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MD Research Degree Thesis

“Aspects of Lupus Nephritis”

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Declarations

I, Eleana Ntatsaki confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Dedications

This is the labour of my academic and research work over the last five years that has culminated in this thesis.

It has been quite a journey…

A move to London, a warm welcome from the UCL research community and the fantastic clinical teams at UCLH and RFH, superb mentors, amazing colleagues…

Great moments of academic inspiration, clinical pearls and life-lessons, musical adventures with Lupus Dave, the honour and fun of becoming a Davette, and performing at the Shakespeare Globe Theatre in aid of Lupus patients…

A lot of hard work, setting up the studies, recruiting the patients, always rushing from the Monday morning UCLH Lupus clinic to the afternoon Lupus clinic at the RFH, questionnaires and surveys, spreadsheet nightmares, stats and graphs…

Many changes and a few challenges too… commuting from Cambridge, moving to London and then back to East Anglia, a new consultant job, a pandemic, a pregnancy and a little baby… cue many sleepless nights; writing up this thesis, finding the motivation and dedication to complete the task in hand, whilst holding my little one in the other…

I would like to dedicate this thesis to my son Jason, the result of my physical labour and my true inspiration for becoming better every day… And to thank my family, especially my husband Vass, who has been my rock and constant support throughout all the ups and downs.

I am grateful for the outstanding mentorship and true support I had from my supervisors, Professors David Isenberg and Alan Salama. As a reflection of this journey and with a clear inspiration from my multi-talented mentors, I have composed "The Researcher" (an alternative take on a classic), as a humorous musical narrative of my academic journey.

Finally, I am very thankful to all the patients that have made my research possible, and I am dedicating the song to them; especially those that sometimes don't comply with their medication, hoping that this research may encourage them to do so!

"The Researcher"

(Alternative take to "The Boxer" by Simon and Garfunkel)

I am just a Rheum Reg from the Eastern Deanery
I have wanted to do research, add some letters to my name,
get an MD (Res) Degree…

All night and day, looking through the pages of the BMJ
For the right job to appear, to start my research career

When I left my home in Cambridge, I was no more than a Reg
In the company of clinicians; in the busy on call rotas of the NHS

Always on the go, seeking out the meetings where academic people go
Looking for the projects, only they would know

"Why oh why, why don't patients take their meds? Why do they not comply?"
asked the Prof in that lecture hall- "*Let's find out"* said I!

Asking only unbanded wages, I come to London for the job, got the perfect offer!
And a welcome to the research teams at UCH and the Royal Free
I do declare there were times when I was busy, just running from here to there…

Why oh why, why don't patients take their meds? Why do they not comply?
Well, I've set my survey up; let's hope they reply!

Then I'm laying out my research kit and wishing I was done doing stats
And the numbers on the spreadsheet keep eluding me, telling me…
"you've got to write up"

In the clinic waits a patient with a long list in her hand,
And she carries the prescriptions of every drug that puts her off
Or tried once… and then threw out… In a rush to cure her pain…
"*I am flaring, I am flaring*", yet all her pills in their box remain

“Why oh why, is my lupus flaring up?” In despair she cries
*“Have you tried to take your meds?” G*uess what she replies

“Why are my kidneys getting worse? Oh, Doctor, will I die?"
“If you never take your meds, the chance is high”

Why don’t patients take their meds? Why do they not comply?
And when we ask them if they do, well… sometimes they lie

Why don’t patients take their meds? Why do they not comply?
It seems they just forget or think they can get by

Why don’t patients take their meds? What else can we try?
Why not use my adherence tool, and if their risk is high

Sit them down and have a chat, and find out why
Why they do not take their meds… convince them to try!

This song was recorded by the band “Lupus Dave and the Davettes” on Saturday 3rd July 2021 at the Rayne Institute, UCL. An audio recording of the song can be found here:

http://bitly.ws/rrjU

Contents

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Abbreviations

AAV ANCA-Associate Vasculitides

ACR American College of Rheumatology

AFLP Acute fatty liver of pregnancy

ANCA Anti-neutrophil cytoplasmic antibodies

ALMS Aspreva Lupus Management Study

APLS Antiphospholipid syndrome,

AZA Azathioprine

BSR British Society of Rheumatology

BVAS Birmingham Vasculitis Activity Score

CQR Compliance Questionnaire-Rheumatology

CNIs Calcineurin inhibitors

CsA Cyclosporine

CT Computer Tomography

CYC Cyclophosphamide

DCVAS Diagnosis and Classification Criteria in Vasculitis

Dx Diagnosis

ECG Electrocardiogram

EDTA European Dialysis and Transplant Association

EGPA Eosinophilic granulomatosis with polyangiitis

ER Oestrogen receptor

ERA European Renal Association

ESRD End-stage renal disease

ESRF End-stage renal failure

ESLN End-Stage Lupus Nephritis

EULAR European League against Rheumatism

FGF Fibroblast Growth factor

GC Glucocorticoids

GPA Granulomatosis with polyangiitis

GPRD General Practice Research Database

GWAS Genome-Wide Association Study

HCQ Hydroxychloroquine

HD Haemodialysis

HELLP Haematolysis, Elevated Liver enzymes and Low Platelets

Ig Immunoglobulin

IL Interleukin

ISN International Society of Nephrology

IVC Intravenous cyclophosphamide

LN Lupus Nephritis

LupusQoL Lupus Quality of Life

MAQ Medication Adherence Questionnaire

MARS Medication Adherence Report Scale

MGLS Morisky Green Levine Medication Adherence Scale

MHC Major histocompatibility complex

MI Myocardial Infarction,

MMAS Morisky Medication Adherence Scale

MMF Mycophenolate mofetil

MPA Microscopic polyangiitis

MPS Sodium mycophenolate

MRI Magnetic Resonance Imaging

MTX Methotrexate

NICE National Institute of Health and Care Excellence

NIH National Institutes of Health

NSAIDS Non-Steroid Anti-inflammatory

OCR Ocrelizumab

PD Peritoneal Dialysis

PLEX Plasma Exchange

PML Progressive multifocal leukoencephalopathy

RCT Randomised Clinical Trail

RFH Royal Free Hospital

RMD Rheumatic and musculoskeletal diseases

ROC Receiver Operating Characteristic

RPS Renal Pathology Society

rTp Renal Transplantation

RTX Rituximab

SNP single-nucleotide polymorphisms

SEAMS Self-Efficacy for Appropriate Medication Use Scale

SELENA Safety of Estrogens in Systemic Lupus Erythematosus National

SOC standard of care

SLE Systemic Lupus Erythematosus

SLEDAI Systemic Lupus Erythematosus Disease Activity Index Assessment

SLICC Systemic Lupus International Collaborating Clinics

TB Tuberculosis

TAC Tacrolimus.

TIA Transient Ischaemic Attack.

TNFα Tumour necrosis factor-α

UCLH University College London Hospitals

US Ultrasound

VAS Visual Analogue scale

VCS Voclosporin

VDI Vasculitis Damage Index

Thesis Abstract

This thesis explores the clinical outcomes of patients with systemic lupus erythematosus (SLE), focussing on Lupus nephritis (LN), specifically on the impact and results of renal replacement therapies on patients and their disease with reference to adherence to treatment. It comprises three separate but related studies. It also reviews the risk factors for renal disease in SLE and their clinical implications as well as the safety of pharmacological treatment options for lupus nephritis.

This thesis reviews a combined cohort of adult SLE patients receiving renal transplants (rTp) over a 40-year period (1975-2015) in two tertiary United Kingdom centres, the Royal Free Hospital (RFH) and University College London Hospital (UCLH), and investigates factors influencing mortality, transplant outcome and disease relapses. My research examines the impact of pre-transplant time on dialysis on survival in patients with LN, and investigates the role of non-adherence in graft survival. It also explores further adherence patterns in the LN population of the combined cohort in UCLH and RFH and compares it with one other autoimmune condition, notably vasculitis.

Study 1 investigated the time spent on dialysis before rTp and survival following rTp in a cohort of SLE patients. This was a retrospective analysis of 40 adult SLE patients receiving rTp over a 40-year period (1975-2015) and identified that time on dialysis before rTp was the only modifiable survival risk predictor (with a hazard ratio of 1.01 for each additional month spent on dialysis) and suggested that more than 24

months on dialysis adversely affected mortality. No other modifiable predictors associated with mortality, supporting that longer time on dialysis pre-transplantation is an independent modifiable risk factor of mortality in LN.

Study 2 examined whether non-adherence is associated with increased rTp graft rejection and/ or failure in patients with LN in the same cohort as Study 1. The role of non-adherence and other potential predictors of graft rejection/ failure were investigated using logistic regression. During a median follow-up of 8.7 years, 17/40 (42.5%) of the patients had evidence of non-adherence. Non-adherent patients had a trend towards increased graft rejection, odds ratio 4.38, (95% confidence interval= 0.73-26.12, p = 0.11.) Interestingly, patients who spent more time on dialysis before rTp were more likely to be subsequently adherent to medication, p=0.01.

Study 3 determined self-reported adherence to medication utilising an anonymised questionnaire-based survey and explored influencing factors in LN and renal vasculitis clinics at UCLH and RFH. I compared 114 patients with LN and 80 patients with renal vasculitis to identify emerging patterns, behaviours and differences that could potentially introduce barriers to adherence. Lupus patients were more likely to be female, younger and with longer disease duration ($p<0.001$). Their adherence decreased with time compared to vasculitis patients ($p<0.001$). Conversely, the patients with vasculitis had higher attendance at clinic appointments ($p=0.02$), and were more confident they could manage to take their tablets correctly. "Forgetfulness" regarding medication, and keeping track of hospital appointments were the most common reasons given for non-adherence rather than deliberate non-

adherence. Increasing age and taking prednisolone associated with better adherence. In contrast, missing even one outpatient clinic appointment associated with worse adherence. Utilising responses from the survey, a prediction model was proposed to further risk-stratify patients regarding their potential adherence patterns that can identify the "at-risk" patient and alert clinicians to the possibility of poor adherence.

Impact statement

My research has focused on exploring aspects of LN, including patients that had undergone renal transplantation for LN, and examining the impact of poor adherence in this and another group of patients. The novel concept arising from my research study 1, is that patients that remain on dialysis for longer periods tend to have a worse overall outcome in terms of mortality. Specifically, for every additional month on dialysis, there was a statistically significant deterioration in prognosis. This suggests that aiming to transplant LN earlier, and ideally before spending 24 months on dialysis, could be pivotal in optimising outcomes. Interestingly, the second study found that adherence is better the longer one stays on dialysis. This highlights that undertaking earlier transplantation (including pre-emptive transplantation) whilst it will be beneficial for patients (study 1) might lead to worse adherence (study 2). Therefore, taken together, these studies suggest that vigorous adherence assessment and support should be offered for patients who have spent little or no time on dialysis prior to early transplantation in order to ensure the best outcomes.

My final study investigated independent factors of adherence in Lupus and Vasculitis patients. This was a mixed qualitative and quantitative survey. Factors associating with adherence included age, poorer outpatient clinic attendance, using steroids, specific beliefs/ attitudes in relation to medication use and their side effects. Utilising these factors, two models were created to identify poor adherence based on *Age/ Prednisolone use/ Full clinic attendance record* for the first model and *Age/ Prednisolone use/ dislike towards taking tablets/ concerns about side-effects* for the second model. Both models showed a good C-statistic for identifying poor adherence. Particularly the first model utilising *Age/ Prednisolone use/ Full clinic*

attendance record can be automatically incorporated and calculated by hospital's Electronic Patient Record (such as EPIC at UCH or VitalData in RFH). Therefore, when reviewing the patients in the clinic or virtually, the physician in charge can be pre-alerted about the risk of poor adherence in the individual they are about to see. Thus, the physician can be aware of this risk and prompt a bit more into adherence patterns and offer educational support to improve this.

Key Points

- Risk assessment for poor adherence in patients with autoimmune disease is essential, and patients with SLE and LN have a higher chance of poor adherence than vasculitis patients.

- Early risk assessment for adherence in all patients with SLE and LN is vital and could be facilitated automatically through electronic patient records.

- Earlier rTp for patients with LN on dialysis leads to better outcomes.

- Adherence is better in patients who have spent longer time on dialysis. Patients who received renal transplantation pre-emptively, or spent little time on dialysis, might be more at risk of poor adherence.

CHAPTER 1

Introduction

Systemic Lupus Erythematosus (SLE)

Definition

Systemic lupus erythematosus (SLE) (or lupus for short) is a multisystem heterogeneous autoimmune rheumatic disease [1]. Its highest prevalence is among women of childbearing age, and it is characterised serologically by the presence of pathogenic antinuclear antibodies which are the primary cause of tissue damage.

Etymology

Origin of the terms "Systemic Lupus Erythematosus" and "lupus"

"Lupus" (n.) from Medieval (late 14th century) Latin lupus meaning "wolf" was used to describe several diseases that cause ulcerations of the skin, apparently because it "devours" the affected part.

"Erythematosus" (Ερυθηματώδης) originates from the Greek word "ερύθημα" describing redness or blushing.

"*Systemic"* from the Greek word" Συστηματικός" describes how the disease affects many different organs and systems in the body.

Historical origin of SLE

Hippocrates first described cutaneous ulcerations calling them "*herpes esthiomenos*" (έρπης εσθιόμενος) which literally translates to "something that spreads by eating"; it

has been proposed that SLE was included under this term [2]. However, the first time the term lupus was used in English literature was in the tenth century by Hebernus of Tours, who was the Archibishop of Tours in France. In his book “Miracles of St. Martin” he presented the case of Eraclius, the bishop of Liège who was suffering from a serious dermatological disease causing him open skin ulcers and sores, which was named as “lupus” [2]. The first actual description of the systemic nature of lupus was reported by Kaposi in 1872. It was not until later, between 1895 and 1904 however, that Osler first described the relapsing/ remitting course of lupus [3].

Clinical presentation

The multisystem clinical presentations of lupus are diverse, ranging from rashes and arthritis to anaemia, thrombocytopenia, serositis, seizures, psychosis and renal involvement. However, lupus nephritis (LN) remains one of the most common severe manifestations of SLE and is associated with significant morbidity and mortality [4]. Although there is considerable variation in the presentation, pathology, course and outcome, at least one-third of SLE patients will develop overt renal disease, with 10–25% reaching end-stage renal failure (ESRF) and 10–20% of patients dying within 10 years [5].

Aetiopathogenesis

The pathogenesis of SLE is multifactorial, involving the interaction of genetic, hormonal and environmental factors that induce antibody production and a systemic inflammatory response leading to the clinical manifestations of the disease [1]. Despite

recent advances in discovering specific genetic loci linked with increased risk of developing SLE and better insights into the cells and molecules implicated in the pathogenesis, the precise aetiopathogenesis remains incompletely understood [6,7]. Different risk factors relate to the expression of specific clinical features, and certain clinical manifestations may be more common in some patient groups that share common characteristics. Genetic, ethnic and hormonal factors influence the presence and severity of specific disease manifestations such as LN [7]. As most of the data come from observational studies, there is still debate and uncertainty regarding the strength of association for many of these factors. For renal involvement, these associations appear to contribute additionally to disease outcome and overall prognosis.

Epidemiology

The incidence of SLE appears to be increasing, though the data may be influenced by better awareness and the development of more sensitive diagnostic criteria. However, SLE remains an uncommon disease [8,9]. Furthermore, there is significant variability in the incidence and prevalence across different countries, with the burden of the disease being considerably higher among non-white racial groups [6,10].

A systematic review of epidemiological studies of SLE by Rees et al. in 2017 [9] reported that North America had the highest incidence and prevalence of SLE, [23.2/100 000 person-years (95% CI=23.4- 24.0) and 241/100 000 people (95% CI=130-352) respectively]. In contrast, Africa had the lowest incidence (probably influenced by under-reporting) and Australia the lowest prevalence. In northern

Europe, the prevalence of lupus starts from approximately 40 cases per 100,000 in white people and exceeds 200 per 100,000 persons among black people. Europe's highest prevalence was reported in Sweden, Iceland and Spain [11].

In the UK, based on the population of the General Practice Research Database (GPRD) , a study by Nightingale et al. from 1992-1998, estimated the overall incidence at rate at 3.02/100000/year [12] and prevalence at 0.041%, with a reported male and female prevalence of 0.01% and 0.07%, respectively. The crude annual prevalence of SLE was reported at 25/100000 in 1992 rising to 40.7/1000000 in 1998.

A more recent retrospective study using the Clinical Practice Research Datalink (CPRD) [13] which was the successor of the GPRD from 1999-2012 found the incidence of SLE to be 4.91/100000 person-years with a declining trend. The incidence estimates difference compared to previous studies in the 1990's may reflect a variation in how the study population was defined and how incident cases were captured. Specifically, in this study Rees et al. used a more comprehensive method for case capture, with three different definitions for cases that allowed inclusion of all cutaneous and systemic subtypes (e.g. renal or cerebral lupus) that potentially allowed a wider estimation of the full breadth of lupus cases in the community. Furthermore, the wider use of electronic records in the new millennium may have enabled more accurate recording. After adjusting for length of data contribution and age standardised analysis, the researchers found a persistent decrease in incidence despite an increase of prevalence with time. Thus they

highlighted that the noticed increase in prevalence suggests that SLE is no longer as “rare” as previously considered, which may have long term implications in terms of healthcare planning .

Classification

For many years the most widely used classification criteria for SLE has been the American College of Rheumatology (ACR) classification criteria, first published in 1971 [14], revised in 1982 [15] and 1997 [16]. These require four or more out of 11 criteria to be present, simultaneously or serially, during any interval of observation for the diagnosis of SLE to be made (Table 1.1)

	ACR criteria for the classification of SLE
Criterion	**Definition**
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion
Serositis	Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/day or > 3+ if quantitation not performed OR
	Cellular casts: may be red cell, haemoglobin, granular, tubular or mixed
Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance OR
	Psychosis: in the absence of offending drugs or known metabolic derangements, e.g. uraemia, ketoacidosis or electrolyte imbalance
	Haemolytic anaemia with reticulocytosis OR

	ACR criteria for the classification of SLE
Criterion	**Definition**
Haematologic disorder	Leukopenia <4000/mm^3 total on two or more occasions OR
	Lymphopenia <1500/mm^3 on two or more occasions OR
	Thrombocytopenia <100 000/mm^3 in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titre OR
	Anti-Sm: presence of antibody to Sm nuclear antigen OR
	Positive finding of aPLs on: • an abnormal serum level of IgG or IgM aCL; a positive test result for LA using a standard method, or; a false positive test result for at least six months confirmed by *Treponema pallidum* immobilisation or the fluorescent treponemal antibody absorption test
ANA	An abnormal titre of ANA by immunofluorescence, or an equivalent assay at any point in time and in the absence of drugs associated with drug-induced lupus syndrome

Table 1.1 The ACR criteria for the classification of SLE

The proposed classification is based on 11 criteria [17]. For the purpose of identifying patients for clinical studies, a person shall be considered to have SLE if at least four of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Adapted from Tan EM *et al.* [15], The 1982 revised criteria for the classification of systemic lupus erythematosus.

In 2012 the Systemic Lupus International Collaborating Clinics (SLICC) group published new validated classification criteria with higher sensitivity than the revised ACR criteria, albeit at the cost of lower specificity [8]. In order to confirm the diagnosis of SLE using the SLICC classification, at least four criteria from a list of clinical and immunological features- including at least one clinical criterion and at least one immunological criterion- should be present, as described in Table 1.2.

In order to fulfil the renal criterion as shown in Table 1.2, the presence of either persistent proteinuria exceeding 0.5g per day (or more than 3+ of protein on urinalysis if quantification had not been performed) or the presence of cellular casts (including red cell, haemoglobin, granular, tubular or mixed) is required. It is worth noting that the renal criterion has remained unchanged throughout all the ACR revisions, confirming that renal involvement is indeed a key clinical manifestation of SLE bearing significant weight when it comes to making the diagnosis and assessing the severity of the disease. The SLICC criteria allow biopsy-proven LN together with ANA and anti-dsDNA alone to be sufficient for making a diagnosis of SLE [8]. However, in addition to the useful diagnostic information for both SLE and LN, a renal biopsy can confirm LN even in asymptomatic patients with silent renal disease, indicating that often clinical features cannot predict the severity of nephritis seen histologically.

The 2012 SLICC classification criteria
Clinical criteria
Acute cutaneous lupus including: • Lupus malar rash (do not count if malar discoid) • Bullous lupus • Toxic epidermal variant of SLE • Maculopapular lupus rash • Photosensitivity lupus rash • Subacute cutaneous lupus
Chronic cutaneous lupus, including: • Classic discoid rash, localised (above the neck) or generalised (above and below the neck) • Hypertrophic (verrucous) lupus • Lupus panniculitis (profundus) • Mucosal lupus • Lupus erythematosus tumidus • Chilblain lupus • Discoid lupus/lichen planus overlap
Oral ulcers including palate or buccal or tongue or nasal ulcers
Non-scarring alopecia
Synovitis involving two or more joints, characterised by swelling or effusion or tenderness in two or more joints and at least 30 min of morning stiffness.
Serositis • Typical pleurisy for more than 1 day or pleural effusions or pleural rub • Typical pericardial pain or pericardial effusion or pericardial rub or pericarditis by ECG (electrocardiograph)
Renal • Urine protein-to-creatinine ratio (or 24-h urinary protein) representing 500 mg protein/24 h • Or red cell casts
Neurologic • Seizures • Psychosis • Mononeuritis multiplex • Myelitis • Peripheral or cranial neuropathy • Acute confusional state
Haemolytic anaemia
Leucopenia (<4000/mm^3 at least once) or lymphopenia (<1000/mm^3) at least once
Thrombocytopenia (<100,000/mm^3) at least once

The 2012 SLICC classification criteria
Immunologic criteria
ANA
Anti-dsDNA antibody
Anti-Sm
Antiphospholipid antibody positivity as determined by any of the following: • Positive test result for lupus anticoagulant • False-positive test result for rapid plasma reagin • Medium- or high-titre anticardiolipin antibody • Positive test result for anti-b2-glycoprotein I
Low complement
Direct Coombs' test in the absence of haemolytic anaemia

Table 1.2 The 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. Reference: Petri et al. *2012* [8]

More recently, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have jointly developed new classification criteria set for SLE published in 2019 [18]. This was prompted by the perceived need for criteria that were both highly sensitive and specific. This set requires positive ANA together with a more extensive list of weighted criteria improved sensitivity and specificity as shown in Table 1.3.

These criteria also perhaps reflect the current thinking about SLE more accurately and, thus, may have better utility in SLE research. However, these are not diagnostic criteria and are not widely used in clinical practice yet. The new classification criteria were developed with multidisciplinary and international input. The rigorous methodological process included 23 expert centres, with each contributing up to 100 SLE patients and non-SLE patients.

	ACR 1997	SLICC 2012	ACR/EULAR 2019
Derivation			
Sensitivity %	85	97	**98**
Specificity %	95	90	**96**
Validation			
Sensitivity %	83	97	**96**
Specificity %	93	84	**93**

Table 1.3 Comparison of SLE classification criteria.
The ACR/EULAR 2019 offer the best sensitivity and specificity compared to the ACR 1997 and SLICC 2012 criteria.

Essentially, they include positive ANA at least once as an obligatory entry criterion; this is then followed by additive weighted criteria grouped in seven clinical (constitutional, haematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and three immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) categories, and weighted from 2 to 10. Patients accumulating ≥10 points are classified. The 2019 EULAR/ACR classification criteria algorithm is shown in Table 1.4.

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Table 1.4 The new ACR/EULAR 2019 SLE classification criteria.

Lupus Nephritis

Although the classification of LN has also evolved over the past 40 years, renal biopsy findings remain of paramount importance in correlating pathological features with clinical symptoms, allowing optimisation of the treatment and improving the prognosis of lupus patients. It is worth noting that lupus patients may present without any specific renal symptoms, but with evidence of microscopic haematuria or proteinuria on routine testing, hypertension or more commonly with a 'nephritic' picture. LN may present as acute renal failure much less frequently or be accompanied by other severe systemic features such as myocarditis or cerebritis.

The importance of screening for renal disease has been highlighted in all SLE guidelines and urine analysis has been found to be a sensitive screening tool. The recent BSR Lupus audit in the UK in 2018 [19] identified appropriate urine protein quantification was one of the key audit standards, and reported that routine clinical practice globally did not reach the proposed standard of 90%. Furthermore, there was significant variation depending on whether care was provided in dedicated versus general clinics (with 85%vs 76% compliance rates to audit standards respectively) and with favourable compliance when patients were seen in specialised centres compared to non-specialized centres (84% vs 78% respectively).

Renal biopsy is recommended in all SLE patients with clinical or laboratory evidence of active nephritis as treatment and prognosis may vary depending on the class [5]. A repeat biopsy should also be considered if the clinical picture changes, as transformation to a different histological class is not uncommon and may be part of

the natural history of the disease or the effect of immunosuppressive treatment. The recommendation from both the European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) [20] and the British Society for Rheumatology (BSR) guidelines [21] for the management of LN is to consider a renal biopsy with any sign of renal involvement in order to guide the treatment choices.

Classification of Lupus Nephritis

The most widely used classification, produced by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003 [22], provides clear, concise and functional categories that reflect the pathogenesis of the various types of renal injury in SLE nephritis (Table 1.5).

A more recent revision of those classification criteria in 2018 by Bajema et al. [23] proposed new definitions for mesangial hypercellularity and cellular, fibrocellular and fibrous crescents. In addition, the term "endocapillary proliferation" was eliminated and the definition of endocapillary hypercellularity reviewed extensively. Class IV-S and IV-G subdivisions of class IV lupus nephritis were also eliminated, and the active and chronic designations for class III/IV lesions replaced by a proposal for activity and chronicity indices.

Summary of the abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)	
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis *The proportion of glomeruli with sclerotic lesions needs to be indicated*
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis *The proportion of glomeruli with fibrinoid necrosis and cellular crescents needs to be indicated*
Class V	Membranous lupus nephritis *May occur in combination with class III or IV*
Class VI	Advanced sclerosing lupus nephritis
In all classes the grade of tubular atrophy, interstitial inflammation and fibrosis, the severity of arteriosclerosis or other vascular lesions must be indicated (mild, moderate, severe)	

Table 1.5 Summary of the abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003) [22].

Lupus nephritis epidemiology

Various studies report on the frequency for renal involvement across patients with SLE. The proportion of patients presenting with LN at the time of SLE diagnosis ranges from 7% to 31% [24]. However the proportion of patients with SLE that ever

develop LN is slightly higher at 31-48% [24–28]. In addition, there are racial, ethnic and regional variations in the incidence, prevalence and prognosis of LN [29,30].

In a retrospective study of 1.5 million renal patients from the US Renal Data System, Sexton et al. calculated standardised incidence ratios and outcomes of more than 15,000 End Stage Lupus Nephritis (ESLN) patients from 1995-2010. The authors suggested that although the increase in end-stage renal disease (ESRD) from LN appears to have stopped in the last decade, racial disparities with worse outcomes in African-Americans continue to exist [31].

The manifestation of LN also appears to be age-dependent with the vast majority of patients developing nephritis early in the course of their disease and usually when younger than 55 years of age, with children having a higher likelihood of developing severe nephritis compared to elderly patients [32]. Specifically, male sex, younger age (<33 years) and non-European ancestry associated with earlier development of renal disease in some reports. African-Caribbean, African-American and Asian ethnicities usually present with more severe renal involvement when compared to other ethnic groups [33]. Moreover, Black and Hispanic patients with LN tend to have a worse prognosis and a higher risk of renal disease and mortality [26,34–39]. Previous studies have also reported greater risks of LN among African and Hispanic Americans compared with European Americans [33,35].

Risk factors

As discussed, demographic and social factors including age, sex, race and socioeconomic status undoubtedly play a role in the development, severity and outcome of LN. However, there are potentially other additional factors predisposing individuals to LN, including genetic, immunological and hormonal causes, as well as clinical and laboratory findings as outlined in Table 1.6, addressed in more detail in the next section.

Ethnicity and social-economic factors

Many studies explore the roles of race and ethnicity as potential powerful drivers of disease. However, these concepts are often not clearly articulated and may cause confusion. To clarify the use of these terms in the context of this thesis, I use the term “ethnicity” as inclusive of cultural and environmental influences, whereas I use “race" as being purely related to genetic inheritance and susceptibility. Although both appear to influence the phenotype, there is still debate as to whether this is primarily genetic (i.e. race) or whether environmental and cultural factors (i.e. ethnicity) also significantly contribute to this observation.

It is well documented that SLE patients from most non-European populations develop renal involvement more frequently than patients of European descent. Such patients are also more likely to be treatment-resistant (specifically to intravenous cyclophosphamide) and generally have a poorer outcome, i.e. develop renal insufficiency and ESRD more commonly and have increased risk of death [26,30,35,38,40–42].

The association between ethnicity, social and renal outcomes has been a subject of much research. There have been many attempts, particularly from the USA, to clarify whether this is due to socioeconomic, sociocultural or other factors, but the results are still controversial. Some studies also suggest that African ethnicity may be an independent risk factor for a worse renal outcome [35,43], whereas others have found it to be significant in univariate analysis only, and losing significance in multivariate analysis when wealth, insurance status and non-adherence with medication were adjusted for [36,37,44–46].

In the UK, an assessment of renal failure over a 25-year period within the UCL SLE cohort with particular reference to ethnicity and race included 401 patients (white patients 64%, black patients 19%) followed since 1978 [30]. Interestingly, black patients were still disproportionately represented in the renal failure group (62% vs 19% for white patients). As health care for patients in the UK is free at the point of delivery, this weakens the hypothesis from the USA that the black population had worse renal outcomes due to socioeconomic reasons and poor access to treatment due to cost. A higher proportion of patients in the renal failure group, however, were non-adherent with treatment. In addition, patients in the renal failure group were also found to have persistently low C3 compared with the rest of the cohort. Although there may still be cultural and other reasons for this observation, the results support the notion that genetic factors, rather than socioeconomic status, are likely to be more significant in predisposing to renal failure. Furthermore, a recently updated review of the same cohort after 40 years of follow up noted that the proportion of non-white LN patients increased throughout the decades [34].

The issue of ethnicity, geographical region, and race is also pertinent to evaluating response to specific treatment options. For example, data from the Aspreva Lupus Management Study (ALMS) trial [39], comparing mycophenolate mofetil (MMF) with intravenous cyclophosphamide (IVC) as an induction treatment for LN by race, ethnicity and geographical region, suggested that severe LN in Black and Hispanic patients may respond better to treatment with mycophenolate mofetil (MMF) than with intravenous cyclophosphamide (IVC) plus corticosteroids. This finding encourages vigilance when deciding on therapy for patients with LN and suggests that race and ethnicity should also be considered, particularly if no benefit is seen with IVC [38,47–49].

Genetic factors

There is ample additional indirect evidence that supports a genetic aetiology both in SLE and LN. The rate of SLE concordance in monozygotic twins is 24%-35%, compared to 2%–5% in dizygotic twin pairs [50–52]. Furthermore, familial aggregation studies in SLE show that more than 10% of SLE patients have first or second degree family members that also have lupus (compared to <1% in controls) with the sibling risk ratio estimated around 30 [50].

Nevertheless, in the last decade, extraordinary progress has been made thanks to the Genome-Wide Association Study (GWAS) technology, which has allowed the number of confirmed loci predisposing to SLE to increase to more than 40. Unfortunately, less effort has focused on the genetics of LN, but this appears to be changing. The International Consortium for Systemic Lupus Erythematosus Genetics

recently published a meta-analysis of three genome-wide association studies of SLE to identify lupus nephritis-predisposing loci [53]. Through genotyping >1.6 million markers were assessed in 2000 unrelated women of European descent with SLE (588 patients with LN and 1412 patients with lupus without nephritis). Logistic regression adjusting for population substructure was used to identify any association. Interestingly the strongest evidence for association was observed outside the major histocompatibility complex (MHC). This included markers localised to 4q11-q13 (relating to the PDGF receptor-α that plays a regulatory role in inflammation), 16p12 (relating to SLC5A11, a sodium-dependent glucose cotransporter responsible for active cellular uptake of glucose) and 8q24.12 (relating to hyaluronan synthase 2 (HAS2) that leads to the production of the extracellular matrix component hyaluronan that accumulates in the renal cortex in immune-mediated kidney disease, producing scarring and pathologic renal fibrosis).

This is important, as MHC genes are linked to an immune response to self-antigens and, therefore a risk of autoimmune diseases such as SLE. In particular, *HLA-A1, B8,* and *DR3* have long been related to Lupus [6,54]. The GWAS study showed evidence of association with lupus nephritis for both HLA-DR2 and HLA-DR3 ($p=0.06$ and $p=3.7\times10^{-5}$, respectively). Another more recent meta-analysis looking into whether specific HLA-DRB1 alleles confer susceptibility or resistance to SLE and LN suggested that HLA-DR4 and DR11 alleles might be protective factors for LN, whereas DR3 and DR15 may be predisposing factors [55]. Their results also suggested that HLA-DR3, DR15, DR4 and DR11 might associate with LN and SLE. The emerging results from this large-scale genome-wide investigation of LN are starting to provide additional and important evidence of multiple biologically

relevant LN susceptibility loci that lead to key proteins, each of which contributes a small increase to the overall risk.

Despite identifying genes associated with an increased risk of developing SLE, the genetic association with LN or end-stage renal disease remains fairly understudied. The main gene polymorphisms relating to LN include the ABIN1 (A20-binding inhibitor of NFκB), APOL1 (apolipoprotein L1 gene), and FcγRIIB (Fc gamma receptor -FcγR) which play a significant role in the clearance of immune complexes. These genes have been associated with an increased risk of LN and vary based on sex and race.

Hormonal issues

SLE is typically considered a disease affecting females of childbearing age with a reported female:male ratio of 8–15:1 [56,57]. However, the ratio drops to 2–6:1 and 3–8:1 for pre-pubertal and post-menopausal populations respectively, thus, suggesting that this difference may be the effect of endogenous sex hormones [58].

The role of oestrogens

The higher incidence of SLE in women suggests that hormones are essential in disease pathogenesis and manifestations. The influence of sex hormones is also seen in animal models. Typically, in mouse models, females have worse outcomes. Indeed, administration of oestrogens may exacerbate the disease whereas androgens tend to ameliorate the disease manifestations [59].

The relationship of sex hormones increasing serum levels of certain cytokines and the oestrogen receptor (ER- from the American spelling estrogen) may be significant in disease development [60]. ERs are nuclear hormone receptors that may directly bind to oestrogen response elements in gene promoters or act as cofactors with other transcription factors. Thus, ERs have significant effects on immune function in the innate as well as the adaptive immune responses. Oestrogen's main effects are mediated via two isoforms of ER, alpha and beta (ER α/β), that are expressed on most immune cells. They can modulate the cytokine production (increased interferon-*γ* (INF*γ*), TNF*α*, TGF*β*, interleukin (IL)-1, IL-5, IL-4, and IL-10 production) and affect many different key target cells of the immune system, such as T cells, B-cell precursors, and circulating B cells, as well as dendritic cells.

In addition to the oestrogen exposure, other proposed contributors for the female predominance in SLE are genetic and epigenetic mechanisms and microbiota gut changes [61]. SLE-associated single-nucleotide polymorphisms (SNPs) and epigenetic modifications such as DNA methylation and histone modification play an important role in the sex predilection in SLE. Furthermore, the aberrant X chromosome gene dosage is implicated in the development of sexual dimorphism in SLE, as it may have a pathogenetic role in SLE, which is more prevalent in cases of rare X chromosome abnormalities.

Finally, microbiota dysbiosis may play a role in this sexual dimorphism, the altered gut environment with increased permeability possibly contributing towards a female

predominance in SLE. However, the majority of data referring to the contribution of gut microbiota come from murine studies. Therefore, for the pathophysiological mechanisms to be extrapolated to humans, further studies are necessary to elucidate any potential pathogenic role of the microbiota gut [62].

SLE phenotype in males

Despite males being protected in terms of incidence of disease, probably as a result of a difference in oestrogens and other gonadal hormones leading to an alteration in the immune cell function [63–66], some European and US studies appear to show an increased incidence of renal involvement in men [67]. In the last 20 years however, there have been around 25 attempts to distinguish a distinct male lupus phenotype- and only a small number of studies have suggested that more aggressive disease is found in males with SLE [68,69].

A review study by Murphy et al. looked into whether gender exerts an influence on the clinical presentation and outcome of SLE. It specifically compared the incidence of LN in men and women in four different geographical domains including Asia, Europe, USA and Latin America and concluded that there did not appear to be a significant difference in terms of LN, objective indices of disease activity and mortality between the two sexes [58]. Surprisingly, only two of the studies reviewed demonstrated an increase in renal failure in male subjects [67,69] with no evidence to suggest a predilection for any particular histological class of LN. Thus, Murphy et al. [58] concluded that the association between male gender and nephropathy in SLE remains questionable. Furthermore, multiple other confounding factors such as

hypertension (typically more prevalent in males), race and age at diagnosis also influence renal disease and few studies made the relevant statistical adjustment to account for those variables.

Therefore, despite the suggestion that men with lupus demonstrate a distinct and different disease profile and perhaps a more aggressive disease course particularly when it comes to LN, the available evidence to date does not appear to support this notion, but rather implies that the presence and outcome of LN in men and women appears to be broadly similar.

Pregnancy and lupus nephritis

Pregnancy represents a period of intense hormonal changes. Mild flares of SLE are common throughout pregnancy; however, renal involvement is less common. Nonetheless, severe renal flares with permanent impairment of renal function, even though relatively uncommon, can still occur [70]. Pregnancy in women with LN is associated with an increased risk of foetal loss (up to 75%), and some researchers report worsening of the renal and extra-renal manifestations during pregnancy; however, this is not universally supported [71,72].

The best outcome in pregnancy is obtained if the disease is quiescent for more than six months pre-conception and if the renal parameters at conception are well controlled (i.e. serum creatinine less than 140 micromole/l, proteinuria less than 3 g/24 hours and normal blood pressure) [71]. Pregnancy success rate varies from 20% to 95% depending on baseline creatinine [48], and the risk of foetal loss is significantly

increased by at least 2-3 times compared to the non-SLE population (often linked to the presence of antiphospholipid antibodies). Unfortunately, because of overlapping clinical features, like worsening proteinuria between LN and pregnancy complications such as pre-eclampsia, diagnostic delays may occur. In women with chronic renal disease, pregnancy may accelerate the decline in renal function and exacerbate existing hypertension and proteinuria, with a higher risk of maternal (e.g. pre-eclampsia) and foetal complications (e.g. intrauterine growth restriction and intrauterine death); with all of these complications strongly correlating with the degree of renal impairment peri-conception. Secondary complications such as HELLP (Haematolysis, Elevated Liver enzymes and Low Platelets) and AFLP (Acute Fatty Liver of Pregnancy) can also cause acute on chronic renal failure for the mother. The complexity of these patients makes it universally accepted that they should be managed in a multidisciplinary team of physicians, obstetricians and counsellors.

Age

Hormonal changes may also be implicated in age-related factors and SLE, explaining some differences noted in the type and severity between early and late-onset LN with more aggressive phenotypes noted at the younger age spectrum. A prospective study on the effect of age on renal damage in a cohort of new-onset SLE patients with renal disease by Mak et al. [32] used a linear regression model on 149 SLE patients (134 women and 15 men), including 28 childhood, 107 adult and 14 late onset SLE patients. They found that the prevalence of renal disease was 53% in

childhood onset (age <16 years), 50% in adult onset and 58% in late onset (≥ 50 years) SLE patients. In addition, their study concluded that the prevalence of renal disease, histological classes of nephritis and initial response to treatment did not differ significantly among the patients of different ages of onset. However, patients with late onset SLE had more renal damage accrual, but age failed to correlate with renal damage after adjustment for various clinical parameters.

Paediatric lupus nephritis

Papadimitraki and Isenberg [73] suggested that paediatric lupus patients present with slightly different phenotype when compared with the adult-onset population. An increased male-to-female ratio, with a higher prevalence of nephritis and cerebral involvement and a higher prevalence of progression to end-stage renal disease, were reported as distinguishing features of childhood-onset lupus.

A European study on paediatric lupus nephritis by Ruggiero et al. [74] analysed 161 Italian paediatric patients with LN from 1978 to 2010 and estimated that 55% of patients had LN at disease onset. They reported that although many children present with severe renal disease at SLE onset, they may not fulfil an adequate number of the ACR criteria to be diagnosed with SLE. Hence, they also suggested that the clinical picture of SLE may often be less characteristic in paediatric patients, thus making the correct diagnosis more challenging.

Adolescent-onset SLE nephritis

Although there have been limited studies in adolescents, there are data to suggest that adolescent-onset SLE is associated with a more aggressive phenotype of disease and increased risk of LN with a marked increase in mortality. In a large tertiary referral centre UK based cohort [75], 124 individuals diagnosed with SLE between 11-18 years of age associated with more frequent LN on both univariate and multivariate analysis when compared to the adult onset SLE control group. The standardised mortality rate was also significantly increased in females with adolescent-onset SLE, with a risk almost fifteen-fold compared with patients with adult-onset SLE.

Adherence to treatment in adolescents with chronic diseases is an ongoing challenge, with rates varying widely, from 10% to 89% [76] and can contribute to worse outcomes and faster progression to more severe disease. For example, a study specifically in SLE patients found that 29% of adolescents and young adults were non-adherent as defined by undetectable blood hydroxychloroquine (HCQ) concentration, and that medication adherence estimates using blood HCQ concentration correlated with adherence rates as measured using pharmacy refill information (Pearson correlation coefficient $r = 0.50$, $p < 0.0001$) [77].

Antibody profile

Over 100 different autoantibodies have been identified in the serum of patients with SLE. Of these only a few however, including antibodies to single and double-stranded DNA, RNP, poly (ADP-ribose), anti-histone, anti-nucleosome and anti-C1q, have been found in more than 30% of the patients. Of this relatively small number,

only antibodies to dsDNA, C1q and nucleosomes have been linked strongly to LN. It is however true that some others, including anti-Sm and anti-Ro, have been eluted from the kidneys of patients with lupus [78], which suggests they may have a pathogenetic role, although this is not proven yet.

There is extensive literature on the topic of anti-dsDNA antibodies and lupus nephritis [79]. From animal model studies and clinical observations, it does seem highly likely that at least some anti-dsDNA antibodies are genuinely pathogenic. Moreover, there are many reports of an increase in anti dsDNA (and anti-nucleosome) antibodies rising concomitantly with, or in advance of, the overt development of LN [80] and the recent use of rituximab as a first-line agent in LN was in many cases associated with improvement both in the nephritis and in the level of anti dsDNA antibodies [81].

Antibodies to C1q have also been linked to the presence of LN, although not in every study [82]. A rise in the levels of these antibodies predicts renal flare in some but not all patients.

Clinical Implications

Mortality, morbidity, ESRF and outcome predictors

LN is a significant cause of mortality and morbidity amongst SLE patients. The survival, renal outcome and long-term prognosis of LN have been studied in long-term follow-up cohorts spanning over decades in different geographic areas [83–85]. Several clinical outcome predictors among findings registered at the time of the first renal biopsy have been identified as prognostic factors, as shown in Table 1.6.

A large Danish cohort of 100 patients diagnosed with LN (World Health Organization classes I–VI) had a median follow-up duration of 15 years [83]. The cumulative renal survival after 5, 10, and 20 years of follow-up was 87%, 83%, and 73%, respectively. Systolic blood pressure ≥180 mmHg, focal segmental nephritis, and advanced sclerosing nephritis were identified as baseline predictors of mortality in multivariate regression analyses, while systolic blood pressure ≥180mmHg, serum creatinine level ≥140μmoles/L and diagnostic delay predicted progression to ESRD. At the histologic level, they identified advanced sclerosing (WHO class VI) LN and focal segmental (WHO class III) LN as strong baseline predictors of death. It was also noted that the risk of ESRD did not change significantly across calendar-year periods.

The Systemic Lupus International Collaborating Clinics inception cohort (≤15 months of SLE diagnosis) study reported that patients with nephritis had a higher risk of

death (HR = 2.98, 95% CI=1.48- 5.99; p = 0.002) [25]. Similar findings have also been reported from other European cohorts.

A 30 year period review of the University College London cohort by Croca et al. [84] reviewed 156 LN patients followed up between 1975 and 2005. They reported a 60% decreased rate in the 5-year mortality between the first and second decades, which thereafter remained stable over the third decade. There was a clear increase in ESRD development and mortality among Afro-Caribbean patients. In addition, there was a strong association between Afro-Caribbean patients and higher prevalence of Class V type nephritis. Type V nephritis is usually associated with heavy proteinuria and hypoalbuminemia and resistant hypertension [86] and in its pure form occurs in 10–20% of patients with LN. Typically, the proliferative types of nephritis (Classes III and IV) are associated with a poorer prognosis. A recent follow-up study of the UCLH cohort to 2015 by Gisca et al. confirmed that the 5–year mortality rates stabilised from 1995 onwards and the progression to ESRD remained stable over the decades [34].

Risk factors for Lupus Nephritis	
Demographical Age Sex Race/Ethnicity **Environmental** Geographical Socioeconomic status **Genetic** Genetic polymorphisms GWAS Epigenetic Microbiota gut changes **Hormonal** Age Sex **Immunological** Autoantibody profile Anti-dsDNA Anti-C1q Anti-phospholipid Anti-Sm Nucleosomes Anti Ro Podocyte protein phosphorylation (Tubulin) Alpha actinin **Histopathological** Light microscopy, immunofluorescence WHO /ISN-RPS Classification	**Clinical and laboratory markers** Elevated serum creatinine Glomerular filtration rate Urinary abnormalities Hypocomplementemia Low haematocrit Nephrotic syndrome Proteinuria Persistent arterial hypertension **Activity and chronicity indices on biopsy** Cellular crescents and fibrinoid necrosis Tubular atrophy and interstitial fibrosis Histological transformation Location of immune deposits Capillary thrombosis **Treatment regimens/ Drug exposure** -Non-adherence to treatment -Delay in institution of cyclophosphamide -Cyclophosphamide/corticosteroid combined versus corticosteroid alone -Maintenance immunosuppression -Nephritic renal flares -Failure of remission in the first year

Table 1.6 Factors that may influence the presentation and/ or prognosis of lupus nephritis [87].

Assessment of SLE

A systematic approach should be taken to assess and monitor disease activity and damage because of the diversity and complexity of clinical and laboratory manifestations in SLE patients. The presentation and different clinical manifestations observed may be due to one or any combination of the following:

- disease activity (from active inflammation or thrombosis)
- acute drug toxicity
- chronic damage
    - due to the effects of the disease
    - due to treatment (e.g. atherosclerosis or lung fibrosis)
    - due to concomitant disease (e.g. myositis)
- co-morbidity (e.g. infection)

Taking a detailed history (including review of drugs, vaccinations and adherence concerns) and performing a thorough clinical examination (including vital signs and urinalysis) are of paramount importance in the context of SLE in order to establish the likely differential diagnoses and investigate appropriately further.

The BSR guidelines for SLE suggest a combination of laboratory and other investigations as indicated at initial assessments and then at appropriate intervals for monitoring of progress (1-3 months in active disease and 6-12 months for monitoring stable disease) [21].

These investigations include:

- Basic blood tests
    - Full blood count and other tests for anaemia, renal function, bone profile, liver function tests, Creatine kinase, CRP, vitamin D3 and thyroid function.
- Immunology
    - ANA, Anti-dsDNA titre, C3/C4 level, aPL antiphospholipid antibodies (aPL) (Lupus Anticoagulant (LA), anti-cardiolipins (aCL), anti-beta2-glycoptroteinI), Anti-Ro/La, anti-RNP and anti-Sm antibodies , Immunoglobulins, Direct Coombs' test
- Urine
    - Urinalysis (screen for proteinuria, haematuria, leucocyturia and nitrites to exclude infection)
    - Urine random protein: creatinine ratio or 24-h urine collection for protein
    - Urine microscopy (and culture)
- Other investigations
    - Microbiology, Biopsy (e.g. skin, kidney), Lung function tests, Neurophysiology, ECG (when indicated)
- Imaging
    - Chest X-ray or other imaging (US, CT, MRI) as indicated

It is vital to assess relevant comorbidities and modifiable cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes mellitus, high BMI and smoking. Moreover, when considering disease activity with a view to planning treatment, it is necessary to determine the circumstances that may have led to a lupus flare (e.g.

ongoing or recent infection, hormonal changes, timing of previous therapeutic change, or risk of non-adherence). This will provide a further guide to appropriate investigations, treatment change, non-drug measures and lifestyle advice, required support for maintaining good adherence and finally, the disease monitoring needed thereafter. It is also recommended that patients are managed in centres with experience in lupus, as this is associated with better outcomes.

Regarding disease activity assessment, both the BSR [21] and the EULAR/ACR [20] guidelines recommend using validated assessment tools to assess disease activity reliably. These are defined instruments that are purpose-built and validated for SLE and are widely used in research and clinical practice.

Assessment Tools

Disease activity

Over the last 40 years, the lupus community has invested a lot of time and effort in producing tools to reliably capture disease activity and cover the spectrum of clinical presentations of this complex multisystem disease. More than 60 different scales have been devised, but not all have been validated or shown to be effective, reliable and user friendly.

The currently recommended assessments are the latest revised versions of the BILAG-2004 index by the British Isles Lupus Assessment Group, including data collection form, glossary and scoring); and the SLEDAI-2K (Systemic Lupus

Erythematosus Disease Activity Index) or the SELENA-SLEDAI. The SELENA-SLEDAI is a slightly modified version of the SLEDAI, developed for a National Institutes of Health-sponsored multicentre study of oestrogen/ progesterone hormone use in women with SLE: Safety of Estrogens in Systemic Lupus Erythematosus National Assessment (SELENA) [88].

For these tools to be accurate and reliable and perform well, it is essential that only manifestations/ items due to SLE disease activity are recorded and that the data collection forms are used in conjunction with the appropriate glossary and scoring rules. Furthermore, relevant training in the use of these instruments is advised.

The use of disease activity tools enables the stratification of disease activity to mild, moderate and severe lupus, depending on the scoring on these assessment tools.

Damage

The Systemic Lupus International Collaborating Clinics/ American College of Rheumatology damage index (SLICC/ACR Damage Index (SDI)) [89] is the recommended validated instrument for assessing damage. It is constructed to help capture items of irreversible changes occurring after the diagnosis of SLE is made.

Quality of life questionnaires

It is recommended that the patients' own assessment of their disease and the impact on their health and life is captured using health status or quality of life

questionnaires. The generic Short Form36 (SF-36) has been validated for use in lupus [90]. However, there is also a lupus-specific questionnaire, the Lupus Quality of Life (LupusQoL) that can be used [91].

Disease severity

The utility of these tools is to assist in stratifying disease to mild, moderate or severe and tailor accordingly the management plan. The BSR guidelines have provided an algorithm and a structured approach to diagnosis and management depending on the severity of the above assessment tools. This is summarised in Table 1.7 and Figure 1.1.

Management of SLE

General principles

There is no cure for SLE, and the goals of treatment are to manage symptoms, disease activity and prevent long-term complications.

However, there are general measures for most lupus patients that reduce the risk of flare and improve their general well-being, such as sun protection, smoking cessation, healthy diet, exercise, and avoiding trigger factors and specific medication. All patients should be offered Hydroxychloroquine (HCQ) unless there is a contraindication. Further specific management recommendations are summarised in Table 1.7 showing the BSR recommendations for induction and maintenance treatment for SLE according to disease severity.

Table 1.7 **BSR Guidelines summary**	**Mild activity/flare**	**Moderate activity/flare**	**Severe activity/flare**
	BILAG **Any C scores** **or single B score;** **SLEDAI <6**	**BILAG** **Two or more systems with B scores;** **SLEDAI 6–12**	**BILAG (non-renal)** **One or more A scores;** **SLEDAI >12**
SLE Manifestations	Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia platelets 50–149 × 10^9/l	Fever, lupus-related rash > 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25–49 × 10^9/l	Rash involving >2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets <25 × 10^9/l
INDUCTION Initial typical drugs and target doses if no contra-indications	• Topical Corticosteroids preferred • or oral prednisolone ≤20 mg daily for 1–2 weeks or • or i.m. or IA methyl-prednisolone 80–120 mg	• Prednisolone ≤0.5 mg/day • or i.v. methyl-prednisolone ≤250 mg × 1–3 • or i.m. methyl-prednisolone 80–120 mg	• Prednisolone ≤0.5 mg/day • and/or i.v. methyl-prednisolone 500 mg × 1–3 • or prednisolone ≤0.75–1 mg/kg/day
	• and HCQ ≤6.5 mg/kg/day • and/or MTX 7.5–15 mg/week • and/or NSAIDs (for days to few weeks only)	• and AZA 1.5–2.0 mg/kg/day or MTX (10–25 mg/week) or MMF (2–3 g/day) or cyclosporin ≤2.0 mg/kg/day • and HCQ ≤6.5 mg/kg/day	• and AZA 2–3 mg/kg/day or MMF 2–3 g/day or CYC i.v. or cyclosporin ≤2.5 mg/kg/day • and HCQ ≤6.5mg/kg/day
MAINTENANCE Aiming for typical **maintenance** drugs/doses providing no contra-indications	Prednisolone ≤ 7.5 mg/day	Prednisolone ≤7.5 mg/day	Prednisolone ≤7.5 mg/day
	and/or MTX 10 mg/week	• and AZA 50–100 mg/day • or MTX 10 mg/week • or MMF 1 g/day • or cyclosporin 50–100 mg/day	• and MMF 1.0–1.5 g/day • or AZA 50–100 mg/day • or cyclosporin 50–100 mg/day
	and HCQ 200 mg/day	and HCQ 200 mg/day	and HCQ 200 mg/day
	Aim to reduce and stop drugs except for HCQ eventually when in stable remission	Aim to reduce and stop drugs except for HCQ eventually when in stable remission	Aim to reduce and stop drugs except for HCQ eventually when in stable remission

Table 1.7 shows the BSR Guidelines summary of SLE manifestations and treatment recommendations for induction and maintenance according to disease severity [21].

Hydroxychloroquine

HCQ is an alkalinizing lysosomotropic drug that accumulates in lysosomes, where it inhibits important functions by increasing the pH. Although initially it was used as an antimalarial drug, HCQ has proved to be effective in many autoimmune diseases and has been used in lupus for more than 60 years [92].

HCQ is currently recommended for all patients with SLE and is the cornerstone baseline drug featuring in all SLE and LN management guidelines. There is ample evidence for multiple beneficial effects of HCQ in SLE, yet despite this, poor adherence to treatment is actually very common [93]. Drug blood levels can be used to assess compliance, but currently, this is not routinely done in clinical practice, although it is common to monitor drug levels in the context of research trials.

HCQ is considered a comparatively safe drug and may be prescribed to pregnant women. However, some cautions are needed to prevent retinopathy, a rare but severe complication of prolonged use of HCQ that has led to more sensitive screening techniques, with a prevalence of retinal abnormalities exceeding 10% after 20 years of continuous use. Additional risk factors for retinopathy include duration of treatment, dose, chronic kidney and pre-existing retinal or macular disease [94].

However, the risk of toxicity is very low for doses below 5 mg/kg real body weight, and current recommendations suggest that the daily dose should not exceed this threshold. Thus, the traditionally prescribed dose of HCQ of 6.5 mg/kg/day, which

has been established as efficacious in clinical trials, has been challenged, supporting that dose-optimization is key in balancing the risks of toxicity versus the risk of sub-therapeutic levels.

Treatment for SLE and Lupus Nephritis

When glucocorticoids (GC) were first introduced for SLE treatment in the 1950s, the survival rate for SLE was very poor, at less than 50% at 4 years. Despite concerns about possible adverse effects of GC on renal function, Muehrcke et al. in 1955 [95] first showed GC improved patient outcomes. As new therapies and trials became available, the management of SLE has been modified significantly, including evidence-based potent immunomodulators and biologic agents as shown in Figure 1.1, indicating the currently accepted pathways for SLE management and Table 1.7 for SLE and 1.8 for LN.

In parallel with the advancement in the management of SLE in general, the management of LN has also changed significantly over the last 15 years with emerging evidence and guided the formulation of two key concepts:

- the induction of remission, aiming to minimize damage to the nephrons by dampening inflammation in the kidney, and
- the maintenance phase of immunosuppressive therapy, aiming to consolidate the remission and reduce the long-term risk of relapse [96].

More recently, there has been a proposal for a hybrid concept of continued combination therapy without the distinctive two phases [97], which will be discussed in more detail in the biologic drugs section of this thesis.

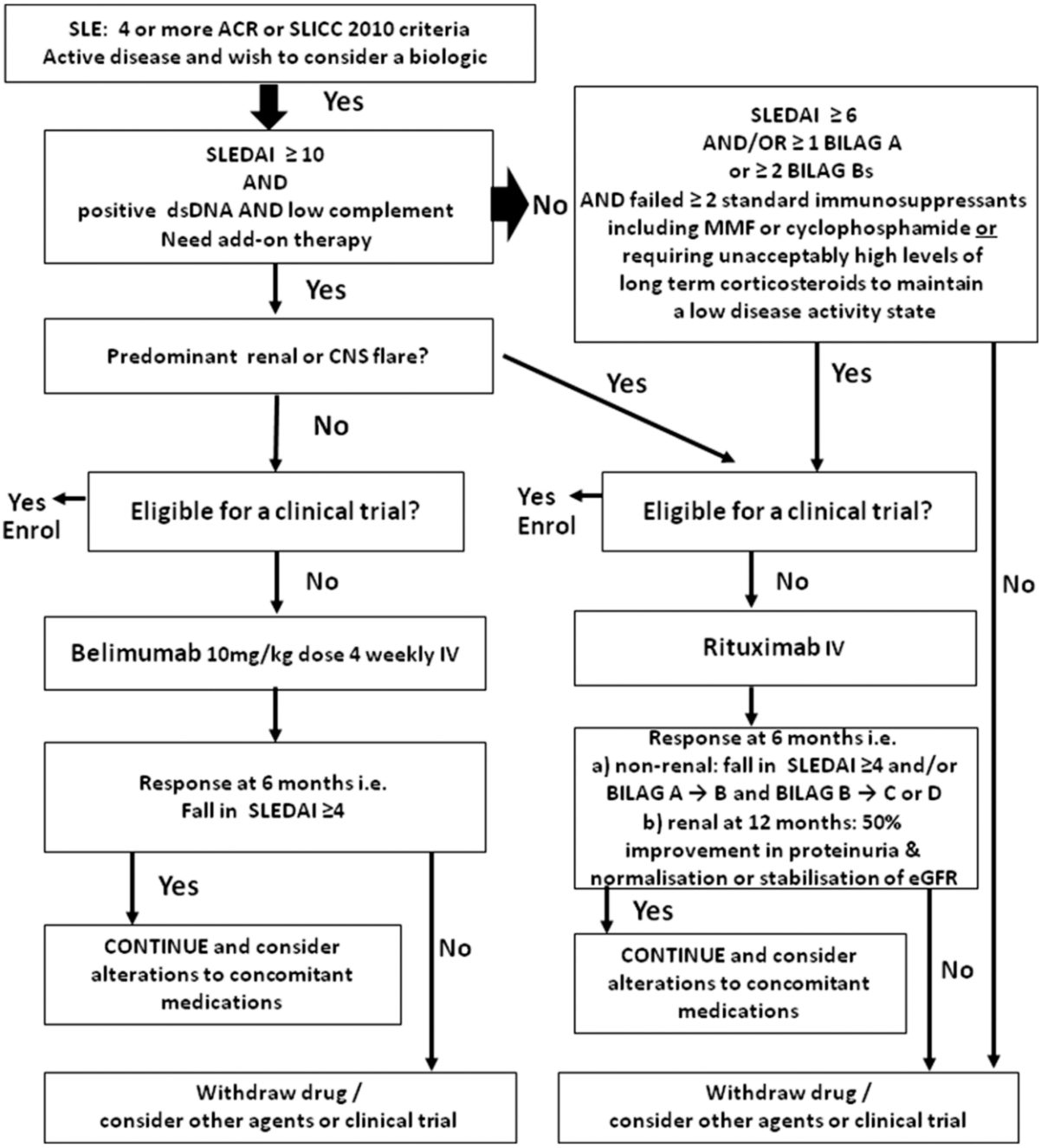

Figure 1.1 Management Algorithm from the British SLE guidelines [21].

Although LN may affect all the compartments of the kidney, what is of significant concern is glomerular involvement. Treatment has largely thus been guided by histological findings as defined by the International Society of Nephrology (ISN)/ Renal Pathology Society (RPS) classification [22] considering the presenting clinical parameters and the degree of renal impairment as shown in Table 1.8.

Initially, optimizing cyclophosphamide and glucocorticoid regiments and the introduction of mycophenolate mofetil for proliferative and membranous LN were pivotal. But despite improving the prognosis, up to a quarter of LN patients could still progress to ESRD [98] with increased morbidity and mortality [99].

Whilst the improvement seen was a step in the right direction, nevertheless, concerns remained about treatment toxicity, especially long-term glucocorticoid use and exposure to cumulative cyclophosphamide doses. In the next section, I will discuss the initial therapies in more detail and the more recent advancements in the management of LN.

LN classification-treatment traditional regimens depending on the Class of LN		
	Induction	**Maintenance**
Class I	Immunosuppression treatment for LN not needed. Treatment should be guided by extra-renal manifestations.	
Class II	Immunosuppression treatment for LN not needed at the beginning. Proteinuria should be considered. - If proteinuria < 1g/daily treatment dictated by extra-renal manifestations. - If proteinuria > 3g/daily treatment GC with or without immunosuppressant drugs (CNIs) to spare dose of GC during 6/12 months. - If proteinuria 1-3g/daily individual evaluations should be made.	
Class III-IV (A)*	GC and immunosuppressant drugs (CYC or MMF).	Lower dose of GC and immunosuppressant drugs (MMF, AZA, and MPS).
Class V	GC and immunosuppressant drugs (CYC, MMF, CsA, TAC or AZA). If non-responder with one of the immunosuppressants, consider the other.	Lower dose of GC and Immunosuppressant drugs (MMF, AZA, CsA).
Class VI	Decreasing immunosuppression unless extra-renal lupus activity.	

LN: lupus nephritis, GC: glucocorticoids, CNIs: calcineurin inhibitors, AZA: azathioprine, MMF: mycophenolate mofetil, CYC: cyclophosphamide, MPS: sodium mycophenolate, CsA: cyclosporine, TAC: tacrolimus.

*Treatment considered for active or active plus chronic lesions.

Based on KDIGO guidelines: Lupus nephritis. Kidney International Supplements (2012) 2, 221–232; doi:10.1038/kisup.2012.25

Table 1.8 shows the LN classification-treatment traditional regimens depending on the Class of LN

Conventional induction and maintenance therapy for LN

Glucocorticoids

Initially, moderate to high doses of GC was the primary therapy used together with a cytotoxic drug for remission induction. However, since the 1980s, a second immunosuppressive agent was co-administered.

Glucocorticoid dosing considerations

The optimum dose of GC remains controversial, trying to balance the effect of GC against the potential side-effects. For induction, most guidelines (KDIGO, American College of Rheumatology and the European League Against Rheumatism/European Dialysis and Transplantation Association) previously recommended either moderate/ high dose prednisolone (or equivalent) of up to 1mg/kg/day during 2 or 4 weeks followed by tapering schedules. In more severe forms of LN, intravenous pulses of methylprednisolone (250-1000mg/day) were considered during the first 3 days. However, more recently, studies [100] showed equivalent efficacy at lower doses and thus, in both British and European guidelines, GC induction reduced intravenous methylprednisolone dose to 500-2500 mg (allowing flexible dosing depending on disease severity), and starting oral prednisone dose to 0.3–0.5 mg/kg/day, reducing to ≤7.5 mg/day by 3–6 months [17,20].

Glucocorticoid safety concerns

Whilst long-term damage and increased mortality are established complications of GC, it is also evident that there is a direct linear correlation between a higher dose of GC and side effects. Serious side effects include increased infection risk, diabetes, high blood pressure and osteoporosis. Other adverse complications include ecchymosis, leg oedema, parchment-like skin, dyspnoea and sleep disturbance. A "threshold pattern" has also been described at >7.5 mg/day of prednisolone for glaucoma, depression, insulin resistance and hypertension and at >5 mg/day for epistaxis and weight gain. But even lower doses can cause complications such as cataracts which can rarely be observed even with <5 mg/day [101].

While susceptibility to major infection usually occurs with doses of >7.5mg/day, this too has a dose-related effect, and clinical vigilance is required to identify opportunistic infections like tuberculosis reactivation, Pneumocystis Jiroveci pneumonia, or overwhelming strongyloidiasis [102]. Cardiovascular risk is another major concern; a study from the Hopkins Lupus Cohort suggested that longer use of steroids, effectively indicating higher cumulative dose taken, was associated with higher cardiovascular disease [103].

Other life-changing complications are also evident, including up to 24% of patients with lupus are found to have osteoporosis, including premenopausal patients, with a 1.2-fold increased fracture risk when compared with age and sex-matched controls [104]. This mineral bone-loss effect of GC in LN patients is aggravated by the

nephropathy. The risk of fracture depends on the dosage and duration of GC therapy. Specifically, after three months of GC use, the relative risk of vertebral fracture increases from 1.55 to 5.18 when the dose is increased from 2.5mg/day to >7.5mg/day [105]. Furthermore, there is a 7-fold increase in hip fractures and a 17-fold increase in vertebral fractures with doses ≥10mg/day [106], indicating that chronic and high use of GC can lead to significant comorbidity.

More pertinent to renal disease, prolonged use of GC may increase proteinuria by increasing the glomerular filtration rate and decreasing tubular reabsorption. This effect is, however, reversible, although there are limited relevant data available for this [107].

Induction without Glucocorticoids?

Although GC have historically been considered a mandatory component for treating LN, emerging evidence has challenged this assumption. An observational trial of Rituximab (RTX) combined with IV methylprednisolone followed by MMF in 50 patients with LN (class III, IV or V) showed that most subjects achieved complete renal remission without any oral GC [108]. A randomized controlled trial (RCT) (RITUXILUP) [109] seeking to answer this very fundamental question of efficacy with steroid-avoiding regimens, to obviate the burden of long-term GC related adverse effects, was unfortunately prematurely terminated. Ironically, this was due to the inability to recruit enough patients that were not on steroids, which paints a picture about the scale of the steroid usage issue.

There is an ongoing desire within the lupus community to explore the concept of steroid-free or steroid “light” regiments. Many of the new trials for novel biologics that will be discussed later in my thesis have supported this paradigm, and it seems that there may be a new era with less use of steroids approaching in SLE management.

Furthermore, steroids are the “marmite” of all medication- either loved or loathed by patients. To that end, there are always concerns regarding adherence, in both ways; either not taking them because of the side-effects or taking more than advised due to the masking of undesired symptoms and energy-boosting effects. However, most patients on steroids have strong feelings and perceptions regarding their effects and side effects that may not always align with that of their clinicians. A study looking at a sample of just over 600 UK-based respondents who were taking GCs for a variety of conditions, including 82 patients with SLE, ranked the GC related side effect of most importance to responders as follows: weight gain was first, followed by insomnia and moon face with equal median score [110]. Three serious side-effects, cardiovascular disease, diabetes and infections, were ranked of lower importance overall. The sub-analysis of the 82 SLE patients showed that the top-ranking concerns were weight gain, reduced bone strength and moon face. Although the three most highly rated side-effects, were not the ones associated with the worse long term clinical outcomes, nonetheless, they remained important to patients, perhaps reflecting their impact on quality of life and high prevalence. Therefore, this ought to be considered when negotiating treatment options with individual patients and planning future studies concerning GC safety or “steroid-free” or “steroid-light” regiments.

Table 1.9 summarizes the main safety concerns regarding steroids and the ranking of the patients' perception of importance of those symptoms in the SLE cohort of the above study by Costello et al. [110]. Chronic damage items are in italics.

Side Effects ***Chronic Damage***	**Patient Ranking**	**Consequences**
• Weight gain / *Obesity* • *Osteoporosis* • Swelling/ Facial swelling • High blood pressure • Infection • Depression/ mood swings • Blurry vision/ c*ataracts/ glaucoma* • *Cardiovascular disease* • Palpitations • Insomnia • Easy bruising • *Type 2 diabetes mellitus* • Indigestion • Acne, hirsutism Other items not ranked • *Muscle atrophy* • *Avascular necrosis*	1 2 3 4 5 6 7 8 9 10 11 12 13 14	• Medication intolerance • Polypharmacy; (additional medications needed to control side-effects attributed to corticosteroids increases medication burden) • Increased cost of care • Chronic debilitating comorbid conditions • **Poor medication adherence**

Table 1.9 Side effects as ranked by patients in SLE. Weight gain, general swelling and facial swelling were the most frequently mentioned side effects by patients.

Conventional Immunosuppressive drugs

Azathioprine.

Azathioprine (AZA), a purine analogue drug acting at the level of DNA replication, can block the "de novo" pathway of purine synthesis [111] and has been used in the treatment of LN since the 1960s mainly as maintenance treatment. A pooled analysis including 250 patients with LN published in 1984 confirmed the superiority of AZA or CYC together with GC than GC alone [112] and established AZA in routine use.

AZA is well tolerated overall, with studies confirming it is at least as well tolerated as Cyclophosphamide (CYC), cyclosporine (CsA), MMF or tacrolimus (TAC)[113]. One rare complication of AZA is in homozygous patients with a genetic polymorphism that reduces the thiopurine methyltransferase enzyme activity (found in about 0.5% of the population) and can lead to significant toxicity. The patients are thus routinely checked for this polymorphism before AZA initiation.

Cyclophosphamide.

Cyclophosphamide (CYC) was the gold standard induction therapy together with GC [114] for severe LN for over 30 years [115]. The National Institutes of Health (NIH) recommended high-dose intravenous CYC as first-line induction treatment for LN (0.5-1g/m^2 monthly x 6 followed by quarterly pulses for 2 years) as it had fewer side-effects than prolonged daily oral CYC regimens [114]. Shorter courses (monthly CYC for six months) were safer than longer courses (notably monthly CYC for six months and quarterly pulse cyclophosphamide for 2 additional years) as they had lower

ovarian failure, at the expense of higher exacerbations [116]. Nonetheless, other side effects including infection risk, haemorrhagic cystitis, gonadal toxicity, leucopenia, alopecia, and predisposition towards malignancies meant that there was an appetite for safer regiments with less cumulative CYC use [47].

Indeed in the 1990's a reduced-dose intravenous (i.v.) CYC regimen (500mg twice a week x 6 doses) was introduced and subsequently compared with the NIH regimen in the Euro-Lupus Nephritis trial (ELT) [117]. Renal response, mortality and relapse rates were similar and encouragingly remained similar in the 10-year follow up study [118]. However, a notable difference was that after 6 CYC doses, the ELT group were given maintenance therapy with AZA at week 12, whereas the NIH regimen continued with quarterly CYC pulses and started AZA at week 44. Therefore, whilst this made it difficult for direct comparisons, it allowed the ELT to introduce the concept of a short induction with a more toxic agent, followed by maintenance with a less toxic one [119].

Whilst both oral and intravenous regimens exist, the latter has a higher side-effect profile, although it may be more effective [120]. Pertinent to this thesis, intravenous pulsed therapy was also more attractive and hence more likely to have higher adherence (as it was supervised) than oral therapy, and this has formed the mainstay of CYC therapy.

Mycophenolate Mofetil

The original pilot study of MMF in LN compared the additional benefit of MMF (2g/day for 6 months and then 1g/24h for 6 months) or oral CYC (2.5 mg/kg/day) [121] to GC. The overall results were very similar with complete or partial remission, relapse rates and rate of kidney disease in both groups.

The largest randomized clinical trial (RCT) comparing MMF with CYC in LN patients tested both induction and maintenance strategies [122]. The induction component of the trial was an international, multicentre 24-week protocol including 370 patients with ISN/RPS III, IV or V LN. The patients received intravenous MMF (3g/day) or CYC every six months (0.5–1.0 g/m2) with GC in both groups. Renal outcomes such as a decrease in urine protein/creatinine ratio, stabilization or improvement in serum creatinine and complete renal remission, as well as adverse events, were similar in the two groups.

However, multiple studies confirmed the superiority of MMF compared to CYC in relation to side effects. MMF showed a reduced risk of ovarian failure, alopecia or leucopenia and [121,122], was not associated with bladder toxicity and had less infection risk than oral CYC. Diarrhoea, nonetheless, was more common in the MMF group [113].

With more evidence, clinical practice changed and moved away from CYC use for maintenance towards MMF and AZA [47] as the latter were safer. MMF and AZA were

shown to have similar safety and efficacy [123,124]. However, other studies showed fewer relapses with MMF making it the usually preferred choice [125,126], unless immunosuppression is needed in pregnancy or during breastfeeding where AZA is currently recommended [127].

Sodium Mycophenolate.

The evidence for the safety and effectiveness of Mycophenolate (MPS) in LN patients is less compelling. A retrospective analysis of 52 paediatric patients with LN treated over 13 years comparing MPS with other immunosuppressive therapies showed higher efficacy and survival rate in the MPS group. The rate of progression to stage 3 chronic kidney disease was similar, and there were no significant differences in adverse events. However, the heterogeneity in the timing of treatment, duration of follow-up and diversity of the control group treatments are important limitations of the study [128]. MFS has also been compared with iv CYC in patients with resistant-type LN with fewer adverse events than the latter [129].

Enteric coated mycophenolate sodium (EC-MPS) was initially developed to ameliorate the known adverse effects relating to gastrointestinal upset that are common with MMF (such as nausea, diarrhoea, abdominal cramps). A recent study of 54 LN patients [130] that compared switching treatment to EC-MPS versus continued therapy with MMF found a similar short term renal response. Furthermore, a comparative study between MMF and MPS in renal transplant recipients did not identify a significant difference in terms of tolerability and efficacy between these two commonly used mycophenolic acid derivatives [131]. Therefore,

since the bioequivalence of EC-MPS and MMF has been well documented on renal transplant patients, one can reasonably deduce based on the pharmacokinetics of MMF and MPS and the results available, that further studies are unlikely to yield significantly different results with regards to efficacy between the two formulations.

Calcineurin inhibitors.

Cyclosporin A (CsA) and Tacrolimus (TAC) are widely used in immunosuppression post organ transplantation [132] and are effective in LN. Calcineurin inhibitors have two potential beneficial modes of action in the LN: their ability to inhibit the transcription of the early activation genes of interleukin-2 (IL2) and suppress T cell-induced activation of tumour necrosis factor-α (TNFα), IL-1β as well as IL-6. Thus, signals for B cell activation, class-switching and immunoglobulin production are indirectly attenuated [133]. The anti-proteinuric effect of CsA relates to its ability to stabilize the actin cytoskeleton in kidney podocytes [134].

Cyclosporine

CsA is as effective as CYC in induction and maintenance treatment in LN patients with preserved renal function [135] and is more effective in membranous LN than induction regimens using GC alone [86]. Maintenance regimes comparing AZA versus CsA in a cohort of class IV and V LN patients were equivalent[136]. However, CsA improved proteinuria and kidney histology in patients with relapsing disease who did not respond to maintenance treatments with CYC or AZA [137] making it thus an option in these patients. Some important side effects associated with CsA, such as hypertension, transient renal function impairment, gingival hyperplasia, hirsutism,

and paraesthesia, are not seen with tacrolimus, for example, making it, therefore, the preferred choice [138].

Tacrolimus

TAC is effective in treating membranous LN and refractory disease and is as efficacious as CYC with fewer side effects [139]. Treatment with TAC and MMF is more effective than iv pulse CYC in mixed proliferative and membranous LN with no increase of adverse events [140], and in class III, IV, V or mixed III–IV and V LN there is a higher complete response rate in the TAC/MMF group. A large multicentre randomised trial of 368 Chinese patients with LN by Liu et. [141] reported a significant superiority of efficacy of a multi-target therapy approach including TAC/MMF and steroid compared to iv CYC at 24 weeks.

The follow on open label trial of this cohort compared the multi-targeted TAC/MMF approach to AZA as maintenance therapy in an 18 month extension period, and used renal relapse rate during maintenance therapy as the primary outcome. The researchers [142] (Zhan et al.) concluded that multi-target therapy as a maintenance treatment for LN resulted in a low renal relapse rate and fewer adverse events, therefore suggested that this approach could be an effective and safe maintenance treatment.

It is worth pointing out that the definition of the primary endpoint was the cumulative rate of renal relapse at 18 months. Renal relapse for this study was defined by the presence of either a relapse of proteinuria (defined as persistent proteinuria ≥1.0 g/24 h after complete remission or an increase of ≥2.0 g/24 h after partial remission

with or without haematuria and a specified increase in serum creatinine levels. However the anti-proteinuric effect of CNIs should be taken into consideration when interpreting the results of this study, as it may have reduced the level of proteinuria observed, therefore reducing the sensitivity of accurately identifying true renal relapse.

Tacrolimus has its own side effects, including alopecia, diabetes, leg cramps and neurological symptoms, and a reversible 30% decline of renal function [143]. The other significant benefit of TAC is its safety in pregnancy [144].

Voclosporin

Voclosporin (VCS) is a novel high potency calcineurin inhibitor, developed with a structural change from CsA incorporating a single carbon extension with a double bond. It has a favourable metabolic profile and a consistent, predictable dose response, indicating that this could potentially allow elimination of the need for therapeutic drug monitoring whilst at the same time it is almost four times as potent as CsA. In the AURORA 1 randomized study [145], Rovin et al. compared VCS with placebo on top of MMF and rapidly tapered GC, and reported that the addition of VCS led to better preservation of renal function at 52 weeks by a factor of 2.65. It needs to be noted however, that the background treatment in both arms included MMF and a rapid tapering oral steroid regime, which would not be considered the standard of care for the majority of patients (in the absence of an additional steroid-sparing agent). Furthermore, the MMF dose of 1g bd used, could be considered less than the higher doses usually used in standard of care. Therefore, it is unclear if the

benefit of VCS would have been as evident in the presence of a more gradual tapering steroid regime. Nonetheless, the benefit of the results was sufficient for VCS to be approved by the Federal Drug Administration for use in LN [146].

As with all CNI, it is important to appreciate VCS's intrinsic anti-proteinuric effect, and how that may interfere with trial outcomes interpretation in lupus nephritis trials.

A summary of the conventional drugs for LN and their main side effects are seen in Table 1.10.

Drug name	Mode of action	Main use	Main adverse effects
Hydroxychloroquine	Alkalinizing lysosomotropic effect	Baseline	Retinopathy (uncommon), Cardiotoxicity (very rare), cutaneous eruption
Glucocorticoids	Trans repression Transactivation	Induction Maintenance	Osteoporosis, cardiovascular risk, increased infections risk
Azathioprine	Block the "de novo" pathway of purine synthesis	Maintenance	Herpes Zoster
Methotrexate	Antimetabolite and folate analogue	Baseline	Liver toxicity Nausea/GI mouth ulcers malaise

Cyclophosphamide	Interfere with DNA replication	Induction	Infections, nausea and vomiting, alopecia, gonadal toxicity, haemorrhagic cystitis, malignancies
Mycophenolate	Reversible inosine monophosphate dehydrogenase (IMPDH) inhibition	Induction Maintenance	Diarrhoea, herpes Zoster, pregnancy loss, foetal malformations
Cyclosporine	Transcription of the early activation genes of IL2 inhibition.	Induction Maintenance	Gum hypertrophy, hypertrichosis, hypertension, arthralgia, GI symptoms
Tacrolimus	Suppress T cell-induced activation of tumour necrosis factor-α (TNF a), IL-1β, and IL-6.	Induction	Pneumonia, herpes zoster, tremor, reversible increase in serum creatinine
Voclosporin	High potency calcineurin inhibitor	Induction Maintenance Continuous therapy	Headache, hypertension, infection, diarrhoea

Table 1.10 Conventional drugs for LN, mode of action, main use and main side effects.

Biologic Therapies

Despite the progress made in the treatment of SLE with conventional therapies, the long-term prognosis of LN has changed little in the last 30 years [84]. The need for newer effective drugs that may facilitate earlier remission and reduce relapse rates has driven clinical research towards the direction of targeted treatments [147]. The "biologics era" has seen many targeted novel biologic agents being developed, and combination therapies of conventional with biologic agents have become the treatment paradigm in diseases such as rheumatoid and psoriatic arthritis.

Pathogenesis and potential targets

Understanding the role of specific cells and molecules in the pathogenesis of SLE and LN has facilitated the development of biologic agents. Although SLE is predominately a B-cell driven phenomenon influenced by genetic, hormonal and environmental factors, there are also proposed roles for both B and T-cells in the induction of glomerular inflammation in the pathogenesis of lupus nephritis [41,40,96]. The pathways implicated in LN and the potential targets with the respective drugs are explained in Figure 1.2.

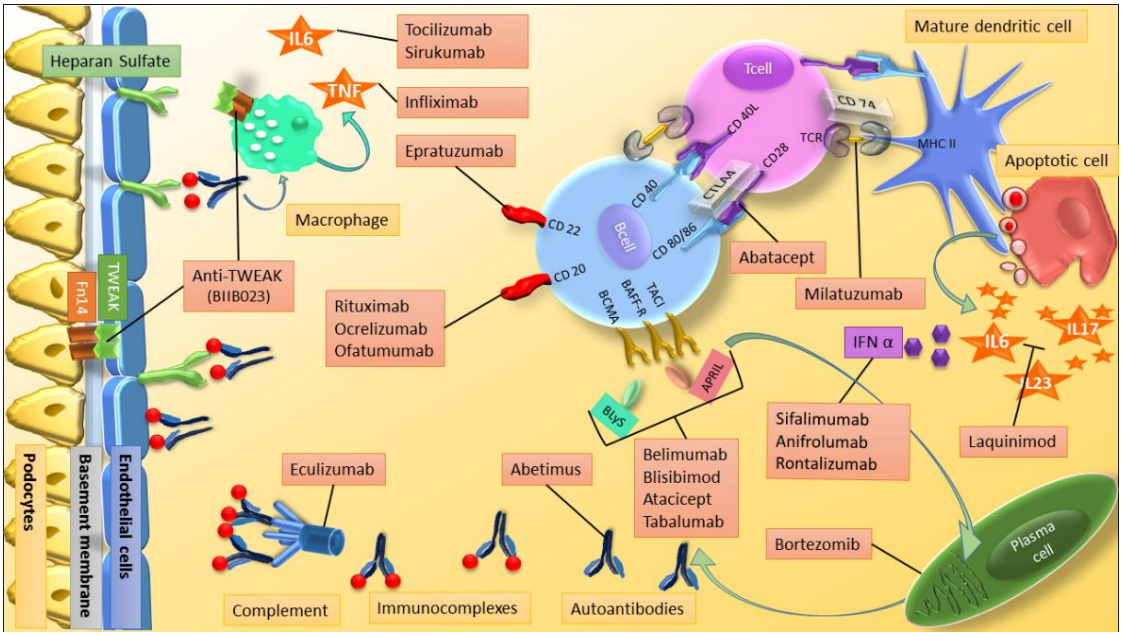

Figure 1.2 Target molecules and drugs in the pathophysiology of LN adapted from Ntatsaki & Garcia-Velo et al [149].

In this figure the pathogenesis pathway of LN and its possible biological targets is explained.

When the mononuclear-phagocytic system fails to clear apoptotic cells, an inflammatory response occurs. The surface apoptotic vesicles containing nuclear debris such as dsDNA and RNA antigens activate dendritic cells, which in turn trigger INF-α production and T-cell response with interleukin production. IFN- α contributes to the differentiation of monocytes to macrophages which present self-antigens to T and B cells. IFN- α also leads to the differentiation of B-lymphocytes to plasmatic cells, activation of T-Lymphocytes and maturation of dendritic cells.

Simultaneously B and T-lymphocytes interact and co-stimulate each other. The activation of B-lymphocytes leads to the expression of BlyS/BAFF and APRIL and their differentiation into plasmatic cells that produce autoantibodies. The immunocomplexes formed by the autoantibodies and the nuclear antigens activate the complement system. In the kidney, both the autoantibodies and antigen/antibody complexes may cause inflammation by deposition at the level of the glomerular basement membrane or by binding to basement membrane components (e.g., heparan sulfate), leading to tissue damage. Activated effector T-cells can also inflict tissue injury with chemokine receptors and activation markers, allowing them to migrate into the kidney.

On the other hand, Fibroblast Growth factor (FGF)-inducible molecule 14 (Fn14) is expressed on a wide variety of cell types, including mesangial, tubular cells, interstitial fibroblast and podocytes. In normal tissues, it is expressed at relatively low levels, but it can quickly rise in response to inflammation. When the cytokine tumour necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) joins with its receptor (Fn14), it activates multiple downstream signalling pathways, with the nuclear factor kB (NFkB) pathway being the most relevant. These activated pathways also lead to glomerular and tubular injury.

For each of the above-mentioned pathogenic mechanisms, there are targeted biologic drugs annotated in the figure.

Use of biologics in LN

Although many target molecules and pathways have been trialled to treat non-renal SLE and other rheumatic conditions, there are far fewer studies specifically designed for LN. Until recently, none of them has reached its primary endpoint, highlighting the challenge SLE trial endpoints pose. However, this has changed in the last year with two studies, at long last, showing positive trial results, with one of them being an RCT for LN (BLISS -LN) [150]. A summary of the key biologics with the mode of action and side effect profile is described in Table 1.11, and the trial acronyms are explained in Appendix 1.

The use of biologics in the context of a LN regimen could be broadly categorized in the following roles in the induction setting:

i) an “add on” treatment to conventional therapies (usually GC and immunosuppressant like MMF or CYC) (e.g. LUNAR, BELONG, BLISS-LN)

ii) a potential steroid-sparing agent (e.g. RITUXILUP concept, BEAT -LUPUS) where the biologics allow for a low dose or GC free approach

iii) an option for refractory cases with suboptimal approach to the standard of care therapy (e.g. RING)

iv) a biologic agent could be used as a potential long-term maintenance agent after induction. However, there are no specific trials for biologics as stand-alone maintenance agents.

v) Finally, a biologic drug can be part of a continued combination therapy option, thus moving away from the traditional induction-maintenance therapeutic paradigm. Indeed, in recent years newer drugs have been trialled (e.g.

Belimumab, Obinutuzumab). Novel treatment concepts retain the early use of steroids but rather involve the continued use of a combination of immunosuppressive drugs to control the underlying chronic systemic autoimmune disease [97]. This different strategy allows the physician to taper corticosteroids faster, hence overlapping with category ii.

In terms of safety, most of these biologics have an established side-effect profile when tested in SLE and other rheumatic conditions. Long-term toxicity data in patients with renal disease are scarce. However, the burden of disease in the LN population and the complexity of medication clearance through an affected filtering mechanism is an additional cause for caution.

B- cell depletion therapies

Rituximab

Rituximab, a humanized monoclonal antibody against CD20, was the first biologic to be used in the treatment of SLE. Most investigators consider RTX to be effective in treating refractory SLE, although two large trials, LUNAR (study of lupus nephritis) [151] and EXPLORER [152] (study of non-renal patients), did not meet their primary endpoints. However, both the ACR /EULAR and BSR guidelines for the treatment of SLE and LN mention RTX as a possible therapy [153]. NHS England also permits its use in SLE.

In the LUNAR study, 72 patients with LN (class III or IV) were randomized in each arm to receive 2 courses of RTX or placebo, in addition to standard-of-care (SOC) treatment, of MMF and GC. The trial concluded that in proliferative LN, the addition of rituximab to induction therapy with MMF did not provide better (short-term) results [151]. The LUNAR has been criticized because of its poor design relating to its statistical power defined on a highly optimistic superiority effect favouring RTX. Interestingly, although this did not reach statistical significance in LUNAR, it was within the range of the statistically significant effect of belimumab in the two main non-renal lupus trials (BLISS) [154].

RTX has also been trialled as a GC sparing agent. The RITUXILUP trial was based on published pilot data of 50 patients, involving the addition of RTX to MMF without oral GCs and showing that it is at least as effective at inducing a renal response as the standard of care therapy comprising MMF and high dose oral GCs [108]. RITUXILUP [155] was a proof of concept, open labelled multicentre RCT multicentre trial aiming to demonstrate whether the addition of RTX to MMF therapy is helpful in treating a new flare of LN and whether it has a long-lasting steroid-sparing, beneficial effect with equal efficacy and greater safety than a conventional regimen of MMF and oral prednisolone. If successful, this trial had the potential to be genuinely "game-changing" and dramatically alter the management of lupus nephritis. Unfortunately, the trial ended prematurely, as discussed earlier.

Finally, although not licensed for this indication, RTX has been broadly used by experienced lupologists as a potential option for refractory LN. It has been

extensively used off label in Europe (0.5-1.5%) for patients with refractory disease or LN [156].

Side-effects include infusion reactions (fever, bronchospasm, rash and hypotension) which usually settle on stopping the infusion. Patients are screened pre-infusion and usually followed up for infections such as tuberculosis and hepatitis B or C. The effect of B cell depletion lasts for 6-12 months usually, and it is vital to monitor immunoglobulin levels and CD19+ B cell counts bimonthly until B cells normalize, as accumulated doses of rituximab may cause hypogammaglobulinaemia linked with a higher risk of infection [157,158]. Progressive multifocal leukoencephalopathy (PML) has been rarely reported in SLE. However, it is now clear that immunosuppression- however achieved- is the cause for this, rather than a specific agent [159].

Ocrelizumab

Ocrelizumab (OCR) is a fully human monoclonal antibody against CD20 tested for efficacy in patients with LN in a phase III RCT (BELONG). Despite reaching an overall response rate of 66-67% in the ocrelizumab treatment arm, the difference in response versus standard of care treatment did not reach statistical significance [160]. The BELONG trial was terminated early because of severe infection rates in the OCR arm when the study drug was combined with MMF as background immunosuppressive therapy.

Obinutuzumab

This is a type II antiCD20 monoclonal antibody that has shown superiority to rituximab (a type I drug) in depleting tissue B cells in lymphoma, is being compared to the standard of care. The NOBILITY trial [161] was a positive RCT for LN patients with proliferative nephritis with Obinutuzumab used as an add-on to glucocorticoids plus MMF. At 76 weeks, significantly more patients from the Obinutuzumab group achieved the endpoint of complete renal response, p=0.007.

Belimumab

Belimumab is a monoclonal humanized immunoglobulin that binds to the BLyS protein approved for the treatment of mild to moderate SLE affecting the skin and joints. It has been the main approved B cell depleting therapy for non-renal SLE, and recently there has been evidence of efficacy in LN with a positive trial, albeit with altered endpoints. The main trials (BLISS and BLISS -LN) [150], have been some of the few trials in SLE to yield positive results.

Trials that have looked at combinations of rituximab followed by Belimumab in LN include the CALIBRATE and BEAT LUPUS trials. THE CALIBRATE trial concluded that the addition of belimumab to rituximab and CYC was safe and diminished the maturation of transitional to naïve B cells during B cell reconstitution and enhanced negative selection of autoreactive B cells. However, it did not improve clinical efficacy compared to B- cell depletion alone [162], and there was no increased safety concern. Pooled data from one phase II and two phase III RCT reported adverse events rates ranging from 13.5% to 19.5%, with placebo at 16.6%, which were not

dose dependant [163]. THE BEAT Lupus trial recruitment has been completed, and results are expected in 2021. The use of belimumab preceding RTX is also currently trialled as a steroid-sparing combination.

Other targets

Atacicept

Atacicept is a transmembrane activator and calcium-modulator, and cyclophilin-ligand interactor (TACI) fusion receptor protein. It inhibits both B lymphocyte stimulator (BLyS) and A proliferation-inducing ligand (APRIL) in B-cells, ranging from immature to mature. By inhibiting BLyS and APRIL, it causes a reduction in B-cell proliferation, interferon gamma and immunoglobulin production. The doses used in the phase II/III RCT in lupus were 75mg or 150mg [164]. The 150mg arm of the APRIL-SLE randomized trial was terminated early due to two fatal infections. This was unfortunate as the monoclonal agent clearly showed serological benefit and some clinical improvements. In addition, in most SLE trials, a small number of deaths are noted; nine, for example, in the first Mycophenolate vs Cyclophosphamide trial [122]. The LN study of atacicept was terminated after the enrolment of only 6 patients (2 placebo) because of the severe decrease in immunoglobulins, although it turned out that in most cases, the fall in IgG levels was linked to the concomitant MMF usage.

Abatacept

Abatacept is a combination of human IgG (Fc portion) and CTLA-4 that blocks the stimulation of B cells leading to a reduction in antibody formation and immune

response. The phase II/III trials in LN [165]compared a combination of abatacept with CYC and MMF, respectively, versus placebo. They did not meet the primary outcomes, although when the same data were analyzed using different criteria (LUNAR trial response criteria), there was a 20% response rate in the abatacept arm compared to placebo [151]. The side effect profile is comparable with other biologics, notably infections such as herpes zoster and gastrointestinal symptoms.

Anti-Interferon Alpha

Anifrolumab, sifalimumab and rontalizumab and are anti-IFNα monoclonal antibodies. Neutralization of IFNα leads to a reduction of inflammation by reducing BAFF/BLyS levels, mature B cells, antibody production and T-cell activation. Anifrolumab is a human monoclonal antibody to type I interferon receptor subunit 1 and was investigated for the treatment of SLE. It did not reach significance for the primary endpoint [SRI-4] in the initial phase 3 trial TULIP-1, but TULIP-2 using the BICLA endpoint resulted in a positive trial. Patients receiving anifrolumab had some side effects; notably, herpes zoster and bronchitis occurred in 7.2% and 12.2% of the patients, respectively. One death from pneumonia was noted in the anifrolumab group.

Future Targets

There are many other potential target molecules such as other B cell surface receptors (CD22, CD20), BLyS, BAFF, complement targets, TWEAK with many respective novel drugs as seen in Figure 1.2. Many of these have been or are currently trialled in SLE and other rheumatic conditions.

Biologic drugs in SLE and LN			
Drug name	**Mode of action**	**Main use**	**Main adverse effects**
Rituximab	Monoclonal antibody Anti-CD20 IgG1 (chimeric murine/ human)	Induction Combination	Leucopenia and lymphoma, opportunistic infections, infusion reaction, infection risk, PML
Belimumab	Monoclonal antibody binds to BLyS (Humanized)	Induction Combination	Nausea, diarrhoea, headaches, URTI, fever, cystitis, infusion reaction
Obinutuzumab	type II anti-CD20 monoclonal antibody	Combination	Infusion reactions, rash, rhinitis, nausea, URTI, headaches, fatigue, flushing.
Anfrolimumab	Human monoclonal antibody to type I interferon receptor subunit	Induction Combination	Herpes zoster, Bronchitis, Pneumonia, Infusion reaction, fatigue, URTI/UTI, Sinusitis, dizziness, arthralgia, headache, lymphopenia, anaemia
Atacicept	TACI-Ig fusion protein that inhibits BLyS and APRIL	Induction	LRTI/URTI, injection site reaction, fever, arthralgia, dizziness, depression
Abatacept	Human IgG1 heavy chain fused with CTLA4 that blocks T cell activation by B cells	Induction	Herpes Zoster, GI symptoms, headache, infusion reaction, fever, hypertension, back pain, infections
Ocrelizumab	Fusion protein of Fc region of IgG1 fused to CTLA-4, which inhibits T cell co-stimulation	Induction	Increased infection risk
GI: gastrointestinal, PML: Progressive multifocal leukoencephalopathy, LRTI: low respiratory tract infections, URTI: upper respiratory tract infections.			

Table 1.11 Key biologic drugs in SLE with their mode of action & side effect profile

Lupus Nephritis Treatment summary

The armamentarium of therapies for LN may have expanded somewhat over the last 30 years. However, the emphasis in treating LN patients necessitates striking the right balance between giving a robust and effective immunosuppressive regimen that is potent enough to control inflammation and preventing long-term kidney and extra-renal damage.

LN is a challenging and complex entity, and although there have been encouraging steps towards novel and safer therapies, sadly, up until recently, the clinical trials for most of the newer biologic agents have been disappointing. Some possible reasons of why trials of biologic drugs in SLE have often been unsuccessful, may include poor design (low numbers and short follow up period), difficulty in recruitment, excessive use of concurrent GC and immunosuppressive agents or early termination due to unexpected toxicity [147]. It is therefore essential to standardize clinical trial outcomes and define the endpoints for LN trials carefully. By improving the trial design, and recruiting from a more diverse ethnic population via collaborative and networking bodies, eventually, there will be evidence-based guidance for novel therapies based on good quality trial data. This is very pertinent, not only from a clinical perspective but also from a health economic perspective. Although some of the novel treatments may be significantly more expensive than the conventional therapies, being mindful of the high cost of renal replacement therapy, avoidance of only a few cases of end-stage renal disease might be cost-effective in the LN population.

However, there are also improved regimens of conventional therapies such as MMF and AZA, with long-term safety data now being available, as well as novel "conventional" drugs such as voclosporin. It may be that the effect of biologics drugs, over and above these already established and very effective treatments is small, hence biologics trials may be underpowered to detect such small differences in outcomes.

However, the toxicity profile of long-term GC use and cumulative CYC exposure are suboptimal and may become unacceptable options, especially in the light of newer target specific biologic agents with equivalent efficacy and favourable adverse effect profiles. It is conceivable that in the future, for some LN patients it might be possible to be treated at diagnosis using biologic agents and multitarget pathways (e.g. B cell depletion/ Interferon blockade) in continued combination therapy avoiding oral steroids, which carry a significant morbidity burden [108]. Treatment paradigms are shifting, and concepts such as induction and maintenance therapy are challenged. Nevertheless, the potential for unexpected toxicity and the absence of long-term follow-up data with novel therapies and combinations is a significant and challenging consideration when exploring new treatment concepts and regimens.

Finally, adherence to treatment is very often relating to the patients' perception of potential side effects. Therefore, it is important when contemplating the pharmacological safety of treatments to use common sense and a tailored approach for the individual patient. The efficacy and safety of pharmacological treatments in LN are ultimately based on applying a balanced combination of sound clinical

judgement, careful evaluation of robust evidence from well-designed trials. In the near future, individualized patient genetic and genomic characteristics may guide clinical decision making and facilitate appropriate treatment. The introduction of a wider selection of validated and well-tested treatment options may decrease the mortality and morbidity for LN patients reducing or abolishing progression to end-stage renal disease.

Renal transplant

Historical background of renal transplant

The first long-term successful kidney transplantation was performed in 1954 by Joseph Murray between monozygotic twins, with graft survival of 8 years and Murray received the Nobel Prize in medicine in 1990 for his pioneering contributions to medicine [166]. The development of the first immunosuppressive drugs permitted the first successful graft from a cadaver to be undertaken in 1962, opening the door to modern transplantation. The first successful kidney transplant in UK was performed in Edinburgh by Sir Michael Woodruff and his team on 30th October, 1960 [167]. This was a milestone in history of transplantation for the UK.

The first two case reports of renal transplantations for patients with SLE and LN were reported in 1965 in Cleveland clinic by Roenigk et al. but nether patient survived more than 3 months [168]. However, things have improved considerably since then. Over the last century, organ transplantation has overcome major technical limitations on the surgical aspect, but also has seen the development of much more effective

immunosuppressive medication and organ donor matching techniques that have allowed a considerable expansion in renal transplants [169].

There is an increasing number of renal transplants globally. More specifically, in the USA with total number of adult kidney transplants was observed to be rising from 45,008 in1996-1999 to 76,885 in 2016-2019.The outcomes and long term survival has shown gradual improvements in patients and graft survival[170]. In the year 2000 according to the WHO transplant observatory database there were 23,084 renal transplants performed globally rising to 102,403 in 2019. In the UK the rate of renal transplantations gradually increased from 1855 in 2005 to 3649 in 2019 However one of the remaining limiting factors and challenge from the outset is to overcome the shortage of suitable donor organs [171].

The most common indications for renal transplant include glomerulonephritis, cystic kidney disease, diabetic nephropathy and systemic immunological disease which combined amount to more than 60% of all cases [172].

Renal transplant for SLE

As discussed above, LN remains one of the most common and severe manifestations of SLE. In patients reaching ESRF, renal transplantation (rTp) has now become the preferred treatment. However, in the early era of renal transplantation, SLE patients were not considered favourable candidates. This was due to an assumed risk of recurrent LN. From 1975 however, when it was first

suggested that transplant outcomes in SLE are comparable to non-SLE patients [173] multiple reports worldwide, including different ethnic populations, have shown low recurrence rates of LN in kidney transplant recipients ranging from 2-30% [118,174–176]. Nonetheless, some studies have raised concerns regarding worse graft and patient survival in SLE when compared to other patient groups (e.g. diabetes), with unfavourable comparative outcomes, especially for the recipients of deceased donors [177]. It is without a doubt however, that rTp can be a life-prolonging therapy. Patients with LN who do receive an rTp have better survival and fewer cardiovascular and infectious complications than LN patients on dialysis, indicating that when rTp is an option it should be the preferred strategy [178].

Whilst all centres in the UK undertake pre-emptive transplantation for their patients when possible, in reality most patients still undergo dialysis for months until the disease is quiescent and thus potentially reduce the risk of recurrence, or delays occur until a match is identified. The recurrence of LN varies from 2-4% in some studies [179–181] and reported as high as 30% in a different study [182]. LN recurrence in the allograft can lead to early or late graft loss ranging in different studies from 30-50% of the patients who have a recurrence [183–185]. However, it is essential to highlight that with the use of newer immunosuppressants like TAC, LN recurrence is likely to be in the lower end of the range given. Furthermore, graft failure could also occur from other aetiologies and specific risk factors such sex, ethnicity, age at the time of SLE, LN and ESRF diagnosis and time between those diagnoses, as well as comorbidities (diabetes, hypertension, APLS, cardiovascular disease) which are non-modifiable risk factors [184].

Poor adherence to immunosuppressive treatment is common in patients with SLE and may identify those with LN who have a poorer prognosis [30,186,187]. This poor adherence to immunosuppressive therapy has also been associated with increased graft failure in renal transplant patients necessitating a return to dialysis [188]. Not surprising, up to 16% of graft losses are attributed, in part, to poor adherence [189,190] and returning to dialysis after a failed renal transplant is associated with 78% mortality risk compared to patients on the transplant waiting list receiving dialysis [191]. However, despite the available evidence linking non-adherence to adverse outcomes in patients with transplantation, little specific is known regarding adherence in patients with lupus nephritis following renal transplantation and whether fewer adherent patients have worse outcomes.

Similarly, whilst in other patient cohorts undergoing rTp, need for dialysis (vs pre-emptive transplantation) or increasing time on dialysis before the rTp associated with worse overall survival after the transplantation [192–196], this has not been specifically clarified for lupus patients and will thus form an important aspect of this thesis, as there is controversy on this matter. An early study by Roth et al. in 1987 [197], on 15 patients with LN and transplantation suggested that patients with less time on dialysis did worse in terms of patient and graft survival; they supported the notion of delaying renal transplantation by at least one year, to ensure disease quiescence and help avoid recurrence of lupus nephritis. Other later studies however, showed no adverse effect of the time spent on dialysis prior to renal transplantation on the outcome of patient and graft survival [198,199] . Furthermore, some small studies even supported a beneficial effect of earlier transplantation [183,200]. Given that time spent on dialysis before rTp is a potentially modifiable factor, it is necessary to investigate

whether this is indeed a risk predictor in lupus patients specifically. In addition, to see whether there is a "safe maximum" time on dialysis before transplantation. Other modifiable risk factors include parameters such as the type of dialysis, donor source, and notably adherence to treatment, as seen in Table 1.12.

Ultimately, however, the sparsity of suitable donors and frequent allo-sensitisation of lupus patients due to prior pregnancies and receipt of blood products means that most patients spend significant time on dialysis before transplantation.

We therefore find ourselves trying to balance the benefits of earlier, or even pre-emptive transplantation, against the benefit of disease quiescence and lack of donor availability, in an evidence-free zone. However, what is backed by evidence, is that both morbidity and mortality are improved with rTp, thus making it the preferred intervention [178].

Risk factors for mortality in renal transplant for SLE

Risk factors for mortality in renal transplant for SLE	
Modifiable risk factors	**Non-modifiable risk factors**
Time on Dialysis	Sex
Dialysis type- haemodialysis vs peritoneal dialysis	Ethnicity
Donor source- cadaveric vs living	Age of SLE diagnosis
Adherence to treatment	Age of LN diagnosis
	Age of ESRF
	Time between SLE and LN diagnosis
	Time between LN and Dialysis
	Diabetes Mellitus (type 1 or 2)
	Hypertension
	Dyslipidaemia
	APLS
	Cardiovascular disease (MI, stroke, TIA)
	Decade of renal transplantation

Table 1.12: Modifiable and non-modifiable potential risk factors

APLS-Antiphospholipid syndrome; MI-Myocardial Infarctions, TIA-Transient Ischaemic attack SLE- Systemic Lupus Erythematosus; LN- Lupus Nephritis; ESRF-End-stage renal failure.

Vasculitis

Definition

The vasculitides are a heterogeneous group of rare disorders characterized by vessel inflammation leading to impairment of distal organ function.

Etymology

The word “vasculitis” comes from the Latin *vāsculum* meaning "small container, vessel" and from the Ancient Greek -ῖτις (*-îtis*, “pertaining to”), which is a suffix denoting disease characterized by inflammation. The term “vasculitis” literally means inflammation of the vessels and is used to describe a group of relatively rare conditions with a broad spectrum of clinical presentations that can cause significant morbidity and mortality.

Aetiopathogenesis

The aetiopathogenesis is still unknown, but as with most autoimmune diseases, these conditions are thought to arise from an interaction between a genetically predisposed host and an environmental factor.

Epidemiology

Individual vasculitides are rare diseases in general. The incidence and prevalence of the vasculitides vary with age, time, ethnicity and geography, which generates various hypotheses about the aetiology and pose considerable challenges to epidemiologists. These challenges include difficulties in capturing cases and

correctly defining a case with a lack of clear distinction between the different disorders [201]. The ANCA-associated vasculitides (AAV) are particularly rare, and therefore a large population is required to determine the incidence and prevalence, thus raising feasibility issues. The majority of the data come from Caucasian populations of European descent. The overall annual incidence is approximately 10-20/million, with a peak age of onset in 65 to 74 years. Giant cell arteritis presents in the elderly, most commonly those of Northern European ancestry; ANCA-associated vasculitis seems to have a consistent overall occurrence, but with differences in the presence of MPO and PR3 vasculitis between populations. Kawasaki disease occurs mainly in Asian populations, especially Japanese, and predominately in less than 5 years [202]. Although the epidemiology of vasculitides is increasingly well studied, there are still gaps in our knowledge of the occurrence of vasculitis in the third world and in those populations whose health care systems do not permit the easy collection of accurate epidemiological data [203].

Classification

The classification of the vasculitic syndromes is usually made according to the size of the vessels affected, but also according to the presence of specific antibodies, mainly ANCA antibodies, that characterize the pathology of some of the individual conditions [204,205].

In addition, vasculitides can be either primary or secondary to an underlying systemic disease, malignancy, or infection (Figure 1.3 and Table 1.13).

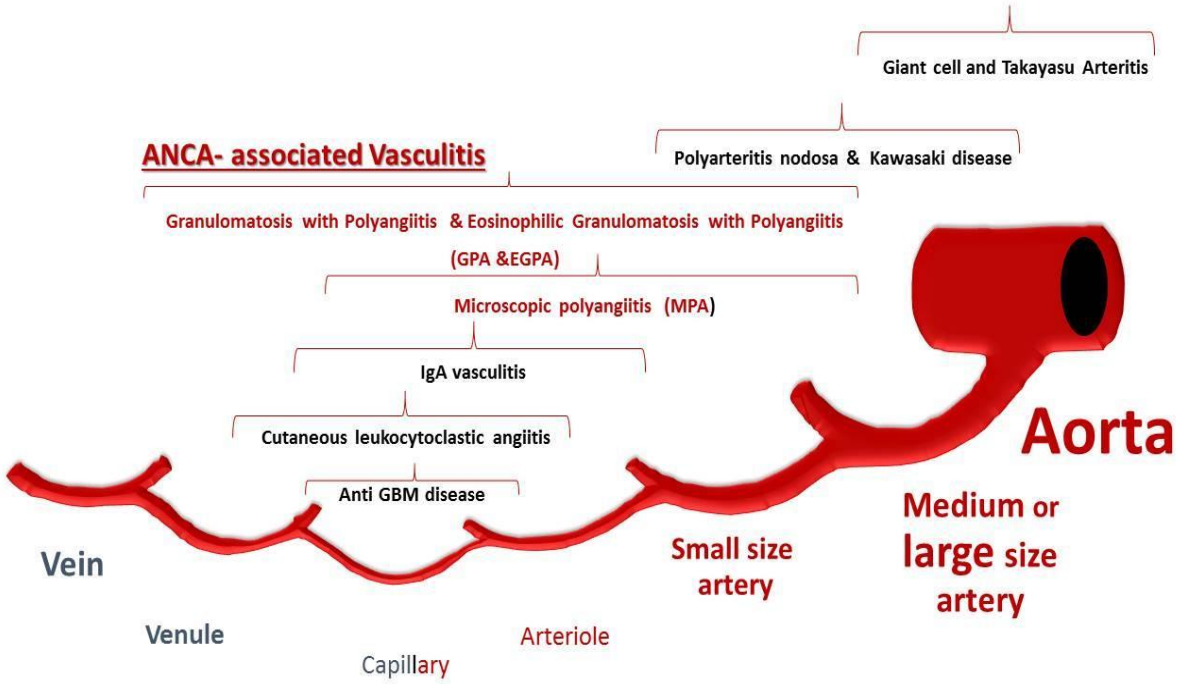

Figure 1.3 Classification of vasculitis according to vessel size. From Ghani and Ntatsaki [206]. The ANCA associated vasculitides are shown in red.

GBM – glomerular basal membrane; Ig A – immunoglobulin A.

PRIMARY VASCULITIDES

According to vessel size

Large Vessel	Medium Vessel	Small Vessel	Variable Vessel
Takayasu Arteritis Giant Cell Arteritis	Polyarteritis Nodosa Kawasaki Disease	ANCA-Associated Vasculitis (GPA, MPA & EGPA) Anti-GBM Disease Immune Complex • Cryoglobulinaemic Vasculitis • IgA Vasculitis (Henoch-Schönlein) • Hypocomplementaemic Urticarial Vasculitis (Anti-C1-q Vasculitis)	Behçet's Disease Cogan's Syndrome

Single Organ

Isolated Aortitis	Cutaneous Arteritis	Cutaneous Leucocytoclastic Angiitis	

C1q- complement fraction; EGPA- eosinophilic granulomatosis with polyangiitis; GPA- granulomatosis with polyangiitis; Ig A- immunoglobulin A; MPA- microscopic polyangiitis

SECONDARY VASCULITIDES		
Vasculitis Associated with Probable Aetiology		
Infection-related	Hepatitis C Virus-Associated Cryoglobulinemic vasculitis Hepatitis B Virus-Associated vasculitis Syphilis-Associated Aortitis	
Drug - Associated	Drug-related Immune Complex	e.g. sulfonamides, penicillins, thiazide diuretics
	Drug-related ANCA-Associated vasculitis	e.g. carbimazole, propylthiouracil, hydralazine and allopurinol (mainly with induction of MPO-ANCA)
Vasculitis associated with systemic disease	Lupus Vasculitis Rheumatoid Vasculitis Sarcoid Vasculitis Spondyloarthropathy-related Vasculitis and others	
Cancer	Malignancy developing in patients with a diagnosis of primary systemic vasculitis	Bladder cancer Lymphoma Leukaemia Non-melanoma skin cancer Renal cell carcinoma
	Malignancy associated with subsequent development of vasculitis	Myelodysplasia Lymphoma Hairy cell leukaemia Myeloma Solid tumours
Other	Miscellaneous vasculitides	

Table 1.13 Classification of Vasculitides (based on data from the 2011-2012 International Chapel Hill Consensus Conference Nomenclature of the Vasculitides [205,206].

ANCA associated vasculitis

Three distinct clinicopathological syndromes, often associated with ANCA antibodies, known as ANCA-associated vasculitis (AAV), have been identified and collectively comprise the most common subgroup: granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss Syndrome, and microscopic polyangiitis (MPA) (see Table 1.13 and 1.14). A small subset of these patients may present with typical clinicopathological features of ANCA-associated disease, despite not having a detectable ANCA; these patients are usually described as having ANCA-negative small vessel vasculitis. These should not be confused with other forms of vasculitis, which are not ANCA-associated and are defined by their clinicopathological features (see Table 1.14).

Small Vessel Vasculitis
ANCA-Associated Vasculitis
Microscopic Polyangiitis Granulomatosis with Polyangiitis Eosinophilic Granulomatosis with Polyangiitis
Non-ANCA-Associated Vasculitis
Anti-GBM Disease Immune Complex Cryoglobulinaemic Vasculitis IgA Vasculitis Hypocomplementaemic Urticarial Vasculitis

Table 1.14 Small Vessel Vasculitis Sub-Classification (based on data from the 2011-2012 International Chapel Hill Consensus Conference Nomenclature of the Vasculitides)

C1q- complement fraction; GBM- glomerular basal membrane; Ig A- immunoglobulin A.

The American College of Rheumatology (ACR) criteria were developed in the 1980s and published in 1990 [207], before the broader use of ANCA testing and the availability of imaging techniques such as MRI and PET scanning. These criteria are not current, or fit for use in the 2020s. The Chapel Hill Consensus Conference provided a framework for defining various types of vasculitis [205]. In 2017, ACR/EULAR proposed new provisional criteria for classifying GPA using further information based on data from 1500 adult patients in the Diagnosis and Classification Criteria in Vasculitis (DCVAS) initiative. However, their finalization is still in progress and presented only in abstract form [208].

Diagnostic Criteria in Vasculitis

There is no validated or generally accepted systemic diagnostic criteria for the systemic vasculitides. It is important to note that classification criteria should not be used as diagnostic criteria [202].

Clinical Diagnosis

A high index of suspicion is required to achieve an early diagnosis, as in the early phase of the disease, the symptoms can be non-specific. Symptoms such as unexplained systemic disturbance, arthritis or arthralgia, polymyalgia, episcleritis, neuropathy, microscopic haematuria, proteinuria, pulmonary infiltrates or nodules, and maturity-onset asthma and upper airways symptoms should prompt consideration of a diagnosis of vasculitis [209].

The diagnosis usually becomes more evident when major organ involvement occurs. However, more advanced disease at the time of diagnosis is generally associated with worse outcomes. The combination of delayed diagnosis and advanced disease limits the potential benefit of any therapy. Patients with multisystem illness or pyrexia of unknown origin should be assessed for vasculitic syndromes; however, clinicians should be mindful that many conditions can mimic vasculitis, including infections and non-infectious inflammatory diseases, malignancy, drugs and factitious illnesses.

Detailed clinical history, examination and laboratory assessments are essential in obtaining a complete picture of the disease presentation. Imaging studies are also helpful in confirming a clinical diagnosis but can be of limited value in the absence of clinical signs. A biopsy is often necessary, depending on the clinical features (e.g. skin, lung, kidney), especially when there is suspicion of renal involvement.

Renal involvement

Renal involvement is present in most patients with MPA and GPA and may be asymptomatic until advanced renal failure occurs. Therefore, renal involvement in AAV must be diagnosed before the creatinine increase through detection in the urine of microscopic haematuria, erythrocyte casts and non-nephrotic proteinuria. The consequences of a missed or delayed diagnosis of renal involvement are potentially life-threatening because the survival and the risk of ESRD are closely associated with renal function at presentation [210].

Disease Assessment

As in lupus, to measure outcomes and response to treatment, it is crucial to have appropriate tools to estimate damage and activity relating to the condition. The most commonly used measures of disease activity, severity and damage are the Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Damage Index (VDI) [211,212]. Both the updated version of BVAS (BVAS v3) and VDI are validated scores widely used in clinical trials as measures of disease severity, activity and damage [214]. Although they were originally designed and used for trial purposes, they are becoming more frequently used in everyday clinical practice.

Treatment Paradigm

Like the traditional treatment of SLE, the treatment of AAV is divided into two distinct phases, induction and maintenance. Rapid and effective induction of remission can be achieved with the initial immunosuppressive therapy, and maintenance treatment thereafter needs to keep control of the disease and prevent relapse. The main stages in treatment follow these key principles of management:

- Rapid diagnosis
- Rapid initiation of treatment
- Early induction of remission to prevent organ damage
- Maintenance of remission with the aim of eventual drug withdrawal
- Prevention of drug toxicity
    - GC sparing effect (emerging concept)

The standard of practice and current guidelines recommend using CYC or rituximab with steroids as an induction treatment, followed by maintenance with either azathioprine (AZA) or methotrexate (MTX) or continue with rituximab. The treatment algorithm proposed by the BSR for the management of AAV is seen in Figure 1.4.

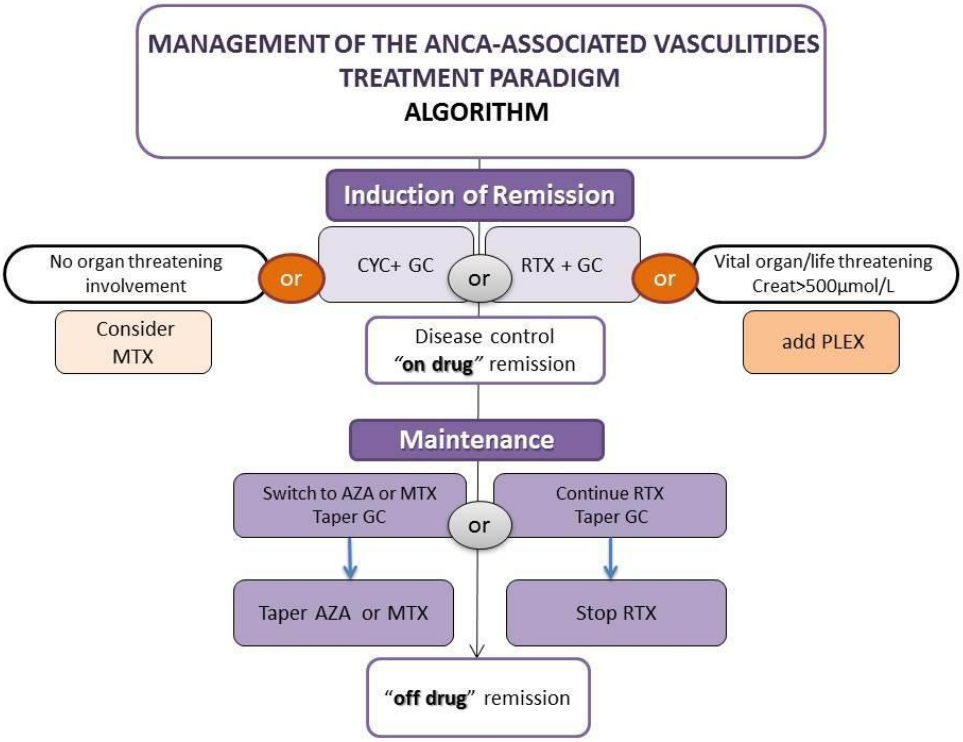

Figure 1.4 Algorithm for the management of ANCA-Associated Vasculitis according to the British Society of Rheumatology Guidelines, by Ntatsaki et al [209]

AZA- azathioprine; CYC- cyclophosphamide; GC- glucocorticoids; MTX- methotrexate, PLEX- plasma exchange; RTX- rituximab

Although the AAVs comprise three separate syndromes, the main principles of treatment are shared. However, most trials have focused on GPA and MPA, with some additional treatments relevant to EGPA only.

The impact of novel therapies is becoming more apparent, and the prognosis for AAV has improved considerably over the past 20 years. This change is reflected in the emerging guidelines where biologic drugs, and rituximab in particular, have been established both for induction and maintenance of remission.

Moreover, similarly to lupus, there are now more innovative treatment paradigms for steroid-free or steroid-light regimens in AAV. It has been shown recently, that brief exposure to glucocorticoids with combined cyclophosphamide and rituximab results in similar remission rates to standard therapy, but with fewer infections and lower rates of diabetes [215–217]. Glucocorticoid avoidance may allow effective remission with reduced adverse effects in both the short and long term and should be tested in a formal RCT. Pepper et al. showed in a prospective open-label trial of 46 patients with severe AAV that early GC withdrawal is as effective for remission induction as the standard of care and associated with reduced GC-related adverse events [218].

As discussed earlier, the notion of early GC withdrawal or avoidance has been successfully introduced both in the treatment of lupus nephritis [108] and in renal transplantation [219,220]. More recently, in AAV, the use of Avacopan, a C5a receptor inhibitor, was shown to be effective in replacing high dose GC together with cyclophosphamide or rituximab [221], in an RCT of patients with milder AAV disease followed for just 12 weeks.

Nevertheless, despite the advances in therapy, the natural history of untreated GPA and MPA remains one of a rapidly progressive, usually fatal disease.

Treatment options

The main conventional immunosuppressants used are CYC, MTX and AZA, whose mode of action and main side-effects have been discussed earlier at the SLE section (see Table 1.10 page 79) relating to their mode of action and key side effects.

The role of plasma exchange (PLEX) has been reviewed in a recent RCT (PEXIVAS), and it was shown that mortality or ESKD was not reduced with the use of PLEX among patients with severe ANCA-associated vasculitis. However, a reduced-dose regimen of glucocorticoids was non-inferior to a standard-dose regimen for death or ESKD.

I will not discuss the specifics of each drug option for the treatment of vasculitis in much detail, as the main drugs have been covered in the lupus section, which is the main focus of this thesis. A list of the main biologic drugs used in vasculitis is in Table 1.15.

Biologic	Mechanism of action	Main clinical use in vasculitis
B Cell depleting agent		
Rituximab	IgG1 chimeric, murine/human monoclonal antibody against CD20	GPA and MPA induction and maintenance Case reports in PAN, KD, UV, IgAV and CV
Anti B cell-activating factor		
Belimumab	human monoclonal IgG1 antibody against B lymphocyte stimulator (BLyS)	Under investigation as a potential therapeutic option in GPA
Interleukin inhibitors		
Tocilizumab	humanized monoclonal antibody against interleukin 6 receptor (IL6R)	Randomized controlled trial in GCA is currently underway

Mepolizumab	humanized monoclonal antibody against interleukin 5 (IL5)	Resistant cases of EGPA
Anakinra	interleukin1 (IL1) receptor antagonist	Successful case report in UV
Canakinumab	humanized monoclonal against IL1β antibody	Open-label study of 10 patients with severe UV some success
IgE antibody		
Omalizumab	humanized monoclonal antibody against IgE	Severe refractory EGPA-related asthma. Case reports of beneficial effects in UV.
Tumour necrosis factor (TNF) inhibitions		
Etanercept	p75 Fc fusion protein which acts as a receptor blocker for TNF	GPA. Prospective study open-label trial using etanercept as adjunctive therapy for IVIG in acute KD was safe and effective.
Infliximab	chimeric murine/human monoclonal antibody against TNFα	GPA and MPA. Multicentre RCT showed infliximab effective and safe in refractory KD
Adalimumab	humanized monoclonal antibody against TNFα	AAV with renal involvement
Anti-T cell therapy		
Alemtuzumab	humanized anti-CD52 monoclonal antibody (CAMPATH-1H) selectively depletes the peripheral circulation of T lymphocytes, monocytes and macrophages.	No widespread use for AAV yet
Abatacept	fusion protein composed of the Fc region of IgG1 fused to the extracellular domain of CTLA4, which inhibits T cell co-stimulation	Open-label study of AAV patients with mild relapsing GPA reported remission induction in the majority of patients (80%) and overall good tolerance.
Complement therapy		
Avacopan	C5a receptor inhibitor	RCT of AAV patients with moderate disease as GC sparing adjuvant treatment

Table 1.15. Summary of Biologic Drug Use in Medium and Small Vessel Vasculitis

AAV- ANCA-associated vasculitis; BLyS- B lymphocytes stimulator; CTLA4-cytotoxic T lymphocyte-associated protein 4; CV- cryoglobulinaemic vasculitis; EGPA-

eosinophilic granulomatosis with polyangiitis; Fc- fragment crystallizable region of the antibody; GCA- giant cell arteritis; GPA- granulomatosis with polyangiitis, IgAV- IgA vasculitis; IgG1- immunoglobulin G1; IVIG- intravenous immunoglobulins; KD- Kawasaki disease; MPA- microscopic polyangiitis, PAN- polyarteritis nodosa, RCT- randomized controlled trial; UV- urticarial vasculitis. From [206].

Risk Factors for relapse

Many different factors are associated with relapse in AAV. The most common risk factors relate to either disease parameters (i.e. type and ANCA status, subtype of disease, history of previous relapse) and management parameters (type and timing of therapy) [222].

A list of recognized risk factors is summarised in Table 1.16.

Recognized risk factors for relapse in ANCA-associated vasculitis	
Disease parameters	**Management parameters**
1. PR3-ANCA	1. Early drug withdrawal at 1 year
2. GPA disease	2. Induction therapy type
3. Higher presenting eGFR	3. Maintenance therapy type
4. *Staphylococcus aureus* nasal carriage	4. Antibiotic prophylaxis with co-trimoxazole
5. ANCA positivity at the time of completion of induction therapy	***Poor adherence***
6. Previous relapses	

Table 1.16 Recognized risk factors for relapse in ANCA-associated vasculitis. ANCA- anti-neutrophil cytoplasm antibody; eGFR- estimated glomerular filtration rate; GPA- granulomatosis with polyangiitis; PR3- proteinase 3. Adapted from [222].

However, one of the less frequently discussed management parameters is adherence to treatment. Especially when comparing IV with oral regimens, adherence to the oral regimens may be suboptimal and therefore affect clinical trial outcomes. Furthermore, in real-life practise, poor adherence to treatment is a known risk factor for relapse and indicates a poor outcome in many rheumatological conditions. It is estimated at more than 50% and as high as 82% [223], as I will discuss in more detail later on.

There are very few studies for adherence in the vasculitis population [224]. Despite the lack of specific data for AAV in relation to adherence, this important risk factor should not be underestimated. In the context of clinical trials, where there is a more controlled environment, there should be focused efforts engrained within the study design to assess adherence via drug monitoring methods where possible.

Adherence

Terminology

There is significant variability regarding the preferred terms to describe adherence patterns in different studies [225]. Terms that have often been used include compliance, concordance, persistence, retention rate and discontinuation. Although often used as synonyms to adherence, the terms compliance and concordance, actually describe different aspects of patients' medication-taking behaviour. The definitions and terms used for research purposes in clinical trials can vary significantly amongst different studies, and furthermore, the concept and challenges of adherence in real life practice can be broader and more complex compared to the monitored and structured context of a clinical trial.

Etymology

'*Adherence*', the most commonly used term, comes from the Latin word "adhaerere", which means to cling to, keep close, or remain constant. In the Oxford English Dictionary, it is defined as 'Persistence in a practice or tenet; steady observance or maintenance', a definition that appropriately depicts the tenacity that patients need to achieve in sticking to a treatment regimen [226].

The word '*compliance*' comes from the Latin word "complire", meaning to fill up, i.e. to complete an action or process. The Oxford English Dictionary definition is 'The acting in accordance with, or the yielding to a desire, request, condition, direction, etc.; a consenting to act in conformity with, an acceding to, practical assent.' In the

medical context, this can be interpreted as acting following the advice given by the prescriber. However, this interpretation implies a paternalistic attitude towards the patient on the prescriber's part and therefore is not as favourable nowadays.

Therefore, the concept of concordance has been introduced in the last decade, suggesting that the prescriber and patient should come to an agreement about the regimen that the patient will take. The definition of '*concordance'* in the Oxford English Dictionary is 'The fact of agreeing or being concordant; agreement, harmony'. Thus, the term concordance also suggests that patients are more involved in the process and should take greater responsibility for their management, and it relates more broadly to the process and outcome of a medical consultation.

Definitions

The National Institute for Health and Care Excellence (NICE) guideline on optimising medicines adherence has summarised these terms as follows [227]:

Compliance- commonly used and implies that the patient complies with the doctor's orders; most doctors no longer practise medicine in such a paternalistic way.

Concordance- is a complex concept that is not practical in everyday general practice; it covers incorporating patient beliefs and preferences in the decision-making process and includes wider supportive care for the patient.

Adherence- a preferred term that describes the extent to which the patient's behaviour matches advice from the prescriber.

However, the most widely used definition universally is by the World Health Organisation that defines adherence to medicines as "the extent to which the patient's action matches the agreed recommendations" [228]. This presumes an agreement between the prescriber and the patient about the prescriber's recommendations, and is also the term that I will be using in this thesis.

Why is adherence important?

Medicines are taken to improve symptoms and outcomes. However, poor adherence may limit the benefits of medicines. This can result in lack of improvement or, worse, deterioration in health. Moreover, the economic costs are not limited to wasted medicines only, but also include the 'knock-on' costs arising from increased demands for healthcare if the health of poorly adherent patients deteriorates.

Non-adherence is a fundamental limitation in healthcare delivery, often because of a failure to agree fully on the prescription in the first place or to identify and provide the support that patients need later on. Addressing non-adherence should start with an exploration of patients' perspectives regarding the medication and the reasons why they may not want, or be unable, to use them. All healthcare professionals have a duty to help patients make informed decisions about treatment options and use appropriately prescribed medicines to the best effect.

The cost of non-adherence

A systematic review on the financial impact of medication non-adherence by Cutler et al. reported that the annual costings of medication non-adherence range from US$100 to U$290 billion (£73 to £212 billion) in the USA, €1.25 billion (£1.09 billion) in Europe and approximately $A7 billion (£3.87 billion) in Australia [229]. Furthermore, 10% of hospitalisations in older adults were attributed to medication non-adherence, with the typical non-adherent patient requiring three additional medical visits per year, resulting in $2000 (£1462) increased treatment costs per annum. However, the researchers found that methodological differences make the comparison among studies challenging and an accurate estimation of the true magnitude of the cost very difficult. They concluded that research assessing the economic impact of medication non-adherence is failing to provide adaptable data to influence health policy sufficiently.

In the UK, the cost relating to poor adherence is estimated to exceed £500million a year [230].

At the same time, the National Institute for Health and Care Excellence (NICE) also reports that medication adherence is an ongoing challenge. It is estimated that some 35-50% of all medicines prescribed for long-term conditions are not taken as recommended [231]. This represents a personal and economic loss to patients, as well as to the healthcare system and society.

Types of non-adherence

NICE suggests that causes of non-adherence fall into two overlapping categories; unintentional and intentional:

Unintentional non-adherence occurs when the patient is keen to follow the agreed treatment, but external barriers outside their control prevent them from doing so. Such examples include difficulties in understanding and remembering the instructions, inability to access or pay for the treatment, forgetting to take the medication, or developing side effects of the treatment.

Intentional non-adherence, on the other hand, occurs when the patient actively decides not to follow the treatment recommendations. This relates to beliefs and preferences that influence the person's perceptions of the treatment, as well as their motivation to commence and persevere with it. Therefore, clinicians need to understand better the perceptual factors like beliefs and preferences, which can influence both motivations to start, as well as follow through with the treatment. In addition, the practical factors that affect a patient's ability to adhere to the agreed treatment need to be considered.

Factors influencing adherence

Adherence is a complex behavioural process which is determined by several interacting factors [228]. These include:

- attributes of the patient
- the patient's environment
    - social support
    - characteristics of the health care system
    - functioning of the health care team
    - availability and accessibility of health care resources
- characteristics of the disease in question and its treatment.

There are many specific aspects of treatment to which a patient may not adhere, such as appointment-keeping, vaccinations, appropriate medication use, following advice for changing lifestyle behaviour (e.g. diet, physical activity, smoking cessation).

Trends in adherence

The debate regarding the terminology and the adoption of more inclusive and balanced definitions aligns with the evolution of practising medicine in recent years. There is a clear intention to empower patients by involving them in decisions about prescribed medication and their treatment overall, manifested through the current guidelines and the good medical practice principle by the regulatory bodies, including the Good Medical Practice by the GMC [232]. In addition, the principle of working in partnership with patients, sharing with them the information they will need to make decisions about their condition, its likely progression and the options for treatment, including associated risks and uncertainties, is underpinning everyday practice.

Long gone are the days of paternalistic care when patients would merely accept and follow prescriptions and instructions from their "all-knowing" doctors. With the progress of technology and wide access to the advents of internet and increasing media coverage of scientific developments, more and more patients can access information about their disease and treatment options. Of course, the quality of this information is hugely variable, and in the era of "fake" news, not always accurate or indeed from appropriately reviewed sources. Worryingly, even at a time of a global pandemic, there are people that based on misinformation on social media deny the existence and severity of an infectious disease and fail to adhere to public health measures[233]. Even before the pandemic, however, too often patients were seen in the clinic, having purchased "miracle" treatments online or expensive supplements and gadgets to substitute their regular treatments [234]. On the other hand, it is also very common to have patients coming with a “named” agent and list of investigations they would like to have and strong views about their diagnosis and specific medication they want to be prescribed to “cure” them from their ailment, as seen on social or mainstream media.

The difficult task for the clinician nowadays seems to be not only to diagnose and treat the patient but to try to convince them of the correctness of the actual diagnosis and to consider the necessary treatment. Of course, the patient's body is their own, and they have the final say in deciding what is the most suitable treatment for them, in accordance with their understanding, beliefs and wishes. However, the decision of which treatment options should be offered and prescribed is down to the clinician's professional judgement. But adhering to those recommendations ultimately rests with the patients.

There is, therefore, a fine balance to be achieved in negotiating this new relationship in the modern era, accepting the principle of professional expertise and evidence-based knowledge on the clinician's part, and honouring the patient's autonomy. Despite the wealth of available information to the patients, it is still acceptable to assume that a healthcare professional is better equipped to navigate the complexity of scientific literature and provide an appropriate recommendation. This automatically puts the clinician in a position of authority and power that may tilt the balance of the therapeutic alliance.

Although the patients can also access an extended level of information material regarding the disease and therapeutic modalities, the critical and scientific appraisal of the evidence by a trained clinician and the interpretation of the clinical presentation based on their experience and knowledge of medicine is necessary. Healthcare professionals are required to undertake years of training in accordance with stringent guidelines of the governing medical boards and regulators in order to be allowed to treat patients and specifically to become prescribers. Only doctors, and more recently also selected specialist trained nurses and pharmacists, have the licence and authority to prescribe and dispense medications, always with a diagnosis in mind. However, this may be perceived by some as denying the patient the chance to have greater input in decisions regarding their therapeutic options.

To that end, specific guidelines have been issued by NICE on how healthcare professionals can help patients make informed decisions by facilitating patient

involvement in the decision to prescribe and how to adhere to the prescribed medicines can be supported.

Recommendations and guidelines for optimising medicines adherence

These guidelines, initially published in 2009 and recently updated in 2020 [235] stipulate that “healthcare professionals should adapt their consultation style to the needs of individual patients so that all patients have the opportunity to be involved in decisions about their medicines at the level they wish”. Clinicians are encouraged to establish the most effective way of communicating with each patient and, where necessary, consider ways of making information accessible and understandable (e.g. using large print, pictures, symbols, an interpreter, different languages or a patient advocate). The guidelines prompt clinicians to offer patients information relevant to their condition, possible treatments, and personal circumstances, which is easy to understand and free from jargon. It is recommended that all patients should be offered the opportunity to be involved in making decisions about prescribed medicines. However, it is stressed that it is really important to first establish what level of involvement in the decision-making process the patient prefers.

Concerning poor adherence, one of the key recommendations highlights the risk that increasing patient involvement can mean that patients decide not to take or to stop taking a medicine. It is therefore recommended that the information provided to the patient on risks and benefits and the patient's decision should be recorded. As clinicians, we should accept the patient's decision, sometimes to voluntarily not adhere to the recommended medication, even though we might not agree with that

decision, as long as the patient has the capacity to make an informed decision and has been provided with the information needed to make such a decision.

It is recognised that non-adherence is common and that many patients can be non-adherent sometimes. Clinicians are encouraged to assess adherence routinely in a non-judgemental way whenever they prescribe, dispense and review medicines and if non-adherence is identified, explore the reasons for this. Patients' concerns about medicines and whether they believe they truly need them, do affect if and how they adhere to their prescribed medicines. Therefore, it is suggested to review patient knowledge, understanding and concerns about medicines and the patient's view of their need for medicine at specific time intervals agreed with the patient, as adherence may change over time. Furthermore, especially when treating long-term conditions with multiple medications, it is advised to repeat the information and be aware that although adherence can be improved, not one single specific intervention can be recommended for all patients. Hence, tailored interventions to the specific difficulties with adherence the patient is experiencing are preferable.

These guidelines embrace the fact that subjective beliefs may influence patients' acceptance of medical advice, including medication use. Therefore, it is vital to take beliefs into account when giving health advice and/ or providing medical treatment.

Personal and cultural beliefs on medication adherence

Medication adherence is undeniably multi-faceted. The impact of beliefs (be it personal or cultural) on medication adherence of patients with chronic illnesses has been systematically reviewed by Shahin et al. [236]. Factors contributing to medication

adherence include illness perceptions, health literacy, self-efficacy, cognitive abilities like memory, coping and problem-solving skills and psychosocial factors.

Personal beliefs about illness include both psychological elements and emotional representations such as feelings that arise as a result of illness, like anxiety and/ or depression. Social determinants such as spirituality and religiosity have been increasingly identified as influencing health decisions and adherence treatment [237]. Cultural beliefs, defined as "a set of behavioural patterns related to thoughts, manners and actions, which members of society have shared and passed on to succeeding generations", may also impact the behaviour of patients with chronic disease about taking their medication.

The concept of self-efficacy

Albert Bandura, an influential social cognitive psychologist, best known for his social learning theory, first introduced the concept of self-efficacy in 1997 [238]. He stated that the ability to perform certain behaviours is mainly influenced by the belief that someone is actually able to execute that behaviour and defined this as self-efficacy. High self-efficacy for medication-related behaviours can sustain the adherent behaviour longer. Conversely, patients with low self-efficacy have the opposite effect [239]. Promoting self-efficacy leads to improved self-management outcomes, increases life expectancy and reduces the use of health care resources [240]. As self-efficacy has the potential to affect motivation and adherence to prescribed regimens, it is not surprising that interventions aimed at promoting self-efficacy have been studied in chronic diseases [241].

Moreover, specific assessment tools have been designed and validated to measure this behavioural aspect of adherence, and often questions relating to self-efficacy are included in adherence surveys.

One such example, the Long-Term Medication Behaviour Self-Efficacy Scale (LTMBSES), was developed by De Geest et al. [242] and validated by Denhaerynck et al. [243], to measure self-efficacy in relation to long-term medication behaviour in renal patients. This is a Likert scale instrument consisting of 27 items addressing skills related to medication use. It has three substantive dimensions with mutually influencing sub-themes derived from Bandura's self-efficacy theory, i.e. personal attributions (7 items), environmental factors (13 items), and task-related and behavioural factors (7 items).

Using this instrument, a Dutch study of 54 chronic kidney disease patients randomised them to control or intervention group and rated their self-efficacy using the Long-Term Medication Behaviour Self-Efficacy Scale (LTMBSES) [241]. The intervention discussed the results of the self-efficacy test with the patients, whereas such a discussion did not take place in the controls independently of the score achieved. Discussing self-efficacy scores with the patients led to increased self-efficacy scores in patients post-intervention (but not with the control), and older patients (defined as over the age of 55) had higher self-efficacy scores.

Assessing adherence

Over the last forty years, many studies on medication adherence have been conducted searching for the ideal adherence measure, but a single tool suitable for all circumstances has yet to be identified. Selecting a method to monitor adherence is thus usually tailored to the individual attributes and targets/ resources of the study and clinical setting, acknowledging that different tools might be used even within the same institution in different situations. Currently, no available method can be considered as the "gold standard", and utilising a combination of methods is often recommended [244].

Generally speaking, measurements of medication adherence are categorised by the WHO as subjective and objective.

Subjective measures are those requiring the provider's or the patient's evaluation of the medication-taking behaviour, such as self-reporting and healthcare professional assessments. The main criticism of subjective methods is that they are vulnerable to bias, and patients tend to underreport non-adherence to “please” their healthcare providers [245] . Similarly, clinicians tend to overestimate good adherence [246].

Objective measures include direct methods such as biochemical quantification of the drug or its metabolite concentration in body fluids or directly observed therapy [247]. Indirect objective methods also exist, such as electronic monitoring, pill counting and secondary database analysis. Objective measures are used often to validate and

correlate with the subjective ones. Tempting as it is to utilise only one measure for identifying non-adherence, a meta-analysis on adherence outcomes in transplantation reported that although employing a single objective measure may have more accuracy, a multi-subjective-measure approach has higher sensitivity [248].

Direct approaches, on the other hand, such as drug level monitoring, are usually more expensive and burdensome to the health care provider. However, measuring levels of specific drugs is a good and commonly used means of assessing adherence. For instance, in renal transplantation, the serum concentration of immunosuppressive agents such as tacrolimus (TAC) and mycophenolic acid (MPA) trough levels usually reflect adherence patterns, whilst subtherapeutic levels can reflect poor adherence or suboptimal dosing [249].

Even with drug levels monitoring however, bias can be introduced if patients choose to take their medication just before the upcoming tests, a phenomenon described as "White coat adherence" [250,251] and which cannot be ignored, allowing a false perception of good adherence around clinic visits.

There are also anecdotal reports of patients so keen to please their treating physician to the extent of undergoing monitoring for toxicity of medication or even undergoing invasive interventions for monitoring purposes (e.g. OCT for HCQ monitoring) or research purposes (blood sample or skin biopsy) and attending for the monitoring procedure, despite knowing that they are not taking the medication being monitored (personal communication “pearls of wisdom” Professor Isenberg).

Surprisingly, even within the context of clinical trials, when patients know that they are specifically monitored for their adherence to a particular drug, some still do not adhere despite having volunteered to participate.

A summary of the most commonly used methods of assessing adherence and the main advantages and disadvantages of each method is summarised in Table 1.17.

Methods of Measuring Adherence	Advantages	Disadvantages
Direct measures		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them impractical for routine use
Drug level monitoring Biologic marker monitoring	Objective Most accurate Can provide physical evidence	Binary result only (Yes/No) Potential issue with drug metabolism Intrusive Expensive Varied drug metabolism Non-quantifiable biomarkers/drug metabolites Drug-drug interactions and drug-food interactions Require qualified staff and techniques to perform Bias occurs if patients know the schedule of the tests (white coat adherence)
Indirect measures		
Measures involving secondary database analysis	Able to assess multidrug adherence Can identify patients at risk for treatment failure	Assumptions are made (the medication-taking behaviour corresponds to prescription refilling, and the medications are taken according to prescription) Fail to identify partial adherence

Methods of Measuring Adherence	Advantages	Disadvantages
Direct measures		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them impractical for routine use
	Provide medication-refilling pattern The complete dataset used is generally verified by a third party for insurance claim purposes	Fail to identify barriers for the detected non-adherence Missing out prescriptions, if obtained outside the system Incomplete records, if drug discontinuation is verbally advised by the prescriber
Measures involving Electronic Medication Packaging (EMP) devices	Highly accurate Identify medication-taking pattern Identify partial adherence	Expensive Technical supports required Overestimation if patients accidentally or purposefully actuate the container Inconvenience due to bulky container Pressure to patients
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect the clinical response
Measurement of physiologic markers (e.g. heart rate in patients taking beta-blockers)	Often easy to perform	The marker may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)

Methods of Measuring Adherence	Advantages	Disadvantages
Direct measures		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them impractical for routine use
Pill count	Low cost Simple Can be used in various formulations Highly accurate	Not for non-discrete dosages or *prn* medications Underestimation due to early refill Arbitrary cut-off value Unable to identify a medication-taking pattern
Patient diaries	Help to correct for poor recall Simple; objective	Easily altered by the patient Susceptible to distortion
Measures involving clinician assessments and self-report	Low cost Easy to administer Real-time feedback Available Flexible to accommodate different conditions Identify belief and barriers to adherence Well-validated	Least reliable Relatively poor sensitivity and specificity Affected by communication skills of interviewers and questions in the questionnaire Patient's desirability can bias

Table 1.17 Comparing advantages and disadvantages of various adherence measuring methods; modified from NEJM and Lam et al. [244].

Although the subjective methods are considered to be less reliable, their low cost, flexibility, simplicity, and real-time feedback have proven very practical and thus are primarily used in clinical practice [252,253]. Different formats used include online assessments, written questionnaires, structured interviews and a voice response system. However, no tool is perfect and false data input by patients (intentionally or unintentionally) can reduce both the sensitivity and specificity of capturing true non-adherence. Furthermore, deficient communication skills and poorly constructed questions by the interviewers, as well as issues with the weak design of surveys (for example, bias may be introduced by negativity in phrasing the questions inferring blame to the patients), are also recognised problems. Nevertheless, despite some drawbacks, these questionnaires can identify individual patient concerns and subsequently tailor appropriate intervention [251].

Surveys, Questionnaires and Scales

The most commonly used subjective measures are surveys and questionnaires. Table 1.18 summarises the most often used ones.

Questionnaires and scales	**Advantages**	**Disadvantages**
Brief Medication Questionnaire	Self-administration Evaluate multidrug regimes Reduce practitioner's training	Time-consuming

Questionnaires and scales	Advantages	Disadvantages
Hill-Bone Compliance Scale (Hill-Bone)	High internal consistency in both primary and outpatient setting	Limited generalizability
The Self-Efficacy for Appropriate Medication Use Scale (SEAMS)	High internal consistency in patients with high or low literacy	Time-consuming
Medication Adherence Report Scale (MARS)	Simplistic scoring Strong positive correlations compared to MAQ	Limited generalizability
Medication Adherence Questionnaire (MAQ) or 4-item Morisky Medication Adherence Scale (MMAS-4)	Quickest to administer Validated in the broadest range of diseases Validated in patients with low literacy Sensitivity 88%	Comparatively short, mainly suitable for initial screening Low Internal consistency (Cronbach's alpha 0.68) Copyrighted
Morisky Green Levine (MGL) scale	Easy to administer Cost-effective	Closed question format with "yes-saying" bias

Questionnaires and scales	Advantages	Disadvantages
	Used in clinic and research Sensitivity 81% On public domain	Lower validity and reliability than MMAS-8 Even lower internal consistency (Cronbach's alpha 0.61) than MAQ
8-item Morisky Medication Adherence Scale (MMAS-8)	Higher validity and reliability in patients with chronic diseases than MAQ Sensitivity 93%	Higher internal consistency (Cronbach's alpha 0.83) Copyrighted
Compliance Questionnaire-Rheumatology (CQR)[254]	Validated for rheumatic conditions Weighted items improving sensitivity	Complex calculations required Limited utility in clinical practice

Table 1.18 Summary of commonly used self-report questionnaires and scales: advantages and disadvantages.

In this section, I will review in more detail some of the commonly used adherence Questionnaires and Scales. Most of these questionnaires are validated against other measures, both subjective and objective. In addition, there is a plethora of questionnaires and scales utilised to accommodate various conditions, some are

generic, whilst others target specific aspects of adherence such as medication-taking behaviours or barriers to adherence or beliefs associated with adherence.

In terms of determining non-adherence, there are two main methodologies used: either utilising an absolute cut-off value or ranking the degree of adherence.

Most scales have a recommended cut-off value. For example, patients that took at least 80% of their medicines, as ascertained by an objective measure, are reported as adherent. Those who took less than this cut-off value are reported as non-adherent. Some cut-off scales may correspond to other self-reporting measures in a binary outcome. However, this can be variable, and often different research studies may define their specific cut-off value according to the population or disease studied or the aspect of adherence assessed.

On the other hand, some scales, such as the Medication Adherence Questionnaire (MAQ), the 8-item Morisky Medication Adherence Scale (MMAS), and the Brief Medication Questionnaire, rank the degree of adherence rather than defining an absolute cut-off for adherence. The rationale of ranking can be determined either by clinical outcomes or the researcher's expertise.

From the different scales identified in Table 1.18, I will discuss those that are more commonly used and are more relevant for chronic disease and specifically rheumatic disease that are the focus of this thesis.

The Compliance Questionnaire-Rheumatology (CQR) [255] is a rheumatology-specific instrument designed to measure patient compliance to medication. The questionnaire was developed and validated in 32 patients through semi-standardised interviews. However, equal weighting of items in this questionnaire did not perform well when compared to electronically measured medication compliance. However, its performance as measured by sensitivity was substantially improved in its ability to detect non-adherence defined as <80%, when the 19-items were differentially weighted using discriminant analysis. Unfortunately, this meant that the use of the CQR in the clinical setting requires a complex calculation, which hampers its utility in clinical practice.

The other two commonly used adherence scales in rheumatic disease are the two Morisky Adherence Scales. Like the CQR, both of these scales perform well compared to semi-standardised interviews but perform poorly compared to electronically measured medication compliance.

Morisky medication adherence scales

The original 4-item scale is often referred to in the literature as the “Medication Assessment Questionnaire” (MGL MAQ), was originally developed in 1986 and applied in baseline and post-intervention interviews with a cohort of patients treated for hypertension [256]. The original MGL MAQ is in the public domain and is widely cited in peer-reviewed journals. The four questions used in the scale address barriers to medication-taking and permit the health care provider to reinforce positive adherence behaviours. (See box 1.1) The MMAS-4 / MAQ scales are very similar but

are copyrighted since 2006 and have been used and validated in broader populations and a wider variety of diseases.

Original MGL Items

1) Do you ever forget to take your medication?

2) Are you careless at times about taking your medication?

3) When you feel better do you sometimes stop taking your medication?

4) Sometimes if you feel worse when you take medicine do you stop taking it?

Adherence Scoring: 0=High, 1-2=Medium, 3-4=Low

Box 1.1 Original MGL Questions and their scoring

The MMAS has since 2008 expanded into a structured eight-question survey. The four-item version (MMAS-4) only includes elements of forgetfulness and symptom severity, whereas the eight-question version (MMAS-8) explores additional situational and emotional aspects of medication adherence, such as non-adherence due to feelings of pressure or reasons other than forgetfulness.

The first seven items are dichotomous response categories with "yes" or "no", and the last item is a five-point Likert response. Compared to the original Morisky scale, it has much better psychometric properties: sensitivity and specificity are 93% and 53%, respectively, whilst Cronbach's alpha value is 0.83 that is above the

acceptance threshold of 0.70. (Cronbach's alpha score is a measure of internal reliability, and a score of 0.70 and above is considered satisfactory).

Adherence in rheumatic disease

The levels of adherence to treatment in patients with rheumatic and musculoskeletal diseases (RMD) vary, and it is estimated that 30-80% of RMD patients do not follow the recommended treatment plan [257,258]. The heterogeneity of different methods and outcome measures of adherence used in different studies makes it challenging to make direct comparisons between studies. For example, Kelly et al. [259] in a recent systematic review included 53 studies and identified 71 outcome domains, 37 different instruments that reported adherence in 115 unique ways (e.g. different adherence definitions and calculations, metric, and method of aggregation) thus, confirming the need for consensus on relevant outcomes to improve comparison of adherence measures and guide strategies to support adherence.

In contrast, a systematic review by Lavielle et al. evaluated interventions to improve medication adherence in RMD classified in five modalities (educational, behavioural, cognitive behavioural, multicomponent interventions or others) reported that educational interventions do improve medication adherence in these conditions and have the highest level of evidence [260]. After reviewing 22 studies (18 studies in RA (72%), four studies in SLE (16%), two studies in SpA (8%) and one study in gout (4%)), they concluded that despite the importance of medication adherence in chronic inflammatory rheumatic disorders, evidence on interventions to improve medication adherence remains scarce.

Recently, the European League Against Rheumatism (EULAR) recognised that non-adherence is the single most untold risk leading to suboptimal outcomes in the care of musculoskeletal disease and has recently commissioned a task force to review the literature and provide perspective and guidance which was published in 2020 [261]. The task force developed four overarching principles and nine points of consideration for healthcare providers, aiming to improve adherence by enhancing communication, building trust, removing structural barriers, fostering a blame-free environment and tailoring the solution to the problem.

The overarching principles state:

- Adherence impacts the outcomes of people with RMDs
- Shared decision making is key since adherence is a behaviour following an agreed prescription
- Adherence is influenced by multiple factors (comorbidities, treatments, cognition and preferences)
- Adherence is a dynamic process that requires continuous evaluation

Adherence in SLE and vasculitis

As one chapter of my thesis compares the adherence patterns seen in SLE against vasculitis, I will discuss some adherence-related features in these conditions.

Pharmacotherapy, including immunosuppressive medication, has significantly improved the prognosis in SLE patients; however, adherence to medication is variable [6]. Impaired adherence leads to poor clinical outcomes in SLE, and the rates of non-adherence in SLE patients range from 3% to 76% depending on the assessment methods used, which are all subject to limitations [77].

Similarly, the systemic vasculitides are a family of complex autoimmune multisystem conditions that, if left untreated, lead to significant morbidity and mortality. As in SLE, treatment with newer and more effective immunosuppressive therapies over the last few decades has improved prognosis substantially [262]. However, despite treatment with remission induction and maintenance regimens, 30% to 60% of vasculitis patients will still experience a relapse, potentially causing organ damage, renal involvement, hospitalisation or death [263]. As a result, they have worse health-related quality of life [264]. Similar to lupus, poor adherence can lead to relapse of disease and worse prognosis [260].

Therefore, understanding the factors associated with adherence in both conditions might enhance further support for the "at risk" patients, resulting potentially in better outcomes.

For both patients with SLE and vasculitis, nephritis carries a significant burden of disease, especially for the poorly adhering patient. Thus, a careful balance between the need for polypharmacy (using various immunosuppressants, prophylactic drugs and those to treat disease or drug-induced complications such as hypertension) and

the ability to comply with them all is clearly required. In addition, non-adherence may be specific to some agents and not others or may be more generalised.

By understanding and improving our insight into the reasons that result in poor adherence to pharmacotherapy in general, but also to taking specific medication, we may be able to identify common patterns of behaviour and practical barriers. We may even identify specific questionnaire answers that could highlight the risks and which could be addressed with targeted patient and staff education, with the overall aim of improving patient adherence and thus outcomes. This identification is especially important as omission or substitution by the treating physicians of certain drugs is now possible with the increasing range of treatment regimens as discussed previously. However, applying more customised therapies is only realistic if a clear understanding of what motivates patients to take certain drugs is better understood [265].

Unfortunately, good adherence to prescribed pharmacotherapy is often overestimated by physicians. Although in SLE adherence is well-researched, comparisons with other rheumatic conditions are mostly limited to Rheumatoid Arthritis [266] and Ankylosing Spondylitis [267]. In addition, there are comparatively limited data specifically on adherence of patients with lupus nephritis or at risk of developing nephritis. Furthermore, to date, no study has compared adherence to treatment in patients with vasculitis and SLE; despite the multiple similarities of these two conditions, including multiorgan involvement, systemic symptoms, similar pharmacotherapy and specifically pertinent for this work, the potential for renal involvement.

Adherence in SLE

Due to the various definitions of adherence used in studies and the different clinical settings, there is a significant variation reported in the adherence rate for the lupus population. For this reason, a systematic review and meta-analysis has been undertaken as part of this thesis and presented in Chapter 7 to identify the overall adherence currently reported in the literature (estimated at 49%). This meta-analysis will provide the foundation and inform the design of the adherence studies described later in this thesis.

The adherence in the studies including SLE patients, ranges from 17% [268] to 93% [93] with a variety of methods used to report adherence, including self-reporting, pharmacy refill data [269,270], and various compliance questionnaires [271] or biomarkers [272]. Furthermore, the clinical setting is different. For some studies, a National Health system mainly covered the prescription fee, whilst for others, the patients had to pay it themselves, possibly partially explaining the difference in adherence seen.

Moreover, as adherence is defined to a specific medication, it is essential to note that the rate of adherence in different studies could vary, even in the same individual, from one medication to the other [273]. There is also a significant difference in the number of participants included in each study, with the smallest one reporting on 32 participants [266] and the largest one by Feldman et al. [268] reporting on 10,406 patients.

Feldeman et al. investigated in 2018 [268] the adherence to HQC using the proportion of days covered in Medicaid data to describe HCQ adherence and defined good adherence as >80% of the days. They identified 10,406 patients with SLE, mainly women (94%), black 41% and white 31% and reported that only 17% were persistent adherers. In addition, they identified that white race (compared to black or Hispanic) was associated with better adherence, older age associated with better adherence and suffering from SLE related comorbidities also increased adherence.

The same group led by Feldman et all in 2019 , using a similar methodology, also published data using the Medicaid database on patients with SLE taking Azathioprine and MMF and identified a total of 4379 patients, 2309 on Azathioprine and 2070 on MMF [273]. In this particular study 17% of patients on AZA were adhering to the medication, whilst this rose to 21% for the MMF. Being of African-American or Hispanic race decreased adherence for AZA use, but not for MMF use. Male sex and multiple medications associated with worse adherence.

In a study by Sun et al. [269] some 121 patients with SLE were included, of who 46% had private insurance. They measured adherence using both pharmacy refill data but also self-reported. They identified that adherence was better with increasing age, being non-Afro-Caribbean and decreased with the need to take more than two medications, worse SLICC score or need to attend the Emergency Room or be hospitalised.

Another study by Liu et al, [274] followed 1956 patients using the Kaiser Permanente Northern California cohort, and calculated adherence using the medication possession ratio dichotomised as adherent (≥80%) or non-adherent (<80%). In adjusted analyses, they identified that increasing age and ≥3 rheumatology appointments per year increased adherence, whereas socioeconomic factors did not influence adherence.

Iudici et al. [272] recruited 83 consecutive patients with SLE and measured their HCQ and desethylchloroquine (DCQ) levels. The researchers concluded that 71% of the patients were adherent. After adjustment, concomitant use of immunosuppressants and the physical summary of the SF-36 questionnaire were associated with worse adherence.

The highest adherence was noted in the single centre French study by Costedoat-Chalumeasu et al. in 2007 at 93% [93]. This study included 203 patients who attended the rheumatology clinic outpatient department in a Paris hospital. The patients were unaware that they might be asked to take part in a study and also provide a blood test. All patients approached consented to participate in the study and have blood tested. Only 14 patients (7%) admitted that they had stopped HCQ and had low levels subsequently, giving an overall adherence of 93% - the highest seen in any study. Those patients cited concerns about potential side-effects and perceived ineffective effect of HCQ compared to other medications for poor adherence. Whilst this is a very reassuring result, it should be emphasised that it is only a reflection of that specialist clinic – and certainly not the result seen in larger cohort-based studies. However, what that study showed was that unscheduled, regular assay of HCQ

levels in whole blood could be a useful tool for identifying poor adherence in patients with SLE. They reported that undetectable or unexpectedly low HCQ concentration could prompt intervention and discussion with the patients regarding adherence and prevent flares by early detection of poor adherence. Furthermore, they suggested that this type of testing may prevent unnecessary and potential harmful escalation of treatment due to misinterpretation of flares and attributing this to lack of response rather than poor adherence.

A follow on international multi-centre study in 19 centres across 10 countries, by the same lead author in 2019 [246], utilised the same principle of unscheduled assays of HCQ blood levels on 305 lupus patients presenting with flares (defined by raised SELENA-SLEDAI score), also triangulating the results with self-reported questionnaires (MASRI) and also physician assessment of perceived adherence. The level of severe non-adherence as defined by drug levels alone was defined at 18.4%, but the overall level of adherence based on questionnaire surveys was estimated at 76.7%.

One of the interesting findings of the study was how different methods can identify different types of adherences better, and the moderate correlation between the three methods used. Drug levels were better in detecting severe non adherence and patient questionnaires were better in picking up infrequent missing of doses, and that those two methods correlated moderately (with Spearman's correlation- r_S=0.43). On the other hand, physicians' questionnaires and drug levels correlations performed much worse (r_S=0.19), with physician assessment often significantly underestimating the degree of poor adherence. This study certainly provided food for thought and

highlighted the importance of combining different methods and understanding their strengths and limitations.

Another study by Heiman et al., followed 632 patients of African-American origin using patient questionnaires for both adherence and depression, as poor adherence is often linked with depression- and identified 54% as poor adherers. In adjusted regression, they identified that younger age, female sex and more severe depressive symptoms were associated with poorer adherence.

Common themes emerging in terms of potential risk factors for poor adherence include young age [269], non-Caucasian ethnicity [274], poor education [271], lack of family support [275], shorter disease duration [276], being single [277] , depression [271], poor literacy and comprehension of instructions [278], side effects [279], forgetfulness [280], alcohol and substance abuse [281], unemployment [246], complicated drug regiments [277], cost and barriers to access of medication [282].

Many different interventions to improve adherence have been proposed for SLE patients such as: educational, motivational interviews and additional support, using pharmacy refill data to monitor non-adherence and prompt discussions surrounding SLE medications during clinic encounters [283], and specific medicine box or memory aids. In the general population similar successful interventions, which are practical and applicable to routine clinical practice, include a) using combination pills to minimise the daily pill burden, b) consultation for disease co-management with allied health professionals and clinical pharmacists, and c) medication-taking reminders

such as telephone calls to prompt refills. These interventions have demonstrated improvements in adherence of 10%, 15%, and 33%, respectively [284].

Younger patients, more specifically adolescents, are considered a challenging cohort of patients for any chronic disease. Useful approaches in optimising adherence to treatment in this sensitive age group include co-managing mental health issues appropriately, building rapport and strengthening the therapeutic relationship [76], and customising the treatment regimen where possible. Furthermore, empowering the adolescents to deal with adherence issues, providing adequate information, building on family and peer support, and motivational enhancement therapy are strongly recommended. However, harnessing technology and adjusting the approaches to their daily routine and habits, may be a potential avenue worth exploring.

In 2012 Ting et al. [285] looked specifically at interventions that may be preferable for this cohort of patients who are inherently more likely to struggle with compliance. In their prospective single centre study, Ting et al. recruited 70 patients with childhood-onset systemic lupus erythematosus (cSLE) and investigated the effects of cellular text messaging reminders on adherence to clinic visits. They utilised a combination of adherence assessment approaches, including drug levels and a self-report survey (MASRI), as well as pharmacy refill adherence at baseline and follow up. Patients with HCQ adherence >80% were considered sufficiently adherent. Although the clinic attendance adherence improved significantly by >80% among those adolescents who were non-adherent to clinic visits at the baseline with the aid of text message reminders, the intervention did not make a significant difference in long term

adherence to taking HCQ. Nevertheless, it suggested that this method could effectively improve visit adherence among adolescents and young adults with cSLE and maybe indirectly allow more opportunities to address the drug-related adherence.

In 2009 in his editorial entitled “Calling yesterday, texting today, using apps tomorrow” Nielsen reported that teens were texting an average of 3339 messages per month [286]. This trend has now been fast forwarded to the 2020s where teenagers are using smartphones and social media for most of their social interactions – this has been reinforced by the pandemic years with a reported increase in teenage smartphone use from 86% in 2012 to 98% in 2019 amongst those aged 16-24 [287] with the percentage of those teenagers spending more than 4 hours a day on screen-time almost doubling during the pandemic (from 32% to 62% before and after the pandemic respectively).

The use of technology and smart devices however, is not limited to the younger population anymore. The smartphone penetration rate in the UK has increased each year, reaching an overall figure of 92% in 2021 with a clear increase in the rate of smartphone ownership among those aged 55 and above. In 2016, less than half of all respondents over the age of 55 owned such a device, a figure that eventually rose to 83% in 2021 in the more mature population [288].

This suggests that there is a potential of harnessing the power of technology and social media to relay health appropriate messages or target adherence

enhancement apps to adolescent and young adults, who are nearly ubiquitous social media users, but also to more mature users that are now becoming more familiar with the newer technologies. Although opportunities to better engage adolescents and young adults through social media exist in healthcare delivery, health education and health policy, the challenges of creating evidence-based frameworks for measuring the impact of social media on health still exist [289].

Despite the growing number of mobile phone apps available to support people in taking their medications and to improve medication adherence, little is known about how these apps differ in terms of quality and effectiveness. An Australian review by Pérez-Jover et al. [289] in 2019 identified 272 medication reminder apps and systematically evaluated them- with 54% of them being rated as an advance quality app based on the use characteristics. However, they were not able to qualitatively evaluate the efficacy of the app in a clinical setting. This is a potential area of further research and expansion, as the utility of such applications may prove a significant tool in the not-too-distant future, and can be targeted at the SLE population specifically.

Adherence in Lupus Nephritis

The number of publications relating to adherence in LN has increased significantly in recent years. In Brazil, a RCT of 122 women with LN [290] showed low levels of adherence at baseline of around 30%, utilising a 5- item clinical questionnaire with follow up over one year. Adherence to specific drugs for SLE improved after

educational interventions led by pharmacists, with the effectiveness of the intervention reaching 64% (95% CI 34–80%).

In the USA, Feldman et al. [273] described above, studied longitudinal patterns and predictors of adherence to AZA and MMF in a nationwide SLE cohort over 10 years and dichotomised adherence at 80%, with ≥24 of 30 days per month considered adherent. Only 17% of 2309 AZA and 21% of 2070 MMF initiators were adherent. Male sex and polypharmacy associated with lower odds of non-adherence to both medications. Interestingly, LN was associated with lower odds of non-adherence to MMF (OR 0.74 [95% CI 0.55-0.99]). Overall, the study concluded that adherence to AZA or MMF over the first year of use was rare. Race, sex, and LN were modestly associated with adherence, but the significance of predictors varied by medication, underlining the complexity of predicting adherence behaviour.

Furthermore, HCQ which is considered one of the cornerstone therapies in SLE and LN management, was associated with very low rates of adherence among Medicaid beneficiaries in the USA. In a study of 10,268 patients between 2000 and 2010 who newly initiated HCQ, less than 20% of patients adhered to taking HCQ (adherence was defined as ≥80% proportion of days covered by medication refills and drug dispensing). Non-adherence was seen more often in younger people of non-white race/ ethnicity and individuals of lower socioeconomic status, requiring higher acute care use (i.e. emergency care visits and/ or hospitalisations) and was associated with comorbidities such as diabetes and depression [268]. Interestingly, a trend

towards worsening HCQ adherence also was noted over the first year of use for most patients, regardless of initial adherence [291].

An international study of adherence in patients with SLE experiencing flares by Costedoat-Chalumeau et al. [246], reported that self-administered questionnaires best captured mild or moderate non-adherence (i.e. tablets missed relatively infrequently and tablet intake frequently interrupted), whereas very low blood drug levels identified better severe non-adherence (i.e. complete discontinuation of treatment). Using drug levels as a criterion, severe non-adherence was unmasked in up to 20% of the patients [292].

A UK based cross-sectional questionnaire-based quantitative study [293] of 98 patients with LN from the Guy's and St Thomas' SLE cohort highlighted the importance of trust in relation to medication adherence. The study also showed that a good understanding of patients' illness is linked to a better relationship with their doctor and increased trust, which consequently resulted in greater participation in shared decision-making. The researchers suggested that tailored psycho-educational interventions could contribute to improving the patient-doctor relationship, which, in turn, might impact medication adherence in patients with lupus nephritis.

An earlier UK qualitative study on adherence patterns in the UCL SLE cohort by Chambers et al. [186], although not studying exclusively LN patients, identified similar patterns in the patients' reasoning for taking or not taking their medications, which

were largely related to their previous experiences with the disease and/ or drugs. In line with the more recent studies, it suggested that improvements in communication between doctors and patients could promote better adherence in patients with SLE.

Furthermore, another national survey study in the UK via the LUPUS UK forum [294] exploring the impact of patient-physician interactions, pre- and post-diagnosis, on lupus and UCTD patients' psychological well-being, cognition and health-care-seeking behaviour, reinforced the message that negative medical interactions pre- and post-diagnosis can cause a loss of self-confidence and a loss of confidence and trust in the medical profession. The study proposed that empowerment, including shared medical decision-making and knowledge acquisition, can mitigate insecurity and improve care, hence also lead to better treatment adherence.

However, the socioeconomic aspects and associated constraints to adherence should not be disregarded, and these can be more prominent in poorer countries or countries where access to healthcare and treatment is not free. A similar study to the UCL UK one conducted in Jamaica by the same lead researcher [295] reported that the high cost and poor availability of medications were the main reasons for poor adherence. However, some patients chose not to take their medications because of side effects, perceived mild severity of their disease and/ or a preference to take drugs only when symptomatic.

In the US, challenges relating to access of care and other treatment barriers also explain partly the poorer adherence and increased rates of acute care use among

patients with SLE and LN. In a separate study of patients with incident LN within a US Medicaid population [296], quality of care was assessed by performance on three measures (receipt of an immunosuppressive, an antimalarial, and a renal-protective antihypertensive agent). Although adherence was not specifically assessed, more than 1 in 8 patients in this study used the Emergency Department (ED) as their primary source of care (with no difference by geographic region), and quality of care as assessed by these metrics was lower in those receiving their care in the ED.

Adherence in vasculitis

There is a relative paucity of studies that have examined medication adherence for vasculitis. Only two studies, the Vasculitis Self-Management study (VSM) [297] and the Accessing Social Support in Symptom Treatment (ASSIST) [298] have focused specifically on vasculitis patients and have used specific scales tailored to their study population.

The scale consists of seven items measured on a five-point Likert scale; the response scale for the first six items ranges from 1="none of the time" to 5="all of the time," The seventh item (percentage of medication doses taken exactly as directed) ranges from 1="0–24 %" to 5="100%." The VSM study medication adherence scale has demonstrated satisfactory internal consistency (Cronbach's α=0.77) and test-retest reliability of 0.60 in a previous study of vasculitis patients

The VSM study was a cross-sectional study of 202 AAV patients that investigated barriers to performing various self-management behaviours, such as medication adherence. Five barriers were identified associating with worse medication adherence, including firstly disruptions to the patient's daily routine and secondly forgetfulness. The other three barriers related to the complexity of the medication regimen (e.g. large number of medications, or complex medication instructions, and/ or complicated dosing schedule.)

The second vasculitis-specific study, ASSIST, was a longitudinal study of 228 vasculitis patients (not only AAV) that examined if social support and conflicting medication information from different sources (e.g. physicians and the internet) adversely affected adherence. Carpenter et al. demonstrated that physician support increased vasculitis patients' adherence self-efficacy and consequently predicted better medication adherence, whereas receiving conflicting information resulted in poorer adherence. A further review and analysis of that study cohort analysed potential predictors for poor adherence and showed that variables that significantly correlated ($p<0.05$) with non-adherence were younger age ($r=-0.23$, $p<0.001$), female sex ($r=0.16$, $p<0.05$), the experience of side-effects ($r=0.15$, $p<0.05$), and more depressive symptoms ($r=0.22$, $p<0.001$).

However, in the regression model, only younger age and more depressive symptoms predicted worse adherence. Over 97% of patients who took steroids in that study reported experiencing drug-related side effects. Moreover, the experience of drug-related side-effects on the initial survey was significantly associated with worse adherence at three months. However, this relationship did not remain significant

when adjusting for other factors. In addition, patients who experienced side effects with specific medication were found to be less adherent compared to those that had no side effects. Interestingly, clinical characteristics were not significantly correlated with adherence.

Overall, vasculitis patients reported a high level of medication adherence. But even among this highly adherent sample, patients who were younger and had more depressive symptoms were less adherent to therapy at 3-month follow-up [224]. The researchers concluded that multiple factors are associated with medication non-adherence for vasculitis patients. They suggested that healthcare providers should discuss medication adherence and drug-related side effects with their vasculitis patients and particularly target younger patients and patients with clinical signs of depression.

Conclusion of Literature review

SLE with kidney involvement can lead to ESKD, and that is in part relating to non-adherence. Despite every physician's hopes and wishful thinking, as with many other chronic diseases, non-adherence to treatment is very common in SLE, even with LN.

In SLE, the reported levels of non-adherence range from 3% to 83% depending on the methods used, with the worst figures found in studies using objective measures. The overall rate of adherence in all the eligible studies I meta-analysed was estimated at 46%. Furthermore, non-adherence may be even higher in countries without health insurance systems and poor access to specialised care, leading to unintentional non-adherence.

The first step in addressing this fundamental issue of non-adherence is to diagnose it as promptly and as accurately as possible, which can be particularly challenging given the great variability of assessment methods and their many limitations.

Subjective measures are easier and more practical to use; however, self-administered questionnaires may underestimate non-adherence. Even clinicians' assessments can be highly subjective and inaccurate, and attendance at clinic visits might not always correlate with adherence to treatment.

Objective methods (i.e., pharmacy refilling data, pill counts, electronic monitoring devices) are not routinely applied in clinical practice. Indirect assessment utilising the

presence of clinical or biological markers of non-adherence (e.g. absence of Cushing-like features in patients treated with corticosteroids or macrocytosis in patients on azathioprine) can be clinically helpful, but are not always reliable. Unscheduled drug level monitoring (e.g. blood HCQ levels) can be a helpful objective way, and specifically in SLE and LN, HCQ levels monitoring is a promising option given that the majority of patients will be on this drug.

There are now many published recommendations and support mechanisms to optimise medicine adherence in general (e.g. NICE) and more specific for rheumatic disease (e.g. EULAR). All of them advocated a non-judgemental approach and put patient empowerment at the centre of focus.

Despite treatment with remission induction and maintenance regimens in the vasculitis population, 30% to 60% of patients will still experience a relapse potentially causing organ damage, renal involvement, hospitalisation or death, and an overall worse health-related quality of life. Whilst the limited literature suggests that poor adherence is not as common in vasculitis, it can contribute to relapse of disease and worse prognosis.

For SLE and LN patients, non-adherence is frequent and has important clinical implications. Therefore, it should be routinely and repeatedly assessed at each visit because behavioural patterns evolve and vary over time. A timely non-judgmental and open discussion about adherence may avoid renal flares and unnecessary treatment escalation.

Despite the recent advances in therapy, LN remains one of the most common and severe manifestations of SLE, and in those patients reaching ESRF, renal transplantation can be a life-prolonging therapy. Patients with LN who do receive an rTp have better survival and fewer cardiovascular and infectious complications than LN patients on dialysis, indicating that when rTp is an option it should be the preferred strategy. However, poor adherence to immunosuppressive therapy is associated with increased graft failure in renal transplant patients necessitating a return to dialysis, with up to 16% of graft losses being attributed, in part, to poor adherence.

The progress in therapeutic options and emerging treatment paradigms for SLE and vasculitis promise a more optimistic outlook in regards to steroid dose reduction. Prescribing newer and fewer medications that are simpler to administer and with better side-effect profiles may also help to improve adherence. However, it is very unlikely that these advances alone will entirely solve the problem of poor adherence. Devoting time to diagnosing non-adherence and investing effort to build rapport with each patient, allowing them to improve self-efficacy and actively participate in their care decision-making, will undoubtedly remain essential for improving adherence and consequently patient prognosis and quality of life.

NOTE

Chapter 1 is partly based on the following published articles:

Ntatsaki and Isenberg, Risk factors for renal disease in systemic lupus erythematosus and their clinical implications. *Expert Rev Clin Immunol* 2015*;* 11: 837-48 [87]

Ntatsaki E*, Velo-García A*, Isenberg D. The safety of pharmacological treatment options for lupus nephritis. *Expert Opin Drug* 2016; 15: 1041–1054 [141]

CHAPTER 2

Aims and hypotheses of thesis

Study 1

Aim

To assess the impact of time on dialysis before renal transplantation on survival in patients with lupus nephritis.

Hypothesis

Clinical variables, including time on dialysis before transplantation, have an impact on survival post renal transplantation in patients with lupus nephritis.

Study 2

Aim

To assess the association of poor adherence in renal transplantation, graft rejection and/ or failure in patients with lupus nephritis.

Hypothesis

Poor adherence associates with an increased risk for graft rejection and/ or graft failure for patients with renal transplantation in lupus nephritis.

Study 3

Aims

To assess self-reported adherence to medication in patients utilising an anonymised questionnaire-based survey in the lupus nephritis and renal vasculitis population.

To identify influencing factors and create a risk stratifying prediction model in lupus nephritis and renal vasculitis.

Hypotheses

A patient self-reported survey can identify risk factors associated with poor adherence.

A risk stratifying model based on the identified risk factors can predict adherence.

Study Summaries

Study 1

Objectives

Lupus nephritis (LN) is a significant cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE), often leading to end-stage renal failure (ESRF) and necessitating renal transplantation (rTp). The optimal timing of rTp in SLE patients with ESRF is uncertain and could potentially affect survival. Therefore, I investigated the time spent on dialysis before rTp and survival following rTp in a cohort of SLE patients.

Methods

Retrospective analysis of all adult SLE patients receiving rTp over a 40-year period (1975-2015) in two tertiary UK centres. Cox proportional hazard regression and receiver operator curves (ROC) were used to determine the risk associated with time on dialysis before rTp and other potential predictors.

Results

Forty patients (age 35±11 years, 34 female, 15 Caucasian, 15 Afro Caribbean and 10 South Asian underwent rTp. Eight (20%) patients died during a median follow up of 104 months (IQR 80,145), and the five-year survival was 95%. Univariate analysis identified time on dialysis before rTp as the only potentially modifiable risk predictor of survival with a Hazard Ratio of 1.013 for each additional month spent on dialysis

(95% CI= 1.001-1.026, p=0.03). ROC curves demonstrated that >24 months on dialysis had an adverse effect with sensitivity of 0.875 and specificity 0.500 for death. No other modifiable predictors were significantly associated with mortality, indicating that time on dialysis had an independent effect.

Conclusion

Increased time on dialysis pre-transplantation is an independent, modifiable risk factor of mortality in this cohort of patients with lupus nephritis.

Study 2

Objectives

Poor adherence to immunosuppressive treatment is common in patients with systemic lupus erythematosus and may identify those with lupus nephritis (LN) who have a poorer prognosis. Moreover, non-adherence has also been reported to be a potential adverse outcome predictor in renal transplantation (rTp). Therefore, I investigated whether non-adherence is associated with increased rTp graft rejection and/ or failure in patients with LN.

Methods

Patients with LN undergoing rTp in two major London hospitals were included retrospectively. Medical and electronic records were reviewed for documented concerns of non-adherence as well as laboratory biochemical drug levels. The role of non-adherence and other potential predictors of graft rejection/ failure, including demographics, comorbidities, age at SLE and LN diagnosis, type of LN, time on dialysis before rTp and medication use were investigated using logistic regression.

Results

Out of 361 patients with LN, 40 had renal transplantation. During a median follow up of 8.7 years, 17/40 (42.5%) of these patients had evidence of non-adherence. A total of 12 (30.0%) patients experienced graft rejection or failure, or both. In the adherent group, 2/23 (8.7%) had graft rejection, whilst in the non-adherent this rose to 5/17 (29.4%, p=0.11). Graft failure was seen in 5/23 (21.7%) patients from the adherent

group and 4/17 (23.5%) in the non-adherent group (p=0.89). Non-adherent patients had a trend towards increased graft rejection, odds ratio 4.38, 95% CI=0.73-26.12, p=0.11. Patients who spent more time on dialysis before rTp were more likely to adhere to medication, p=0.01.

Conclusion

Poor adherence to immunosuppressive therapy is common and has been shown to associate with a trend towards increased graft failure in patients with LN requiring renal transplantation. This is the first study to report that shorter periods on dialysis before transplantation might lead to increased non-adherence in lupus patients.

Study 3

Objectives

Identify predictors of self-reported good adherence in a lupus nephritis cohort and secondarily compare it with another multisystem autoimmune condition with renal involvement, namely vasculitis.

Methods

A prospective cross-sectional study to determine self-reported adherence to medication utilising an anonymised questionnaire-based survey, and explore influencing factors in LN and renal vasculitis clinics at UCLH and RFH.

Results

A total of 114 patients with LN and 80 patients with renal vasculitis were compared to identify emerging patterns, behaviours and differences that could introduce barriers to adherence. Lupus patients were more likely to be female, younger and with longer disease duration ($p<0.001$). Their adherence decreased with time compared to vasculitis patients ($p<0.001$). Conversely, the vasculitis patients had higher attendance at clinic appointments ($p=0.022$) and were more confident they could manage taking tablets correctly. "Forgetfulness" regarding medication and keeping track of hospital appointments were the commonest reasons for non-adherence rather than deliberate non-adherence. An increasing age and taking prednisolone associated with better adherence. In contrast, missing even one outpatient clinic appointment associated with worse adherence. Utilising responses from the survey,

a prediction model was proposed to risk-stratify patients further regarding their potential adherence patterns.

Conclusion

LN and renal vasculitis are two chronic conditions sharing many clinical manifestations and treatment options. Patients with these conditions have common risk factors for adherence that can identify the "at risk" patient and alert clinicians to the possibility of poor adherence.

CHAPTER 3

Methodology

Study 1

Study design

This was a cross-sectional study involving a retrospective review of all adult patients with SLE (aged >18 years) from two major London institutions, UCLH and RFH, who developed renal failure and received a renal transplant over a 40-year period (1975-2015).

Data Collection

UCLH has an established lupus cohort that includes all patients diagnosed with SLE dating back to 1975. At every clinic visit, clinical and laboratory data are collected as part of the assessment and recorded in an electronic platform (BLIPS- British Lupus Integrated Programme System) as well as in paper format, which is kept separately in blue folders. A master spreadsheet database containing linked-anonymised data is kept by Professor Isenberg and was the initial source for identifying suitable patients for this study.

The RFH renal department keeps a database of all patients that attend the clinic in an electronic record platform (VITALDATA). I interrogated this database with support from the Renal Systems and Clinical Data Manager (Mr David Wright) to generate a

list of all patients with a documented diagnosis of SLE and LN who had undergone renal transplantation.

I cross-referenced the two databases to exclude duplicate entries, i.e., patients followed up in both institutions, ensuring that the final database included only unique and eligible patients.

Thereafter, I reviewed hospital notes, electronic records and correspondence from family physicians and physicians in other hospitals. All patients with SLE and LN related ESRF (defined as the need for chronic dialysis therapy or kidney transplantation due to primarily lupus nephritis) and who required renal transplantation from January 1975 to December 2015 were included in this study. In all patients six months of disease quiescence was required before transplantation to be included.

All patients fulfilled four or more of the 1982 revised classification criteria for SLE of the American College of Rheumatology [15], and a histological class of lupus nephritis was defined according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system [22], applied retrospectively for the patients who had undergone transplantation before 2003.

Following a literature review, known modifiable and non-modifiable parameters possibly associating with survival were considered, as shown previously in Table

1.12 page 98 and were recorded for this cohort. An example of the template used for this data collection is included in Appendix 2.

I wanted to investigate the potential role of these risk factors in relation to mortality. The primary endpoint was patient death. Mortality and cause of death were assessed from dedicated SLE-Transplant clinics, where deceased patients are recorded on the electronic record systems. In addition, I also cross-checked this information with the Office on National Statistics, a dedicated national registry where all the deaths in the UK are recorded.

Statistical analysis

I undertook the initial data analysis utilising the functions on Excel spreadsheet software (Microsoft Office) for descriptive statistics. I presented continuous variables as mean and standard deviation and categorical variables as numbers and percentages. I prepared and formatted the database for further statistical analysis, which was undertaken using IBM SPSS version 22 (IBM Corp., Armonk, NY, USA) with the help of an independent statistician. Cox proportional hazard regression and receiver operating characteristic curves (ROC) are used to determine potential predictors. The cumulative survival curves are drawn using the Kaplan–Meier method. Patient characteristics are summarised and expressed as mean ± SD (if normally distributed) or otherwise median and interquartile range (IQR). Comparison between living and dead patients was undertaken using Chi-square, t-test and Mann-Whitney non-parametric t-test. A $p<0.05$ was considered significant.

Ethical approval and funding

This study was a retrospective review of a long-term observational registry for which University College London does not require formal ethical permission.

Funding for this study was supported by a grant from Lupus UK (Grant number award 172153). This research was undertaken at UCLH and RFH who received a proportion of funding from the Departments of Health's NIHR Biomedical Research Centres funding scheme.

Study 2

Study design

For this study, I utilised the same cohort as identified and described for Study 1.

Data collection

As the hypothesis and focus of this study were concerning adherence to treatment, additional information was extracted from the clinical notes of the eligible patients. For this, I retrospectively reviewed hospital electronic and paper records, correspondence with family practitioners and with other hospital physicians to identify any documented concerns about non-adherence to prescribed immunosuppressive treatment. Such concerns would usually be documented if the patients volunteered that they were not adherent to the medication themselves, by family members or admitting to this following direct questioning. Furthermore, in the United Kingdom, repeat prescriptions are facilitated by the General Practitioner

looking after the patients in the community. Therefore, if the patients do not renew their prescriptions in the community, the General Practitioner or the pharmacist will quickly become aware of this and will bring this to the attention of the clinical team for further evaluation.

It is known that whilst patient reporting could detect even relatively infrequently missed tablets, drug monitoring could also identify severe non-adherence [187]. Thus, I also reviewed the trough blood levels recorded for patients on tacrolimus or ciclosporin and mycophenolate mofetil (MMF) to help ascertain evidence of non-adherence. As there is no standard biochemical definition of non-adherence for patients with a renal transplant, I took a realistic and pragmatic approach (after discussion with my supervisors) of defining non-adherence as either:

i) evidence of poor adherence on documentation by a member of the clinic team in the medical records, or

ii) evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least six months after the renal transplantation.

This was to avoid levels taken during the initial introduction of the medication and individual dose adjusting. I used the percentage of sub-therapeutic trough levels of immunosuppressant medication as a surrogate marker of poor adherence rather than trough level variability, as the former has been reported to be more strongly associated with graft rejection after kidney transplantation [189].

Finally, I examined potential associations with poor adherence including sex, ethnicity, age at SLE diagnosis, age at LN diagnosis, age when dialysis was started, duration of SLE diagnosis to LN histological type of LN, time on dialysis before transplantation, other existing conditions such as diabetes mellitus, hypertension, dyslipidaemia and prior cardiovascular disease.

The primary endpoint was renal graft rejection (defined as acute deterioration in graft function with rejection confirmed histopathologically) occurring >12 months after transplantation. Secondary endpoints included renal graft failure (defined as the need for dialysis or re-transplantation) and a composite endpoint of graft rejection and/ or failure >12 months from the transplant.

For patients that had had more than one transplant, the following process was followed:

If the transplant failed due to renal graft rejection, then the patient would meet the primary endpoint and hence no further information was collected. If, however, graft failure (secondary endpoint) was identified the patients were censored for the purposes of the secondary outcomes only, but continued to be monitored for the primary endpoint of renal graft rejection in the second transplant. This means that they were followed during their second transplantation. If the first transplant was lost from an entirely different reason (neither primary nor secondary outcomes as defined in this study), then the follow up was continued until either the primary endpoint was met or the patient died.

Statistical analysis

A similar statistical analysis plan was followed as for study 1. In addition, I used logistic regression to investigate the potential association between non-adherence and renal graft rejection or failure. IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses and a $p<0.05$ was considered significant.

Ethical approval and funding

As per study 1.

Study 3

Study design

The primary aim of this part of my thesis was to identify predictors of self-reported good adherence in the LN cohort and secondarily compare it with another multisystem autoimmune condition with renal involvement, namely vasculitis.

Thus, I have specifically sought to look for adherence patterns only in patients reviewed in dedicated tertiary specialist SLE or SLE/ vasculitis renal clinics at UCLH and RFH respectively. Such patients required input from a renal physician due to established renal disease or deemed at high risk of renal involvement, and thus necessitating specialist renal input.

I designed a prospective cross-sectional study to compare a cohort of patients with SLE and vasculitis with established, or at high risk of developing, renal involvement. I used patient reported questionnaires to identify emerging patterns of behaviours and demographic differences which could constitute barriers to adherence.

Data collection

Consecutive patients with SLE or vasculitis reviewed at a weekly renal clinic dedicated to SLE and vasculitis patients at the RFH (nephrology department) or the monthly SLE renal clinic at UCLH (rheumatology department) were approached. As discussed above, both clinics are based in tertiary referral centres and serve a largely urban and ethnically diverse population.

The study was conducted over a six-month period from June to December 2016. As most patients in this clinic are seen at least once every six months, after discussion with my supervisors, it was felt that this duration would be sufficient to produce a representative sample.

Ethical approval, funding and consent

Institutional approval as an audit was obtained as there was no need for formal ethics approval due to the nature of the study. Funding was as per Study 1 and 2.

The data collected were completely anonymised and the treating physician was not informed whether the patient had participated in the study or not, although the patients themselves could volunteer this information. At the preface of the survey of both the hard copy questionnaire and the online version, there was a patient information sheet explaining that by submitting the response (hard copy or online), consent to participation was implied (see Appendices 3 and 4).

Design of questionnaire

With patient input, I designed a questionnaire-based survey on the assessment of self-reported adherence and factors influencing this in the specialist renal lupus and vasculitis clinics (see appendix 3).

The first draft of questions was based on a previously devised survey targeting patients with renal disease by the Renal Department at RFH (in collaboration with Dr Sally Hamour, a co-investigator for this study). A previous qualitative study of reasons leading to low adherence in our general lupus cohort in UCLH had identified specific themes and patterns [186], which were included in formulating this survey and tailored for LN patients. In addition, risk factors noted in the literature review as discussed in Chapter 1, (Table 1.6 Page 54) were also considered for the questionnaire formulation.

I utilised a step-wise approach to writing the questionnaire considering key survey writing principles [299] building on previous surveys at our institutions [186]. The

principles of the NHS guide for writing an effective questionnaire were also taken into consideration to modify the survey [300]. The language was kept simple, avoiding jargon, the questions were specific without phrasing in the negative where possible. There were no double-barrelled questions or "leading" questions to prevent social desirability bias. Once formulated, the questionnaire was trialled amongst five clinician colleagues for content validity and feedback. It was also reviewed for suitability by a clinical psychologist with experience in working with renal patients. It was then piloted in a group of 12 patients at a patient engagement event that took place at the RFH. This piloting facilitated "cognitive testing": i.e. understanding and clarity of the questions and the user-friendliness of the online software. Following this, the questions were modified to encompass the feedback given by the patient group, mainly resulting in a change in the wording or additional options in the multiple-choice questions.

At the end of this process, the complete questionnaire included 60 questions split into six sections:

a) Patient demographics; including ethnicity, marital status, religion/ faith, education, work status and country of birth

b) Patient diagnosis; duration of disease, self-reported disease activity, and self-reported kidney function

c) Medications; including number and type of all tablets taken and specific questions about commonly used immunosuppressants and steroids

d) Adherence to medication; including a Visual Analogue Scale (VAS), Likert scale, patterns of adherence over time and medication cost to the patients

e) Attendance at clinic appointments; Likert scale of frequency and potential barriers

f) Exploring patient behavioural factors including health beliefs; medication side effect concerns, illness-relevant cognitions, perceptions of disease, self-efficacy and involvement in treatment decisions

These domains were clearly defined and separated in the document with respective layman headings to allow better navigation and user-friendliness for the patients, as seen in box 3.1 below. Similarly, the domains were also clearly marked and separated at the online survey in designated sections.

A. Tell us about you... Some basic information to help us analyse our data
B. About your diagnosis...
C. About your medication…
D. About taking your medication…
E. Getting to the clinic...
F. Helping us understand any difficulties you may have with taking your medication…

Box 3.1 indicating the domains (A-F) of the questionnaire survey

The questionnaire comprised ‘closed’ questions with strength of agreement statements or multiple choices and, to a lesser degree, some open questions offering a free text option. I utilised a bipolar scale where the range of options went from positive to negative with balanced options on each side. In the final section (f) exploring patient behaviours, a strength of agreement was sought.

To reduce "gratitude" and "desirability" bias, it was made explicit at the beginning of the survey that the questionnaire was kept entirely anonymous and the treating clinician would not know whether the patient had participated in the study (unless the patient volunteered this information) or access to the data.

For defining the adherence outcome, I used a Visual Analogue Scale (VAS) from 1-10 as previously published by Chambers et al. [295].

I also utilised Likert scale questions to interrogate adherence levels with descriptive anchors relating to the frequency of missed doses in the response options [301,302].

Questions from a validated scale, the Morisky-Green-Levine (MGLS) Medication Adherence Scale [256], were also embedded in the survey to allow comparison of our results.

A copy of the questionnaire can be seen in Appendix 3 together with screenshots from the online version of the survey (Appendix 4). This can also be viewed here:

https://opinio.ucl.ac.uk/s?s=42000

The questionnaire was the same at both two sites, except for the cover page, which referred to the specific clinics at the individual hospital and named co-investigators from that clinic.

The questionnaire was printed on two A4 size sheets of paper, and the additional cover page was a different colour paper for the two sites to simplify data entry and avoid errors. The time needed to complete the survey length was approximately 10 minutes at the pilot event, and the patients usually had about an hour (after they reported to the clinic, but prior to being called for their appointment) to complete and return the survey if they decided to do this in the clinic.

Distribution of questionnaire

The questionnaire was made available to all the patients in the selected clinics on arrival, either by myself, the nurse, or the receptionist. The option of a hard copy or the online version was offered. The information sheet made it explicit that the study was voluntary and would not affect their clinical care, and this was reiterated verbally when offered the questionnaire, avoiding coercion. Any questions about the questionnaire were directed to me. The patients could review the questionnaire whilst waiting to be called in the clinic, return it following the clinic review or complete the survey online during or after their clinic visit. Clipboard and pens were provided to the patients that completed the hardcopy survey. The completed survey was returned by the patients (or their relatives) into a dedicated sealed box.

Provision was made to support the patients in completing the questionnaire by members of staff, for example, using a language line if the patients did not speak English or reading out the questions if they were visually impaired. Family members were also allowed to help with this if needed.

At the end of the clinic, the questionnaires were retrieved from the box, the data extracted and added into the secure online software system utilised for this work (UCL Opinio) [303]. The hard copies were stored in a secure research dedicated office in line with Good Clinical Practice guidelines.

UCL Opinio is a secure web-based survey tool, which provides a framework for authoring and distributing surveys and a range of reporting facilities. The software was also used to collect and store the online completed questionnaires. In addition, the responses from the hard copy questionnaires were manually entered to the UCL Opinio, effectively, therefore, converting the hard copy responses to an online web-based database and merged with the online survey responses.

Definition of adherence

Given the absence of a gold-standard definition for adherence [228], for the purposes of this study in relation to an outcome measure, it was decided to:

a) use the Visual Analogue Scale (VAS) out of 10, to measure self-reported adherence

b) calculate the median value of all VAS responses for this cohort

c) consider as adherent those patients who scored above the median value on the VAS score

Thus, around 50% of the cohort would be deemed as adherent. This proportion is also in line with the results of my systematic review and meta-analysis on the prevalence of adherence in SLE cohorts from 32 studies, introduced in Chapter 7- page 267 which calculated adherence in SLE to be 49%.

Statistical analysis

I reviewed the data utilising the UCL Opinio software and undertook preliminary analysis in Opinio. Subsequently, the results were exported directly from UCL Opinio to Microsoft Excel and IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) for further analysis. Categorical variables are presented as the number and percentage, whilst continuous variables are presented as mean and standard deviation (if normally distributed) or otherwise median and interquartile range. Comparisons between groups were performed using Student's t-test for normally distributed data or the Mann–Whitney U test for non-parametric data and ANOVA for multiple comparisons. With the help of an independent statistician, logistic regression was used on the whole cohort, and then the Lupus cohort was sub-studied to investigate the potential association between the adherent and non-adherent patients. Univariate and multivariable logistic regression models were generated, and forward step-wise selection used to predict adherence. Using the regression results, statistical models to predict adherence were devised and compared using Receiver Operator Characteristic curves, boxplots and scattergrams. A $p<0.05$ was considered significant.

CHAPTER 4

Study 1

Results

A total of 361 patients with LN were identified (155 from RFH and 206 from UCLH). During a 42-year period of follow up, 121 progressed to ESRF and 40 received a renal transplant. Eight patients had been seen in both hospitals and are included in the hospital where they were seen first. Patient characteristics and demographics are presented in Table 4.1.

Demographic characteristics	Total Patients (n=40)
Sex/ female	34
Ethnicity	
Caucasian	15
Black	15
Asian	10
Age at SLE Diagnosis (years)	21.1 ± 9.2
Age at rTp (years)	35.5 ± 11.0
Age at ESRF (years)	31.6 ± 10.4
Time on dialysis (months)	43 (13-49)
Time of follow up (months)	104 (80-145)
Type IV LN	18
Donor Source / cadaveric	22
Graft failure	9

Table 4.1: Demographic, clinical and histological features of the patients.
SLE- Systemic Lupus Erythematosus, rTp- renal transplantation, ESRF- End Stage Renal Failure, LN- Lupus nephritis

Mean age at transplantation was 36±11 years and 34 (85%) were female. The self-reported ethnic distribution was similar to that seen in the general lupus cohort of the two hospitals, with 15 Afro-Caribbean (37.5%), 15 Caucasian (37.5%), and 10 South Asian (25.0%) undergoing rTp.

Five patients were re-transplanted, of who two patients received a total of two transplants, and one patient received a total of three transplants.

For patients with more than one transplant the following process was applied:
The time of dialysis used for statistical purposes related to the time before the first transplant and the follow-up time was initiated after the first transplant. This means that any additional time on dialysis between transplants was not recorded.

Two patients (5%) had pre-emptive transplantation and the dialysis time for them was included as zero.

During a median follow up of 104 months (IQR 80, 145) eight (20%) patients died (Table 4.2) and the five-year survival was 92.5% which is not statistically different between the decades (Table 4.3). Patient characteristics in the tables are summarised and expressed as mean ± SD (if normally distributed) or otherwise median and interquartile range (IQR). Comparison between living and dead patients was undertaken using Chi-square, t-test and Mann-Whitney non-parametric t-test. A $p<0.05$ was considered significant.

Three patients (37.5%) died as a consequence of sepsis, two secondary to malignancy (25%), two as a consequence of uraemic complications (25%), and one from coronary artery disease (12.5%).

Parameters	Alive (n=32)	Dead (n=8)	P value
Sex (female)	26	8	0.318 ◘
Age at Lupus diagnosis (years)	20.8 ± 9.7	21.8 ± 8.8	0.773 #
Age LN (years)	26.4 ± 8.1	26.3 ± 9.2	0.968 #
Age at ESRF (years)	31.3 ±9.3	32.8 ± 15.3	0.734 #
Age at renal transplantation (years)	36.4 ± 10.5	38.8 ± 13.5	0.335 #
Duration on dialysis before renal transplantations (months)	31 (12-39)	84 (68-90)	0.013 ^
Ethnicity			
Caucasian	11 (34%)	4 (50%)	0.940 ◘
Black	15 (47%)	0	
Asian	6 (19%)	4 (50%)	
Type of Dialysis, HD/PD*	17/9	3/3	0.640 ◘

Table 4.2 Comparison of clinical demographics between patients who survived and who died after the renal transplantation.

* Eight patients required both PD and HD and therefore not included in the direct comparison between PD and HD. However, even when compared with PD or HD, there was no evidence that those who required both dialysis types had worse outcomes (p=0.885).

LN- Lupus Nephritis, ESRF- End Stage Renal Failure, HD- Haemodialysis, PD- Peritoneal Dialysis

Patient characteristics are summarised and expressed as mean ± SD (if normally distributed) or otherwise median and interquartile range (IQR). Comparison between living and dead patients was undertaken using Chi-square, t-test and Mann-Whitney non-parametric t-test. A $p<0.05$ was considered significant.
t-test
^ Mann-Whitney
◘ Chi-square

Five-year mortality according to the decade of transplantation			P value
Decade of rTp	**Patients per decade**	**Deaths/ 5- year mortality**	0.11□
1975-1985	2	0/2	
1985-1995	3	1/3 (33%)	
1995-2005	8	2/8 (25%)	
2005-2015	27	0/27	

Table 4.3 Comparison of 5-year mortality according to the decade the transplant was received. Survival to five years only was considered. Therefore, even if patients died after this period, for the purposes of this table they are included as alive at five years. This explains why only three patients are included as dead in this table. Whilst there was a trend for improved outcomes with time, this did not reach statistical significance. □ Chi-square

rTp: renal transplant

Using univariate Cox regression, time on dialysis and the other potential predictors of survival were investigated. Univariate analysis identified only time on dialysis before rTp as a predictor of survival with a Hazard Ratio of 1.013 for each additional month (95% CI= 1.001-1.026, p=0.03). No other variable reached statistical significance as shown in Table 4.4.

In particular, ethnicity (p=0.99), sex (p=0.44), age at SLE diagnosis (p=0.55), age at LN (p=0.94), time between SLE diagnosis and LN (p=0.37), time between LN and dialysis (p=0.54), age at rTp (p=0.43), or indeed any other co-existing clinical diagnosis; such as hypertension (p=0.32), DM (p=0.56) or dyslipidaemia (p=0.91)

had no effect on survival. There was no difference in which decade the transplant took place and the outcome (p=0.71). However, this should be interpreted cautiously given the low number of rTp undertaken in the earlier decades.

I also compared the length of time on dialysis before transplantation in the patients who received the transplant before or after the year 2000, which was not statistically different (p=0.181). Therefore, these results suggest that the time on dialysis was the only independent modifiable risk factor associated with mortality, irrespective of the decade the transplantation took place.

Regarding treatment regiments, nine patients had received Mycophenolate Mofetil (MMF)/ Tacrolimus combination only, with no previous azathioprine (AZA) or cyclosporine (CSA) use, with the other patients having used AZA or CSA at any stage. The nine patients who received only MMF/ Tacrolimus had an overall mortality of 11.1% compared to the patients who ever received AZA/CSA, who had a mortality of 22.5% (p=0.45).

Finally, there was no difference between the type of dialysis undertaken pre-transplantation, haemodialysis or peritoneal dialysis and outcome (p=0.64).

Factor	P value	HR	95% CI
Time on Dialysis/ per month	**0.031**	**1.013**	**1.001-1.026**
Sex/ male	0.442	0.038	0.001-161.3
Ethnicity	0.987	0.995	0.537-1.844
Age at SLE diagnosis /year	0.552	1.021	0.953-1.094
Age of LN /year	0.941	1.003	0.920-1.092
Age of ESRF /year	0.836	1.008	0.935-1.087
Age at rTp /year	0.431	1.026	0.963-1.092
Dialysis PD (vs HD)	0.764	0.706	0.073-6.862
Time between SLE Dx and LN	0.373	0.996	0.987-1.005
Time between LN and Dialysis	0.540	0.999	0.994-1.003
LN Duration before Dialysis	0.152	1.066	0.977-1.164
Type IV LN	0.398	2.533	0.294-21.82
Dialysis Decade	0.712	0.872	0.420-1.807
Diabetes Mellitus	0.561	0.038	0.001-2319
Hypertension	0.323	0.329	0.360-2.987
Dyslipidaemia	0.905	0.872	0.092-8.234
APLS	0.508	0.036	0.000-672.6
CVS disease (MI, stroke, TIA)	0.873	1.071	0.463-2.476
Donor source living	0.353	0.459	0.089-2.372
Graft Failure post rTp	0.314	2.073	0.501-8.567

Table 4.4: Univariate Cox proportional hazard modelling investigating the association of various parameters and mortality, showing that the single risk factor associated with prognosis was time on dialysis, with longer time on dialysis associated with worse prognosis.

APLS- Antiphospholipid syndrome, Dx- Diagnosis, ESRF- End Stage Renal Failure, HD- Haemodialysis, LN- Lupus Nephritis, MI- Myocardial Infarction, PD- Peritoneal Dialysis, rTp- renal transplantation, SLE- Systemic Lupus Erythematosus, TIA- Transient Ischaemic Attack.

Utilising specifically the time spent on dialysis before transplantation, a Receiver Operating Characteristic (ROC) curve was used to identify the optimal maximum time spent on dialysis before conferring an adverse outcome (Figure 4.1), showing that being on dialysis for >24 months conferred an adverse effect on survival, with an area under the ROC curve of 0.80, sensitivity of 0.88 and specificity 0.50 for death.

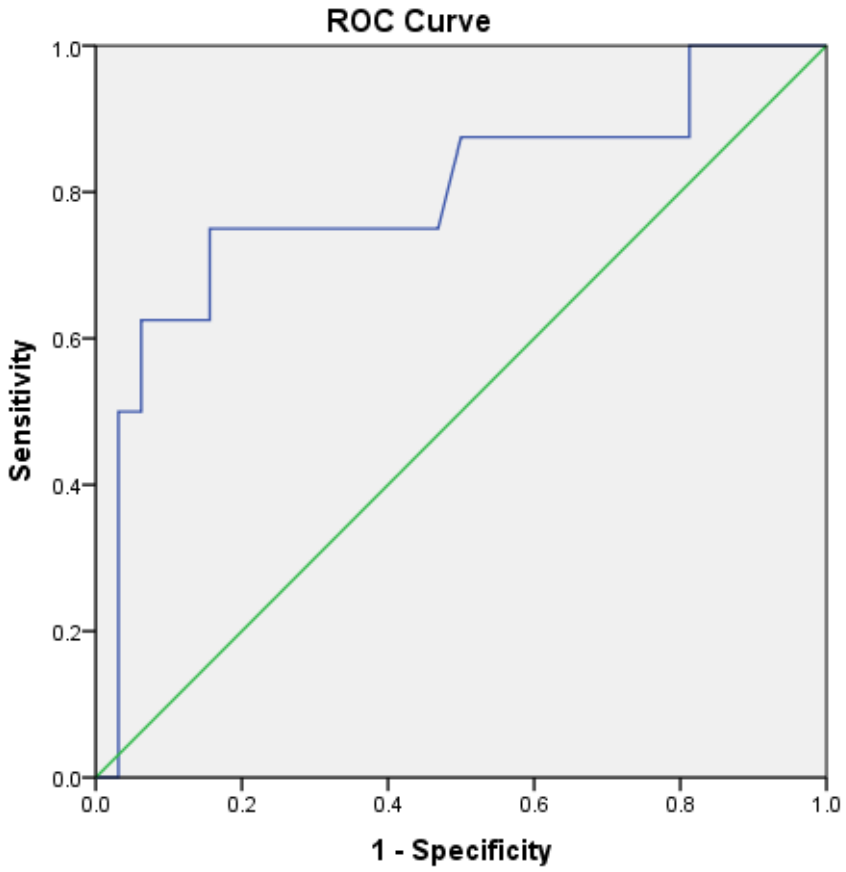

Figure 4.1 Receiver operator characteristic (ROC) curve between time on dialysis and survival. The area under the ROC curve was 0.80. Patients on dialysis for >24 months had a sensitivity of 0.88 and specificity of 0.50 to associate with mortality.

Utilising this dichotomous value, there was a 2.8-fold higher risk of mortality in those patients who spent longer than 24 months on dialysis using Kaplan-Meier curves (Figure 4.2), although there was only a trend towards statistical significance seen

(log-rank p=0.15). This, however, supports the results from the Cox regression, showing mortality was increased by 1.3% for each additional month on dialysis (or 15.6% for every additional year on dialysis) and that most likely if transplantation could be facilitated by 24 months on dialysis, or even earlier, it could be beneficial to the patients.

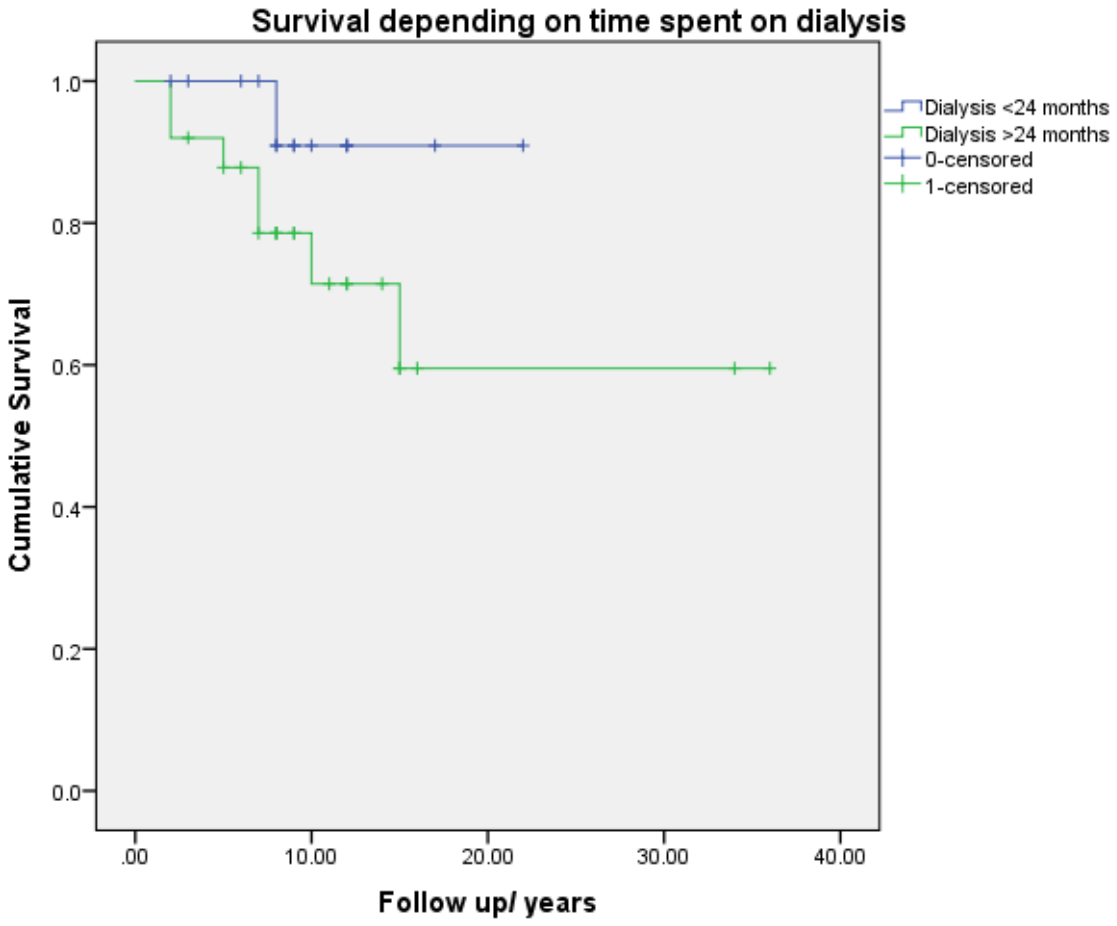

Figure 4.2 Kaplan-Meier estimator plot between patients who had <24 months of dialysis (blue line) or >24 months (green line), suggesting a trend of almost threefold risk of survival in those spending longer time on dialysis, HR 2.84 log-rank p=0.15.

Although not the aim of this study, I also compared the overall survival of the patients with LN-related ESRF receiving a transplant vs those who were not transplanted. In total, 45/81 (56%) died in the non-transplanted patients compared with 8/40 (20%) in

those who received at least one renal transplant (p=0.0002). Although the superiority of renal transplantation in this context is well recognised [178], this result could have been confounded by a higher comorbidity burden in the patients not selected for transplantation.

Discussion

Patients with LN represent a complex cohort of patients which should be managed optimally to ensure longer-term survival. In the present study, I focused on time spent on dialysis pre-transplantation for renal nephritis as a potentially modifiable predictor of patient mortality. I also investigated other potential predictors of survival, both modifiable and non-modifiable. I included patients going back to the early times of rTp in LN from 1975, and I present data on the longest reported follow up period for a dedicated cohort of patients with LN undergoing renal transplantation.

I identified a five-year survival of 92.5%, which is in line with or better than other published studies [176,177,304]. In addition, survival did not appear to differ in relation to the decade the rTp took place. However, this should be considered in the context of the low numbers of rTp in the early decades, appreciating that the study might have been underpowered to detect a small but clinically relevant difference.

The only variable offering prognostic association with mortality was the time spent on dialysis before the transplant. For every additional month on dialysis, the prognosis worsened by 1.3%. In this cohort, if patients exceeded a binary cut-off of 24 months on dialysis, there was a suggestion that it conferred almost a threefold increase in

mortality. No other factors appeared to affect mortality, as they did not reach significance in univariate analysis.

As discussed in Chapter 1, page 96, the optimal timing of transplantation in patients with LN and ESRF has been a focus of much debate, with earlier studies[197] supporting delaying transplantation to ensure quiescent disease activity and more recent studies advocating earlier transplantation if possible [183]. In non SLE cohorts earlier transplantation is beneficial [305], however due to the concerns or relapsing LN when adequate remission has not been achieved prior to transplant in SLE, it is not possible to extrapolate from non SLE studies to the lupus population. Nevertheless, this study supports earlier transplantation if feasible. This is similar to recent work, showing that increased time on dialysis led to increased graft failure [176,306]. Indeed, my cohort included two patients with pre-emptive transplantation and both remain alive at 12 and 22 years respectively, supporting the idea that earlier rTp may be beneficial. Although my research identified a cut-off of 24 months which could be used to prioritise rTp in LN patients, further larger and prospective studies are necessary to identify whether the time relationship to survival up to 24 months is linear, or whether an even earlier and possibly pre-emptive transplantation should be considered and recommended in the guidelines.

Limitations

Despite combining the data from two large institutions, I only had 40 patients in the analysis. However, this number is in line or larger than other similar published studies [176,304]. My cohort also included a mixture of Caucasian, Afro-Caribbean and South Asian patients, and I cannot necessarily extrapolate my results to patients

from other ethnicities. Larger studies including multiple ethnicities will also allow further comparisons.

Moreover, despite a very long follow up of 422 patient-years, only eight patients reached the study endpoint. This may have reduced the identification of the impact of other potentially predictive variables, for example, sex and the presence of antiphospholipid syndrome in particular, which had a wide confidence interval. In addition, although I could only undertake univariate analysis due to the small number of outcomes, this still allowed me to identify individual predictors and trends towards mortality accurately. Given that only the time on dialysis was significant, with patients spending similar times on dialysis across the 40-year period, we can be confident that this was not influenced or affected by other parameters. Nonetheless, I propose that ultimately multicentre interventional studies are required to provide adequate power to address this specific question.

NOTE

Chapter 4 is partly based on a published article, Ntatsaki et al. Impact of pre-transplant time on dialysis on survival in patients with lupus nephritis. *Clin Rheumatol* 2018; 37: 2399-2304 [307].

CHAPTER 5

Study 2

Results

For this study, I interrogated the combined database across the UCLH and RFH as outlined in the methods Chapter 3, page 167, and identified 361 patients with SLE and LN. The vast majority of patients diagnosed with LN were biopsy-confirmed (>90%), and 40 had renal transplantation for LN. A total of 17/40 (42.5%) patients were identified as non-adherent to prescribed treatment for LN (Figure 5.1).

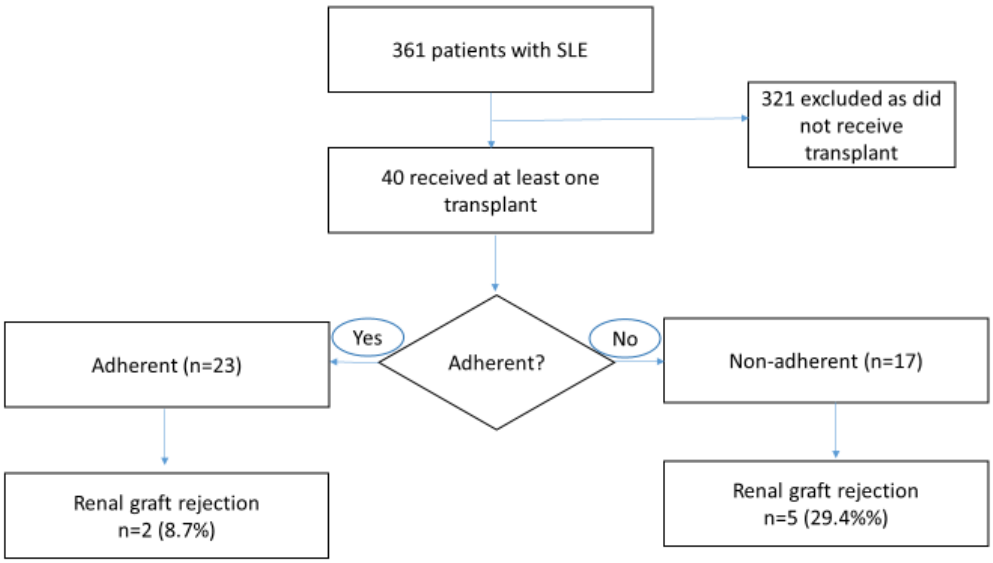

Figure 5.1 Flow diagram indicating the study population included in this cohort.

For the purpose of this study I defined non-adherence as either:

i) evidence of poor adherence on documentation by a member of the clinic team in the medical records, or

ii) evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least six months after the renal transplantation.

As shown in Table 5.1, the only significant difference between the adherent and non-adherent groups was the amount of time spent on dialysis with the adherent group spending 33 (27-79) months on dialysis vs the non-adherent group spending 17 (10-24) months on dialysis, p=0.01. There were no other significant differences between adherent and non-adherent patients. In particular, there was no difference between the groups in this cohort with regards to the age at SLE diagnosis or renal transplantation, sex, diagnosis duration, medication prescribed, ethnicity, or donor source. Moreover, there were no significant differences in other comorbidities between the two groups as shown in Table 5.1 (all values p>0.05).

In addition, there was no difference in adherence vs non-adherence patterns in patients who had received rTp before the year 2000 or after this time. Furthermore, there was no difference in the group that had ever received azathioprine or ciclosporin to those patients that had never received either of these medications in terms of adherence (all values p>0.05). This would support the idea that even if immunotherapeutic regimes were modified during the study period, this was unlikely to affect the pattern of adherence/ non-adherence.

One patient received three rTp in total and had a rejection after the initial transplant. Two more patients received two rTp each. One had a rejection following the initial

graft, whilst the second patient did not have evidence of rejection either after the first or second graft.

The primary endpoint was renal graft rejection (defined as acute deterioration in graft function with rejection confirmed histopathologically) occurring >12 months after transplantation. Secondary endpoints included renal graft failure (defined as the need for dialysis or re-transplantation) and a composite endpoint of graft rejection and/ or failure >12 months from the transplant.

For patients that had had more than one transplant, the following process was followed:

If the transplant failed due to renal graft rejection, then the patient would meet the primary endpoint and hence no further information was collected. If, however, graft failure (secondary endpoint) was identified the patients were censored for the purposes of the secondary outcomes only, but continued to be monitored for the primary endpoint of renal graft rejection in the second transplant. This means that they were followed during their second transplantation. If the first transplant was lost from an entirely different reason (neither primary or secondary outcomes as defined in this study), then the follow up was continued until either the primary endpoint was met or the patient died.

Parameters	Adherent n=23	Non-adherent n=17	P value
Sex/ female	20 (87%)	14 (82%)	0.70 ¤
Ethnicity Caucasian Afro-Caribbean Asian	 8 10 5	 7 5 3	0.46 ¤
Age at SLE diagnosis (years)	22 ± 9	21 ± 11	0.55 #
Age at LN (years)	27 ± 8	26 ± 9	0.63 #
Time on Dialysis	33 (27-79)	17 (10-24)	0.01 ^
DM	2 (9%)	0 (0%)	0.50 ¤
HTN	3 (13%)	6 (35%)	0.12 ¤
Dyslipidaemia	3 (13%)	1 (6%)	0.62 ¤
APLS	2 (9%)	2 (12%)	0.76 ¤
CVS	2 (9%)	3 (18%)	0.43 ¤
Histology type IV	9 (39%)	6 (35%)	0.55 ¤
Donor living	8 (35%)	10 (59%)	0.20 ¤
rTp time Before year 2000 After year 2000	 6 (26%) 17 (74%)	 2 (15%) 15 (88%)	0.41 ¤
Age of ESRD	30 ± 9	32 ± 12	0.59 #
Age at rTp	36 ± 11	34 ±12	0.57 #
Graft rejection	2 (9%)	5 (29%)	0.11 ¤
Graft failure	5 (22%)	4 (24%)	0.89 ¤
Failure or rejection	5 (22%)	7 (41%)	0.21 ¤

Table 5.1: Patient demographic comparison between adherent and non-adherent groups.

Non-adherence was defined as either evidence of poor adherence on documentation by a member of the clinic team in the medical records, or evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least six months after the renal transplantation.

Patient characteristics are summarised and expressed as mean ± SD (if normally distributed) or otherwise median and interquartile range (IQR). Comparison between living and dead patients was undertaken using Chi-square, t-test and Mann-Whitney non-parametric t-test. A $p<0.05$ was considered significant.
t-test
^ Mann-Whitney
¤ Chi-square

Recording a concern for non-adherence either following a medical consultation or biochemically, supported a trend towards increased graft rejection. During a median follow up of 8.7 years, 17/40 (42.5%) of patients had evidence of non-adherence (Table 5.1). A total of 12 (30.0%) patients experienced either graft rejection or failure or both. From the adherent group 2/23 (8.7%) had graft rejection, whilst from the non-adherent group, this was 5/17 (29.4%, p=0.11). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group (p=0.89).

Using Logistic regression, non-adherent patients had a trend towards increased renal graft rejection (OR 4.38, 95% CI 0.73-26.12, p=0.11). There were no other significant predictors for graft rejection or failure or the composite endpoint as shown in Table 5.2, apart from presence of class IV LN on pre-transplant histology, which was associated with a trend towards a higher risk of graft rejection/ failure (p=0.061).

Parameters	Odds Ratio	95% Confidence Interval	P-value
Sex male			
Rejection	-		
Failure	0.650	0.066- 6.410	0.650
Rejection or Failure	0.418	0.043-4.024	0.450
Ethnicity			
Rejection	0.758	0.333-1.727	0.510
Failure	0.697	0.268-1.810	0.458
Rejection or Failure	0.597	0.263-1.359	0.219
Age at SLE Diagnosis			
Rejection	1.016	0.949-1.089	0.647
Failure	1.064	0.976- 1.160	0.158
Rejection or Failure	1.048	0.970-1.131	0.236
Age at LN			
Rejection	0.979	0.880-1.089	0.696
Failure	1.033	0.943-1.132	0.482
Rejection or Failure	1.021	0.938-1.111	0.627
Age starting dialysis			
Rejection	1.042	0.966-1.123	0.287
Failure	1.052	0.980-1.129	0.165
Rejection or Failure	1.044	0.976-1.116	0.209
Time on dialysis			
Rejection	0.999	0.982-1.016	0.871
Failure	1.001	0.987-1.015	0.860
Rejection or Failure	0.998	0.985-1.012	0.829
DM			
Rejection	-		
Failure	3.333	0.180-61.686	0.419
Rejection or Failure	2.250	0.125-40.656	0.583

HTN			
Rejection	2.500	0.389-16.049	0.334
Failure	1.750	0.296-10.340	0.537
Rejection or Failure	2.090	0.391-11.061	0.390
Dyslipidaemia			
Rejection	1.200	0.101-14.195	0.885
Failure	3.600	0.400-32.366	0.253
Rejection or Failure	2.286	0.266-19.658	0.451
APLS			
Rejection	1.133	0.096-13.440	0.921
Failure	0.889	0.077-13.300	0.925
Rejection or Failure	2.143	0.248-18.498	0.488
CVS history			
Rejection	-		
Failure	2.000	0.256-15.623	0.509
Rejection or Failure	1.238	0.166-9.253	0.835
Histology type IV			
Rejection	-		
Failure	7.000	0.647-75.735	0.109
Rejection or Failure	9.800	0.899- 106.845	0.061
Donor source			
Rejection	1.619	0.309-8.478	0.568
Failure	1.538	0.342-6.928	0.575
Rejection or Failure	1.909	0.477-7.638	0.361
Non-adherence			
Rejection	4.375	0.733-26.116	0.105
Failure	1.108	0.248-4.944	0.893
Rejection or Failure	2.520	0.632-10.054	0.190

Table 5.2: Logistic regression modelling investigating non-adherence and other potential predictors and graft-failure. Where a (-) is present it indicates too few events in that group to allow statistical modelling.

Non-adherence was defined as either evidence of poor adherence on documentation by a member of the clinic team in the medical records, or evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least six months after the renal transplantation.

Interestingly, longer time on dialysis before the transplantation was associated with decreased non-adherence. For every additional month on dialysis, non-adherence was reduced by OR 0.96, 95% CI 0.93-0.99, p=0.02. In addition, a receiver operating characteristic (ROC) curve (Figure 5.2), identified that spending more than 25 months on dialysis was more likely to lead to better adherence with sensitivity 0.77, specificity 0.82 and good discrimination with AUC=0.76. These data support the notion that patients spending more time on dialysis are more likely to be adherent, and thus those with less time spent on dialysis before transplantation more likely to become non-adherent.

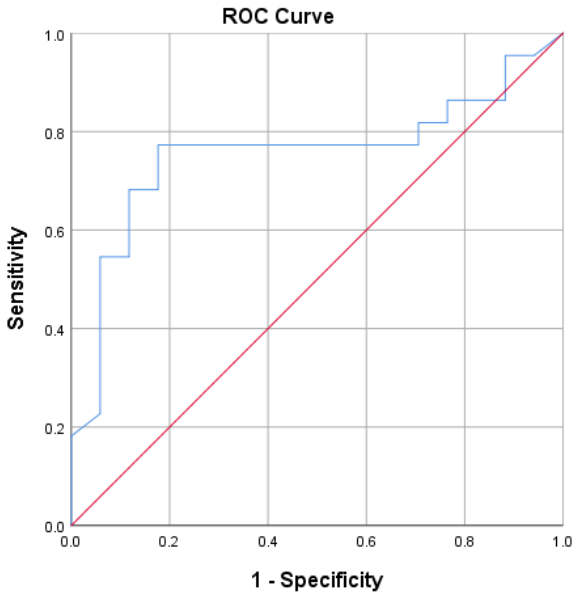

Figure 5.2 Receiver operating characteristic (ROC) curve supporting that dialysis time of more than 25 months before renal transplantation associated with improved adherence (sensitivity 0.77, specificity 0.82 and good discrimination with AUC=0.76)

The role of adherence in graft survival was investigated with Kaplan-Meier estimator plot as shown in figure 5.3, which did not show a statistical difference in survival, Log rank p=0.19

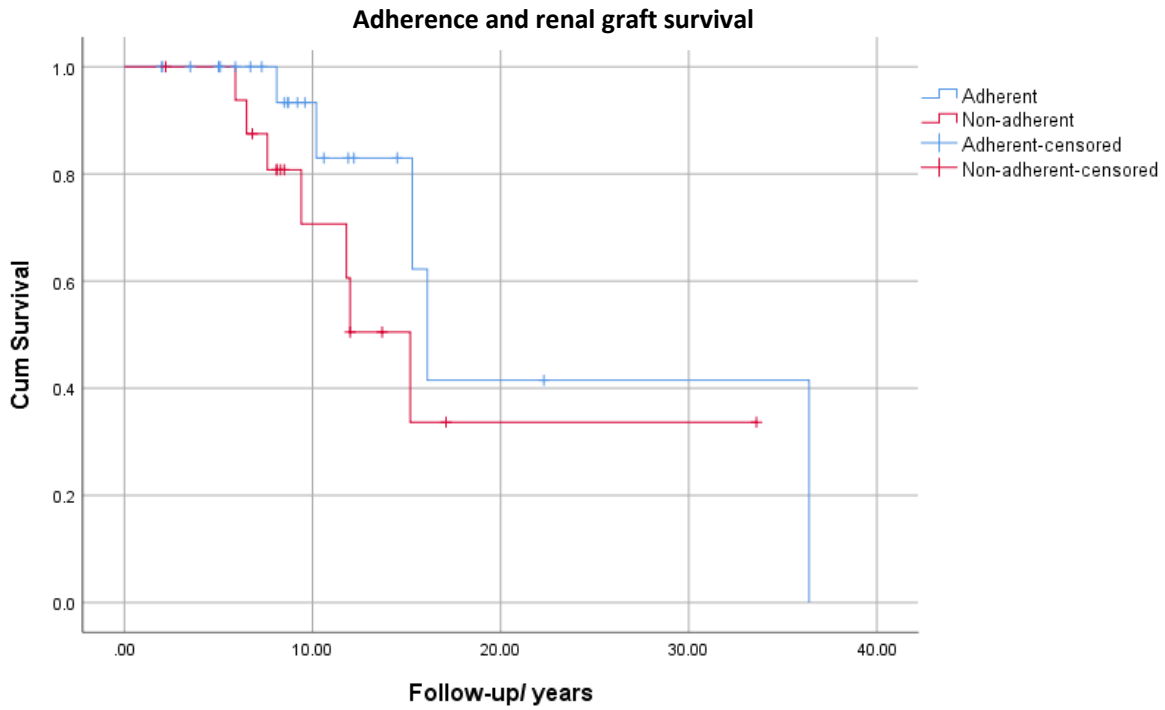

Figure 5.3 Kaplan-Meier estimator plot between patients who deemed adherent (blue line) or non-adherent (red line) for graft survival. There was no evidence of statistically significant difference between the 2 groups, p-log rank =0.19

Furthermore, the role of adherence in overall patient survival was investigated with a Kaplan-Meier estimator plot as shown in figure 5.4, which did not show a statistical difference in survival.

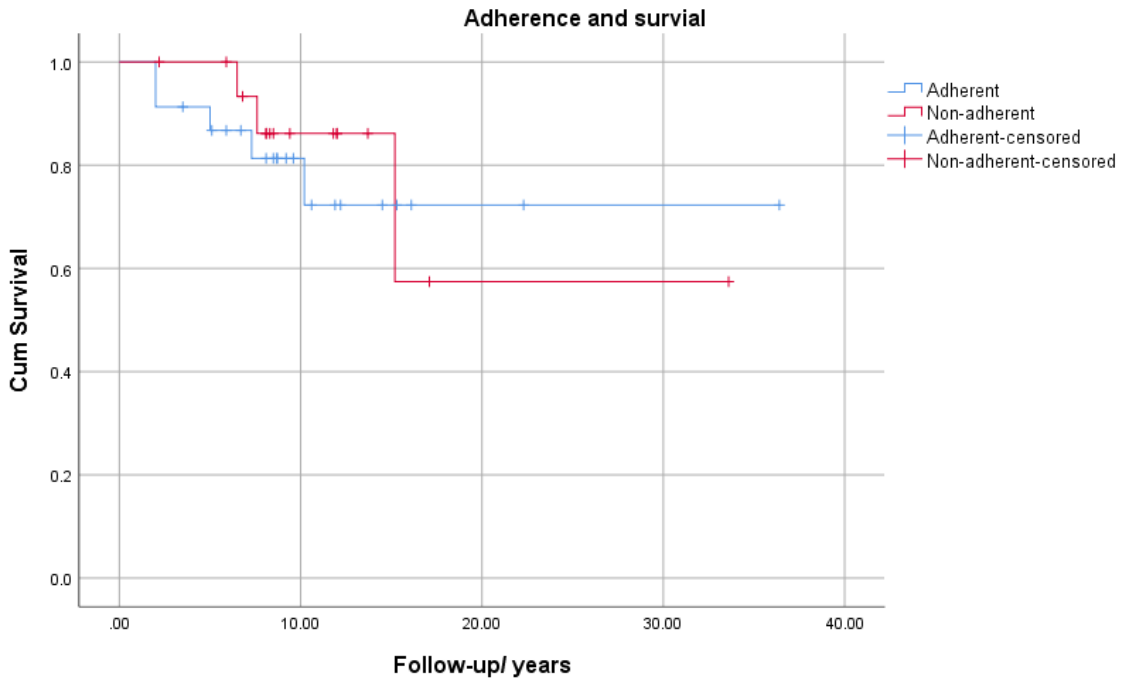

Figure 5.4 Kaplan-Meier estimator plot between patients who deemed adherent (blue line) or non-adherent (red line) and patient survival. There was no evidence of statistically significant difference between the 2 groups, p-log rank=0.67

Discussion

In this study, I considered the role of adherence to immunosuppressive treatment in patients with LN requiring renal transplantation. I documented for the first time the adherence patterns specifically for this cohort of patients and also investigated whether non-adherence was associated with increased risk of graft rejection and/or failure. My results confirmed that more than 40% of patients with lupus nephritis in this cohort, even after renal transplantation, were deemed to be non-adherent, either based on medical record evidence or biochemically based on drug level testing.

What is more worrying, for the first time I showed that once a concern about non-adherence was documented, either in the medical notes or from biochemical assays,

there was a trend to more than a four-fold higher risk of graft rejection, supporting that poor adherence could have potentially significant adverse effects.

As this was an observational retrospective study, it was not possible to investigate causality leading to non-adherence. However, my results raise the strong possibility that patients who spend more time on dialysis are, in fact, more adherent to medication following transplantation. This is an important novel finding and suggests that the time spent on dialysis indirectly encourages better adherence post-transplant. This could be perhaps because patients are more motivated to avoid returning to dialysis. With an increasing number of pre-emptive transplantation [178,308], it is also possible that non-adherence could increase and therefore, the clinicians and other health care professionals should be aware and vigilant in recognising this.

In Study 1, described in Chapter 4, I showed that increasing time on dialysis before rTp adversely affects prognosis specifically in lupus patients [307]. This result is supported by previously published literature in patients with renal disease of mixed aetiology receiving rTp [192]; therefore, minimising the time on dialysis should remain the aim. However, given the current study results (study 2), I also propose that particular attention should be paid for patients who spent little or no time on dialysis to ensure that the potential risk of non-adherence does not compromise the beneficial effects of early transplantation.

Limitations

Although I included patients from two large hospitals in London over a four-decade period, I was only able to identify 40 eligible transplanted patients from an original cohort of 361 patients. This modest number is in line or larger than other similar

published studies of LN [176,304]. Whilst my study was retrospective, I endeavoured to reduce bias by only considering strong pre-defined surrogates for non-adherence, such as clear documentation in the notes or biochemical markers of non-adherence and a well-defined endpoint of graft rejection and failure. Nevertheless, as in all retrospective studies, there is a risk of misclassification, by underestimating the non-adherent patients due to poor attendance in clinic, not being specifically screened for adherence during routine clinical care or having blood tests elsewhere, that needs to be acknowledged.

Moreover, although I had a mixture of Caucasian, Afro-Caribbean and South Asian patients, my results cannot necessarily be extrapolated to other populations. Because of this and also the relatively modest numbers, my study might have been underpowered to detect a small, but significant difference in ethnicity and adherence. Furthermore, as I focused my research only in the LN renal transplant patients, I cannot comment about whether adherence in this cohort is higher or lower than the patients remaining on dialysis. In addition, the retrospective nature of the study did not allow me to screen accurately for depression, a factor recognised to associate with non-adherence in the general lupus population [309]. Finally, despite one of the longest recorded follow up periods exceeding 422 patient-years, I only had 12 patients with graft rejection or failure, which may have impacted on identifying smaller potential associations with the other variables included in this study.

NOTE

Chapter 5 is partly based on a published article, Ntatsaki et al. Renal transplantation for lupus nephritis: non-adherence and graft survival. *Lupus* 2019; 28:651-657 [310].

CHAPTER 6

Study 3

Results

Descriptive statistics

A total of 207 patients responded to the questionnaire. Some 114 (55%) with lupus and 80 (39%) with vasculitis. Their demographics are shown in Table 6.1. A further 13 (6%) patients reported that they had other conditions or were unsure of their diagnosis, and were excluded from further analysis. Therefore, for the purpose of the analysis 194 patients were eligible and are included in the statistical calculations. Furthermore, as not all questions were answered by all patients, the denominator for each variable may differ.

In order to calculate the denominator population for this study, I interrogated the UCL Lupus cohort database, the RFH renal, lupus and vasculitis database, I reviewed clinic appointment slot template records and after discussion with the lead clinicians of each site and my supervisors, the target population for this study was estimated at 460 unique patients. The study was conducted over a six-month period across both sites. As most patients in this clinic are seen at least once every six months, it was felt that this duration would be sufficient to produce a representative sample.

Using the denominator population of 460 potentially eligible patients, the estimated overall response rate was 45.0%, taking into account all 207 patients that responded

to the survey. This value drops to 42.1%, when only considering the 194 patients that were eligible for the study and were included in the statistical analysis.

When considering the whole cohort, I noted significant differences between the Lupus and Vasculitis patients as expected and shown in Table 6.1. There were 77% women in the study (90% in SLE vs 58% in vasculitis, $p<0.001$) and 28% were aged over 60 years (SLE 13% vs 51% vasculitis, $p<0.001$). A total of 53% were white Caucasian (42% in SLE vs 69% in vasculitis, $p=0.003$) and 42% were born outside the UK (SLE 39%, vasculitis 45%, $p=0.67$).

Almost half (48%) were educated to university level (SLE 53% vs 41% in vasculitis, $p=0.09$). In terms of marital status 58% were either married/ civil partnership or long-term relationship (SLE 59% vs vasculitis 56%, $p=0.12$) and 74% had a religion/ faith (SLE 72% vs vasculitis 75%, $p=0.15$).

Similar numbers of completed responses were noted in both centres (UCLH 88 and RFH 107), reducing bias.

Furthermore, the lupus patients had a longer duration of disease ($p<0.001$) and commented that they were more likely to become less adherent with time ($p=0.01$) compared to the vasculitis cohort. On the other hand, the vasculitis cohort had higher attendance at outpatient clinic appointments ($p=0.022$). The two groups were similar

in terms of confidence that they could manage to take the tablets correctly, as indicated on the Likert scale (9.1 vs 9.3, p=0.43 for lupus vs vasculitis).

Notably, more patients with vasculitis (65%) vs lupus (48%) reported adherence 10/10 on the VAS adherence scale (p=0.04).

The median adherence for SLE on the Likert scale was 9/10, whilst it was 10/10 for vasculitis. As such, adherent patients were considered for the purposes of the regression models, those who scored 10/10 on the VAS. With this definition 53/110 (48%) lupus patients and 50/77 (65%) vasculitis patients were defined as adherent.

	Lupus (n=114)	**Vasculitis (n=80)**	P value (ALL)
Female	102/113 (90%)	45/78 (58%)	**<0.001**¤
Age average/ years	49.1 ± 16.5 (min 19, max 90)	57.8 ± 14.8 (min 24, max 90)	**<0.001**#
>60 years 40-60 years <40 years	14/107 (13%) 42/107 (39%) 51/107 (48%)	37/ 73 (51%) 27/ 73 (37%) 9/ 73 (12%)	**<0.001**¤
Education (university degree)	58/110 (53%)	30/73 (41%)	0.094¤
Ethnicity White Afro-Caribbean Asian Other	 47/113 (42%) 29/113 (26%) 27/113 (24%) 10/113 (9%)	 55/80 (69%) 8/80 (10%) 9/80 (11%) 8/80 (10%)	**0.003**¤
Duration of disease >10 years 2-10 years <2 years	 63/109 (55%) 37/109 (34%) 9/109 (8%)	 20/80 (25%) 32/80 (40%) 28/80 (35%)	**<0.001**¤
Disease Activity (Self-rated)	4.54 (average)	4.80 (average)	0.110#

Likert scale out of 10, with 10 being most active disease	5 (median)	5 (median)	
High Disease Activity (Self-rated) ≥7 (out of 10) on the Likert scale	17/109 (16%)	15/71 (21%)	0.324¤
Kidney function (Self-rated) Moderately or severely affected Normal or mildly affected	 31/93 (33%) 62/93 (67%)	 21/75 (28%) 54/75 (72%)	0.659¤
Self-medicating	101/106 (95%)	75/77 (97%)	1.00¤
Total number of tablets (average)	8.5 mean, 8 median	6.8 mean, 6 median	**0.012**#
Concerning side-effects of steroids (in order of reported concern frequency)	Weight gain Osteoporosis Eye problems Skin changes High blood pressure	Osteoporosis Weight gain Sleep disturbance Diabetes Mood problems	
Managing well with taking tablets correctly self-rate Likert scale, out of 10 with 10 being the best management	9.12 (mean) 9 (median)	9.31 (mean) 10 (median)	0.375#

Adherent 10/10 on VAS scale	**53/110 (48%)**	**50/77 (65%)**	**0.036**¤
Becoming worse with adherence as Time progresses	17/105 (16%)	3/71 (4%)	**0.011**¤
Paying for own prescription	20/ 110 (18%)	6/75 (8%)	0.082¤
Attending 100% of clinic appointments	56/108 (94%)	65/77 (100%)	**<0.001**¤

Table 6.1 Comparing demographic parameters and variables between lupus and vasculitis patients. The absolute value represents the number of completed responses for the specific questions and therefore might not reach the total number of patients.

Patient characteristics are summarised and expressed as mean ± SD (if normally distributed) or otherwise median and interquartile range (IQR). Comparison between living and dead patients was undertaken using Chi-square, t-test and Mann-Whitney non-parametric t-test. A $p<0.05$ was considered significant.
t-test
^ Mann-Whitney
¤ Chi-square

Only a minority of patients needed to pay for their prescriptions, with no difference between the cohorts. Concerns about potential weight gain and osteoporosis worried patients the most concerning steroid therapy. Changes in appearance or weight followed by nausea or fatigue were the most common side-effects leading to missed medications.

Furthermore, as shown in Figure 6.1, non-deliberate forgetfulness was the most common reason for non-adherence in both groups. Figure 6.2 demonstrated patients' beliefs, behaviours and attitudes towards their illness and taking their medication.

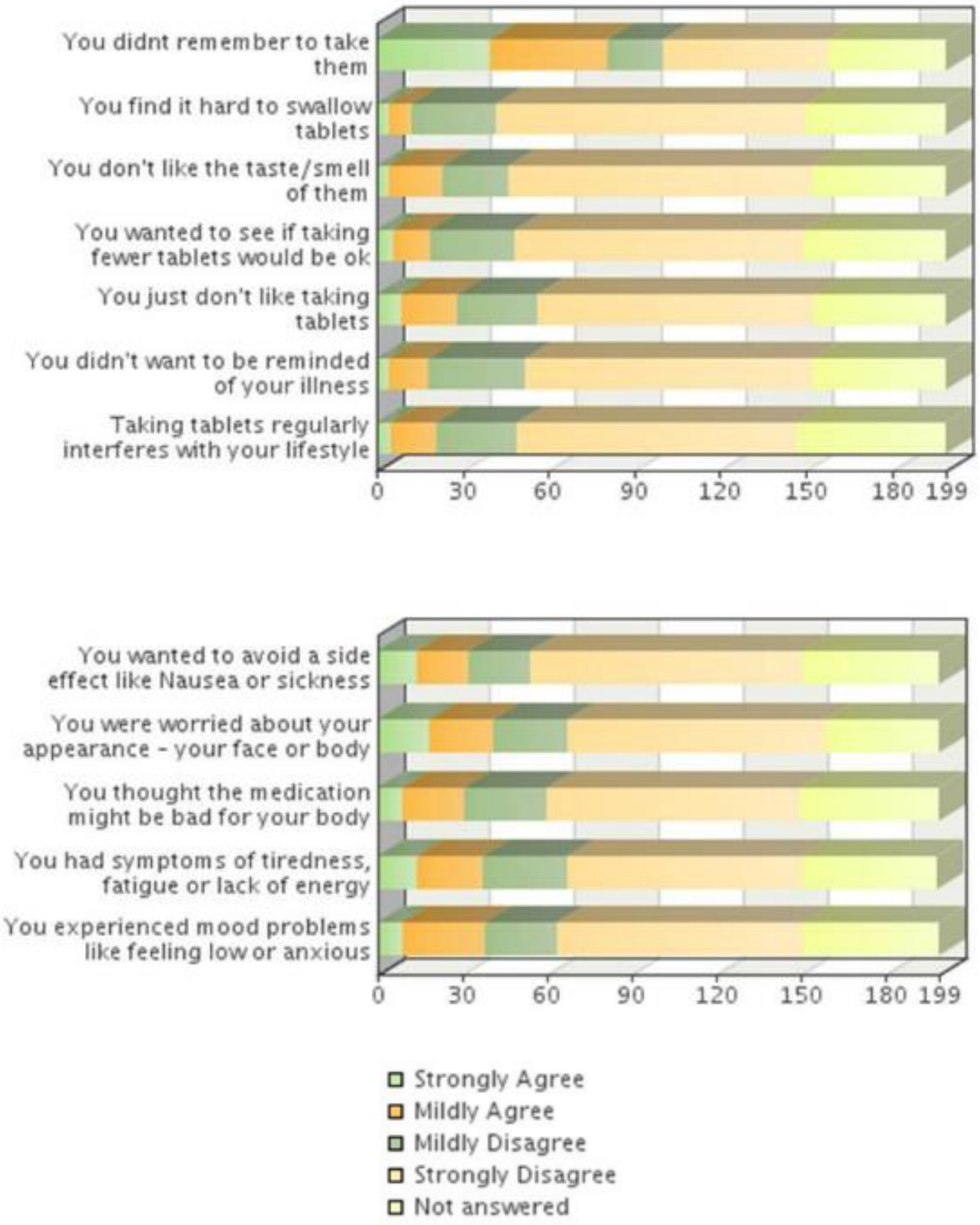

Figure 6.1 Showing reasons leading to poor adherence as identified by the patients from both cohorts (created using UCL Opinio). Forgetting to take the tablets was the most common reason leading to non-adherence.

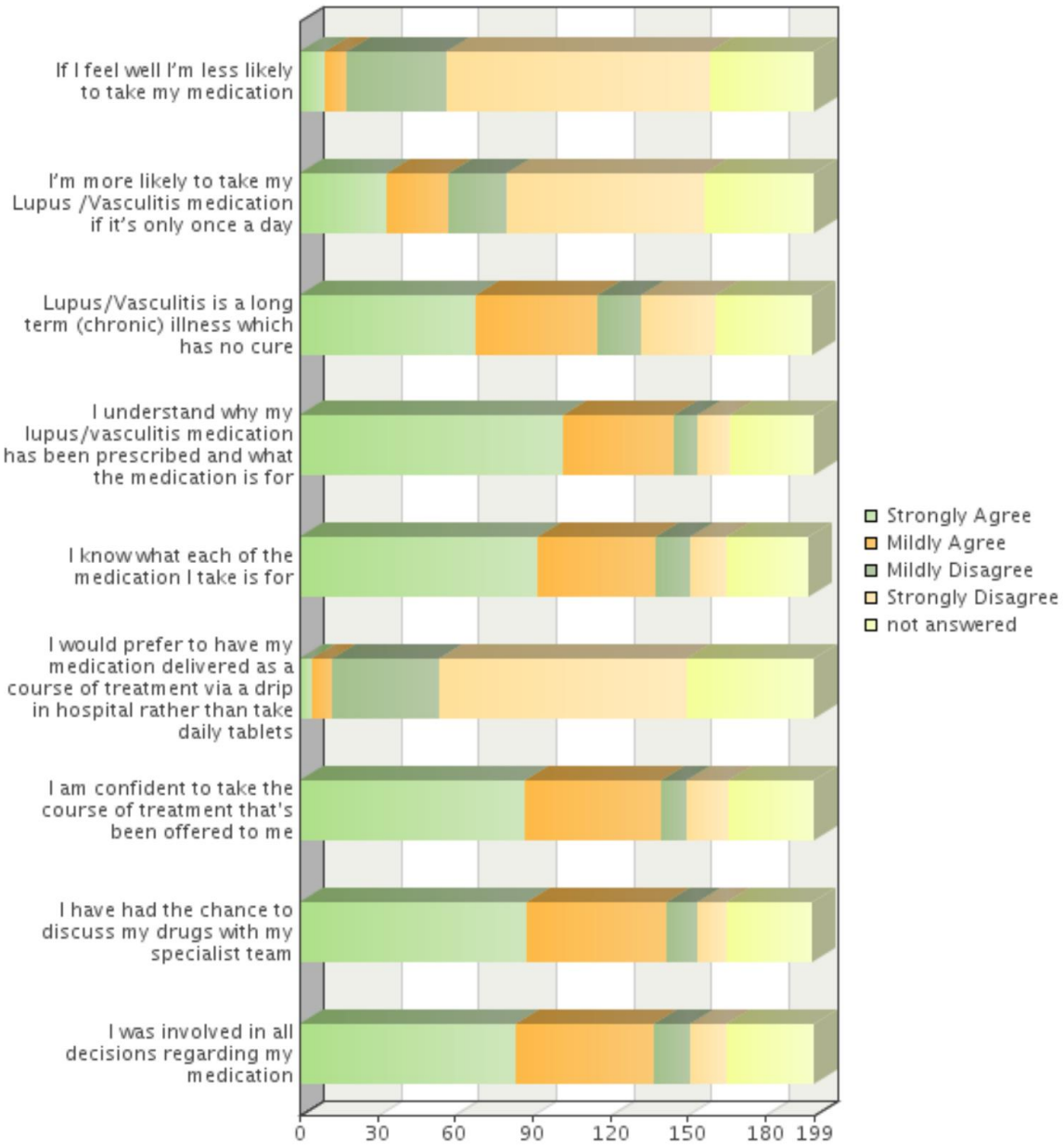

Figure 6.2a Bar chart describing patient behavioural factors including health beliefs, medication side-effect concerns, illness-relevant cognitions, perceptions of disease, self-efficacy and involvement in the treatment decision.

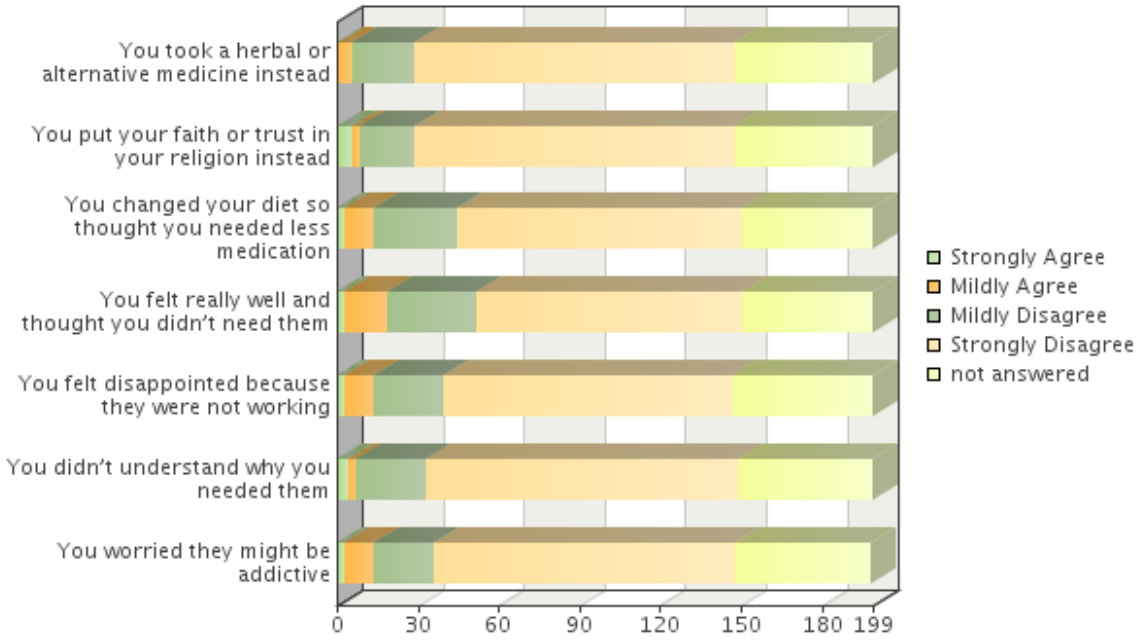

Figure 6b Bar chart exploring patient behavioural factors including health beliefs; medication side-effect concerns, illness-relevant cognitions, perceptions of disease and self-efficacy.

Patients appeared to have a good understanding of why they were taking their medication and felt involved in the decision-making regarding the treatment. They also felt confident to take the course of treatment offered to them. Whilst having to take medication only once daily seemed to be favourable if given the choice of an intravenous drip instead of tablets, this did not seem very appealing. Only a very small number of patients cited religious beliefs, or alternative therapies, as a reason for poor adherence. On the contrary, a change in diet and feeling better was given by more patients as an explanation for worse adherence. Finally, worries about medication being addictive and disappointment due to lack of effect also contributed to being less adherent.

Qualitative data

When directly asking about their medication via a multiple-choice question, the majority of patients were on prednisolone (61%) followed by hydroxychloroquine (45%), MMF (34%) and azathioprine (27%) as shown in Table 6.2 and Figure 6.3 below. Both subcohorts had a similar proportion of patients on steroids. As expected, most lupus patients were on hydroxychloroquine (67%), whereas a bigger proportion of vasculitis patients were on azathioprine (27%).

MEDICATION Distribution and Dislikes	Number of patients on that medication N (%)	Number of dislike responses N (%)	Number of Lupus patients on that medication N (%)	Number of vasculitis patients on that medication N (%)	Lupus vs vasculitis medication P Value
Steroids	100/165 (61%)	27/100 (27%)	66/106 (62%)	34/59 (58%)	0.341
Azathioprine (AZA)	44/165 (27%)	10/44 (23%)	22/106 (21%)	22/59 (38%)	**0.021**
Methotrexate (MTX)	12/165 (7%)	9/12 (75%)	6/106 (6%)	6/59 (10%)	0.285
Mycophenolate Mofetil (MMF)	56/165 (34%)	6/56 (11%)	39/106 (36%)	17/59 (29%)	0.300
Hydroxychloroquine (HCQ)	75/165 (45%)	4/75 (5.3%)	71/106 (67%)	4/59 (7%)	**<0.001**

Table 6.2 Table showing the overall number of patients taking each medication, the proportion of relative dislikes in the whole cohort, and the lupus vs vasculitis cohorts. The p values refer to a comparison between the proportion of patients with lupus and vasculitis medications. Analysis was undertaken using Chi-square.

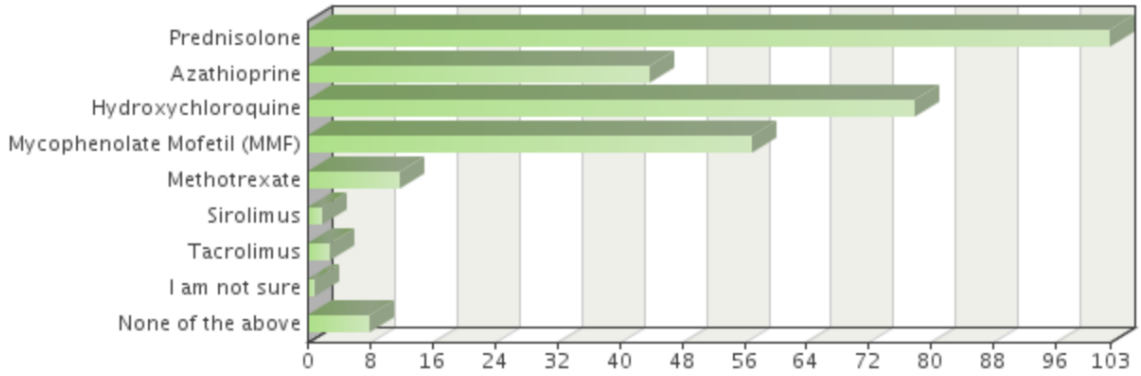

Figure 6.3 Distribution of immunosuppressive medication taken

Patients taking steroids were given the opportunity to express any specific concerns in relation to their steroid treatment. Weight gain and osteoporosis were the most frequently quoted concerns as shown in Figure 6.4.

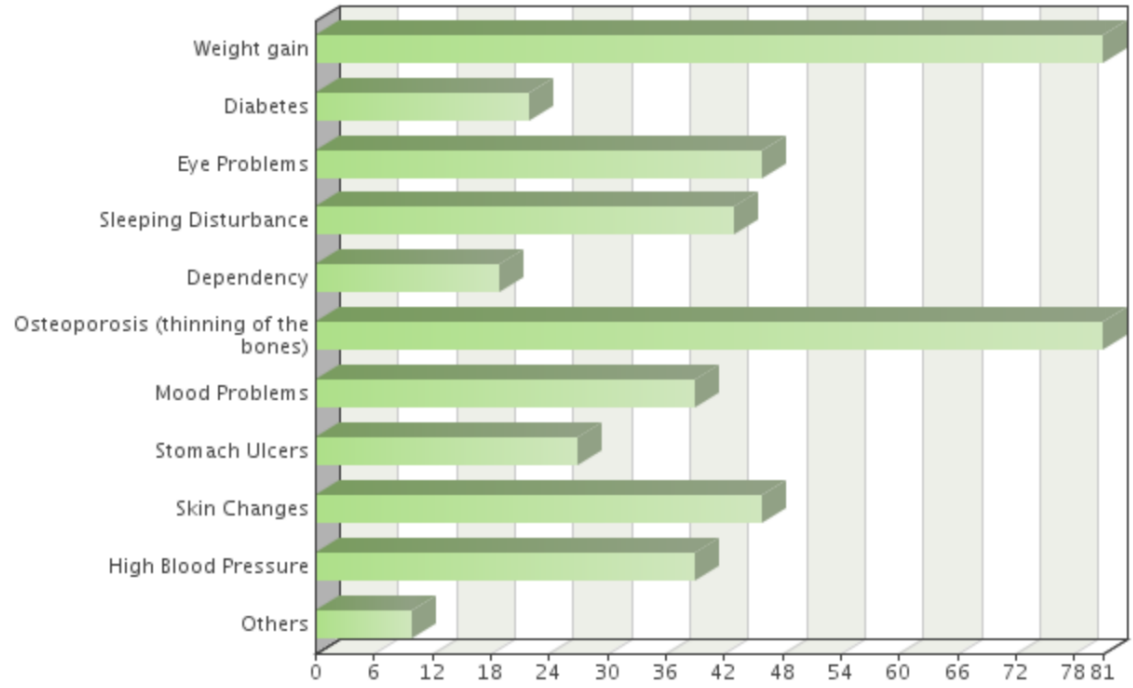

Figure 6.4 Bar chart and list of steroid-related potential side effects that caused concern to those patients that have been on steroids.

Qualitative data- Free text responses

Within the survey, there were questions inviting the patients to utilise free text for additional comments. The free text questions related to medication dislikes, change of adherence over time and reasons for missing hospital appointments as shown below.

Medication dislikes

Interestingly when asked if there was a specific medication the patients particularly disliked, only 66 patients responded positively (commenting on 72 medications) and provided further details about why as a "prompted" free text as shown in Box 6.1.

Is there a specific medication which you particularly dislike taking?

□ No problems with any medication □ Not applicable to me

□ Yes

I dislike taking …… because ……

Box 6.1 showing the question regarding medication dislikes.

The responses are thematically summarised in the following pie charts (Figure 6.5). The most “disliked” medications in absolute values were steroids, followed by azathioprine and methotrexate.

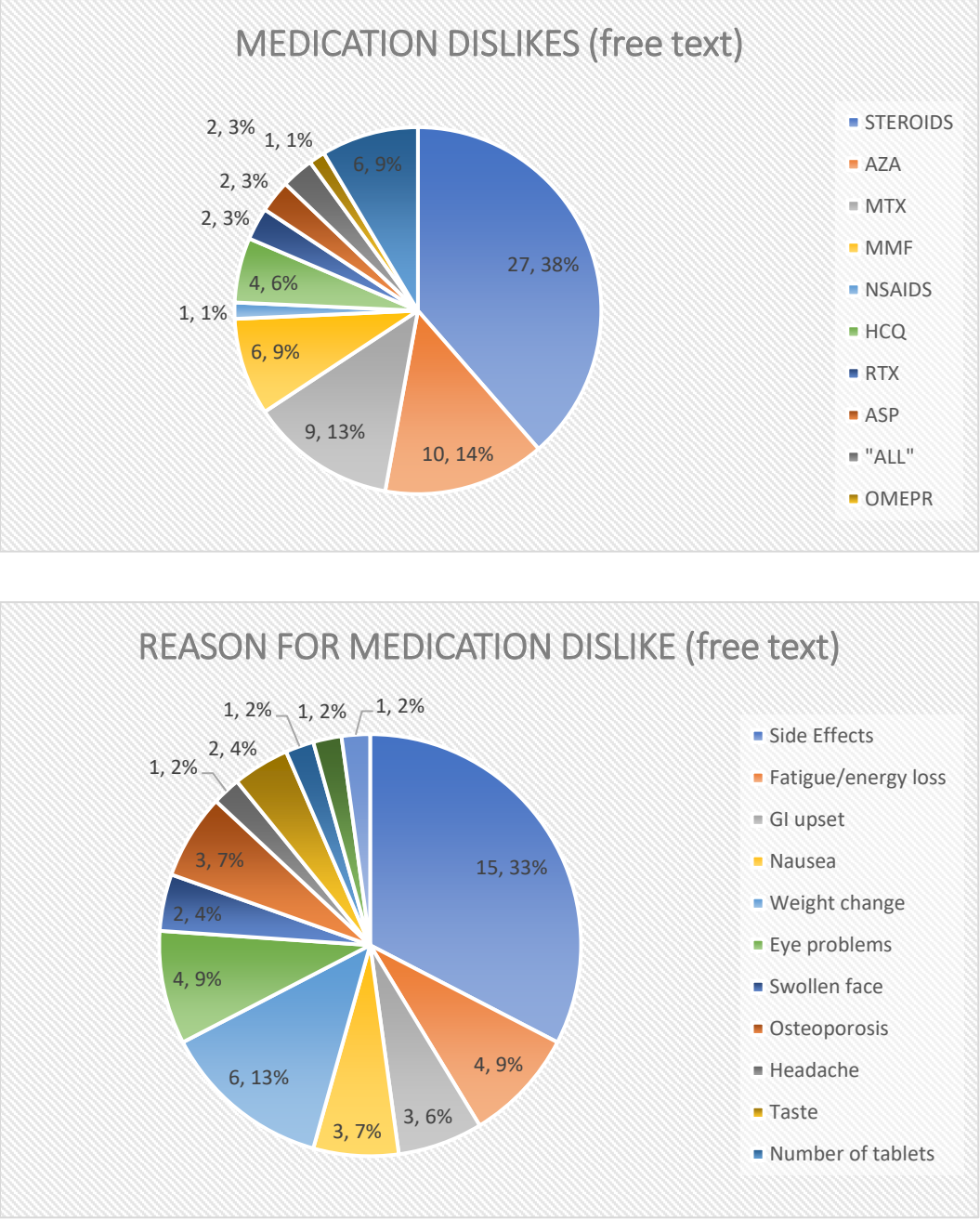

Figure 6.5 Top panel: Distribution of free-text answers for the question relating to specific medication dislikes and reasons for that. The % represents the proportion of patients who responded to this question, indicating they dislike at least one medication. As some patients disliked more than one medication, the overall number of "dislikes" exceeds the number of patients. For example, in the top panel, 27/72 responses were positive as a dislike for steroids (38%). Bottom panel: Reasons for “dislikes” for specific medication as reported in the free text comments allowing comparison with the pre-selected options as shown in Figure 6.4.

AZA- Azathioprine, MTX- Methotrexate, MMF- Mycophenolate mofetil, NSAIDS- non-steroidal anti-inflammatory drugs, HCQ- hydroxychloroquine, RTX- Rituximab, ASP- aspirin, OMEPR= omeprazole

However, proportionately more patients disliked methotrexate (75%) followed by steroids (27%) and then azathioprine (23%). Hydroxychloroquine was relatively well tolerated with only 5% dislikes as shown in Figure 6.6. This also depicts the relevant frequency of taking the specific medication according to the diagnosis.

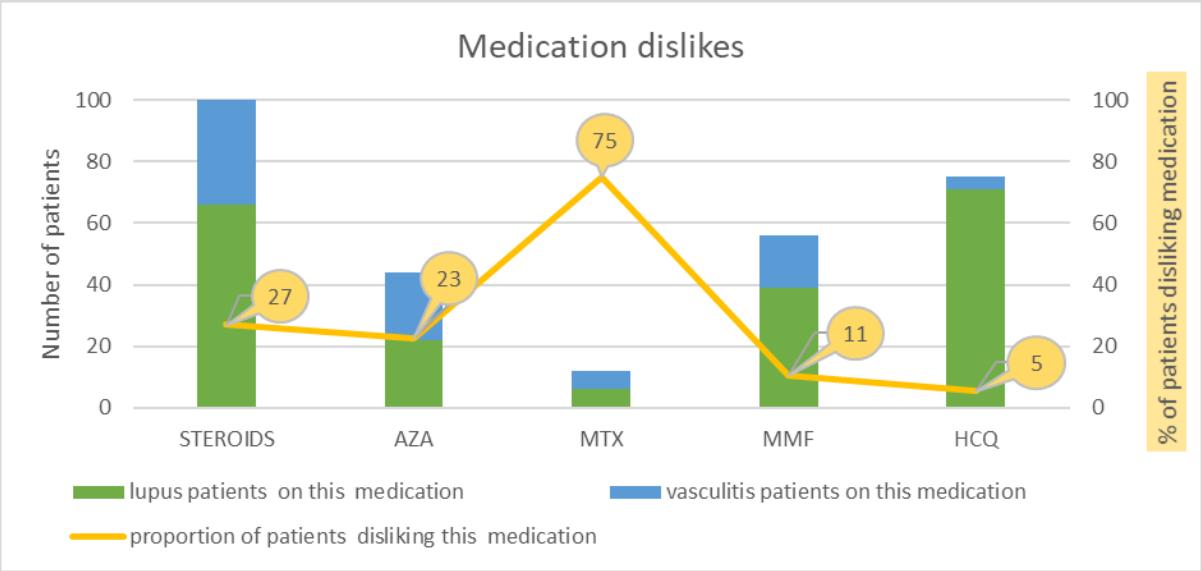

Figure 6.6 Column chart of the total number of patients on each medication divided in the lupus (green column) and vasculitis (blue column) cohorts.
Overlapping (yellow) line chart depicting the overall proportion of patients who disliked each medication.

Clinic Attendance

The majority of patients 121/185 (65%) responded that they attended 100% of their clinic appointments. The 64 patients that admitted to missing appointments were asked about the reasons for this. The most common responses related to unintentional reasons, such as forgetfulness or inability to go to clinics due to travel issues/ cost. There were proposed options in an MCQ format as well as a domain for free text, as shown in Figure 6.7 below.

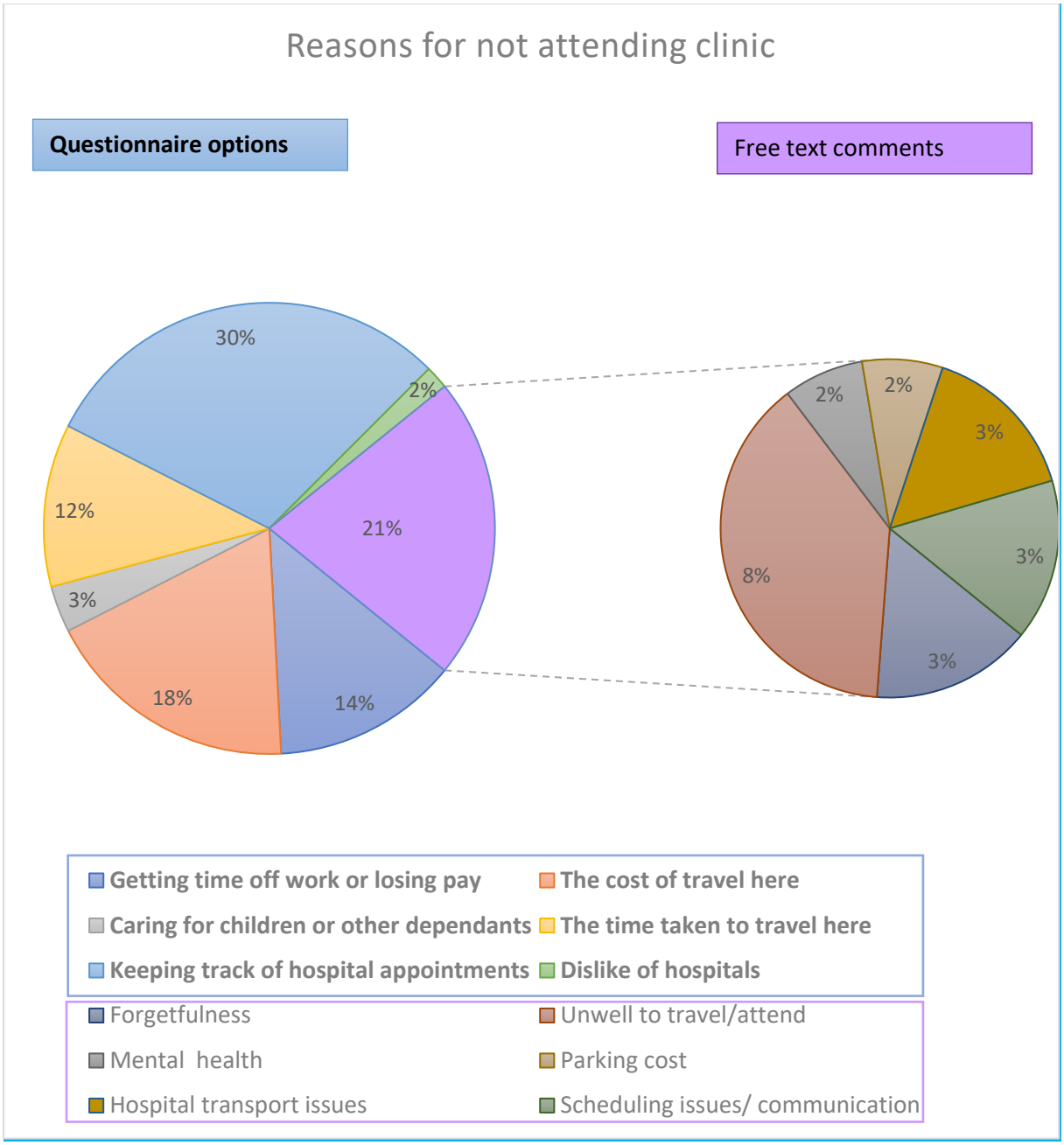

Figure 6.7 : Pie charts demonstrating the distribution of reasons given for not attending clinic from the suggested choices in the questionnaire (pie chart on the left) with the side pie (on the right) elaborating on the 21% of "Other causes" according to free-text responses.

Changes in adherence over time

Patients were asked whether their adherence had changed over time and given the opportunity to explain why that may be the case. The majority reported they got

better or much better over time (48.1%), some 41.4% suggested there was no change, and 10.5% suggested they got worse. Those who said they had become worse provided the following reasoning in the free text response:

- confusion and fatigue
- forgetfulness
- lack of support at home to remind them to take medication (*"easier to forget when living alone and without parents to remind you"*)
- concerns about side-effects
- being "fed up" with taking them

Conversely, those that became better at taking medication suggested in the free text that reasons for this included:

- being more organised (having a pill organiser)
- feeling less fatigue on treatment
- realisation of impact of medication (*"I've realised how much not properly taking my medicine negatively affects my disease*")
- improvement in disease symptoms with medication

Triangulation of adherence outcome scores

Whilst the VAS was the chosen outcome for adherence, I additionally triangulated this by asking the patients to report on the frequency of missed doses in a multiple-choice option, using a Likert scale format as shown below in box 6.2.

If you are taking any of the above medications, which statement best describes how you manage to take these tablets?

□ I always take them as prescribed
□ I miss a dose once or twice a month
□ I miss a dose once or twice a week
□ I take them less than half of the time
□ I rarely take them
□ I never take them

Box 6.2 showing assessment of adherence using a Likert scale for triangulation.

Furthermore, embedded within the survey were four questions that are also included within the MGL scale, a generic validated adherence tool which, however, has not been specifically validated in LN or vasculitis. The MGL scale has a sensitivity of 81% and a specificity of 44% in correlating with good adherence at 42 months [256] and therefore can offer some prognostic value.

As described in Chapter 1 (Introduction page 133) the MGL scale includes four questions and is scored based on patients' binary response to "Yes or No" questions with "Yes" scoring 0 and "No" scoring 1. Thus, a sum score of 0 indicated the highest level of adherence, whilst 1 or 2 indicated a medium level of adherence, and a score of 4 indicated the worst adherence.

The following graph (Figure 6.8) shows the correlation between the three types of adherence assessment used in our study, notably:

- The VAS from 1 to 10 (orange colour, higher value better adherence)

- The Likert scale incorporating six possible answers based on missed dose frequency; “how frequently they missed tablets”, and quantify this as “always missing”, “missing monthly”, “missing weekly”, “missing half of the time”, “rarely” and “never” (“rarely” and “never” merged for the purposes of the graph), depicted by the blue bar chart.
- MGL scale comprised of four questions (grey colour, lower value better adherence)

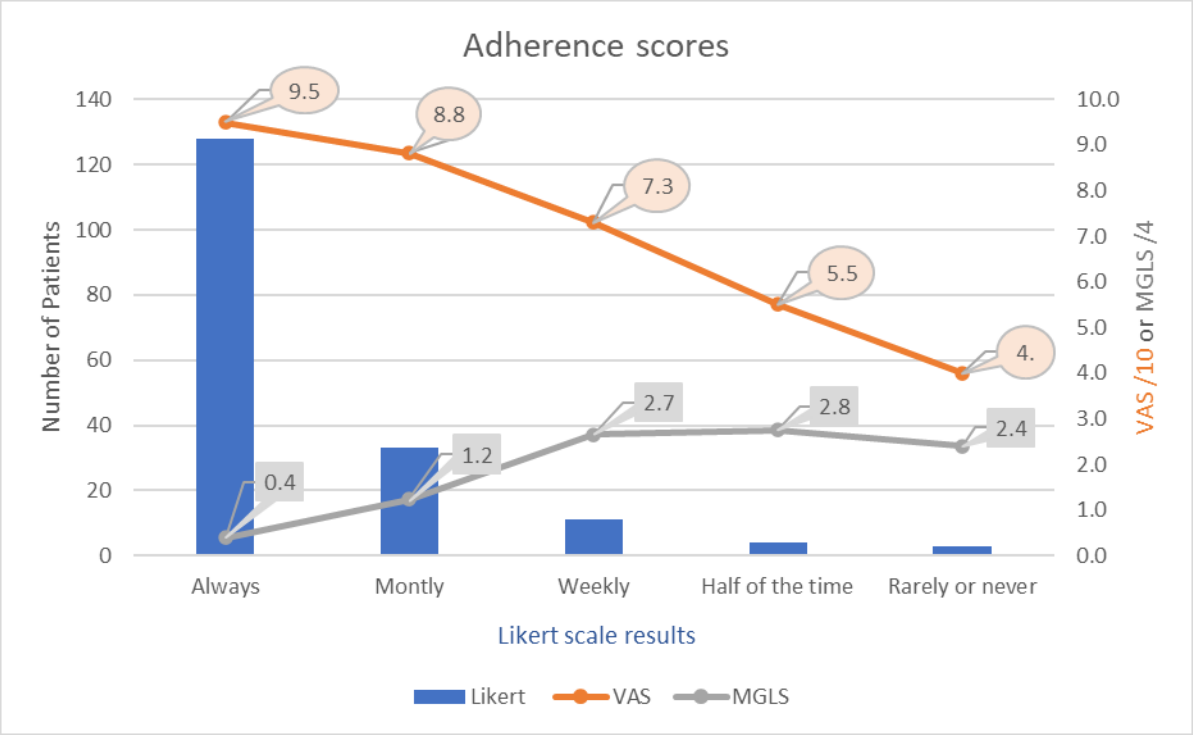

Figure 6.8 Combined column and line chart depicting the correlation between Likert (orange), VAS (blue) and MGLS (grey) adherence scales used indicating good agreement.

The VAS line consists of the mean VAS score for each category of the Likert scale. Patients responding on the Likert scale as “always” adherent had the highest mean scores on the VAS scale and the lowest score on the MGLS, thus suggesting high levels of adherence.

Univariate analysis results

Univariate analysis undertaken across all patients identified various factors associating with better or worse adherence, as shown in Table 6.3 (patient characteristics) and Table 6.4 (patient beliefs, behaviours and attitudes). Increasing age was associated with better adherence (OR 1.039, 95% CI 1.019-1.060, p=0.001) for each additional year, as well as taking prednisolone which was also associated with better adherence (OR 2.263, 95% CI 1.1215-4.217, p=0.01)

On the other hand, taking hydroxychloroquine was associated with worse adherence (OR 0.416, 95% CI 0.225-0.769, p=0.005). Similarly, concerns about potential side effects from medication were also associated with worse adherence. Notably, concerns about diabetes decreased adherence threefold (OR 0.333 95% CI 0.127-0.877, p=0.026) and concerns about mood problems also decreased adherence (OR 0.406 95% CI 0.188-0.877, p=0.022).

If the patients paid for their medication, this reduced adherence by a factor of 2.6 (OR 0.371 95% CI 0.156-0.882, p=0.025). Furthermore, those patients who declared they failed to attend any of their outpatient appointments were three more times less likely to be adherent (OR 0.333, 95% CI 0.180-0.615).

Comparing patients with lupus and vasculitis, the latter were twice as likely to be adherent (OR 1.992 95% CI 1.094-3.626, p=0.024).

Univariate analysis of whole cohort for adherence			
Variable	**OR**	**95% CI**	**P**
A. Patient Demographics			
Sex (Female)	0.682	0.339-1.375	0.285
Age (per additional year)	1.038	1.018-1.060	**<0.001**
Birthplace (outside UK vs UK)	1.429	0.761-2.682	0.267
Ethnicity (Others vs white)	1.032	0.577-1.843	0.916
Ethnicity (0White/ 1Mixed/ 2Asian/ 3Black)	1.064	0.869-1.304	0.548
Any religion vs no religion	1.027	0.537-1.962	0.936
Marital status (married/long-term relationship vs single/ separated/ widowed)	1.442	0.799-2.602	0.224
Education (university vs secondary school vs primary school)	0.868	0.650-1.159	0.337
Employment or student vs unemployed, retired, unable to work due to illness	1.271	0.707-2.283	0.424
B. Disease characteristics			
Vasculitis vs Lupus	1.920	1.055-3.496	**0.033**
Duration (>5 years vs <5 years)	1.071	0.590-1.943	0.822
Disease Activity Severity	1.102	0.955-1.272	0.185
Kidney function moderate/severe/dialysis vs mild/none	1.638	0.854-3.142	0.137
Participation in a clinical trial (yes vs no)	6.480	0.728-57.656	0.940
C. Medication			

Who administers tablets (someone else vs self)?	0.308	0.058-1.630	0.166
Number of tablets taken daily	1.023	0.966-1.084	0.434
Types of different medication	1.093	0.976-1.224	0.125
Medication taken for lupus or vasculitis	0.894	0.767-1.042	0.152
Currently taking Prednisolone/ Steroids	2.598	1.364-4.951	**0.004**
Currently taking Azathioprine	1.637	0.804-3.333	0.174
Currently taking Hydroxychloroquine	0.398	0.211-0.748	**0.004**
Currently taking MMF	0.742	0.388-1.418	0.367
Currently taking Methotrexate	0.445	0.125-1.584	0.211
Number of Immunosuppressive medications taken	0.941	0.629-1.407	0.768
Ever received immunosuppression as iv drip	1.107	0.568-2.154	0.766
Concerns for side-effects relating to steroids			
Fear of weight gain	1.434	0.724-2.843	0.301
Fear of diabetes	0.367	0.136-0.988	**0.047**
Fear of eye problems	1.058	0.513-2.183	0.879
Fear of sleep disturbance	1.348	0.639-2.842	0.433
Fear of dependency	0.761	0.282-2.055	0.590
Fear of osteoporosis	0.931	0.469-1.846	0.837

Fear of mood problems	0.425	0.196-0.918	**0.030**
Fear of stomach ulcers	0.417	0.173-1.002	0.051
Fear of skin changes	0.996	0.481-2.062	0.991
Fear of hypertension	1.222	0.568-2.630	0.608
D. Adherence to medication			
Change in adherence with Time worse vs no change/ better	0.474	0.298-0.756	**0.002**
Potential barriers- Cost of tablets (pay vs free)	0.355	0.149-0.846	**0.019**
E. Attendance to clinic			
Outpatient attendance (miss even one appointment worse adherence than full attendance)	0.337	0.180-0.632	**0.001**

Table 6.3 Table showing all patient-related variables included in logistic regression univariate analysis.

QUESTIONNAIRE SECTION F Behaviours /Beliefs /Perceived barriers	**OR**	**95% CI**	**P**
(strength of agreement Likert scale) (strongly disagree/ disagree vs agree/ strongly agree)			
In relation to tablet taking/ medication			
You didn't remember to take them	2.246	1.652-3.055	**<0.001**
You find it hard to swallow tablets	1.588	0.974-2.590	0.064
You don't like the taste/ smell of them	1.685	1.098-2.595	**0.018**
You wanted to see if taking fewer tablets would be ok	1.462	0.946-2.261	0.087
You just don't like taking tablets	1.664	1.136-2.437	**0.009**
You didn't want to be reminded of your illness	1.601	1.020-2.513	**0.041**
Taking tablets regularly interferes with your lifestyle	1.268	1.934	0.270
In relation to health beliefs			
You took herbal or alternative medicine instead	1.511	0.805-2.837	0.199
You put your faith or trust in your religion instead	1.101	0.693-1.751	0.683
You changed your diet so felt you needed less drugs	1.171	0.743-1.848	0.496
You felt really well and thought you didn't need them	1.548	0.983-2.438	0.059
You felt disappointed because they were not working	1.135	0.705-1.826	0.603
You didn't understand why you needed them	1.003	0.603-1.668	0.991

You worried they might be addictive	1.198	0.740-1.940	0.462
In relation to side effects			
You wanted to avoid side effects like nausea or sickness	1.456	1.043-2.032	**0.027**
You were worried about weight gain or changes in your appearance in your face or body	1.154	0.857-1.554	0.345
You thought the lupus/vasculitis medication might be bad or toxic for your body	1.504	1.044-2.166	**0.029**
You felt your medication was causing you symptoms of tiredness, fatigue or lack of energy	1.219	0.870-1.709	0.249
You experienced mood problems like feeling low or anxious	1.740	0.818-3.702	0.150
In relation to understanding disease/ confidence to treatment			
If I feel well, I'm less likely to take my medication	2.087	1.326-3.286	**0.001**
I'm more likely to take my medication if it's only once a day	1.632	1.236-2.157	**0.001**
Lupus/Vasculitis is a long term (chronic) illness which has no cure	1.072	0.808-1.423	0.629
I understand why my medication has been prescribed	1.076	0.764-1.517	0.674
I know what each of the medication I take is for	0.884	0.636-1.227	0.460
I prefer to have my medication given via a drip/injection instead of tablets	1.130	0.731-1.747	0.583
I am confident to take the course of treatment that's been offered to me	0.976	0.702-1.355	0.884
I have had the chance to discuss my drugs with my specialist team	1.027	0.721-1.463	0.883
I was involved in all decisions regarding my medication	0.977	0.694-1.378	0.896

Table 6.4 showing univariate analysis for Behaviour responses with logistic regression.

The most significant responses related to unintentional non-adherence (e.g. forgetting to take medication), followed by intentional non-adherence (e.g. concerns about the medication and side-effects, a general dislike in taking tablets and more specifically the taste/ smell or difficulty swallowing them). Table 6.5 summarises the stronger predictors of non-adherence from section F of the questionnaire (Behaviours / Beliefs / Perceived barriers)

	Reasons for poor adherence	P value
1	You didn't remember to take them	<0.001
2	If I feel well, I'm less likely to take my medication	0.001
3	I'm more likely to take my medication if it's only once a day	0.001
4	You just don't like taking tablets	0.009
5	You don't like the taste/ smell of them	0.018
6	You wanted to avoid side effects like nausea or sickness	0.027
7	You thought the lupus/vasculitis medication might be bad or toxic for your body	0.029
8	You didn't want to be reminded of your illness	0.041
9	You felt really well and thought you didn't need them	0.059
10	You find it hard to swallow tablets	0.064

	Unintentional
	Side-effects
	Beliefs
	Attitude

Table 6.5 : Top 10 reasons for low adherence categorised in themes and ranked according to the strength of association.

Multivariate analysis results

I then undertook multivariable regression using patient characteristic parameters that are already known to the clinicians (e.g. age, medication of patients, cost of medication, diagnosis and outpatient attendance) without the need to rely on a patient questionnaire. Importantly, on forward stepwise multivariate regression (Table 6.6) the diagnosis of vasculitis itself was not associated with better adherence

per se, indicating that similar factors influence adherence in both lupus and vasculitis patients.

Older age continued to associate with better adherence (OR 1.04 95% CI 1.019-1.071, p = 0.004) and was the likely mediator of the better adherence seen in the vasculitis patients. Taking prednisolone continued to associate with better adherence (OR 3.021 85% CI 1.412-6.461, p=0.004) and declaring suboptimal attendance at outpatient clinics was associated with worse adherence (OR 0.411, 95% CI 0.188-0.899, p=0.026). I then put these parameters in a model which was based solely on patient characteristics.

All the other positive predictors on univariate analysis associating with worse adherence, notably taking hydroxychloroquine, paying for medication, concerns about diabetes or mood problems and diagnosis of lupus vs vasculitis failed to reach significance in the multivariable model.

Model 1: Patient characteristic parameters only is showin in Table 6.6.

Variable	OR	95% CI	P value
Age	1.044	1.019-1.071	0.001
Taking Prednisolone	3.021	1.412-6.461	0.004
OPD attendance	0.411	0.188-0.899	0.026

Table 6.6 Multivariate analysis forward stepwise model results for Model 1, confirming that increasing age and taking Prednisolone improved adherence, whereas missing even one clinic outpatient appointment associated with decreased adherence.

I then extended a stepwise forward regression to include all the variables which were significant in the univariate analysis. In addition to the patient characteristic parameters used in Model 1 (i.e. demographics, diagnosis-related facts) patient beliefs/ behavioural pattern results from the questionnaire were then included to create Model 2.

As shown in Table 6.7 four variables remained predictive of better adherence including: age, taking prednisolone and the response indicating agreement or disagreement to the following two questions:

i) “You just don’t like taking tablets”, and

ii) “You wanted to avoid side effects like nausea or sickness”.

Model 2: Patient characteristic and behavioural parameters is shown in Table 6.7.

Variable	OR	95% CI	P value
Age	1.039	1.007-1.073	0.017
Taking Prednisolone	4.432	1.694-11.598	0.002
Disagreement with comment “You just don’t like taking tablets”	7.412	1.826-30.083	0.005
Disagreement with comment “You wanted to avoid side effects like nausea or sickness”	3.798	1.171-12.321	0.026

Table 6.7 Multivariate analysis forward stepwise model results for Model 2, indicating increasing age and taking prednisolone associated with better adherence, whilst disagreement with the questions "You just don't like taking tablets" and "You wanted to avoid side effects like nausea or sickness", again associated with better adherence.

Development of prediction models for adherence

I utilised the positive predictors from the multivariable analysis and built two potential models for predicting adherence; one based on known clinical parameters (Model 1, Box 6.3) and a second one using a combination of patient characteristics and responses to the two specific questions that yielded additional predictive value as shown in Table 6.7 (Model 2, Box 6.4). The odds ratio risk was utilised to attribute relative weight to each predictor and incorporated in an excel spreadsheet. The Models were constructed using data for adult patients and hence would not apply to patients <18 years of age. Thereafter, they were calibrated to have an adherence score ranging from 0-100, with higher scores indicating an increased likelihood for better adherence.

A binary outcome of non-adherence risk (High/ Low) based on a cut-off value rather than a broader range of adherence levels was used for these models. The calibration of the cut-off point is explained later in this chapter.

$$Model\ 1 = \big((Age - 18) * OR(Age)\big) * OR(Pred) * OR\ (attendance)/7.512$$

Where OR Age=1.044;

OR(Pred) = 3.021 if on pred or 1 if not on pred;

OR(attendance) = 3.308 if full attendance or 1 if not.

Model 1		Data Entry	
	Age	18-90	
	Taking Prednisolone	Yes or No	
	Full attendance at OPD	Yes or No	
	Adherence Risk Score	0-100	
	Risk for Poor Adherence?	**HIGH** **0-10.5**	**LOW** **10.6-100**

Box 6.3 depicting the clinical variables and mathematical formula used in Model 1 (top panel) as well as an electronically programmed excel calculator to identify the risk of adherence (bottom panel).

$$Model\ 2 = \big((Age - 18) * OR(Age)\big) * OR(Pred) * OR\ (dislike\ taking\ tablets) * OR\ (wish\ to\ avoid\ side\ effects)$$/ 73963.46

Where OR Age=1.039;

OR(Pred) = 4.432 if on pred or 1 if not on pred;

OR (wish to avoid side effects) = 7.412^0 if response to question “I don’t like taking tablets” is “strongly agree” or 7.412^1 if response is “agree” or 7.412^2 if response is "disagree" or 7.412^3 if response is “strongly disagree”

OR(wish to avoid side effects) = 3.798^0 if response to question “You wanted to avoid side effects like nausea or sickness” is “strongly agree” or 3.798^1 if response is “agree” or 3.798^2 if response is “disagree” or 3.798^3 if response is “strongly disagree”

Model 2	Data Entry	
Age	18-90	
Taking Prednisolone	Yes or No	
I don’t like taking tablets	Strongly Disagree or Disagree or Agree or Strongly Agree	
I want to avoid potential side effects like nausea or sickness	Strongly Disagree or Disagree or Agree or Strongly Agree	
Adherence Risk Score	0-100	
Risk for Poor Adherence?	**HIGH** **0-1.95**	**LOW** **1.96-100**

Box 6.4 depicting the clinical variables and mathematical formula used in Model 2 (top panel) as well as an electronically programmed excel calculator to identify the risk of adherence (bottom panel).

Model calibration

Both predictive models were calibrated using ROC curves to identify cut-off scores for adherence, with values below the cut-off indicating higher risk for non-adherence. These values were incorporated into a spreadsheet utilising Microsoft Office Excel software programme, thus creating an "excel tool" that automatically does the mathematical calculation. The "excel tool", in addition to calculating the risk-score, also indicates if there is likelihood of good adherence (highlighted by the automatically applied green colour) or poor adherence (which is indicated by the automatically applied red colour). It is therefore user friendly and can easily be used in clinical practice. Utilising automatic risk calculators is common in clinical medicine and specifically in rheumatology (e.g. FRAX score for osteoporosis).

The excel calculator of both models can be found and downloaded through this link, allowing utilisation with all the excel functionality options:

http://bitly.ws/rrk8

Using these models, the individual score for each patient was calculated and a ROC curve (Figure 6.9) used to compare against the adherence as determined by the VAS score. Model 2 performed slightly better with an AUC=0.75, whilst Model 1 had an AUC=0.71. These are encouraging results indicating that they could support identifying the adherent and non-adherent patients in clinical practice.

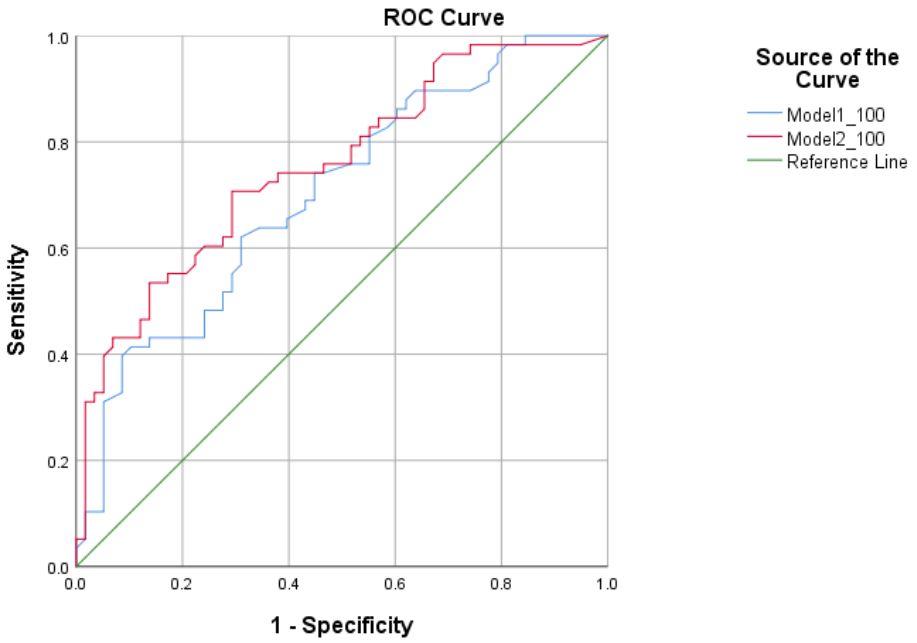

Figure 6.9 ROC curve for Model 1 and Model 2 against VAS adherence, showing AUC=0.71 for Model 1 and AUC=0.75 for Model 2. This can be used to calculate sensitivities and specificities for each value of the score. Clinical values for each score can be utilised as follows:

Model 1 – values >10.5 have a sensitivity of 0.74 and specificity of 0.53 for good adherence, thus used as a cut-off

Model 2- values >1.95 have a sensitivity of 0.74 and specificity 0.62 for good adherence, thus used as a cut-off

This cut off for both models can be modified depending on the clinical setting to reflect the desired sensitivity and specificity; lower value cut-offs will have better sensitivity at the expense of worse specificity for better adherence and vice versa.

Examples of model utility

Print screens of the models are shown below, with relevant patient examples as shown in box 6.5, with the higher value obtained indicating higher probability of adherence. The excel-tool was also programmed to incorporate the cut-off and indicate the likely adherence pattern of the patient.

In the example of Model 1, a 60-year-old patient who takes prednisolone and has good attendance in the outpatient clinics has an Adherence Risk score of 58.9. This is deemed to be good, and in response to the outcome question " Risk for Poor Adherence?" the answer is a "LOW", and Model 1 gets automatically colour-coded GREEN "LOW".

Conversely, the example considered in Model 2 has a low overall score indicating a higher risk of poor adherence, and the colour is automatically depicted as RED "HIGH", indicating an alert sign for the clinician.

Model 1	Patient 1	
	Age	60
	Taking Prednisolone	Yes
	Full attendance at OPD	Yes
	Adherence Risk Score	58.3
	Risk for Poor Adherence?	**LOW**

Model 2	Patient 2	
	Age	45
	Taking Prednisolone	No
	I don't like taking tablets	Agree
	I want to avoid potential side effects like nausea or sickness	Strongly Disagree
	Adherence Risk Score	0.2
	Risk for Poor Adherence?	**HIGH**

Box 6.5 showing Model 1 (top panel) and Model 2 (bottom panel) risk calculator examples from Excel spreadsheet

Comparison with validated scores

I have compared the two proposed models to the MGLS score utilising ROC curves as shown in Figure 6.10 showing fair correlation.

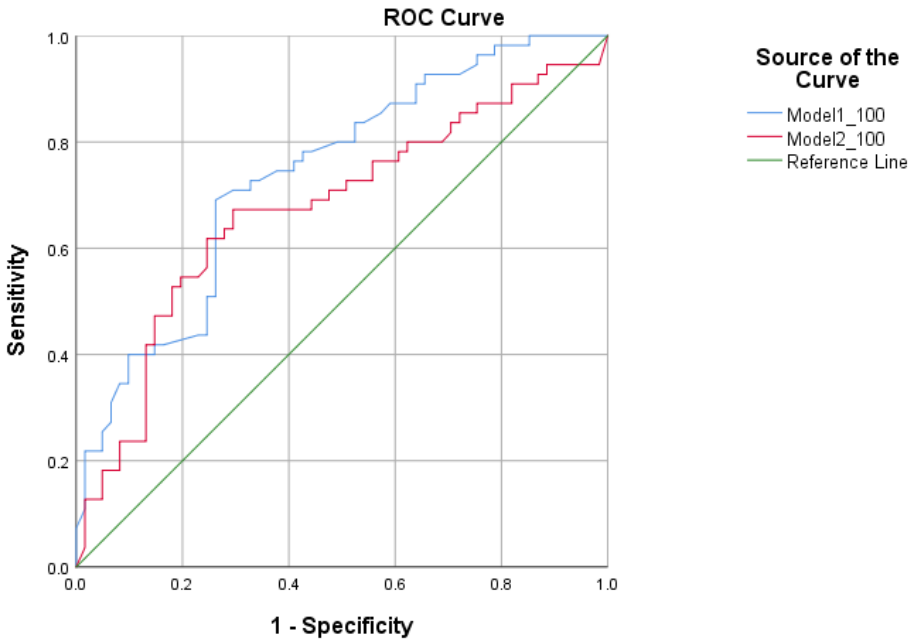

Figure 6.10 showing the ROC curve comparing Model 1 and Model 2 with the MGL scale.

Model 1 had a fair AUC=0.74 whilst Model 2 had a worse AUC=0.68

VAS comparison to MGLS

I have also investigated how the VAS compares with the MGLS scale using ROC curves, and this showed good AUC=0.76 indicating that VAS can be potentially used as a substitute for MGLS to associate with longer-term prognosis.

Furthermore, I calculated the Sensitivity/ Specificity, Positive and Negative Predictive value for the models in comparison to the VAS and MGLS is shown in the Table 6.8 below.

Sensitivity/ Specificity Positive/ Negative Predictive value	VAS	MGLS
Model 1	77% / 56% 67% / 58%	81% / 58% 67% / 74%
Model 2	73% / 61% 65% / 69%	65% / 54% 57%/ 65%

Table 6.8 comparing the ROC identified cut-offs for Model 1 and 2 against the VAS and the MGLS.

Lupus Cohort subanalysis

As the focus of this MD thesis has been LN in particular, I did a further subanalysis in the Lupus cohort of this study.

When looking specifically in the Lupus cohort on univariate analysis age, duration of disease >5 years, taking prednisolone, concerns about diabetes, taking tablets more than once a day and a negative response to the questions “You didn’t remember to take them” and “If I feel well I’m less likely to take my medication” were all significant predictors of better adherence on univariate analysis as shown in the table 6.9 below. Other variables that showed a trend towards significance (i.e. $p>0.05$ but <0.15) included moderate or severe renal failure and taking hydroxychloroquine.

Only the variables that showed significance or a trend to significance are shown in Table 6.9 below.

Univariate analysis of Lupus cohort and good adherence			
Variable	**OR**	**CI**	**P**
Age	1.035	1.006-1.065	**0.018**
Duration of disease >5 years vs <5 years	3.592	1.364-9.460	**0.010**
Kidney function (moderate or severe disease vs mild or normal disease)	2.314	0.968-5.530	**0.059**
Currently taking Prednisolone	2.278	1.008-5.147	**0.048**
Currently taking hydroxychloroquine	0.453	0.196-1.046	**0.064**
Fear of Diabetes	0.244	0.062-0.956	**0.043**
You didn't remember to take them (disagree/ strongly disagree vs strongly agree/ agree)	3.089	1.941-4.914	**0.000**
You find it hard to swallow tablets (disagree/ strongly disagree vs strongly agree/ agree)	1.865	0.985-3.543	**0.057**
You don't like the taste/ smell of them (disagree/ strongly disagree vs strongly agree/ agree)	1.609	0.961-2.692	0.070
You just don't like taking tablets (disagree/ strongly disagree vs strongly agree/ agree)	1.458	0.953-2.230	0.082
If I feel well I'm less likely to take my medication (disagree/ strongly disagree vs strongly agree/ agree)	2.122	1.228-3.666	**0.007**
I'm more likely to take my medication if it's only once a day (strongly agree/ agree vs disagree/ strongly disagree)	1.775	1.244-2.531	0.002

Table 6.9 Univariate predictors of good adherence in the Lupus cohort.

On multivariable regression however, including all significant univariable parameters only age was associated with adherence. For every one-year increase in age, the patients were more likely to be more adherent by a factor of 1.050. In addition, patients on prednisolone had a trend towards a 2.5-fold better adherence (p=0.11), and concerns about diabetes had a trend towards 4-fold worse adherence (p=0.11).

Given that the derivation of the prediction models utilising the whole cohort did not suggest that the actual diagnosis made a difference, it can be concluded that both Model 1 and Model 2 can be used to the same effect in this lupus sub-cohort, even though low power did not produce the same results when analysing the lupus cohort on its own.

Discussion

Non-adherence to medication is a commonly reported problem in chronic inflammatory rheumatic diseases including lupus and vasculitis [260] and is linked to worse outcomes [44]. As discussed in Chapter 1, several studies have investigated adherence patterns in SLE identifying various parameters associating with better or worse adherence. For example, reports in the literature suggest that increasing age [269], being Caucasian [274], higher education [271], family support [275], longer disease duration [276], being married or in a long-term relationship [277] and taking steroid medication [246] tend to associate with better adherence. In contrast, depression [271], limited comprehension of instructions [278], experience of side effects [279], forgetfulness [280], alcohol abuse [281], unemployment [246], having to take medication more than once daily [277], poor availability and cost of medication [282] and poor communication between doctors and patients could all associate with worse adherence [295].

Whilst factors for adherence in lupus patients in general have been extensively studied and compared with other rheumatic conditions such as rheumatoid arthritis, there has been no specific research into factors affecting adherence in LN and comparing such patients with vasculitis, an autoimmune condition that shares multiple similarities including pharmacotherapy and renal impairment.

Comparison of survey responders to overall target population

Lupus population

When comparing the demographics of the responders of my survey to the overall LN cohort, I utilized published descriptions of the UCL lupus and LN cohorts spanning from 1975 to 2015 [34].

Gisca et al. reported on 219 patients with LN, of who 200 were women (91. 3%) with ethnicity distribution amongst the overall cohort very similar to the observed pattern in my study Lupus population. In the Gisca et al. study Caucasians were the majority at 44.7% followed by Blacks at 28.8% and Asians at 24.2%.

In my survey, the corresponding values were Caucasians=42%, Blacks=26%, Asians=24% as seen in table 6.1. There was no statistical difference using Chi Square analysis between my cohort and the Gisca study (p=0.96) for ethnicity. Likewise, the Gisca study had 91.3% women compared to my study which had 90.0% women (p=0.75). Therefore, this suggests that my study is comparable to the overall LN cohort and hence the results reported could be generalizable.

Vasculitis population

With regards to the vasculitis population, there are no published studies of the exact denominator population describing the specific vasculitis cohort, as with the SLE part of the cohort. Therefore, I have reviewed the contemporary epidemiological

literature to critically assess how this broadly compares to the vasculitis sub-cohort findings of my study.

Booth et al. [311] on behalf of the Pan-Thames Renal Research Group conducted a retrospective, multicentre, sequential cohort study and reported presenting features and outcomes of new patients diagnosed with renal vasculitis in London, UK, between 1995 and 2000. The study recruited 313 patients with a new diagnosis of renal vasculitis including diagnoses of ANCA-associated systemic vasculitis (246 patients), Henoch-Schoenlein purpura (25 patients), cryoglobulinaemic vasculitis (seven patients), polyarteritis nodosa(17 patients), and anti–glomerular basement membrane (18 patients). Demographic data were described only in the sub-cohort of ANCA-associated vasculitis patients showing a predominance of white male patients with 57% of patients being men and 83% Caucasian. Other ethnic groups included Hispanic (5%), African or Afro-Caribbean (4%), and Asian (4%).

Another study by Pearce et al.[19] looking at the population of the Nottingham–Derby urban area which is multi-ethnic (and thus may have some similarities to the urban multi-ethnic population served by RFH and UCLH), reported demographic data on patients with ANCA associated vasculitis from March 2007 to June 2013. They identified a total of 107 incident cases of ANCA-associated vasculitis. The majority of cases were men (60%), with a median age at diagnosis of 70.2 (interquartile range: 58.4–78.6) years. Of the total number of cases, 94.4% were white, 1.9% were black, 2.8% were Indo-Asian and 0.9% were other Asian.

In my study, it was not possible to filter down to the specific vasculitis diagnosis and identify which patients had ANCA associated vasculitis for direct comparisons. Therefore, I am unable to compare my population with the two studies mentioned above in a meaningful way. Nevertheless, the ethnic distribution of my sub-cohort was predominately white/ Caucasian as in the above studies and the proportion of men was 42%, which was significantly higher than the SLE sub-cohort.

Comparison of survey sub-cohorts: SLE vs Vasculitis

When comparing the two sub-cohorts, I noted a female predominance in the SLE cohort as expected, with more representation from non-white patients and longer duration of disease despite the younger age. In addition, patients with SLE were taking a higher total number of tablets than vasculitis patients and had worse outpatient clinic attendance.

I looked further into various dimensions of non-adherence including demographic and socioeconomic factors, condition and therapy-related factors as well as patient-related factors including behaviours, beliefs and perceived barriers as reflected in the questionnaire categories.

When considering socioeconomic factors, in contrast to some earlier studies I found no evidence to support an association of adherence with ethnicity, religion, marital status or education, or work status. Whilst partly surprising, not all the previous studies showed a positive association. Further, despite the reasonable numbers of

SLE and vasculitis patients with renal concerns included in this study, the numbers might not have been big enough to be powered to identify smaller associations.

Very few patients had to pay for their medications, nevertheless, not surprisingly, the cost of drugs appeared to impact adherence for the worse on univariate analysis. Although within the UK NHS health care system access to medical care is free at the point of entry, an outpatient prescription is more complex. Each medication has a fixed cost currently at £9.35 per item [312]. However, many patients with chronic conditions, e.g. diabetes or cancer, or if aged over 60, are entitled to completely free prescriptions. Unfortunately, patients with SLE and vasculitis are not allowed to claim free prescriptions. Another option for patients on multiple medications is to buy a pre-paid certificate (currently costing £108.10 for a year), meaning that pre-pay will be cheaper if they require more than 12 items over the 12 months. Importantly, this price of £108.10 sets a cap for the maximum cost to the patients and once paid, a pre-paid certificate allows patients to have any number of medications for any conditions for free. Whilst, therefore the maximum cost that can be incurred for a patient is capped at £108.10, this value might still be too expensive for some individuals and be a deterrent to better adherence. This issue is a more commonly observed phenomenon in countries like the USA, where healthcare costs burden the individual patient directly. Financial constraints contribute to poor compliance, as shown in previous studies by Kennedy and Erb [282].

Related to overall cost, I also noted in the qualitative work that the cost of medication or cost of travel to clinic appointments may also confound differences on

adherence patterns in socioeconomically disadvantaged groups, in which ethnic minorities are overrepresented [313], thus also indirectly potentially affecting disease outcomes.

I then considered disease characteristics and observed that the vasculitis patients are twice as likely to be adherent compared to the SLE patients. However, when adjusting for other variables such as age, this association was no longer significant. I found that increasing age was an independent predictor of better adherence, and therefore, the high rates of non-adherence seen in SLE are less likely to relate to the condition itself, but in part to the younger age of these patients.

One unique aspect of this work was its focus on renal involvement. When reviewing the effect of renal impairment on adherence in the whole cohort, there was no significant difference noted between patients who had normal or mildly affected renal function compared to those who had moderate or severe impairment. Furthermore, there was no difference between the two sub-cohorts of SLE and vasculitis. Work from the Results Chapter 5 study 2 showed that LN patients who spent a longer period on dialysis before renal transplantation tend to be more adherent after the transplantation. I considered that this could translate to the current cohorts as well. However, in this cohort I only had four patients on dialysis and whilst these patients were adherent, they had little effect on the overall results in the cohort. Conversely, if patients had moderate or severe renal involvement, this did not seem to affect adherence.

Another significant aspect of my work was analysing the medication patterns in both qualitative and quantitative ways. As expected, the SLE cohort has a much higher use of hydroxychloroquine, whilst a similar percentage of patients from both cohorts were on prednisolone. However, I also found that if patients were taking prednisolone, they were more likely to be adherent. Although this might seem perverse given the patients reported concerns about steroid side-effects, notably fear of diabetes and mood disturbance, it can be appreciated that patients on steroids might have more severe disease with multiple previous flares, and thus it is important that they adhere to their medications. This important effect has also been recently shown in another multicentre study by Costedoat-Chalumeau N et al [246].

In contrast, whilst hydroxychloroquine was more commonly used in SLE and associated on univariate analysis with worse adherence, when adjusted for other variables it lost its significance. This finding supports the results of other studies [268]. The qualitative part of the study revealed that hydroxychloroquine was tolerated better than other common immunosuppressants, followed by MMF, azathioprine and steroids. Methotrexate was the worst tolerated.

Novel agents such as biologics were less commonly used in our cohort and appeared to be reasonably well tolerated. Having received intravenous medication did not affect the level of adherence to oral medication, though the majority of patients did not prefer to substitute regular tablets for infrequent intravenous medication if given the option.

I also enquired whether patients had ever participated in a clinical trial, as I hypothesised that the experience of intense input with much closer monitoring and access to a supportive environment usually seen within the context of a clinical trial might influence the patient's overall adherence. However, I did not find any suggestion that this was the case in this study.

One obvious finding to emerge from the analysis was that regular attendance in outpatient clinics was significantly associated with better adherence. Whilst this is not surprising, documenting this can allow clinicians to become aware of patients potentially at higher risk of being non-adherent. In addition, with most hospitals now turning to electronic patient records, it should be very easy to programme the system to show the number of missed appointments in the last few years, allowing clinicians to identify patients who are not attending regularly. Reasons provided for lack of clinic attendance included forgetfulness, difficulty in keeping track of appointments which could be categorised as unintentional non-adherence; whilst other factors included time and cost of travel to or park at the hospital and difficulty getting time off work which can be categorised as intentional non-adherence.

Exploring patient-related factors in terms of beliefs and attitudes, there were many different parameters that appeared to affect adherence. However, the most strongly associated behavioural pattern was forgetfulness, which was categorised as non-intentional non-adherence and was the most common cause for missing out tablets. Furthermore, I identified two specific questions that appeared to have a positive predictive value regarding intentional non-adherence –namely i) not liking taking

medication in general and ii) wanting to avoid specific side effects such as nausea- that were thereafter used in a prediction model which will be discussed below.

It is noteworthy that specific beliefs relating to medication toxicity or particular concerns about taste/ smell or difficulty swallowing tablets adversely affected adherence. In addition, the notion that if one is feeling well, one does not need any further tablets appeared to be affecting patient attitudes towards medication adherence and having to take medication more than once daily also adversely affected the likelihood of being adherent. In this context, as depression has been associated with poor adherence [276,314] I also included a question relating to mood, but this was not significantly associated with adherence in the cohorts studied.

One important addition of this work to the existing literature is the utilisation of the patient responses and the generation of two models which could associate with adherence. Model 1 was based on parameters known to clinicians already, notably age, prescription of prednisolone and attendance at outpatients; whilst Model 2 included age and prednisolone prescription in addition to responses to "You just don't like taking tablets" and "You wanted to avoid side effects like nausea or sickness". Both models showed acceptable sensitivity and specificity and could form the basis of clinically valuable models to be used routinely to highlight the "at-risk" patients for non-adherence to clinicians. Furthermore, whilst these models were derived against VAS, they were also compared against a Likert scale for adherence and the validated MGL with good results. Thus, these models can help identify profiles of patients who are more likely to be at risk of poor adherence.

This research and modelling help to understand better why patients with SLE and vasculitis may become less adherent. It implies that clinicians can ensure that when the patients with a higher risk of non-adherence profiles come to the clinic, more effective enquiries can be made about adherence in a targeted and focussed way that is not confrontational. From there, the clinician can initiate measures to improve adherence and, hopefully, prognosis.

Limitations

As with all questionnaire-based research, this study also has certain limitations. Firstly, the type of patients seen in specialist clinics is subject to referral bias, although the catchment area for the two university clinics is large and both receive tertiary referrals across the whole of London and indeed across the whole country.

Secondly, whilst these numbers used in this work are modest for SLE and vasculitis cohorts, the study might still have not been powered sufficiently to identify smaller differences and associations and therefore larger or multicentre studies may be needed to confirm the results.

Thirdly, the study was optional and therefore only represents the cohort of patients who chose to participate. Thus, it may have potentially missed capturing the less adherent patients who might tend to be less engaging and chose not to participate in a study, or indeed those patients missing their appointments hence not being given the option to participate. Whilst this is an inherent limitation of survey-based studies,

to try and limit this, I ensured that the questionnaire was entirely anonymous, giving the non-adherent patients opportunities to admit to that without their clinicians knowing about this. The overall response rate however of 42.1% was also good for a questionnaire based survey, and in line or higher than similar studies[315].

Furthermore, I looked at the representativeness of my sample, in comparison to the whole population of interest (specifically LN for this thesis) and showed that there were no significant differences in sex and ethnicity. Therefore, despite a degree of unavoidable non-response bias, the result of the study could be generalizable.[316]

Moreover, I could not confirm adherence by objective measures such as prescription refills and blood drug level analysis as the survey was intentionally anonymised. However, the lack of an objective measure still lends validity to the results as other studies have shown that questionnaires capture additional aspects of non-adherence over and above blood testing [246]; although including blood testing can be considered in a future study.

In addition, linking the questionnaire survey with blood tests results and retrieving data from medical records regarding clinical attendance, relapse rates, other comorbidities and relevant clinical details, would be very informative, gaining a more accurate picture and correlation to clinical outcomes. However, it would negate one of the strengths of the study, which was the anonymity that potentially enabled higher completion rates and possibly more honest answers.

Finally, it is important to recognize that this study and prediction model can be considered as a feasibility pilot study. Whilst the two proposed models associated with other external scores, indicating that there is a degree of validity and generalisability, it would be essential to validate them with completely external cohorts, ideally from multiple institutions. This would confirm whether the models will work in any setting and any hospital, with any set of patients. External validation is necessary to assess a model's reproducibility and generalizability [317] and until this is done, the model should remain for use only in the research arena.

In order to facilitate larger validation studies for the proposed prediction models, an on line risk score tool and application has been created as a research tool to allow easier calculation of the adherence risk. (see Appendix 10)

CHAPTER 7

Meta-analysis of Adherence in SLE

As discussed in Chapter 1 page 50, there is significant variation reported in the adherence rates for the lupus population due to the various definitions of adherence used in studies, as well as the different clinical settings. I, therefore, undertook a systematic review and meta-analysis to identify and estimate the overall rate of adherence in patients with SLE.

Methodology

I systematically searched PubMed to identify eligible studies from inception to July 2020, following the PRISMA methodology [318] using the following terms:

"(SLE* OR Lupus*) and adherence"

For statistical analysis and results presentation, I used the MedCalc software (version 20.109) for the production of the Forest plot and heterogeneity assessment. Heterogeneity was assessed with the I^2. For data analysis, I planned to use a Fixed-effects model if there was no significant heterogeneity (I^2<50%) or a Random-effects model if heterogeneity was high (I^2≥50%). Publication bias was assessed with funnel plots. All eligible studies identified were included independently of the type of study.

Results

My initial search revealed 676 results. Following abstract and title screening, 460 studies were excluded as they did not refer to adherence in SLE. This left 216 for full article review. All 216 articles were retrieved. Following full review, 174 articles were excluded as they did not include the proportion of adherence leaving 32 articles that provided quantified information on adherence and included in a meta-analysis as shown in Figure 7.1. As heterogeneity was high, a Random-effects model was used.

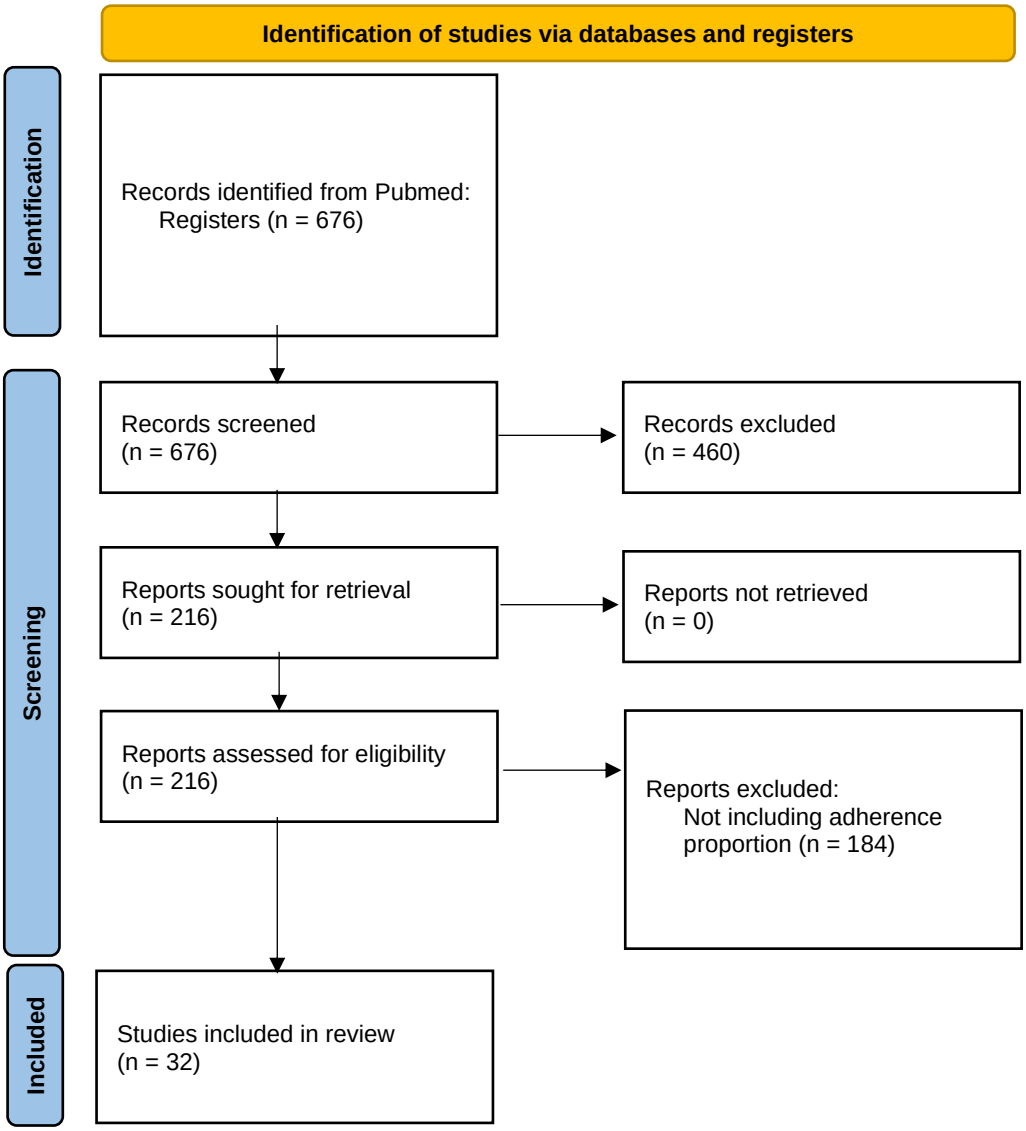

Figure 7.1 shows the PRISMA analysis and algorithm followed or the study selection.

The complete list of the studies with the main details and characteristics is included in Table 7.1.

	Study	Details	Method of assessing adherence	Total patients	Adherent patients	Factors associated
1	Du et al., 2020[271]	Cross-sectional, prospective, single-centre China	Compliance Questionnaire on Rheumatology (CQR) to assess adherence	144	82(56.9%)	Higher Education, lower SLEDAI, lower anxiety, and lower depression were correlated with adherence.
2	Sun et al., 2020 [269]	Cross-sectional, prospective, single-centre, USA	Medication Adherence Self-Report Inventory (MASRI) part A	121	46 (25.4%)	adherence better with increasing age better with being non-Afro-Caribbean worse with >2 medication worse with SLICC damage score worse with >1 ER visit/hospitalisation
3	Hachulla et al., 2020[319]	Prospective, one region, France	MASRI <80% or MMAS-8 or HCP-VAS or HCQ<200micg/L.	158	98 (62.0%)	Younger patients had poorer adherence
4	Ali et al., 2020 # 320	Prospective, one region, Egypt	MGL adherence scale	104	36 (34.6%)	Side effects of medications, forgetfulness and financial difficulties associated with poorer adherence
5	Liu et al., 2019 [274]	Retrospective, Northern California Kaiser Permanente. Patients on Hydroxychloroquine	Adherence was calculated from the hydroxychloroquine possession ratio and dichotomised as < 80% versus ≥ 80%.	1956	1134 (58.0%)	Increased adherence with with increasing age White race ≥ 3 visits in the previous year
6	Xie et al., 2018 [278]	Cross-sectional prospective. Single university hospital, China	self-reported medication adherence was assessed by the eight-item Morisky	140	35 (75%)	Low education, rural residency, childlessness, limited comprehension of medication instructions, side

			Medication Adherence Scale			effects experienced, dissatisfaction with treatment and better physical health were associated with an increased risk of nonadherence.
7	Heiman et al., 2018[321]	Cross-sectional, prospective, on region, USA	MMAS-8	632	291 (46.0%)	Younger age, female sex, and more severe depressive symptoms were associated with low medication adherence.
8	Feldman et al., 2018[273]	Medicaid patients on AZA or MMF with SLE code, USA.	Prescription refill data, adherent if ≥ 80%	4379	Overall 741/4379= (16.9%) AZA 436/2309 (18.9%) MMF 305/2070 (14.7)	Either AZA or MMF patients. Better adherence for males, more medication use. Worse adherence with living in areas below the median household income. African American or Hispanic less adherent, younger less adherent.
9	Chehab et al., 2018[270]	Prospective longitudinal study from Germany, cross-sectional results presented	Morisky Medication Adherence Scale; MMAS-4	458	287 (62.7%)	Use of AZA prednisone ≤7.5 mg, higher age remained independently associated with better adherence, whereas a reciprocal association was observed for patients perceiving medicines as intrinsically harmful.
10	Feldman et al., 2018[268]	Medicaid data, USA, for patients on Hydroxychloroquine	Prescription refill data, adherent if ≥ 80%	10406	1742 (16.5%)	Adherence improved by increasing age, whilst black race or hispanic associated with poorer adherence compared to white. Diabetes associated

						with worse adherence. Depression associated with worse adherence.
11	Prados-Moreno et al. 2018[281]	Observational transversal study, Spain	Adherence assessed with the Haynes–Sackett test. Self-reported>80%. The Morisky–Green test was used to determine adherence and attitudes towards treatment	72	26 (36.1%) using Morisky-Green	The use of NSAIDS associated with better adherence. Use of HCQ associated with worse adherence. Low education or being unemployed associated with worse adherence. Higher SLAQ-Flare associated with better adherence.
12	Alsowaida et al., 2018[309]	Cross-sectional study, Saudi Arabia	Morisky Medication Adherence Scale MMAS-4	140	53 (37.9%)	Younger age and depression associated with poorer adherence
13	Costedoat-Chalumeau et al. 2018[246]	International, prospective study of 19 centres in 10 counties	Assessed by either using HCQ level <200ntg/ml or Part A of the MASRI questionnaire <80%, or both	305	234 (76.7% by questionnaire) 249 (81.6% by HCQ)	Younger age, non-use of steroids, higher body mass index and unemployment, active smoking and current hospitalisation were associated with poorer adherence defined by either HCQ or MASRI.
14	Mazur-Nicorici et al. 2018[322]	Prospective, one region, Moldova	MMAS-8	132	60 (45.5%)	Young age at diagnosis, low disease activity and high education level associated with better adherence, whilst longer duration of diagnosis associated with poorer adherence.
15	Zhang et al., 2017 [267]	Prospective, one region, China	Compliance Questionnaire for Rheumatology-19	121	59 (48.8%)	Use of reminder tools, CQR score and use of biologics associated with better adherence. Side effects, being employed or using

						alternative therapies associated with poorer adherence.
16	Lee et al., 2017[323]	Retrospective longitudinal South Korea. Patients on hydroxychloroquine	Assessed using one-year medication possession ratio (MPR), and non-compliance was defined as a one-year MPR < 0.8	235	47 (20.0%)	Baseline SLEDAI2K >=6 associated with worse adherence
17	Iucidi et al., 2017[272]	Prospective study, based on HCQ levels	Non-adherence defined as HCQ<100ng/ml	83	59 (71.0%)	Use of immunosuppressants and the physical summary of SF-36 associated with poorer adherence
18	Flower et al., 2016[324]	Random selection for prospective study, Barbados	Morisky's Medication Adherence Questionnaire	106	64 (60.4%)	Younger age associated with poorer adherence
19	Resende Prudente et al. 2016[325]	Qualitative cross-sectional, one institution, Brazil.	Morisky-Green-Levine questionnaire	37	17 (45.9%)	Medication expenses associated with reduced adherence. More comorbidities associated with reduced adherence
20	Abdu-Sattar and El Magd. 2015[326]	Single centre, cross-sectional, Egypt	The Compliance Questionnaire for Rheumatology-19, and the patients were classified as non-adherers if they were taking <80 % of their medication	80	43 (52.5%)	Lower education, lower socioeconomic status, rural residency and higher depressive symptoms associated with poorer adherence
21	Lee et al., 2013[327]	Cross-sectional, one area, USA	Measurement of HCQ levels. Undetectable counted as non-adherent	30	27 (90%)	Aim to investigate renal function in patients taking HCQ
22	Marengo et al. 2012[328]	Prospective, one region, USA	Electronic adherence monitoring of oral therapies using MEMS	78	49 (62.8%)	Lower adherence associated with higher number of pills for non-SLE conditions, worse patient-perceived disease activity, worse depression

23	Dalebou dt et al., 2011[279]	Prospective, One region in New Zealand	Measured using part A of the Medication Adherence Self-Report Inventory (MASRI)	106	27 (25.5%) we never intentionally or unintentionally non-adherent stated they were never intentional or unintentionally	Increasing age associated with better adherence Poor cognition associated with poorer adherence
24	Oliveira-Santos et al 2010[329]	Prospective study, One hospital in Brazil	Morisky-Green-Levine questionnaire	246	78 (31.7%)	Family support, schooling and being white associated with better adherence
25	Julian et al., 2009[276]	Prospective cohort, USA	The Medication Item from the Cognitive Symptoms Inventory, 15ever a problem classed as non-adherence	834	454 (54.4%)	Poverty, high SLAQ score and more disease flares associated with poorer adherence
26	Koneru et al., 2008[330]	Face to face interviews of a random sample from four clinics in one area, USA	Pharmacy refill >80%	63	35 (55.4%)	39% non-adherent to pred 51% not adherent to HQC 43% not adherent to other meds 56/101 (55.4%) sufficiently adherent across all meds [but this is an overestimate… as one might be non-adherent to 1 of the 3 medications]
27	Chambe rs et al., 2008[295]	Qualitative study, Jamaica	Patient-reported adherence >85%	75	42 (56%)	Qualitative: cost, poor availability of medication and side effects led to poorer adherence
28	Garcia-Gonzale z et al. 2008[266]	Prospective, cross-sectional, one region, USA	The Compliance Questionnaire for Rheumatology-19,	32	11 (34.4%)	Study reported on 70 RA and 32 SLE. No difference between groups. Running out of pills, forgetting and feeling depressed quoted as reasons for poor adherence.
29	Sailler et al. 2007[331]	Prospective, one region, France	Self-reported compliance on a scale 0-10 with	58	46 (79.3%)	Aim was to investigate the influence of HCQ

			>=8 classed as adherent			concentrations on lymphocyte activation.
30	Costedoat-Chalumeau et al. 2007[93]	Prospective, one region, France	Biochemical analysis of HCQ and then discussion with doctors about adherence	203	183 (90%)	Concern about side effects or not accepting their disease associated with worse adherence.
31	Mosley-Williams et al., 2002[332]	Prospective interview, one region, USA	Patient-reported failure to take medication on a 5-point scale	122	33 (27.0%)	Depression, poorer memory, concern about side-effects of medication, and the need to provide care to a child or elder associated with poorer adherence
32	Petri et al., 1991[333]	Prospective, one state, USA	Physicians' global assessment of compliance	198	105 (53.0%)	Older age and white associated with better adherence

Table 7.1 summarising the characteristics of the patients included in the studies and the adherence rate, as well as factors associating with adherence. Where a # is shown for the study, it indicates that this is a study dedicated in Lupus Nephritis patients. The other studies are from a general SLE population.

The studies were all observational, mainly prospective (n=27) rather than retrospective (n=5), including 21,854 from across the globe. The definition of adherence was variable, with some including patient questionnaires, self-reported adherence, use of visual scales or various blood biomarkers. The interest in publications across three decades has changed significantly. Only one study reported on adherence in SLE in 1990-2000, increasing to eight studies in 2000-2010 and further increasing to 23 studies in 2010-2020, showing that this has become a more researched area indicating its importance.

There was a wide variety in the size and type of studies- importantly pertaining to the number of participants included in each study, with the smallest one reporting on 32 participants [266] and the largest one being by Feldman et al. [268] reporting on 10,406 patients, and this has already been discussed in Chapter 1.

The overall adherence rate in all the studies combined was 49% (95% CI 41-58%), as shown in Figure 7.2, indicating that non-adherence affected one in two patients.

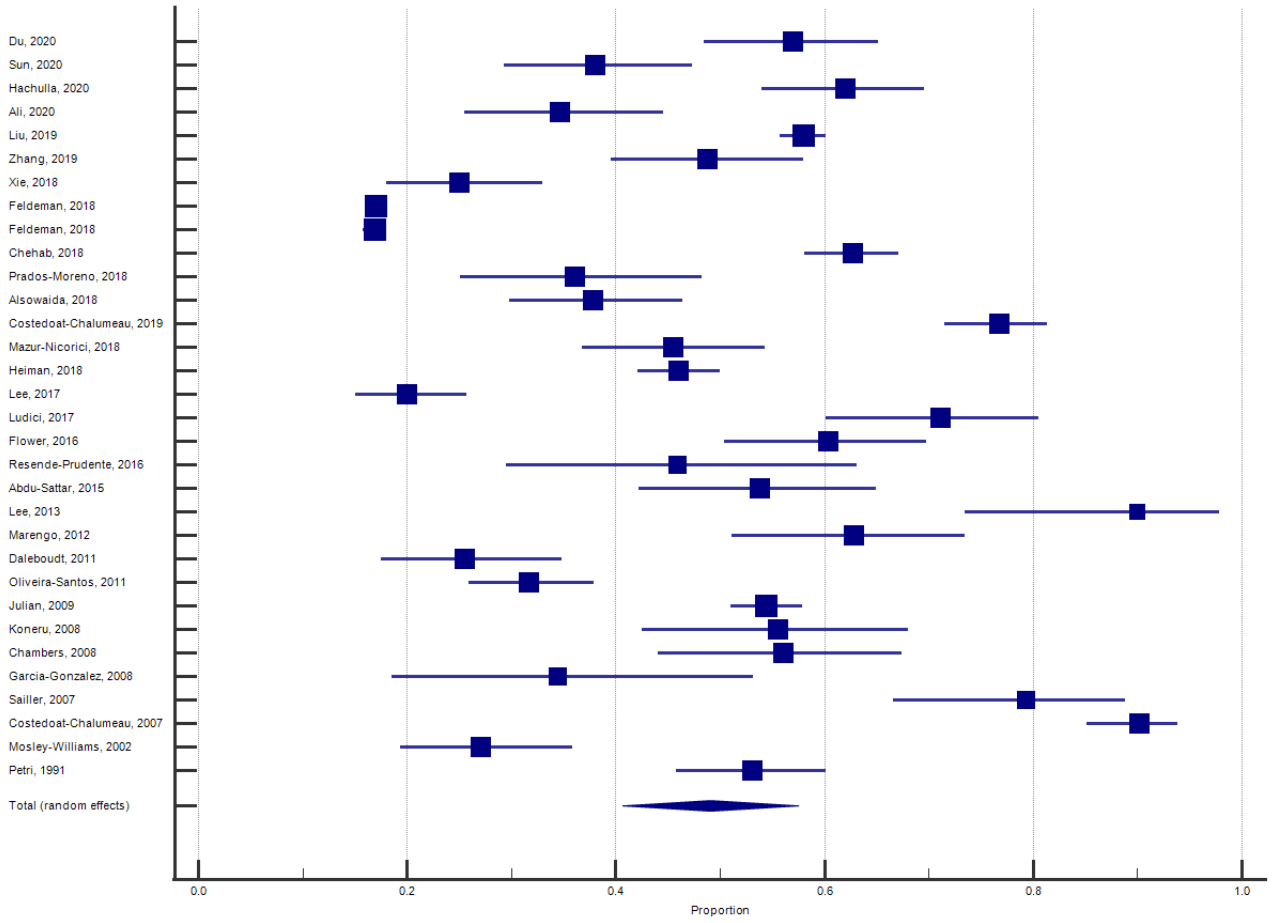

Figure 7.2 Forrest plot of the proportion of adherence using a Random effects model. The overall adherence across studies is estimated at 49% (95% CI 41-58%).

Publication bias was assessed using Funnel plots, as shown in Figure 7.3. This indicated that there might have been some publication bias towards the studies showing higher adherence. Heterogeneity was very high as measured by I^2=99%.

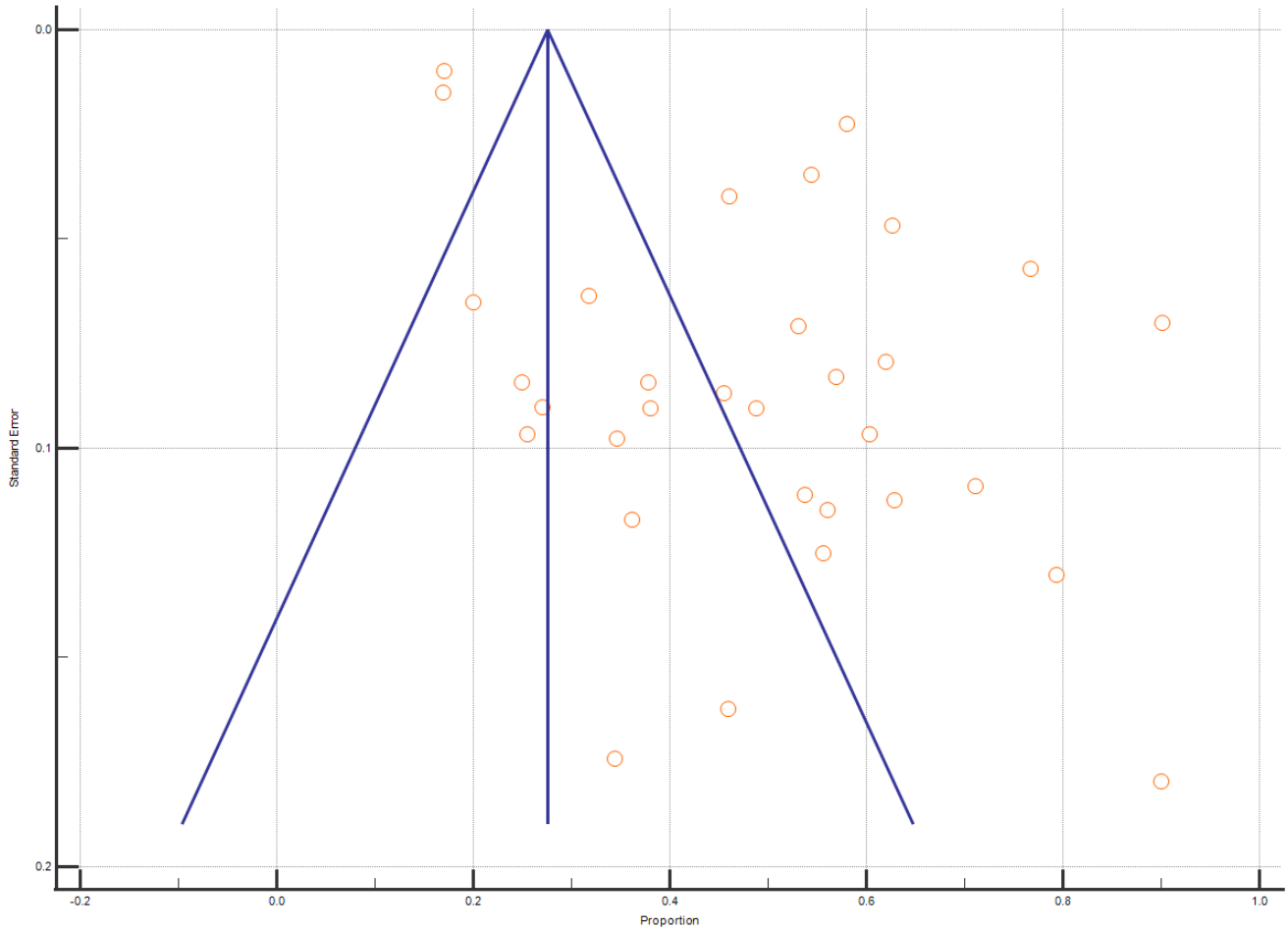

Figure 7.3 Funnel plots for adherence indicating that more studies with higher adherence proportions are being published.

Discussion

This is the first meta-analysis of the proportion of adherence in patients with SLE including all medications used in SLE treatment. I identified 32 eligible studies comprising 21,854 patients across the globe, allowing us to see the true average rate of adherence in lupus patients worldwide. It showed that, on average, one in two patients with SLE is non-adherent and that the degree of adherence can vary depending on the medications the patients take. It nonetheless reinforces the fact

that a large proportion of patients with SLE are poor adherers. Only once this is acknowledged, addressed, and the patients supported to improve their adherence can we expect to see the optimal results from medications.

As described in Chapter 1, page 118, it was interesting to see the common factors associated with worse adherence and some emerging patterns and themes, including age, ethnicity, social and economic status, lower education and coexisting features of depression.

Furthermore, the definition of adherence varied significantly between studies, and this could have also contributed to the range of adherence proportion seen. Some studies used patient questionnaires, asking the patients, visual scales or blood biomarkers. Others also used disease activity scores to triangulate and compare the high level of disease activity related to adherence levels [246].

This work also identified non-intentional causes such as forgetfulness being frequently reported. When it comes to the biochemical assays, HCQ was often used as the focus of adherence, being one of the most commonly used drugs in SLE and one that can be easily measured in the blood and given across a range of severity.

Limitations

Whilst the heterogeneity was high (I^2=99%), this is mainly explained by the different settings in which the studies took place and the different study protocols including the definition of adherence used in each study. Nonetheless, I tried to limit this effect

of heterogeneity using a random effects model allowing the result to give us an indication of the magnitude of adherence in the lupus cohort. This indicates that the studies were very inclusive.

Conclusion

In this meta-analysis of 32 studies and more than 20,000 patients, I confirmed that one in two patients are non-adherent to some medication for their SLE treatment. This result is important, as it would suggest that to expect optimal therapy for our patients, adherence needs to be assessed and the patients supported through their journey to improve their adherence and, ultimately, the management of their condition.

CHAPTER 8

Conclusions and Future Directions

Study 1

In study 1, I investigated the survival of patients with SLE and rTp. This was a long-term follow-up study of 40 such patients from two large institutions spanning four decades. Multiple potential factors that could influence survival were considered, but ultimately, I identified that the only potential modifiable factor to improve survival was reducing the time on dialysis before transplantation. Other factors that did not affect outcome included sex, ethnicity, age of SLE diagnosis or rTp, peritoneal vs haemodialysis and other comorbidities such as diabetes, hypertension or other cardiovascular diseases, dyslipidaemia or APLS. Thus, whilst early on in the transplantation era, patients with SLE were denied rTp, there is now evidence supporting the view that this is beneficial.

My work suggested that each additional month spent on dialysis is associated with worse prognosis (HR 1.013, 95% CI 1.001-1.026, p=0.03), and this adverse effect is more pronounced after 24 months of dialysis. Whilst this finding should be validated in more extensive multicentre studies and help identify the optimal timing of transplantation in LN following ESRF, whether on dialysis or pre-emptively, it does suggest that one should review carefully the SLE patients on the rTp list who have been on dialysis for more than two years and aim to offer rTp as early as possible.

Study 2

In study 2, I investigated the role of non-adherence in patients with SLE who had undergone rTp and whether this could affect graft survival. I screened 361 patients to identify 40 who had undergone rTp. Even in this cohort of patients who had undergone major surgery, poor adherence was seen in 42.5%. Graft rejection was seen in 30% and non-adherent patients had a trend towards higher rates of rejection (HR 4.38, 95% CI 0.73-26.12, p=0.11).

The key novel finding was that patients who had spent more time on dialysis (identified as 25 months on ROC curve analysis) prior to rTp, actually had better adherence than patients spending less than 25 months. This was particularly interesting because this is the first study to document such an effect. A possible explanation for this observed pattern may be that patients who have experienced dialysis for longer wish to reduce the risk of going back to dialysis in the future and thus adhere to medication to achieve that. However, what is important to consider is the fact that from study 1, I showed that longer times on dialysis are associated with worse prognosis. Study 2 highlights, therefore, that if we manage to offer rTp earlier on for patients with minimal or no time on dialysis, it is likely that they may be less adherent.

Identifying patients at risk of non-adherence utilising various methods based on such factors is a key step. More importantly, patients at risk of (such as those with minimal time on dialysis) or with documented concerns about adherence should be closely followed up with regular biochemical testing and a purposeful discussion about the likely consequences of non-adherence in the outpatient clinics may be necessary.

Finally, enhanced education sessions highlighting the importance of immunosuppressive therapy adherence could be considered for all the lupus patients following renal transplantation but also importantly in anticipation of renal transplantation.

Study 3

In study 3, I undertook a prospective cross-sectional study in two major hospitals, investigating patterns of adherence in SLE and vasculitis. A total of 194 individuals with lupus or vasculitis participated, and lupus patients were less adherent than vasculitis patients (48% vs 65% respectively). I identified that increasing age and taking prednisolone associated with better adherence. However, taking hydroxychloroquine associated with worse adherence, and concerns about potential side effects of medication (such as diabetes and mood changes) were also associated with worse adherence on univariate analysis. Not surprisingly, poorer outpatient attendance associated with worse adherence.

Utilising the results of the risk factor multivariable analysis from the study, I built a mathematical model to “predict” adherence in lupus – based on age, prescription of prednisolone and outpatient attendance, which showed good calibration. This is a vital first step in recognising and targeting adherence issues. Using the current electronic records available in each hospital, it is possible to calculate the “risk of adherence” automatically and thus flag this up to the treating team- similar to the CKD risk alert that is seen on patients whose creatinine worsens. Once these patients are highlighted to the team, it is down to the treating team to utilise this

information sensitively and appropriately discussing their barriers to adherence with the patients.

Whilst this study has shown some statistically significant results, an extension of this survey in a non-anonymised way utilising the modelling and identified scores and concordant drug level sampling and clinical assessments may strengthen this research. Larger numbers of responses, ideally through a multicentre study, may be required to have adequate power to make a statistically significant association. Thereafter, external validation of the models can be considered to confirm their availability for clinical use, but this work has laid the foundation for translating the results of a survey to a meaningful "non-adherence score". It can then be utilised to identify patients at risk of poor adherence, thus prompting additional support, improving adherence in the first instance, with prognosis likely to follow in the longer term.

Summary

The studies described in my thesis aimed to identify adverse predictors of survival in patients with rTp due to SLE, the specific role of poor adherence in graft survival following rTp and predictors of adherence. With a central role of adherence in SLE, the three studies together indicate that poor adherence in the SLE cohort is significant, even after a rTp, that survival is dependent on dialysis time but at the same time adherence is dependent on dialysis time. Thus, whilst it might not be possible to change the need for dialysis or time for rTp, working towards identifying the patients at risk of non-adherence and working with them to improve adherence and thus clinical outcomes is feasible.

Reflection on Adherence

The concept of adherence or compliance to medical recommendations has in its core the key principle of allowing an “external authority” to influence and control decisions about one’s body/ health. In my opinion, the cornerstone of the therapeutic alliance between a clinician treating a patient is the trust and confidence that is gained through an effective consultation. Ultimately, this rapport is what may drive an increased chance of inspiring/ convincing a patient to be “adherent” to any advice given, or indeed, any medication prescribed.

Nowadays, only too commonly facts that may have previously been considered undeniable or self-explanatory, are rigorously debated and “attacked” by conspiracy theories. Alternative “facts” and unfounded opinions get regurgitated and enhanced in social and mainstream media echo chambers, leading to them being portrayed as “the hidden truth”. This can be a difficult era to navigate, even for those with a sturdy background in science who are called to convince the public or ‘lay audiences’ of the validity of the scientific method and critical thinking.

Amidst, a pandemic “adherence” to public health advice is desperately needed, not only to protect one's self but also to protect others close to you and the general public. In these exceptional circumstances, it may seem paradoxical, or even an oxymoron, that individual freedom of choice needs to still be preserved and honoured, even more ferociously. Yet “adherence” is demanded, not only to medical therapy on this occasion, but to a series of unusual and strict social distancing and

protection measures in the community, to enable infection regression. This has triggered a number of questions to ponder, which I have deliberated herewith:

How can adherence be improved in our everyday clinical setting?

Is the best way forward making adherence checks mandatory and "policing" the patient as if they lacked the responsibility to take care of themselves? Should the Directly Observed Therapy (extensively utilised for Tuberculosis) be more frequently used? And would "observed adherence" be justified for a non-infectious pathology risking nobody else other than the individual who suffers- in this case from SLE?

On an individual patient level as the “clinician in charge” of their care, should we also be in charge of controlling (in a different way) their adherence by for example measuring drug levels, monitoring with electronic pillboxes or asking for updates from the chemist about cashing of repeat prescriptions?

Or should we just trust that the patients will act with appropriate self-efficacy if they have been given (and understood) the correct information and support for the benefit of their own health?

As clinicians, we are also in charge of the equitability of delivering healthcare on a population basis. Although our focus is always patient-centred, and we have the best interest in mind for each patient we see, it is also our duty to be mindful of the bigger picture of utilising resources and therapeutic options fairly at a public health level.

This broader sense of our clinical responsibility has been put into a sharper perspective for me, having studied in this MD (Res) a cohort of patients with renal transplantation and explored the world of transplantation and its complex ethics; e.g. the responsibility and morality of offering a renal transplant to a non-adherent patient.

My personal view is that the aim should be to empower the patient with appropriate education and boost their self-efficacy, confidence and understanding of the diagnosis and medication in order for them to be willingly taking responsibility for themselves.

However, I have found myself wondering how this balance may shift to a slightly more authoritative and directive pathway when the aim is not just the one person/ patient in front of me but a population. In the context of an infectious disease where under-treatment or poor compliance with advice or vaccination may be detrimental not just to the individual but to the population, can we promote adherence without enforcing it? And can this be realistically achieved, or indeed, should it?

Is it ethical to "police" peoples' behaviour and enforce adherence to restrictive social isolation measures, risking encroaching on their boundaries of free will and personal freedom?

On the other hand, is it moral not to secure adherence to such measures and risk an exponential increase in infection rates with potentially catastrophic consequences in terms of morbidity and mortality?

I propose that a possible and effective way forward is dissecting out any political connotations and sensationalism from the media and promote a scientifically solid message to educate and convince the public (who is now the patient). From the clinician's perspective, in addition to advocating the scientific method and communicating the facts effectively and compassionately, integrity, creativity and resilience are required. The tensioned fine balance between safeguarding the individual's interests and freedom and protecting the public's "greater good" is not always easy to tread and requires great clarity of priorities, professionalism, a sound moral compass and empathy.

Completing this thesis at a time of a global pandemic expanded my direction of thought from the individual to the public. In this thesis, I have considered reasons for poor adherence and discovered the role of and importance of self-efficacy and personal beliefs in medication adherence. I have explored what constructs these behavioural patterns and how the environment plays a role. I have concluded that we, as healthcare professionals, cannot and should not seek to change our patients' personalities, but we can tap into the areas where they need support and help them improve their self-confidence and self-efficacy in taking charge of their own health. And we may have to learn to accept that sometimes, this empowered patient may choose to not adhere to our advice.

Publications

The following publications have been made as part of this thesis and are included in the respective chapters and referenced accordingly.

Peer-reviewed papers

Ntatsaki E, Isenberg D. Risk factors for renal disease in systemic lupus erythematosus and their clinical implications. *Expert Rev Clin Immunol 2015*; 11: 837–848.

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Book Chapter

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Abstracts

Ntatsaki E, Ali B, Hamour S, Isenberg D, Salama AD. AB1242 Comparing adherence to treatment in lupus and vasculitis patients. Annals of the Rheumatic Diseases BMJ; 2018. p. 1717.2-1718. (presented at EULAR, Amsterdam 2018).

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APPENDICES

Appendix 1

Clinical Trial acronyms

CLINCIAL TRIAL NAMES ACRONYMS
ACCESS: Abatacept and Cyclophosphamide Combination Therapy for Lupus.
ADDRESS II: Efficacy and Safety of Atacicept in Systemic Lupus Erythematosus.
ALMS: Aspreva Lupus Management Study.
APRIL-SLE: Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE).
ATLAS: BIIB023 Proof-of-Concept Study in Participants with Lupus Nephritis.
AURORA: Phase 3 Trial of Voclosporin for Lupus Nephritis
BEAT LUPUS: Safety and Efficacy of Belimumab after B cell Depletion Therapy in Systemic Lupus Erythematosus
BELONG: A Study to Evaluate Ocrelizumab in Patients With Nephritis Due to Systemic Lupus Erythematosus.
BLISS LN: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (BLISS-LN)
BLISS: A phase III, randomized, placebo-controlled study of belimumab.
BMS: Bristol-Myers Squibb for Trial Efficacy and Safety Study of Abatacept to Treat Lupus Nephritis.
CALIBRATE: Rituximab and Belimumab for Lupus Nephritis.
ELT: Euro-Lupus Nephritis trial.
EXPLORER: A Study to Evaluate the Safety of Rituximab Retreatment in Subjects With Systemic Lupus Erythematosus
ILLUMINATE: Study to Evaluate the Efficacy and Safety of Subcutaneous LY2127399 in Patients with Systemic Lupus Erythematosus.
LUNAR: Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study.
NOBILITY- Study to Evaluate the Safety and Efficacy of Obinutuzumab Compared With Placebo in Participants With Lupus Nephritis (LN)
PEARL-SC: A Study of the Efficacy, Safety, and Tolerability of A- 623 Administration in Subjects with Systemic Lupus Erythematosus.
RING: Rituximab for Lupus Nephritis with Remission as a Goal.
RITUXILUP: Trial of Rituximab and Mycophenolate Mofetil without Oral Steroids for Lupus Nephritis.
TULIP: Treatment of Uncontrolled Lupus via the Interferon Pathway Anifrolimumab for SLE, TULIP -LN

Appendix 2

Data collection proforma for Studies 1 and 2

DATA COLLECTION PROFORMA

Demographic characteristics
DOB
DOD
Gender
Ethnicity
Clinical Diagnosis and Time to follow-up data
Date of SLE Dx
Age at SLE diagnosis (years)
Date of lupus nephritis diagnosis (biopsy year)
Date of ESRD (dialysis initiation)
Date of renal transplantation (rTp)
Age at renal transplantation (years)
Time between SLE diagnosis and lupus nephritis (months)
Time between lupus nephritis and onset of dialysis (months)
Time on dialysis (months)
Time between diagnosis of lupus nephritis and transplantation (months)
Time of follow up (months) since rTp
Time of follow up (months) since SLE nephritis Dx
Date of last follow up review (if dead is DOD)
Comorbidities
Diabetes
Hypertension
Dyslipidaemia
APLS
Other (specify)
Histological diagnosis at onset of lupus nephritis
Type I to VI
Interstitial nephritis Y/N
Thrombotic microangiopathy Y/N
Number of Biopsies
Change of Type (y/n)
If change of type specify new type
Number of transplantations
Number of transplantations
Date of second transplantations
Date of third transplantation
Time between transplantations
Donor source
Cadaveric donor /Living donor
Related /Non related
HLA identical siblings /parents/other genetically related
Donor age (y)
Cold ischemia time (h) (deceased–donor)
ATG/OKT3/Basiliximab/no induction

Dialysis before renal Tx :
Type of dialysis (HD or CAPD or both)
Viral screen
CMV Y/N
Positive anti-HCV antibodies (patients)
HIV
Other recorded
FINAL Outcome
Graft failure Y/N
Functioning graft
SLE relapse on graft
SLE relapse extra -renal
SLE in remission
Graft failure cause
Rejection
Infection
Delayed graft function Other (specify)
Time to graft failure
Mortality
Alive
Dead
Date of Death
Cause of death
Death related to SLE Y/N

To be measured at following time points

Before rTp (up to 6 months)

At the time of rTp

Post rTp 6 months/12 months/24 months/5 years/10years

Immunologic features at specific time point
Antinuclear antibodies (positive/ negative)
Anti-dsDNA antibodies (value)
Anti-dsDNA antibodies +/-
Anti-phospholipid antibodies +/-
Lupus anticoagulant +/-
Cardiolipin (IgM/IgG/Both/none)
C3 value
Complement (normal/low/high)
ENA status +/-
ENA antibody type
ESR
Albumin value
urinary Protein creatinine ratio
Creatinine value
Clinical assessment
Clinical assessment from letter SLE active or flaring YES/NO
Clinical assessment SLE system?
Clinical assessment form letter renal disease active /flaring YES/NO
Assessment tool used (BILAG/SLEDAI/other/None)
Treatment
MMF/AZA
HCQ
Cyclosporine/tacrolimus/Sirolimus
Rituximab
Cyclophosphamide
Steroids High/Low/none
Compliance concerns documented YES/ NO

Appendix 3

Hard copy questionnaire for Study 3

Survey for treatment adherence in The Lupus (SLE) Nephritis and Vasculitis Clinic

We are conducting this short survey as part of our audit/ service evaluation for all patients attending the Specialist **Lupus /Vasculitis Nephritis** Clinic in our hospital.

We want to see how our patients cope with taking their medication and why some people may find it more difficult than other to take their medication or come to our clinic. We would be very interested in your views and honest feedback.

This survey is anonymised so please answer all questions as truthfully as you can.

This survey should take you no longer than 10 minutes to complete.

If you have any clinical queries as a result of this survey, please raise these and discuss them further with your clinical team or ask to speak to a member of the research/clinical team.

If you have already completed this survey there is no need to complete it again.

Many thanks for taking the time to complete this survey.

Dr Eleana Ntatsaki (Clinical Research Fellow)

Prof David Isenberg (*UCLH Rheumatology Supervisor)*
Prof Alan Salama (*Royal Free Hospital Nephrology Supervisor)*

Information about Consent

By completing the survey and submitting your response you consent to participating in this survey study and acknowledge that once your response is submitted you cannot withdraw it. As this is anonymous, our team cannot identify and remove your response.

You may prefer to complete our survey in its electronic format – please follow this link

https://opinio.ucl.ac.uk/s?s=42000

A. Tell us about you.... Some basic information to help us analyse our data

1. Gender : □ M □ F **2. Age: _____** **3. Country of birth:** □ UK □ Elsewhere

4. Ethnic origin:

□ White □ Asian/Asian British □ Black/ African/Caribbean/Black British

□ Mixed/Multiple ethnic groups □ Other ethnic group_____

5. Marital status:

□ Single □ In a long term relationship □ Married/Civil partnership

□ Separated/Divorced □ Widowed □ Other

6. Religion/ faith :

□ None □ Christian □ Hindu □ Jewish □ Muslim □ Sikh □ Buddhist

□ Any other religion □ Do not want to disclose

7. Which option best describes your highest education qualification?

□ Primary school □ Secondary school (GCSE/ O levels) □ College (A levels)

□ University □ Post graduate degree □ Other

8. Which option best describes your current work status?

□ Full time employment □ Part time employment □ Retired □ Unemployed

□ Student □ Away from work due to illness □ Other

B. About your diagnosis....

1. What is the diagnosis for which you are seen in this Clinic ?(circle and write if other)

Lupus Vasculitis Not sure Other ……..

2. How long have you had this diagnosis?

Weeks Months 1-2 years 2-5 years 5-10 years >10 years Other……

3. Please rate your general well-being level relating to your current disease activity?

Circle a score out of 10 on the lin**e**

(1)_____2_____3_____4_____5_____6_____7_____8_____9____(10)

My disease is **not active at all** My disease is **extremely active**

4. Have you ever participated in a clinical trial for this diagnosis?

Yes No Not sure

5. Which hospital are you attending for your Lupus/ Vasculitis :

Royal Free Hospital UCLH Other……

6. As far as you know, which statement best describes your kidney function?

(Please tick to select all that apply to you)

□ My kidney function is not affected by my disease

□ My kidney function is mildly affected by my disease

□ My kidney function is moderately or severely affected by my disease

□ I have had a kidney transplant

□ I am on dialysis/renal replacement therapy

□ I am not sure

C. About your medication…

1. Who is responsible for giving you your medication? (tick)

☐ I take them myself ☐ Someone else (who?) ……

2. How many tablets do you take daily? (total number of ALL tablets you take **)**

_____

3. How many different types of prescribed medications do you take daily?

_____

(e.g you if you take a type of medication for your blood pressure, that requires you to take a dose of two tables twice daily, it still counts as 1 type of medication (for question 3) but it is 4 tablets in total (for question 2)

3. How many of those types of medication are for your Lupus/Vasculitis?

_____

5. Which of the following medications for immunosuppression do you take for you Lupus? (You can tick more than one option)

☐ **Prednisolone** (Steroid tablet)
☐ **Hydroxychloroquine** *(Plaquenil®)*
☐ **Azathioprine** *(Imuran®)*
☐ **Mycophenolate Mofetil (MMF)** *(Cellcept®/ Myfortic®)*
☐ Methotrexate
☐ Cyclosporin *(Neoral®)*
☐ Sirolimus *(Rapamune®)*
☐ Tacrolimus *(Prograf® /Advagraf®)*
☐ I am not sure
☐ None of these

6. Which of these potential side-effects relating to steroids are you worried most about?
(Please answer only if you are taking/or have ever taken prednisolone/steroids)

☐ Weight gain ☐ Sleeping disturbance ☐ Mood problems ☐ Skin changes
☐ Diabetes ☐ Dependency ☐ Stomach ulcers ☐ High Blood pressure
☐ Eye problems ☐ Osteoporosis (thinning of the bones) Other_____

7. If you are taking any of the above medications, which statement best describes how you manage to take these tablets?

☐ I always take them as prescribed
☐ I miss a dose once or twice a month
☐ I miss a dose once or twice a week
☐ I take them less than half of the time
☐ I rarely take them
☐ I never take them

8. Have you ever had intravenous medications (via a drip) administered to you for your Lupus/Vasculitis? (circle) Yes No Not sure

9. Is there a specific medication which you particularly dislike taking?

☐ No problems with any medication ☐ Not applicable to me

Yes ☐

I dislike taking……..because……

D. About taking your medication…

1. How have you managed with taking your Lupus /Vasculitis medication so far?

Circle a score out of 10 on the line

I never take (1)_____2_____3_____4_____5_____6_____7_____8_____9_____(10) I **always take** my medications as prescribed my medications as prescribed

2. Over time have you become better or worse at taking all your tablets regularly, since you were first diagnosed? (Circle)

Much better Better No change Worse Much worse

If there has been a change, please tell us why do you think that is the case?

3. How often have you had to stop or delay your treatment because of practical difficulties in obtaining your tablets? (Circle)

Never Rarely Sometimes Frequently Almost always

4. How do you usually pay for your medications? (Tick)

□ I do not have to pay for my medications
□ I have a pre-payment prescription certificate
□ I pay for my own prescriptions
□ Someone else pays for my medication
□ Other ……..

5. If you have to pay for your prescriptions have you ever stopped treatment because you couldn't afford it? (Circle) YES NO

6. About taking your medication (Circle)

Do you ever forget to take your medication?	YES	NO
Are you careless at times about taking your medication?	YES	NO
When you feel better do you sometimes stop taking your medicine?	YES	NO
Sometimes if you feel worse when you take medicine, do you stop taking it?	YES	NO

E. Getting to the clinic....

7. Since you have been diagnosed, how many of your clinic appointments have you been able to attend? (Circle)

A few	Some	Most	Almost all	All
(<25%)	(<50%)	(50-75%)	(75-99%)	(100%)

8. Have any of the following kept you from coming to your specialist kidney clinic appointments at the hospital? (You can tick more than one if necessary)

□ Getting time off work or losing pay
□ The cost of travel here
□ Caring for children or other dependants
□ The time taken to travel here
□ Dislike of hospitals
□ Keeping track of hospital appointments
□ Problems with arranging hospital transport
□ Not applicable to me
□ Other reasons such as…….

F. Helping us understand any difficulties you may have with taking your medication…

To help us understand any difficulties that patients may have with following their treatment plan, please rate your level of agreement with the following statements.

- **What are the main reasons why you might have missed doses or tablets?**

1=Strongly agree 2= Agree 3=Disagree 4=Strongly disagree

The tablets/medication	**1**	**2**	**3**	**4**
You didn't remember to take them	□	□	□	□
You find it hard to swallow tablets	□	□	□	□
You don't like the taste/smell of them	□	□	□	□
You wanted to see if taking fewer tablets would be ok	□	□	□	□
You just don't like taking tablets	□	□	□	□
You didn't want to be reminded of your illness	□	□	□	□
Taking tablets regularly interferes with your lifestyle	□	□	□	□

Your health beliefs	**1**	**2**	**3**	**4**
You took herbal or alternative medicine instead	□	□	□	□
You put your faith or trust in your religion instead	□	□	□	□
You changed your diet so felt you needed less drugs	□	□	□	□
You felt really well and thought you didn't need them	□	□	□	□
You felt disappointed because they were not working	□	□	□	□
You didn't understand why you needed them	□	□	□	□
You worried they might be addictive	□	□	□	□

The side effects	**1**	**2**	**3**	**4**
You wanted to avoid side effects like nausea or sickness	□	□	□	□
You were worried about weight gain or changes in your appearance in your face or body	□	□	□	□
You thought the lupus/vasculitis medication might be bad or toxic for your body	□	□	□	□
You felt your medication was causing you symptoms of tiredness, fatigue or lack of energy	□	□	□	□
You experienced mood problems like feeling low or anxious	□	□	□	□

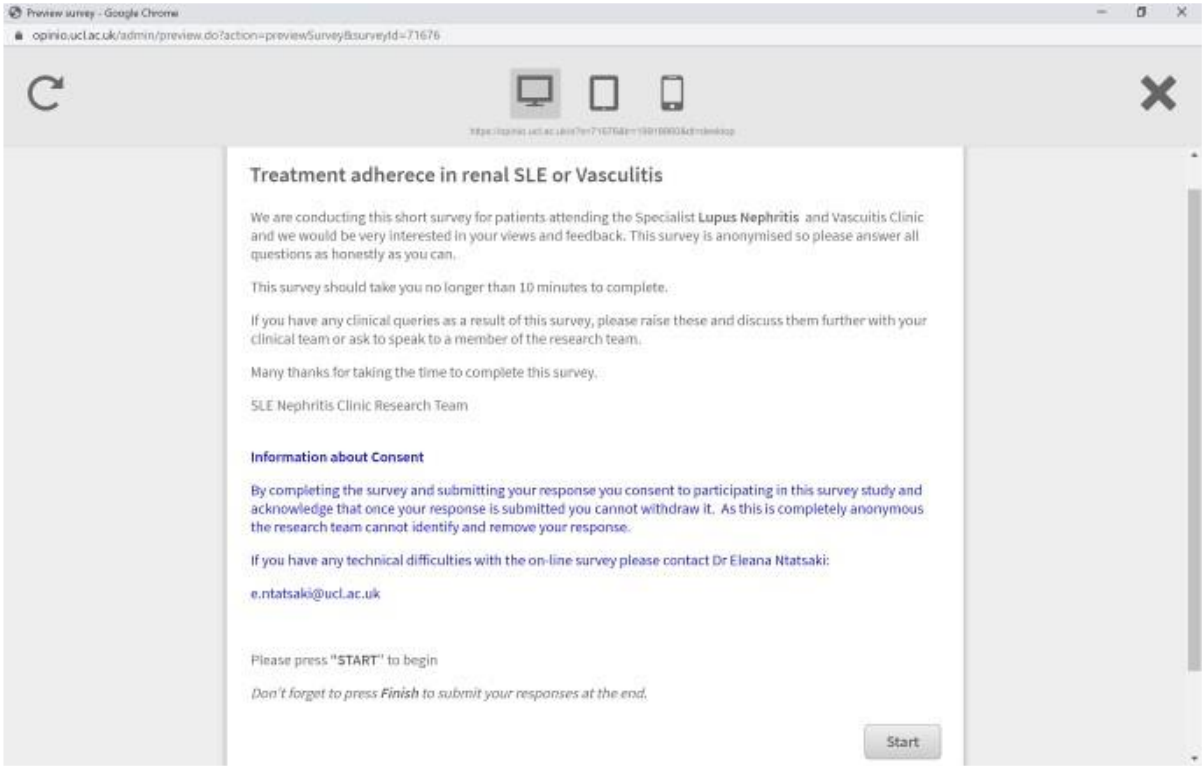
- **How strongly do you agree with the following statements?**
  (Think about your Lupus/Vasculitis medication mainly)

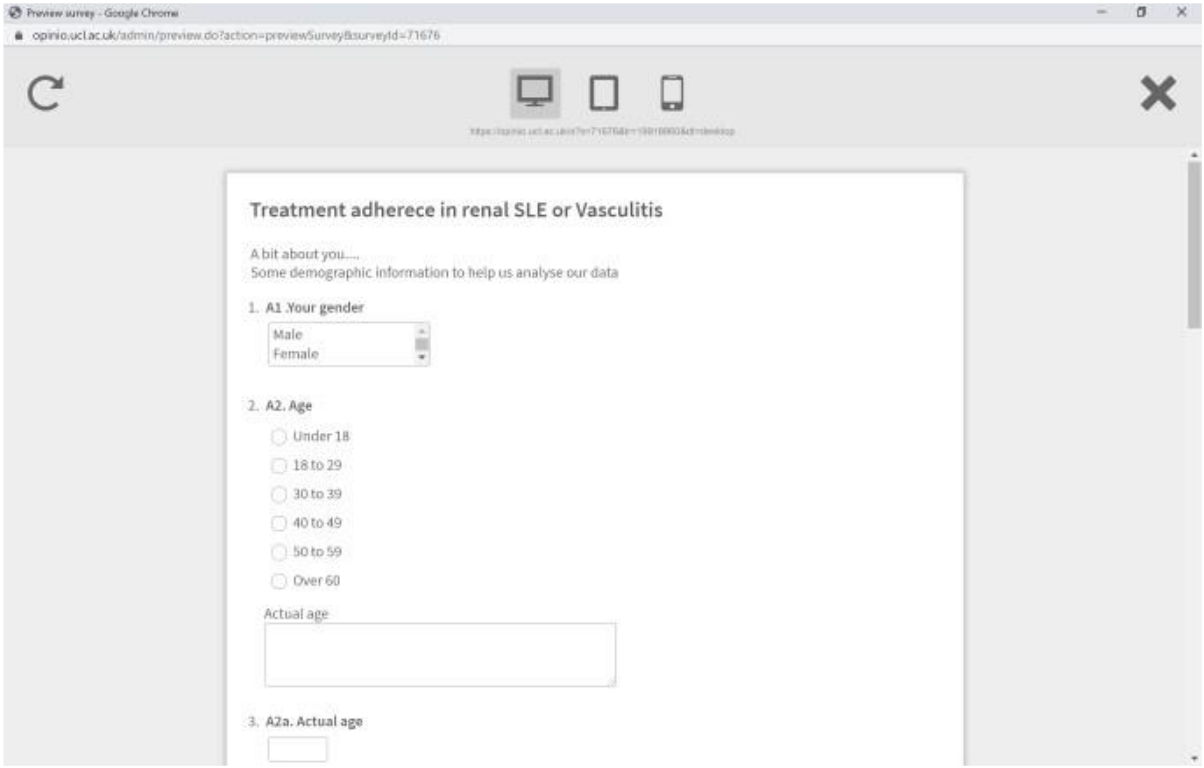
1=Strongly agree 2= Agree 3=Disagree 4=Strongly disagree

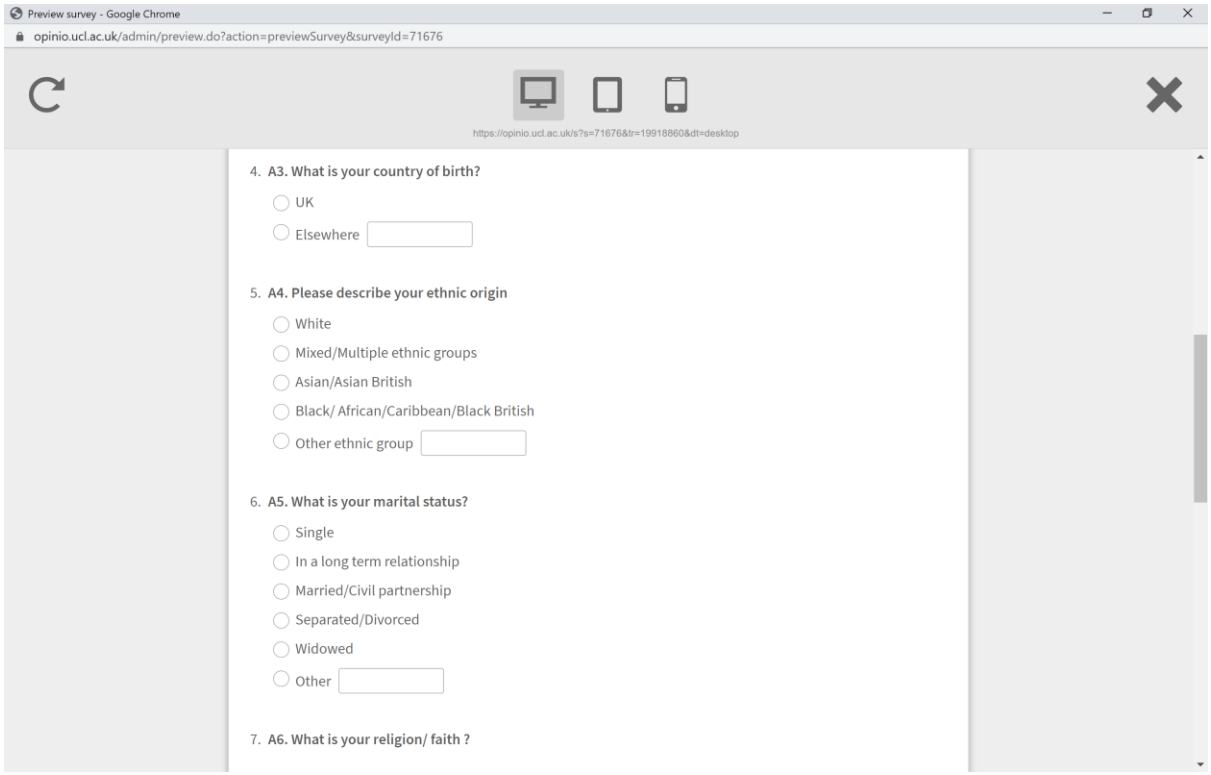
If I feel well, I'm less likely to take my medication	1	2	3	4
I'm more likely to take my medication if it's only once a day	1	2	3	4
Lupus/Vasculitis is a long term (chronic) illness which has no cure	1	2	3	4
I understand why my medication has been prescribed	1	2	3	4
I know what each of the medication I take is for	1	2	3	4
I prefer to have my medication given via a drip/injection instead of tablets	1	2	3	4
I am confident to take the course of treatment that's been offered to me	1	2	3	4
I have had the chance to discuss my drugs with my specialist team	1	2	3	4
I was involved in all decisions regarding my medication	1	2	3	4

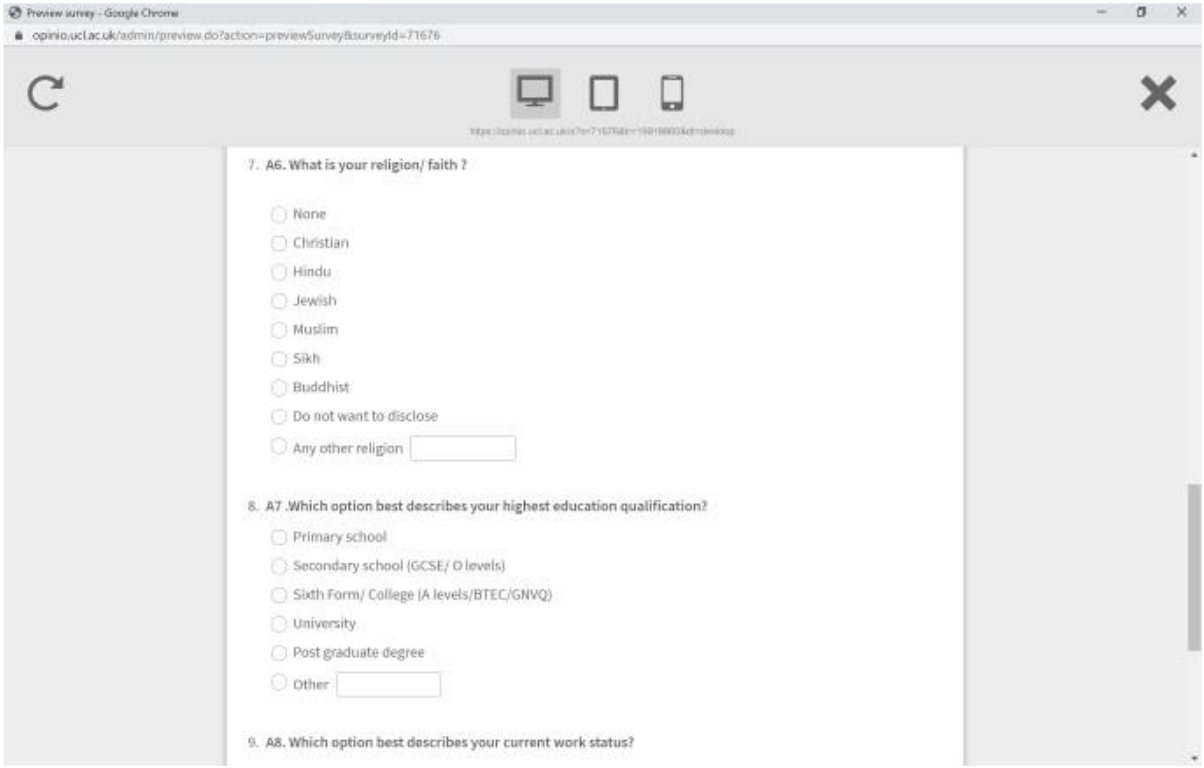
Appendix 4

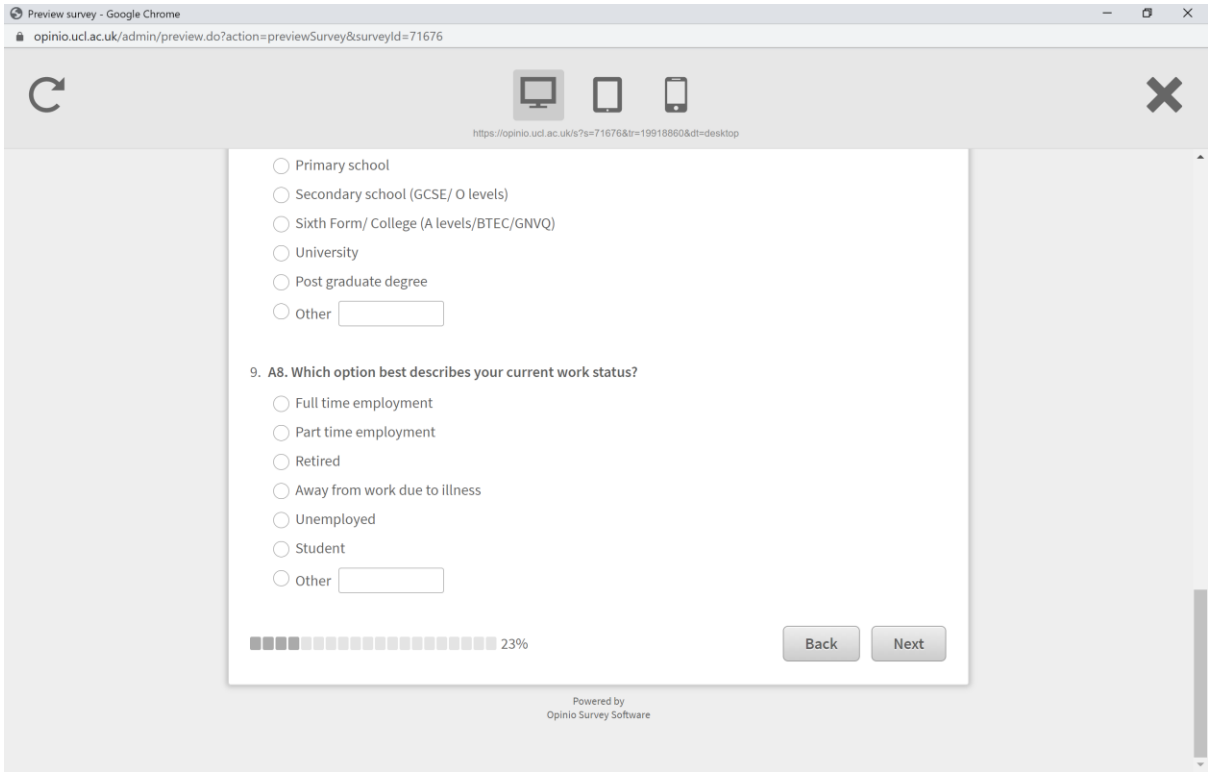
Online questionnaire with screenshots from UCL Opinio for Study 3

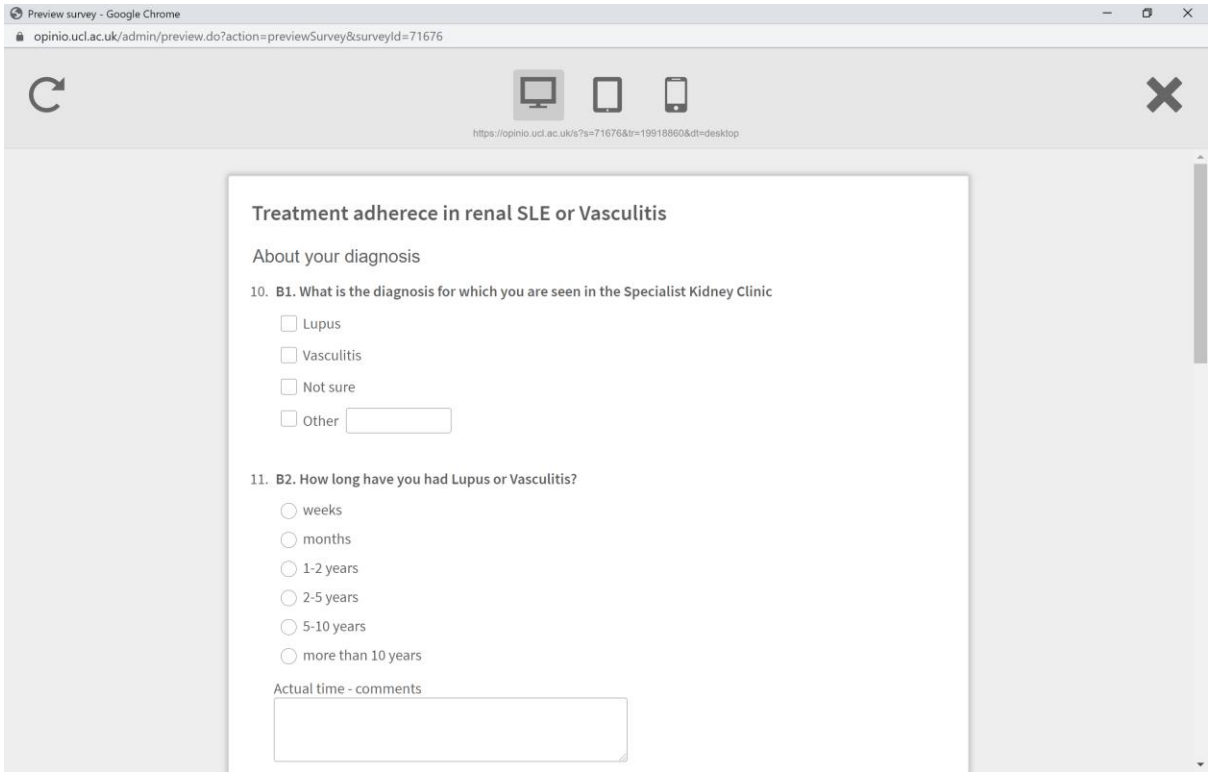

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
We are conducting this short survey for patients attending the Specialist Lupus Nephritis and Vasculitis Clinic and we would be very interested in your views and feedback. This survey is anonymised so please answer all questions as honestly as you can.
This survey should take you no longer than 10 minutes to complete.
If you have any clinical queries as a result of this survey, please raise these and discuss them further with your clinical team or ask to speak to a member of the research team.
Many thanks for taking the time to complete this survey.
SLE Nephritis Clinic Research Team
Information about Consent
By completing the survey and submitting your response you consent to participating in this survey study and acknowledge that once your response is submitted you cannot withdraw it. As this is completely anonymous the research team cannot identify and remove your response.
If you have any technical difficulties with the on-line survey please contact Dr Eleana Ntatsaki:
e.ntatsaki@ucl.ac.uk
Please press "START" to begin
Don't forget to press Finish to submit your responses at the end.
Start

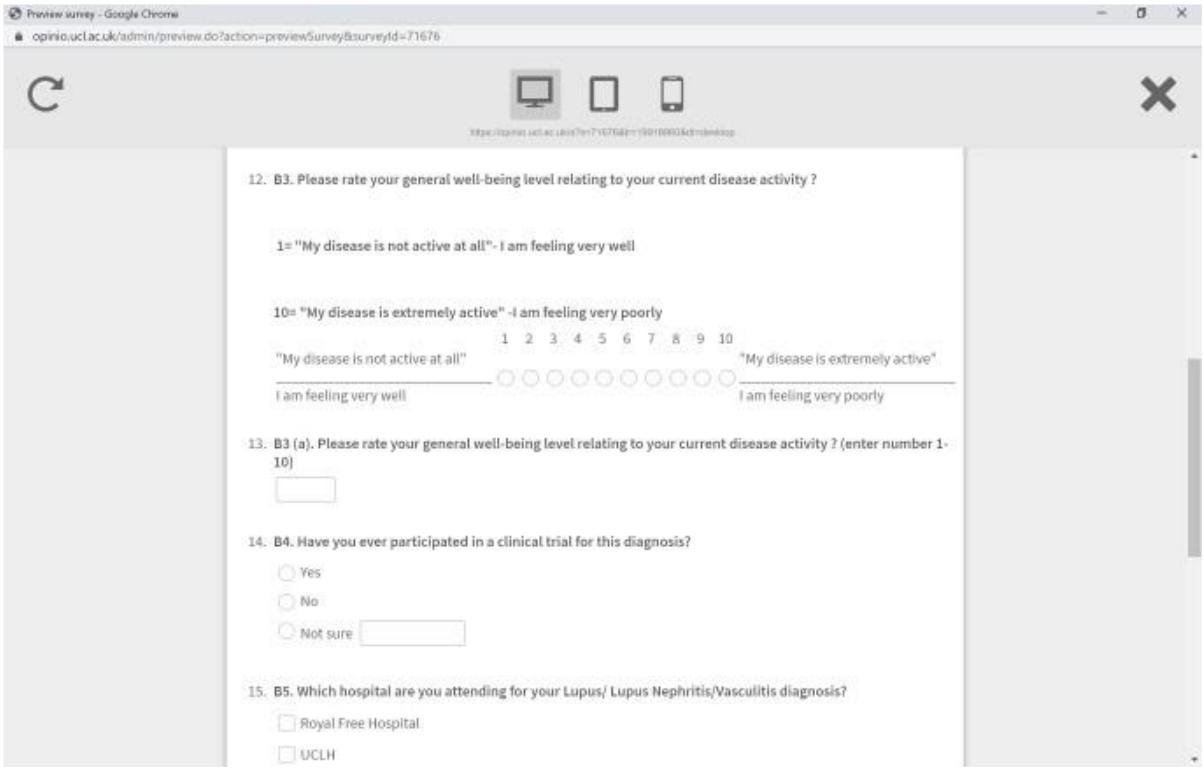

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
A bit about you.....
Some demographic information to help us analyse our data
1. A1 .Your gender
Male
Female
2. A2. Age
Under 18
18 to 29
30 to 39
40 to 49
50 to 59
Over 60
Actual age
3. A2a. Actual age

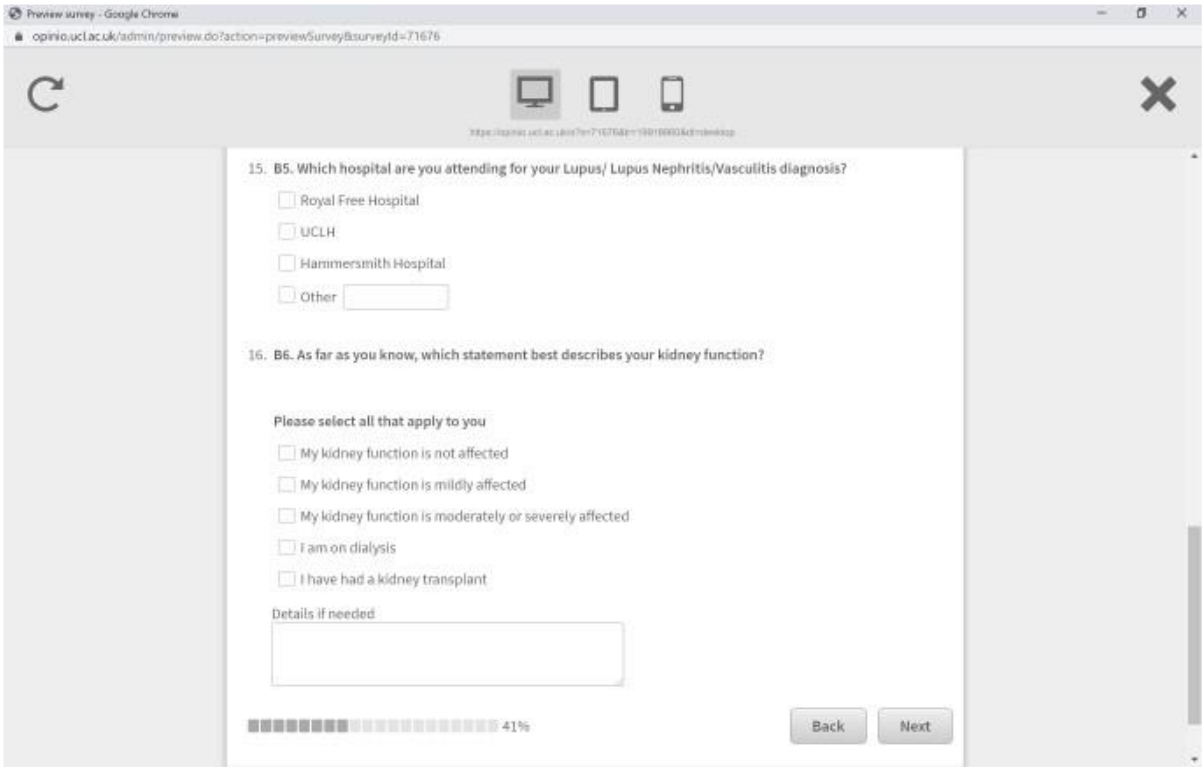

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
4. A3. What is your country of birth?
UK
Elsewhere
5. A4. Please describe your ethnic origin
White
Mixed/Multiple ethnic groups
Asian/Asian British
Black/ African/Caribbean/Black British
Other ethnic group
6. A5. What is your marital status?
Single
In a long term relationship
Married/Civil partnership
Separated/Divorced
Widowed
Other
7. A6. What is your religion/ faith ?

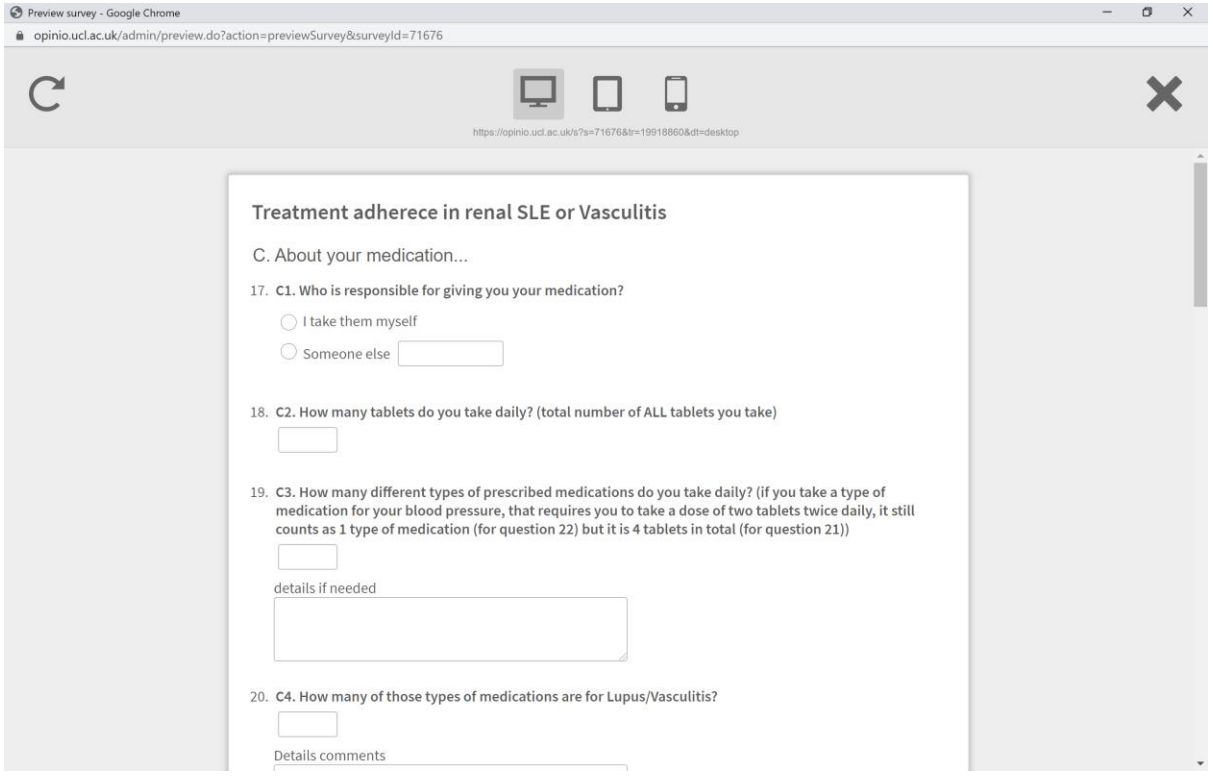

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
7. A6. What is your religion/ faith ?
None
Christian
Hindu
Jewish
Muslim
Sikh
Buddhist
Do not want to disclose
Any other religion
8. A7 .Which option best describes your highest education qualification?
Primary school
Secondary school (GCSE/ O levels)
Sixth Form/ College (A levels/BTEC/GNVQ)
University
Post graduate degree
Other
9. A8. Which option best describes your current work status?

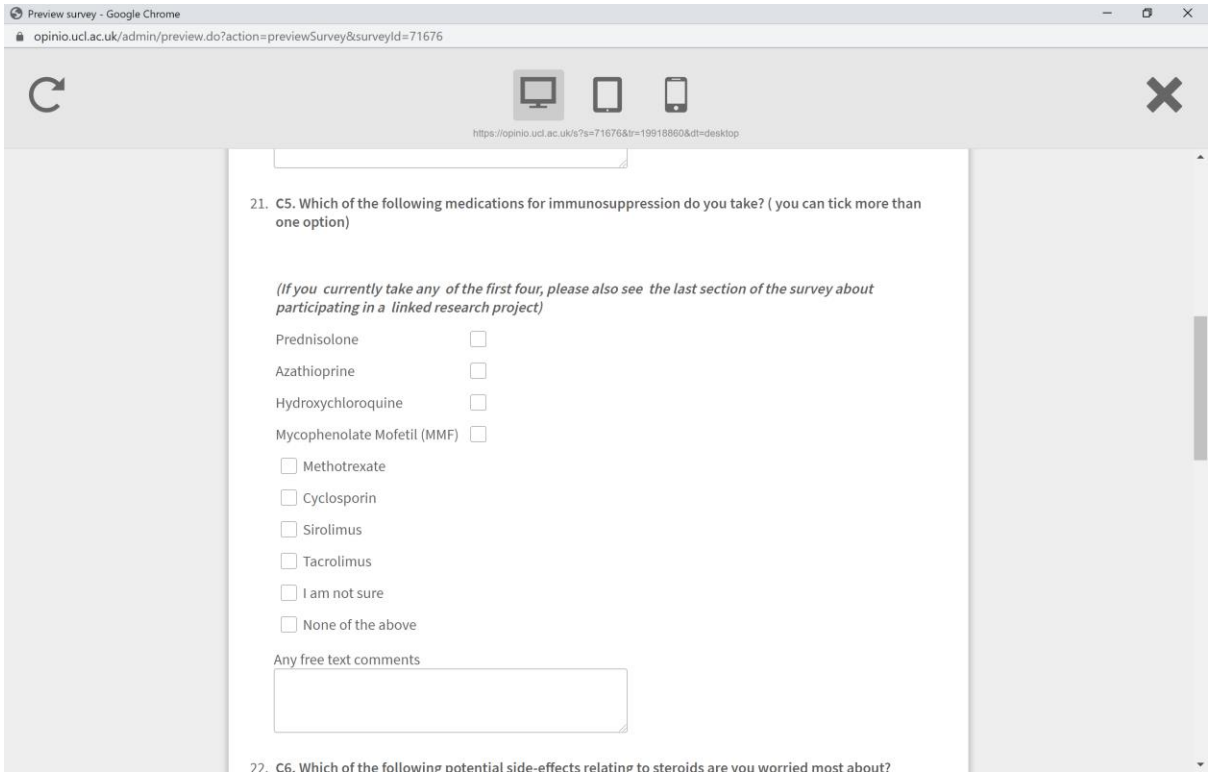

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
Primary school
Secondary school (GCSE/ O levels)
Sixth Form/ College (A levels/BTEC/GNVQ)
University
Post graduate degree
Other
9. A8. Which option best describes your current work status?
Full time employment
Part time employment
Retired
Away from work due to illness
Unemployed
Student
Other
23%
Back
Next
Powered by
Opinio Survey Software


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&r=19918860&dt=desktop
Treatment adherece in renal SLE or Vasculitis
About your diagnosis
10. B1. What is the diagnosis for which you are seen in the Specialist Kidney Clinic
Lupus
Vasculitis
Not sure
Other
11. B2. How long have you had Lupus or Vasculitis?
weeks
months
1-2 years
2-5 years
5-10 years
more than 10 years
Actual time - comments


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
12. B3. Please rate your general well-being level relating to your current disease activity ?
1= "My disease is not active at all"- I am feeling very well
10= "My disease is extremely active" -I am feeling very poorly
1 2 3 4 5 6 7 8 9 10
"My disease is not active at all"
"My disease is extremely active"
I am feeling very well
I am feeling very poorly
13. B3 (a). Please rate your general well-being level relating to your current disease activity ? (enter number 1-10)
14. B4. Have you ever participated in a clinical trial for this diagnosis?
Yes
No
Not sure
15. B5. Which hospital are you attending for your Lupus/ Lupus Nephritis/Vasculitis diagnosis?
Royal Free Hospital
UCLH


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
15. B5. Which hospital are you attending for your Lupus/ Lupus Nephritis/Vasculitis diagnosis?
Royal Free Hospital
UCLH
Hammersmith Hospital
Other
16. B6. As far as you know, which statement best describes your kidney function?
Please select all that apply to you
My kidney function is not affected
My kidney function is mildly affected
My kidney function is moderately or severely affected
I am on dialysis
I have had a kidney transplant
Details if needed
41%
Back
Next


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&r=19918860&dt=desktop
Treatment adherece in renal SLE or Vasculitis
C. About your medication...
17. C1. Who is responsible for giving you your medication?
I take them myself
Someone else
18. C2. How many tablets do you take daily? (total number of ALL tablets you take)
19. C3. How many different types of prescribed medications do you take daily? (if you take a type of medication for your blood pressure, that requires you to take a dose of two tablets twice daily, it still counts as 1 type of medication (for question 22) but it is 4 tablets in total (for question 21))
details if needed
20. C4. How many of those types of medications are for Lupus/Vasculitis?
Details comments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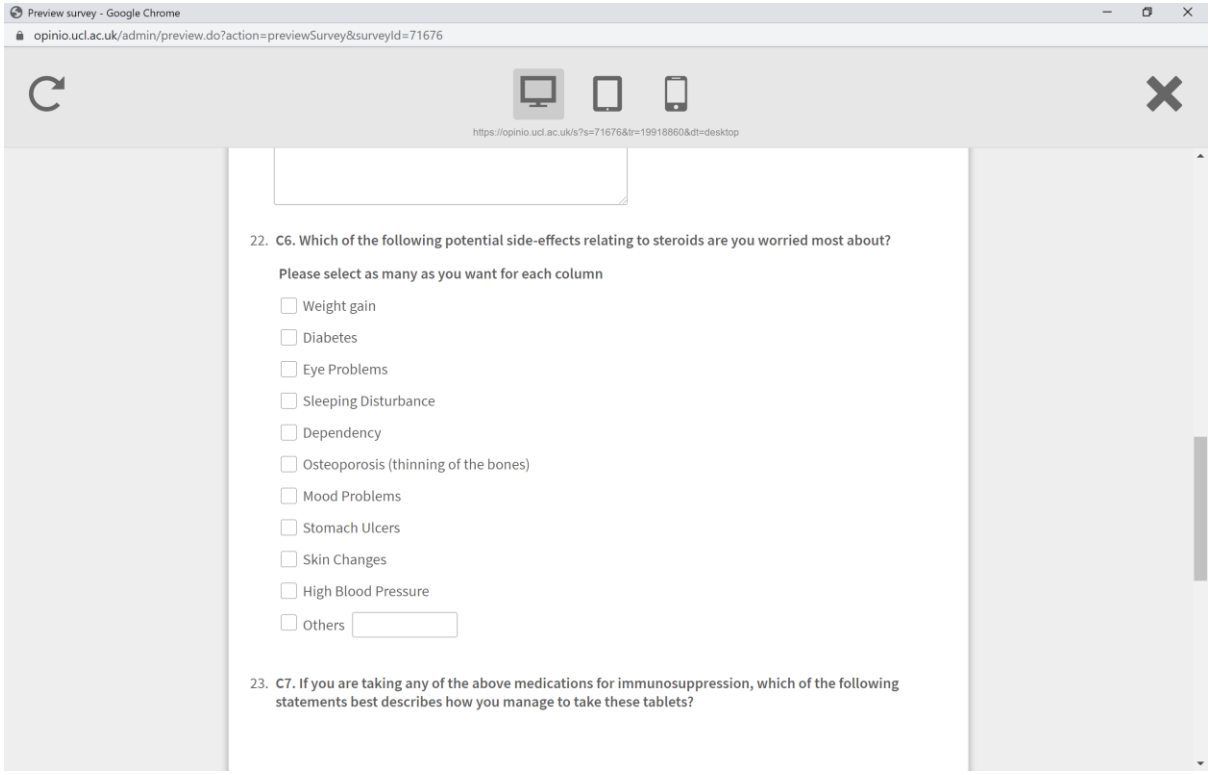
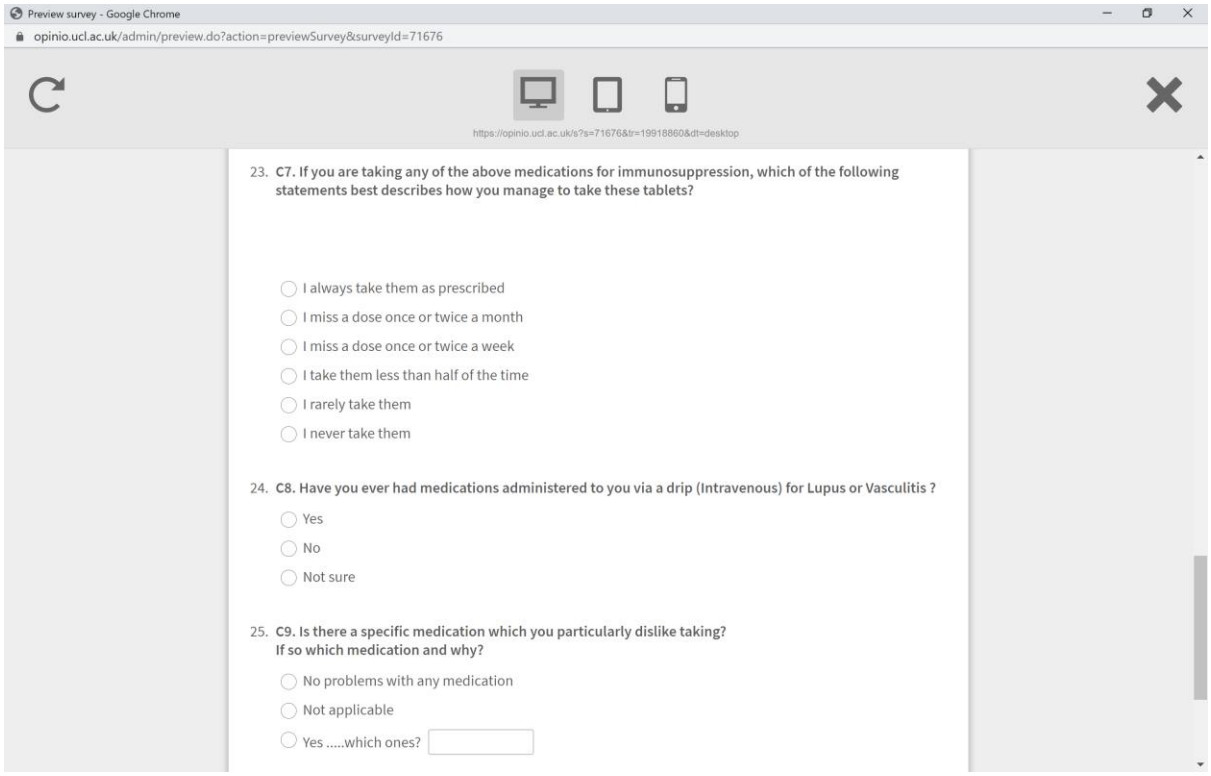
21. C5. Which of the following medications for immunosuppression do you take? (you can tick more than one option)
(If you currently take any of the first four, please also see the last section of the survey about participating in a linked research project)
Prednisolone
Azathioprine
Hydroxychloroquine
Mycophenolate Mofetil (MMF)
Methotrexate
Cyclosporin
Sirolimus
Tacrolimus
I am not sure
None of the above
Any free text comments
22. C6. Which of the following potential side-effects relating to steroids are you worried most about?


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
22. C6. Which of the following potential side-effects relating to steroids are you worried most about?
Please select as many as you want for each column
Weight gain
Diabetes
Eye Problems
Sleeping Disturbance
Dependency
Osteoporosis (thinning of the bones)
Mood Problems
Stomach Ulcers
Skin Changes
High Blood Pressure
Others
23. C7. If you are taking any of the above medications for immunosuppression, which of the following statements best describes how you manage to take these tablets?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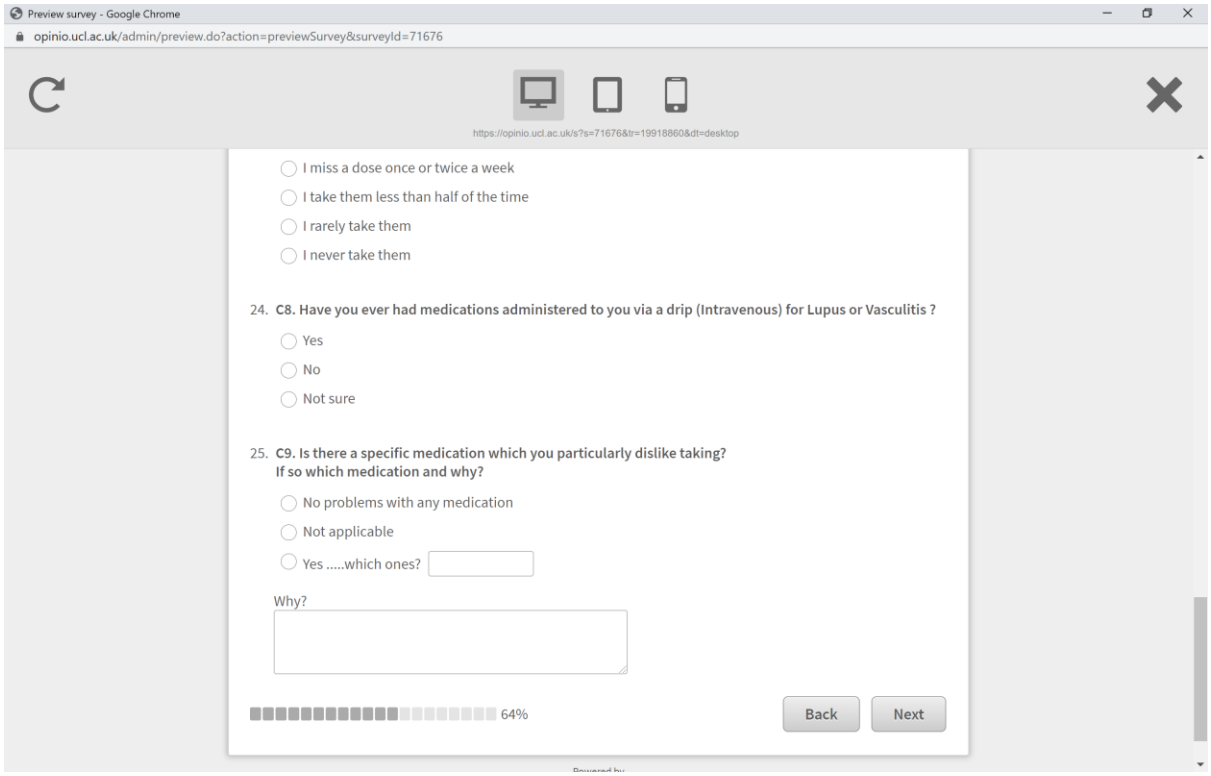
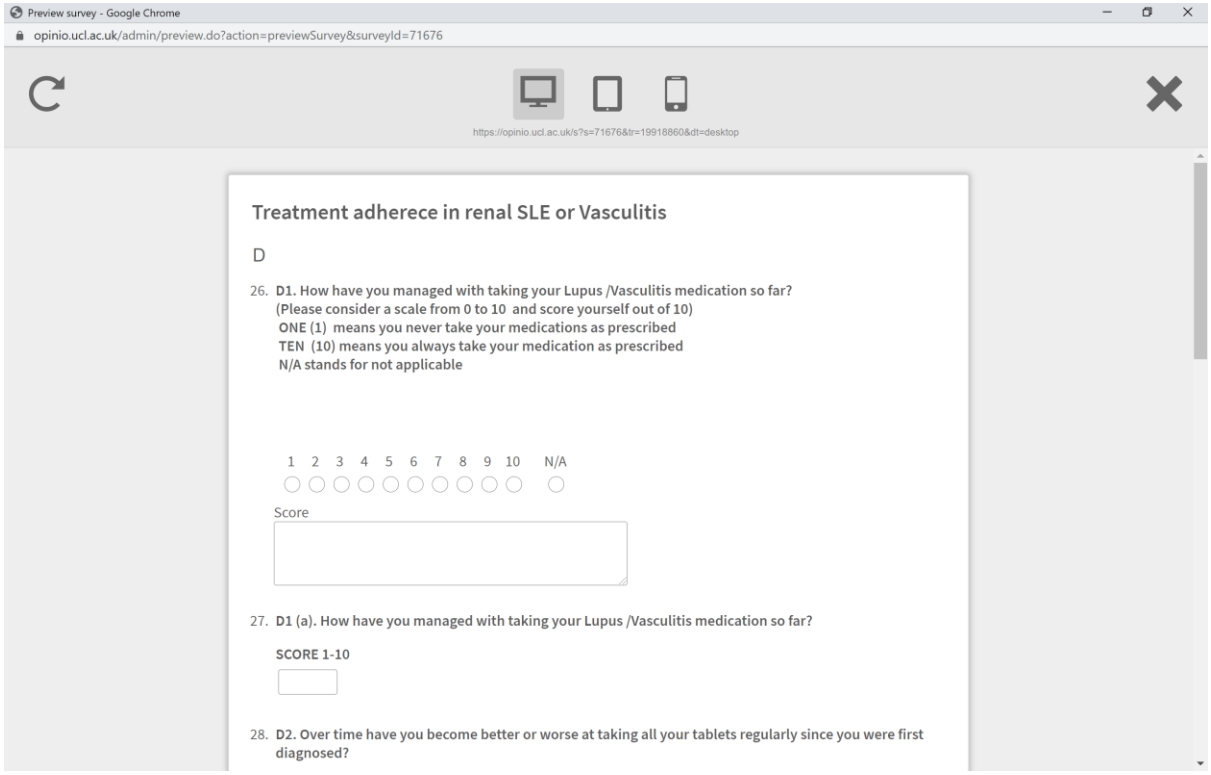
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
23. C7. If you are taking any of the above medications for immunosuppression, which of the following statements best describes how you manage to take these tablets?
I always take them as prescribed
I miss a dose once or twice a month
I miss a dose once or twice a week
I take them less than half of the time
I rarely take them
I never take them
24. C8. Have you ever had medications administered to you via a drip (Intravenous) for Lupus or Vasculitis ?
Yes
No
Not sure
25. C9. Is there a specific medication which you particularly dislike taking? If so which medication and why?
No problems with any medication
Not applicable
Yes .....which ones?


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
I miss a dose once or twice a week
I take them less than half of the time
I rarely take them
I never take them
24. C8. Have you ever had medications administered to you via a drip (Intravenous) for Lupus or Vasculitis ?
Yes
No
Not sure
25. C9. Is there a specific medication which you particularly dislike taking?
If so which medication and why?
No problems with any medication
Not applicable
Yes .....which ones?
Why?
64%
Back
Next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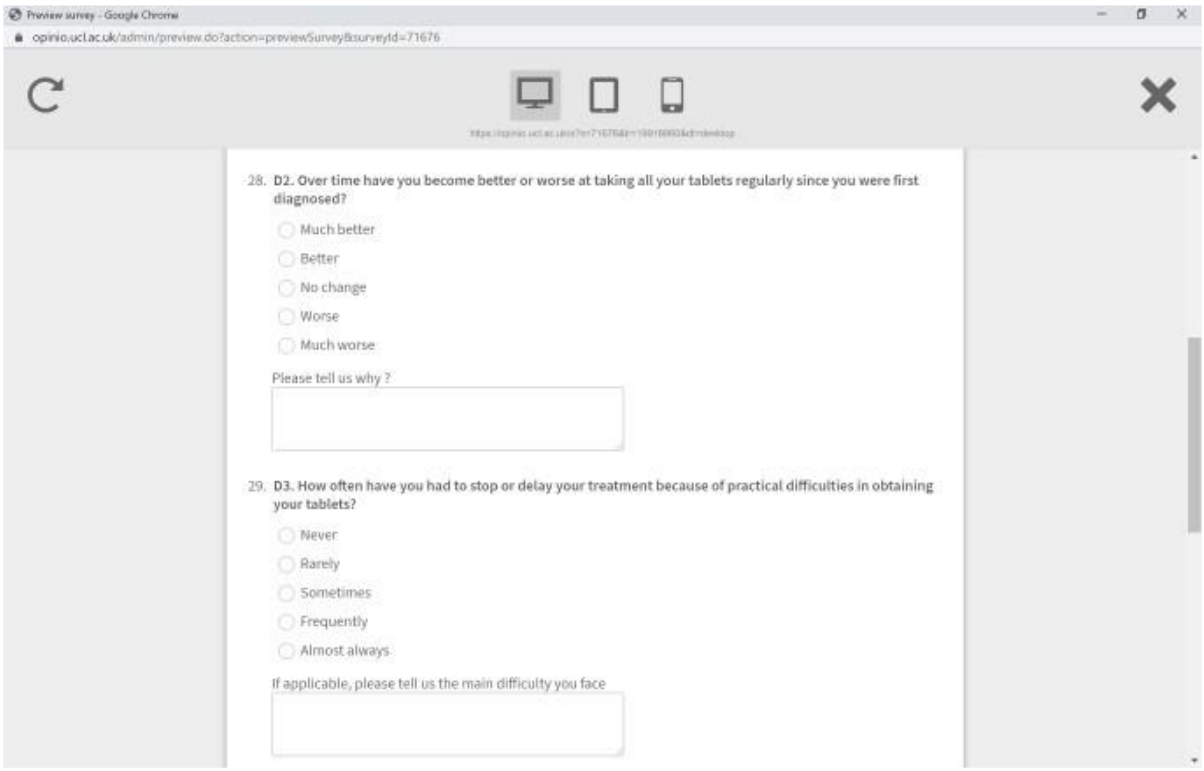
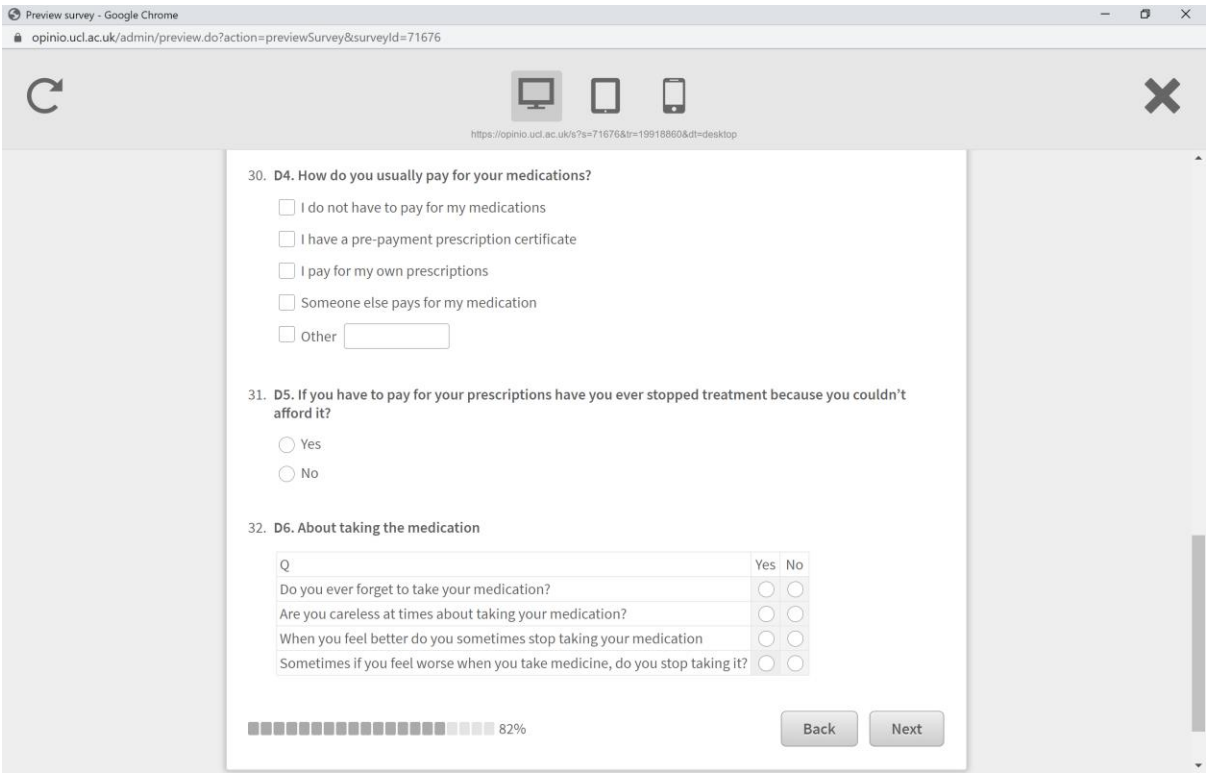
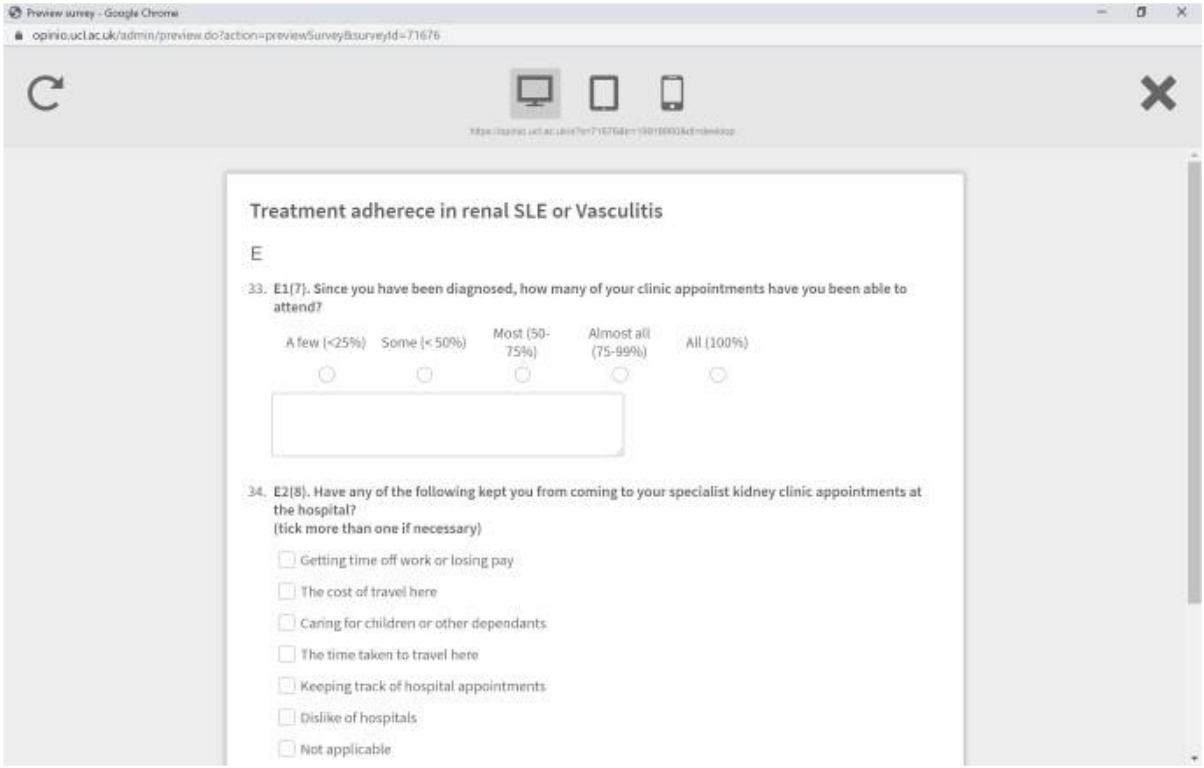
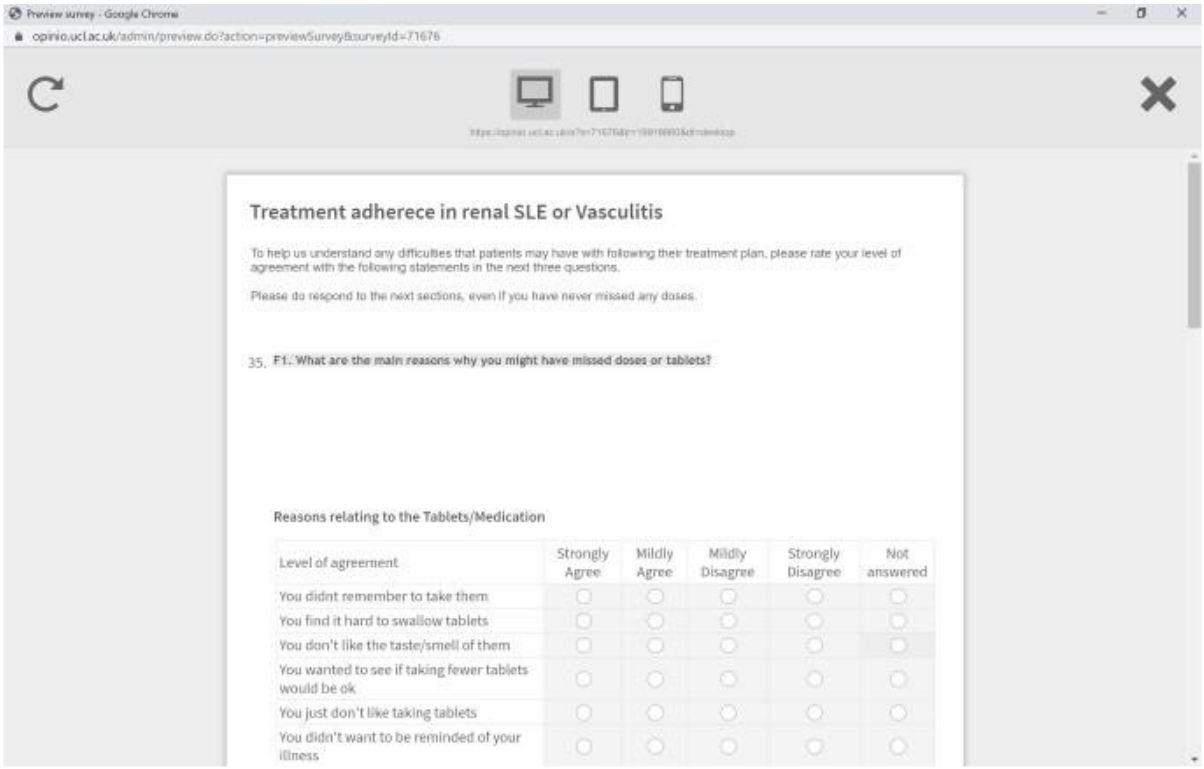
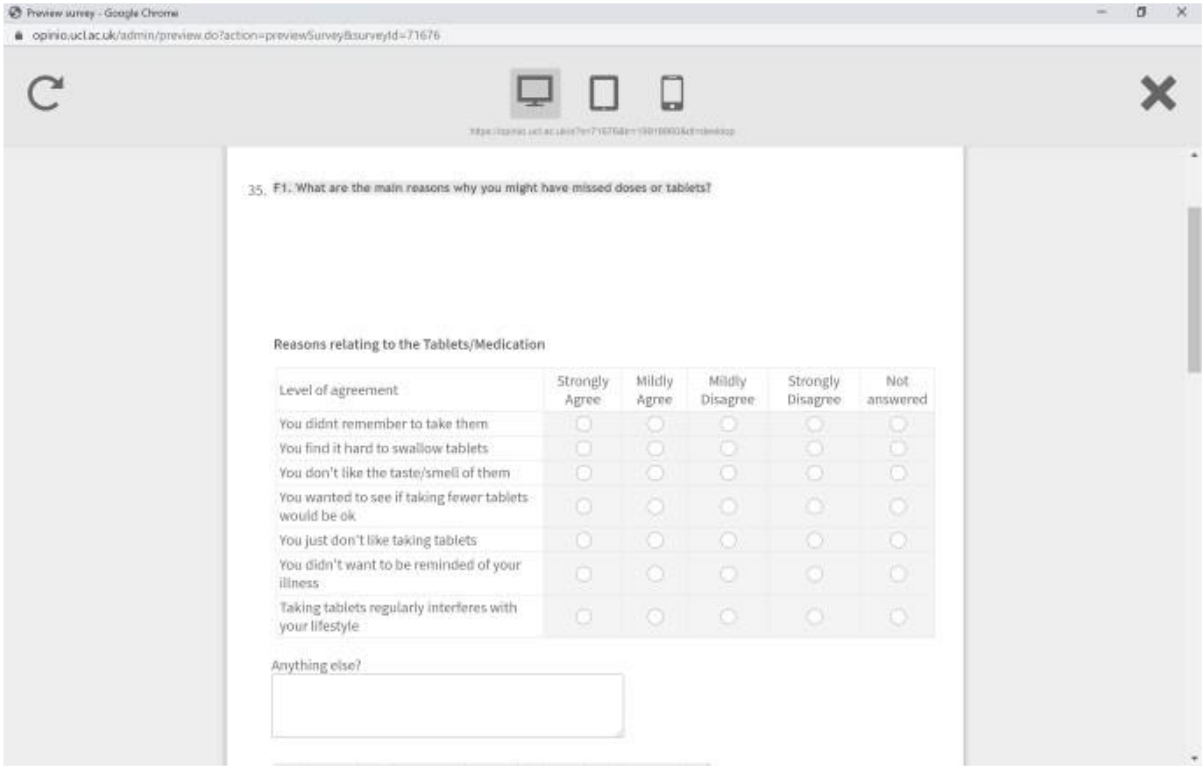
Treatment adherece in renal SLE or Vasculitis
D
26. D1. How have you managed with taking your Lupus /Vasculitis medication so far?
(Please consider a scale from 0 to 10 and score yourself out of 10)
ONE (1) means you never take your medications as prescribed
TEN (10) means you always take your medication as prescribed
N/A stands for not applicable
1 2 3 4 5 6 7 8 9 10 N/A
Score
27. D1 (a). How have you managed with taking your Lupus /Vasculitis medication so far?
SCORE 1-10
28. D2. Over time have you become better or worse at taking all your tablets regularly since you were first diagnosed?

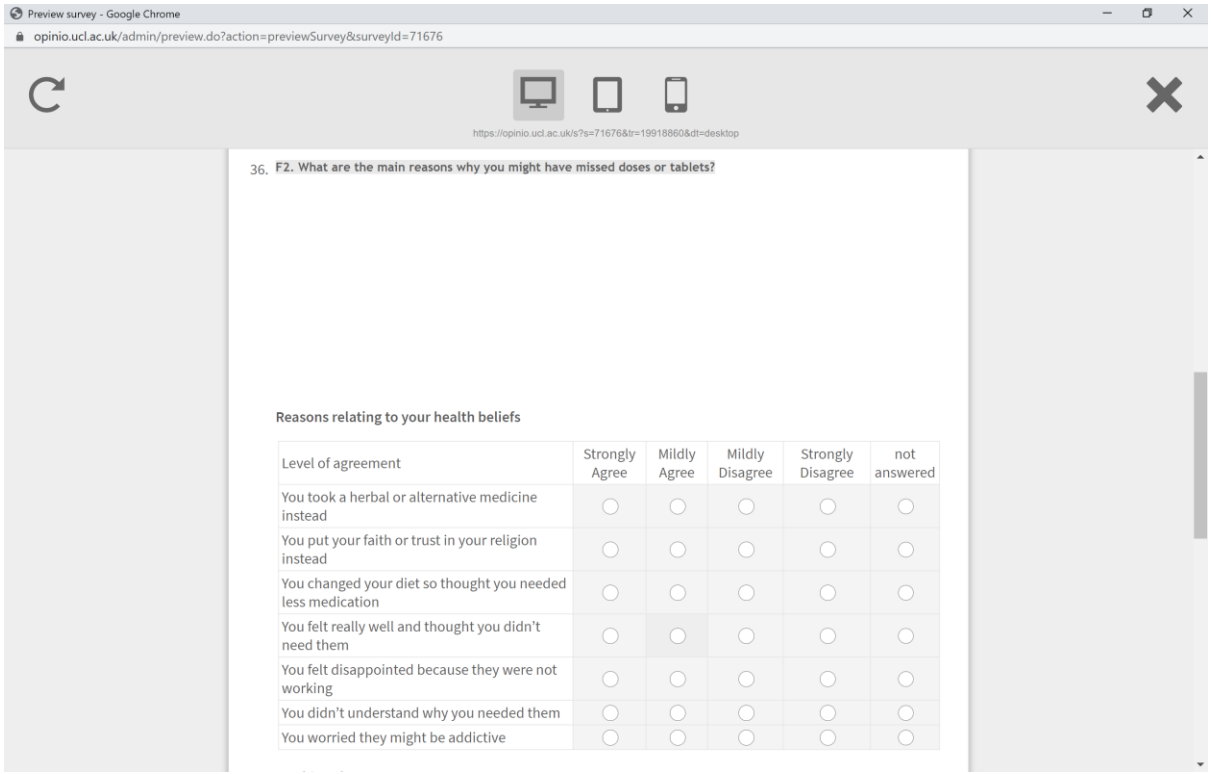

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
28. D2. Over time have you become better or worse at taking all your tablets regularly since you were first diagnosed?
Much better
Better
No change
Worse
Much worse
Please tell us why ?
29. D3. How often have you had to stop or delay your treatment because of practical difficulties in obtaining your tablets?
Never
Rarely
Sometimes
Frequently
Almost always
If applicable, please tell us the main difficulty you face

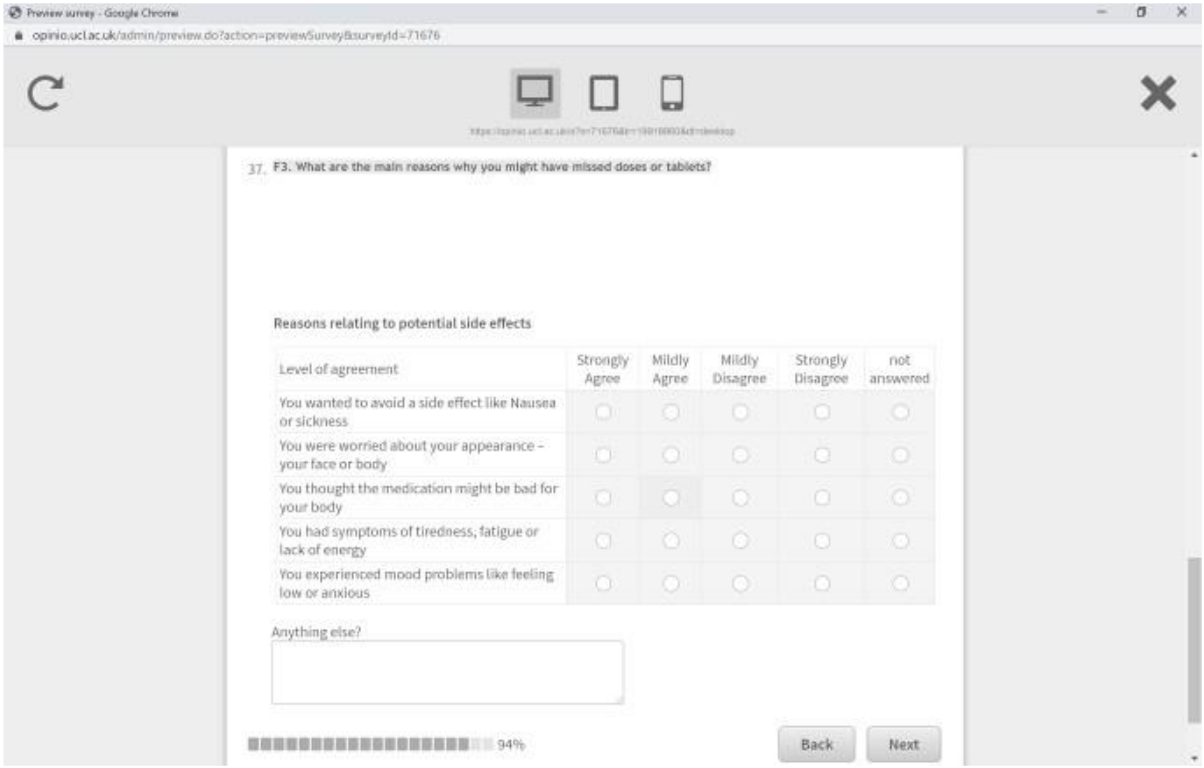

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&r=19918860&dt=desktop
30. D4. How do you usually pay for your medications?
I do not have to pay for my medications
I have a pre-payment prescription certificate
I pay for my own prescriptions
Someone else pays for my medication
Other
31. D5. If you have to pay for your prescriptions have you ever stopped treatment because you couldn't afford it?
Yes
No
32. D6. About taking the medication
Q
Yes
No
Do you ever forget to take your medication?
Are you careless at times about taking your medication?
When you feel better do you sometimes stop taking your medication
Sometimes if you feel worse when you take medicine, do you stop taking it?
82%
Back
Next

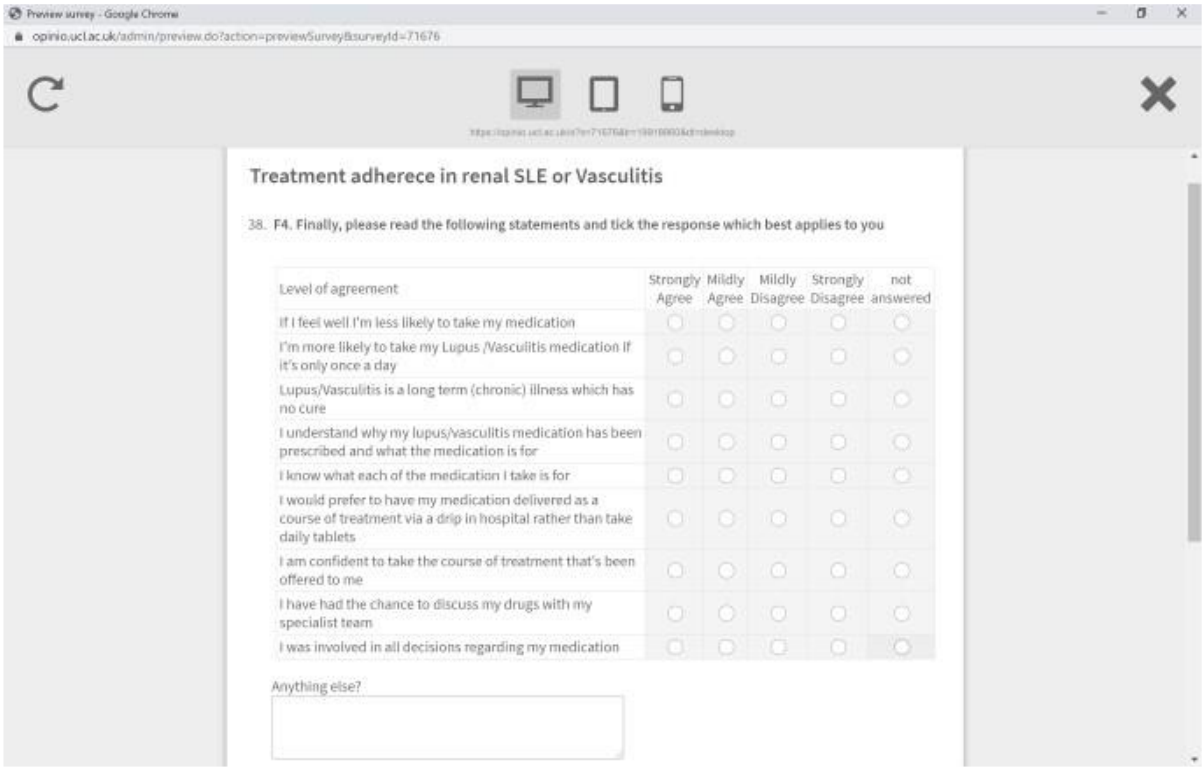

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
E
33. E1(7). Since you have been diagnosed, how many of your clinic appointments have you been able to attend?
A few (<25%)
Some (< 50%)
Most (50-75%)
Almost all (75-99%)
All (100%)
34. E2(8). Have any of the following kept you from coming to your specialist kidney clinic appointments at the hospital?
(tick more than one if necessary)
Getting time off work or losing pay
The cost of travel here
Caring for children or other dependants
The time taken to travel here
Keeping track of hospital appointments
Dislike of hospitals
Not applicable

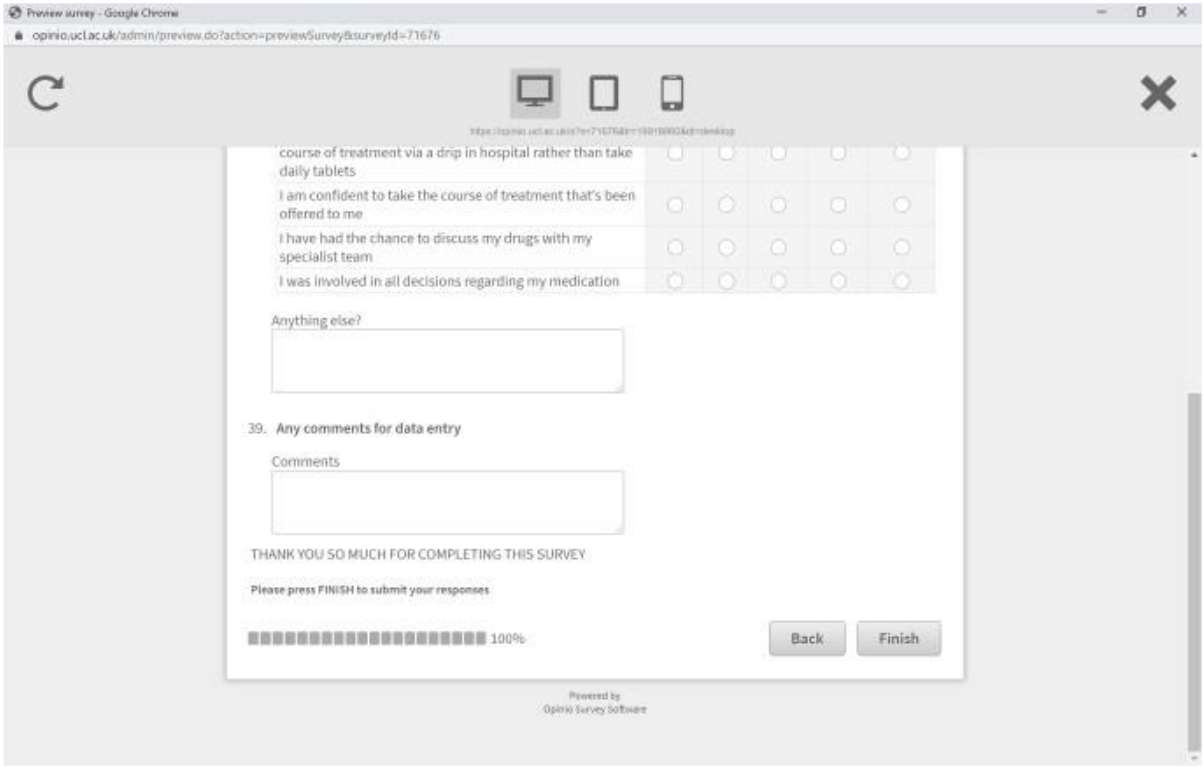

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
To help us understand any difficulties that patients may have with following their treatment plan, please rate your level of agreement with the following statements in the next three questions.
Please do respond to the next sections, even if you have never missed any doses.
35. F1. What are the main reasons why you might have missed doses or tablets?
Reasons relating to the Tablets/Medication
Level of agreement
Strongly Agree
Mildly Agree
Mildly Disagree
Strongly Disagree
Not answered
You didnt remember to take them
You find it hard to swallow tablets
You don't like the taste/smell of them
You wanted to see if taking fewer tablets would be ok
You just don't like taking tablets
You didn't want to be reminded of your illness

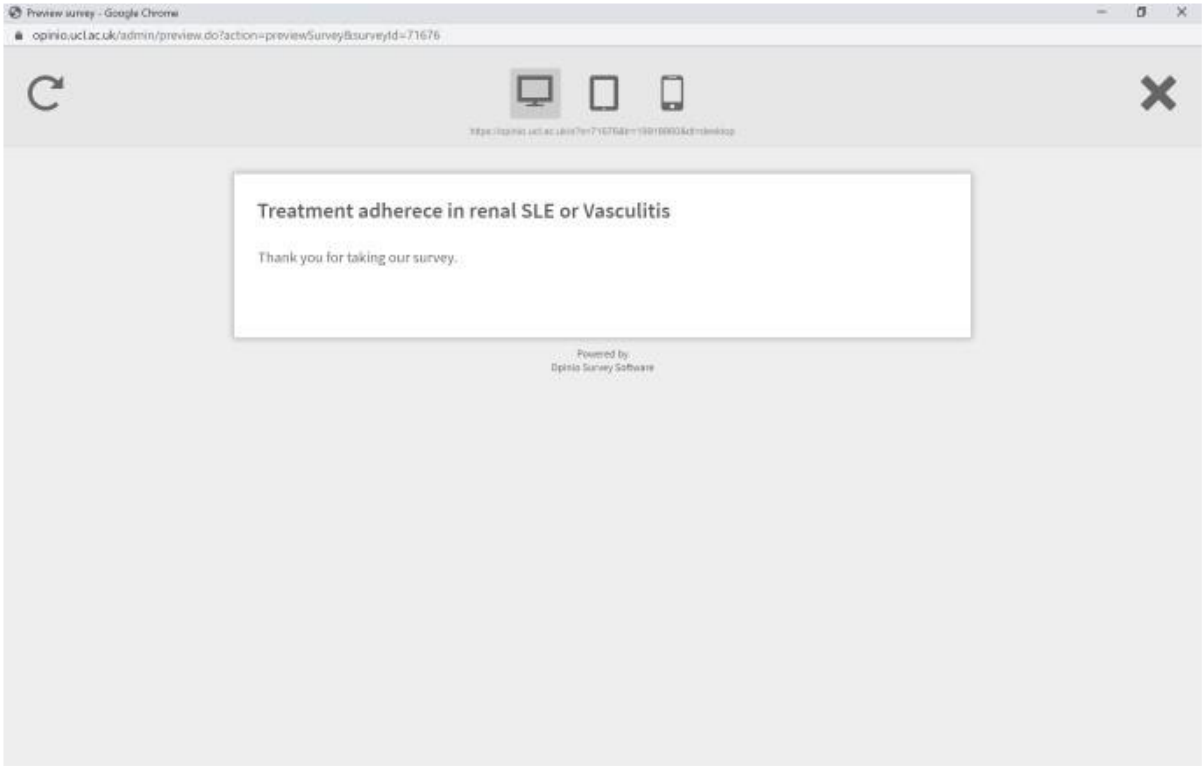

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
35. F1. What are the main reasons why you might have missed doses or tablets?
Reasons relating to the Tablets/Medication
Level of agreement
Strongly Agree
Mildly Agree
Mildly Disagree
Strongly Disagree
Not answered
You didnt remember to take them
You find it hard to swallow tablets
You don't like the taste/smell of them
You wanted to see if taking fewer tablets would be ok
You just don't like taking tablets
You didn't want to be reminded of your illness
Taking tablets regularly interferes with your lifestyle
Anything else?

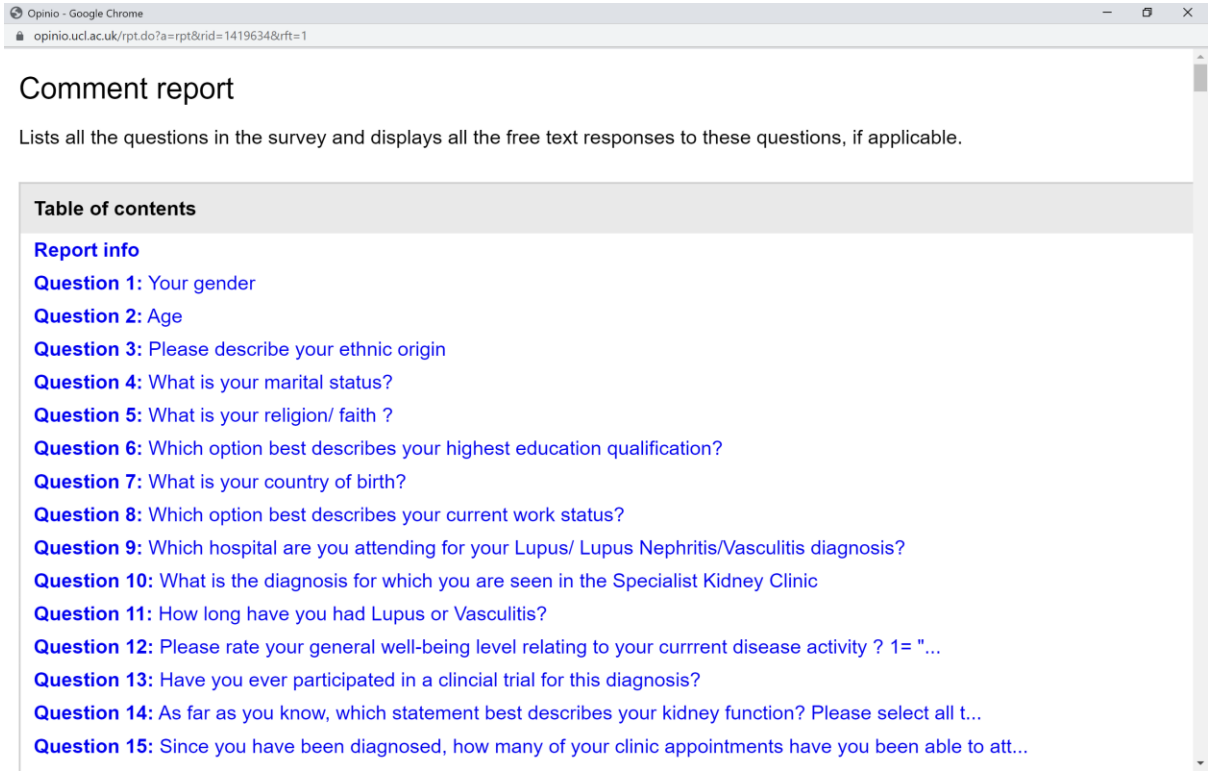

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
https://opinio.ucl.ac.uk/s?s=71676&tr=19918860&dt=desktop
36. F2. What are the main reasons why you might have missed doses or tablets?
Reasons relating to your health beliefs
Level of agreement
Strongly Agree
Mildly Agree
Mildly Disagree
Strongly Disagree
not answered
You took a herbal or alternative medicine instead
You put your faith or trust in your religion instead
You changed your diet so thought you needed less medication
You felt really well and thought you didn't need them
You felt disappointed because they were not working
You didn't understand why you needed them
You worried they might be addictive

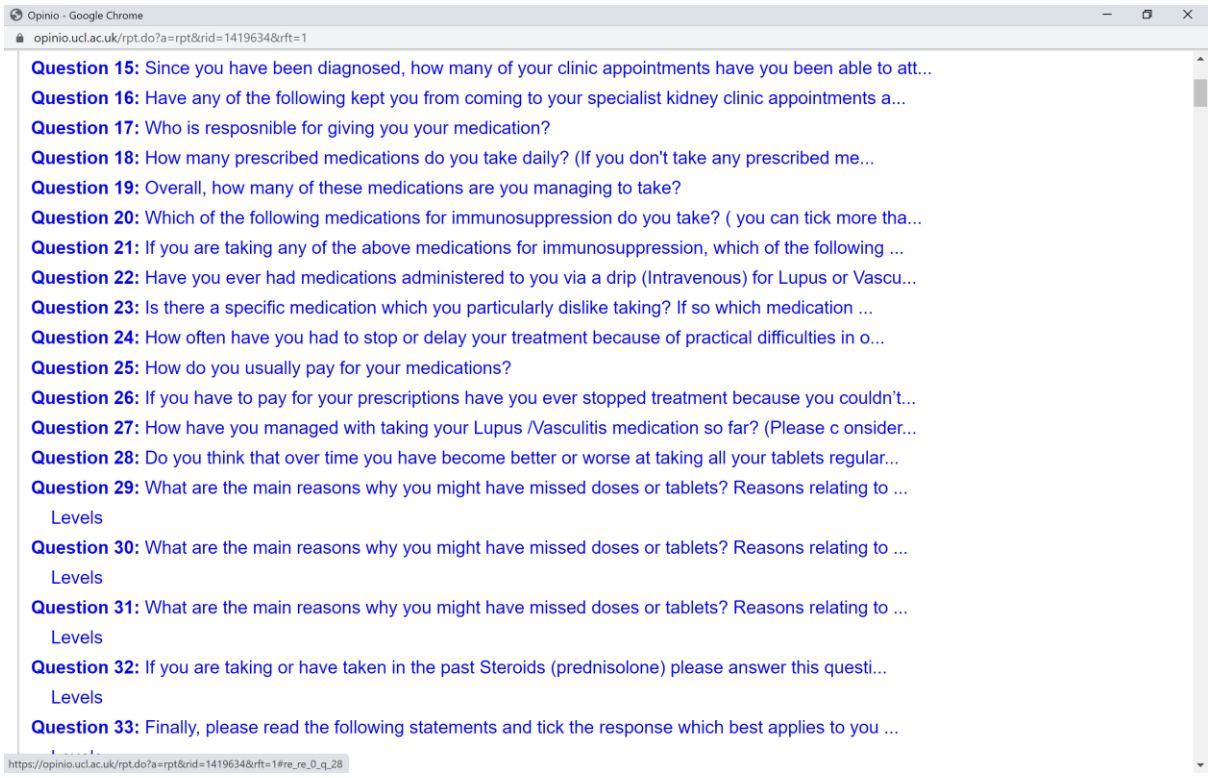

Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
37. F3. What are the main reasons why you might have missed doses or tablets?
Reasons relating to potential side effects
Level of agreement
Strongly Agree
Mildly Agree
Mildly Disagree
Strongly Disagree
not answered
You wanted to avoid a side effect like Nausea or sickness
You were worried about your appearance – your face or body
You thought the medication might be bad for your body
You had symptoms of tiredness, fatigue or lack of energy
You experienced mood problems like feeling low or anxious
Anything else?
94%
Back
Next


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
38. F4. Finally, please read the following statements and tick the response which best applies to you
Level of agreement
Strongly Agree
Mildly Agree
Mildly Disagree
Strongly Disagree
not answered
If I feel well I'm less likely to take my medication
I'm more likely to take my Lupus /Vasculitis medication if it's only once a day
Lupus/Vasculitis is a long term (chronic) illness which has no cure
I understand why my lupus/vasculitis medication has been prescribed and what the medication is for
I know what each of the medication I take is for
I would prefer to have my medication delivered as a course of treatment via a drip in hospital rather than take daily tablets
I am confident to take the course of treatment that's been offered to me
I have had the chance to discuss my drugs with my specialist team
I was involved in all decisions regarding my medication
Anything else?


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
course of treatment via a drip in hospital rather than take daily tablets
I am confident to take the course of treatment that's been offered to me
I have had the chance to discuss my drugs with my specialist team
I was involved in all decisions regarding my medication
Anything else?
39. Any comments for data entry
Comments
THANK YOU SO MUCH FOR COMPLETING THIS SURVEY
Please press FINISH to submit your responses
100%
Back
Finish
Powered by
Opinio Survey Software


Preview survey - Google Chrome
opinio.ucl.ac.uk/admin/preview.do?action=previewSurvey&surveyId=71676
Treatment adherece in renal SLE or Vasculitis
Thank you for taking our survey.
Powered by
Opinio Survey Software

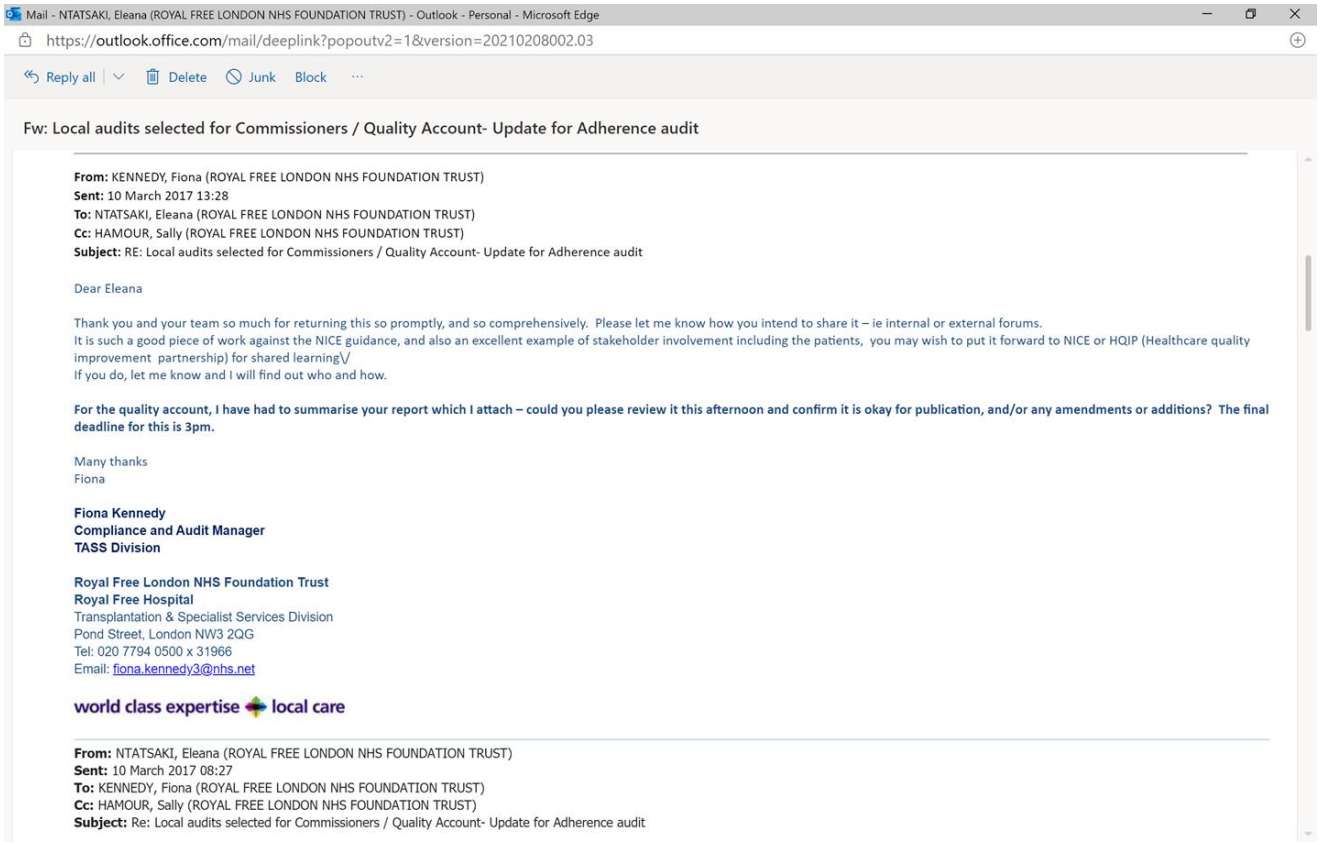

Opinio - Google Chrome
opinio.ucl.ac.uk/rpt.do?a=rpt&rid=1419634&rft=1
Comment report
Lists all the questions in the survey and displays all the free text responses to these questions, if applicable.
Table of contents
Report info
Question 1: Your gender
Question 2: Age
Question 3: Please describe your ethnic origin
Question 4: What is your marital status?
Question 5: What is your religion/ faith ?
Question 6: Which option best describes your highest education qualification?
Question 7: What is your country of birth?
Question 8: Which option best describes your current work status?
Question 9: Which hospital are you attending for your Lupus/ Lupus Nephritis/Vasculitis diagnosis?
Question 10: What is the diagnosis for which you are seen in the Specialist Kidney Clinic
Question 11: How long have you had Lupus or Vasculitis?
Question 12: Please rate your general well-being level relating to your currrent disease activity ? 1= "...
Question 13: Have you ever participated in a clincial trial for this diagnosis?
Question 14: As far as you know, which statement best describes your kidney function? Please select all t...
Question 15: Since you have been diagnosed, how many of your clinic appointments have you been able to att...

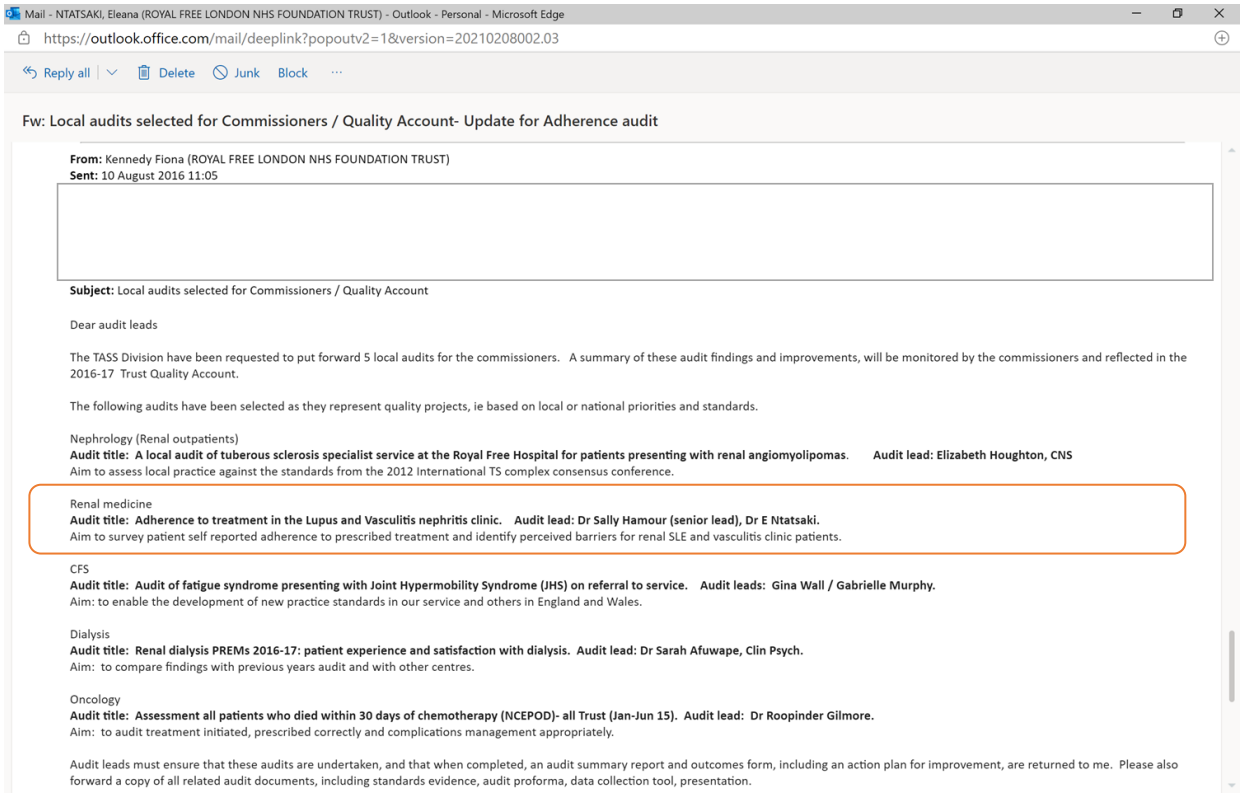

Opinio - Google Chrome
opinio.ucl.ac.uk/rpt.do?a=rpt&rid=1419634&rft=1
Question 15: Since you have been diagnosed, how many of your clinic appointments have you been able to att...
Question 16: Have any of the following kept you from coming to your specialist kidney clinic appointments a...
Question 17: Who is resposnible for giving you your medication?
Question 18: How many prescribed medications do you take daily? (If you don't take any prescribed me...
Question 19: Overall, how many of these medications are you managing to take?
Question 20: Which of the following medications for immunosuppression do you take? (you can tick more tha...
Question 21: If you are taking any of the above medications for immunosuppression, which of the following ...
Question 22: Have you ever had medications administered to you via a drip (Intravenous) for Lupus or Vascu...
Question 23: Is there a specific medication which you particularly dislike taking? If so which medication ...
Question 24: How often have you had to stop or delay your treatment because of practical difficulties in o...
Question 25: How do you usually pay for your medications?
Question 26: If you have to pay for your prescriptions have you ever stopped treatment because you couldn't...
Question 27: How have you managed with taking your Lupus /Vasculitis medication so far? (Please c onsider...
Question 28: Do you think that over time you have become better or worse at taking all your tablets regular...
Question 29: What are the main reasons why you might have missed doses or tablets? Reasons relating to ...
Levels
Question 30: What are the main reasons why you might have missed doses or tablets? Reasons relating to ...
Levels
Question 31: What are the main reasons why you might have missed doses or tablets? Reasons relating to ...
Levels
Question 32: If you are taking or have taken in the past Steroids (prednisolone) please answer this questi...
Levels
Question 33: Finally, please read the following statements and tick the response which best applies to you ...
https://opinio.ucl.ac.uk/rpt.do?a=rpt&rid=1419634&rft=1#re_re_0_q_28

Appendix 5

Commendation from Royal Free Hospital for Study 3

Selection for Commissioners' Quality Account


Mail - NTATSAKI, Eleana (ROYAL FREE LONDON NHS FOUNDATION TRUST) - Outlook - Personal - Microsoft Edge
https://outlook.office.com/mail/deeplink?popoutv2=1&version=20210208002.03
Reply all
Delete
Junk
Block
Fw: Local audits selected for Commissioners / Quality Account- Update for Adherence audit
From: KENNEDY, Fiona (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Sent: 10 March 2017 13:28
To: NTATSAKI, Eleana (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Cc: HAMOUR, Sally (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Subject: RE: Local audits selected for Commissioners / Quality Account- Update for Adherence audit
Dear Eleana
Thank you and your team so much for returning this so promptly, and so comprehensively. Please let me know how you intend to share it – ie internal or external forums.
It is such a good piece of work against the NICE guidance, and also an excellent example of stakeholder involvement including the patients, you may wish to put it forward to NICE or HQIP (Healthcare quality improvement partnership) for shared learning\/
If you do, let me know and I will find out who and how.
For the quality account, I have had to summarise your report which I attach – could you please review it this afternoon and confirm it is okay for publication, and/or any amendments or additions? The final deadline for this is 3pm.
Many thanks
Fiona
Fiona Kennedy
Compliance and Audit Manager
TASS Division
Royal Free London NHS Foundation Trust
Royal Free Hospital
Transplantation & Specialist Services Division
Pond Street, London NW3 2QG
Tel: 020 7794 0500 x 31966
Email: fiona.kennedy3@nhs.net
world class expertise local care
From: NTATSAKI, Eleana (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Sent: 10 March 2017 08:27
To: KENNEDY, Fiona (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Cc: HAMOUR, Sally (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Subject: Re: Local audits selected for Commissioners / Quality Account- Update for Adherence audit


Mail - NTATSAKI, Eleana (ROYAL FREE LONDON NHS FOUNDATION TRUST) - Outlook - Personal - Microsoft Edge

https://outlook.office.com/mail/deeplink?popoutv2=1&version=20210208002.03

Reply all | Delete | Junk | Block | ···

Fw: Local audits selected for Commissioners / Quality Account- Update for Adherence audit

From: Kennedy Fiona (ROYAL FREE LONDON NHS FOUNDATION TRUST)
Sent: 10 August 2016 11:05

Subject: Local audits selected for Commissioners / Quality Account

Dear audit leads

The TASS Division have been requested to put forward 5 local audits for the commissioners. A summary of these audit findings and improvements, will be monitored by the commissioners and reflected in the 2016-17 Trust Quality Account.

The following audits have been selected as they represent quality projects, ie based on local or national priorities and standards.

Nephrology (Renal outpatients)
Audit title: A local audit of tuberous sclerosis specialist service at the Royal Free Hospital for patients presenting with renal angiomyolipomas. Audit lead: Elizabeth Houghton, CNS
Aim to assess local practice against the standards from the 2012 International TS complex consensus conference.

Renal medicine
Audit title: Adherence to treatment in the Lupus and Vasculitis nephritis clinic. Audit lead: Dr Sally Hamour (senior lead), Dr E Ntatsaki.
Aim to survey patient self reported adherence to prescribed treatment and identify perceived barriers for renal SLE and vasculitis clinic patients.

CFS
Audit title: Audit of fatigue syndrome presenting with Joint Hypermobility Syndrome (JHS) on referral to service. Audit leads: Gina Wall / Gabrielle Murphy.
Aim: to enable the development of new practice standards in our service and others in England and Wales.

Dialysis
Audit title: Renal dialysis PREMs 2016-17: patient experience and satisfaction with dialysis. Audit lead: Dr Sarah Afuwape, Clin Psych.
Aim: to compare findings with previous years audit and with other centres.

Oncology
Audit title: Assessment all patients who died within 30 days of chemotherapy (NCEPOD)- all Trust (Jan-Jun 15). Audit lead: Dr Roopinder Gilmore.
Aim: to audit treatment initiated, prescribed correctly and complications management appropriately.

Audit leads must ensure that these audits are undertaken, and that when completed, an audit summary report and outcomes form, including an action plan for improvement, are returned to me. Please also forward a copy of all related audit documents, including standards evidence, audit proforma, data collection tool, presentation.

Appendix 6

Published paper 1

PDFs of all the published papers can be found at this link:

http://bitly.ws/rrkg

EXPERT REVIEWS

Risk factors for renal disease in systemic lupus erythematosus and their clinical implications

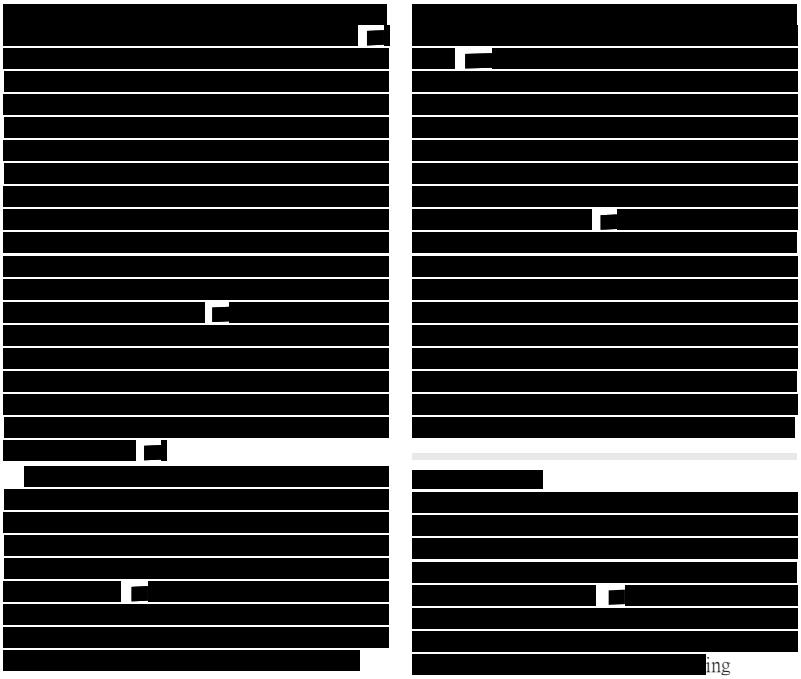
Expert Rev. Clin. Immunol. 11(7), 837–848 (2015)

Eleana Ntatsaki[1] and David Isenberg*[2]

[1]*University College London Medical School, Room GF/664, Royal Free Hospital, London NW3 2 PF, UK*
[2]*Division of Medicine, Centre for Rheumatology, University College London, Room 424, The Rayne Building, 5 University Street, London WC1E 6JF, UK*
**Author for correspondence: d.isenberg@ucl.ac.uk*

Lupus nephritis is one of the most common severe manifestations of systemic lupus erythematosus and is associated with significant morbidity and mortality. Genetic, ethnic and hormonal factors may influence the presence and severity of renal involvement and therefore affect the outcome and overall prognosis of patients. In this review, we will discuss the association of known lupus risk factors in developing renal disease and explore the recent literature to identify potential risk factors and their clinical implications in terms of diagnostic vigilance, management and prognosis.

KEYWORDS: antibody profile · ethnic · genetic · hormonal · lupus nephritis · prognosis · risk factors



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86/1744666X.2015.1045418

ISSN

Appendix 7

Published paper 2

EXPERT OPINION ON DRUG SAFETY, 2016
http://dx.doi.org/10.1080/14740338.2016.1182496

Taylor & Francis
Taylor & Francis Group

REVIEW

The safety of pharmacological treatment options for lupus nephritis

Alba Velo-García[a,b], Eleana Ntatsaki[b] and David Isenberg[b]

[a]Internal Medicine Department, University Hospital Complex of Pontevedra, Pontevedra, Spain; [b]Centre for Rheumatology, Division of Medicine, University College London, UK

ABSTRACT

Introduction: The management of lupus nephritis (LN) has changed significantly over the last 10 years due to emerging evidence from large randomised clinical trials that produced good quality data and guided the formulation of two key concepts: the induction of remission and the maintenance phase of immunosuppressive therapy.

Areas covered: Optimizing cyclophosphamide and glucocorticoid regimens and the introduction of mycophenolate mofetil for proliferative and membranous LN has been pivotal. Nevertheless, concerns remain about treatment toxicity especially long term glucocorticoid use and exposure to cumulative cyclophosphamide doses. Here we discuss the conventional and newer pharmacological options for managing LN focusing on drug safety and toxicity issues.

Expert opinion: The need for effective and less toxic treatments led to the development of the role of targeted biologic therapies in LN. However, evidence from the initial randomized controlled trials has been disappointing, although this reflects inadequate trial design rather than true lack of efficacy.

ARTICLE HISTORY
Received 11 March 2016
Accepted 21 April 2016
Published online
13 May 2016

KEYWORDS
Safety; treatment; lupus nephritis; cyclophosphamide; biologics

1. Introduction

CONTACT David Isenberg d.isenberg@ucl.ac.uk Centre for Rheumatology, Division of Medicine, University College London, Room 424, The Rayne Building,5 University Street, London WC1E 6JF, UK

Alba Garcia-Velo and Eleana Ntatsaki are joint first authors.

NOTE: The ongoing trials are mentioned with the study´s unique identifier NCT number of the registry ClinicalTrials.gov (https://clinicaltrials.gov)

Appendix 8

Published paper 3

Clinical Rheumatology (2018) 37:2399–2404
https://doi.org/10.1007/s10067-018-4115-1

ORIGINAL ARTICLE

Impact of pre-transplant time on dialysis on survival in patients with lupus nephritis

Eleana Ntatsaki[1,2] & Alba Velo-Garcia[1,3] & Vassilios S. Vassiliou[4,5] & Alan D. Salama[6] & David A. Isenberg[1]

Received: 18 January 2018 / Revised: 2 April 2018 / Accepted: 17 April 2018 / Published online: 11 May 2018

Abstract

Lupus nephritis (LN) is an important cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) often leading to end-stage renal failure (ESRF) and necessitating renal transplantation (rTp). Optimal timing of rTp in SLE patients with ESRF is uncertain and could potentially affect survival. We investigated the time spent on dialysis before rTp and survival following rTp in a cohort of SLE patients. Retrospective analysis of all adult SLE patients receiving rTp over a 40-year period (1975–2015) in two tertiary UK centres. Cox proportional hazard regression and receiver operator curves (ROC) were used to determine the risk associated with time on dialysis before rTp and other potential predictors. Forty patients (age 35 ± 11 years, 34 female, 15 Caucasian, 15 Afro–Caribbean and 10 South Asian) underwent rTp. During a median follow-up of 104 months (IQR 80,145), eight (20%) patients died and the 5-year survival was 95%. Univariate analysis identified time on dialysis prior to rTp as the only potentially modifiable risk predictor of survival with a hazard ratio of 1.013 for each additional month spent on dialysis (95% CI = 1.001–1.026, $p = 0.03$). ROC curves demonstrated that > 24 months on dialysis had an adverse effect with sensitivity of 0.875 and specificity 0.500 for death. No other modifiable predictors were significantly associated with mortality, indicating that time on dialysis had an independent effect. Increased time on dialysis pre-transplantation is an independent modifiable risk factor of mortality in this cohort of patients with lupus nephritis.

Keywords Lupus nephritis · Outcome · Renal transplant · SLE · Survival

Introduction

Systemic lupus erythematosus (SLE) is a heterogenous autoimmune rheumatic disease with particularly high prevalence in women of childbearing age [1]. The kidneys are often affected, with at least one-third of SLE patients developing overt renal disease, while 10–25% may reach end-stage renal failure (ESRF) requiring dialysis or kidney transplantation and 10–20% of patients die within 10 years [2]. Lupus nephritis (LN) remains one of the most common and severe manifestations of SLE. There are racial, ethnic and regional variations in the incidence, prevalence and prognosis of LN [3]. Specifically younger age (< 33 years), non-European ancestry and male gender (in some but not all series) were found to associate with earlier development of renal disease. Moreover, African–Caribbean, African–American and South Asian ethnicities usually have worse renal involvement when compared to other ethnic groups. Furthermore, Black and Hispanic patients with LN tend to have poorer prognosis and a higher risk of renal disease and mortality [4].

In those patients reaching ESRF, renal transplantation (rTp) has now become an accepted and preferred treatment. However, in the early era of renal transplantation, lupus patients were considered unfavourable candidates given an assumed risk of recurrent LN. Since 1975, however, when it was first suggested that the outcomes of transplant in SLE are comparable to non-SLE patients [5], there have been reports

* Eleana Ntatsaki
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2 Rheumatology Department, Ipswich Hospital, Heath Road, Ipswich IP4 5PD, UK

3 Internal Medicine Department, University Hospital Complex of Pontevedra, Pontevedra, Spain

4 Norwich Medical School, University of East Anglia and Norfolk and Norwich University Hospital, Norwich, UK

5 Imperial College London, London, UK

6 Centre for Nephrology, University College London, London, UK

Appendix 9

Published paper 4

Lupus (2019) 28, 651–657
journals.sagepub.com/home/lup

PAPER

Renal transplantation for lupus nephritis: non-adherence and graft survival

E Ntatsaki[1,2], VS Vassiliou[3,4], A Velo-Garcia[1,5], AD Salama[6] and DA Isenberg[1]

[1]Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom; [2]Rheumatology Department, Ipswich Hospital, Ipswich, United Kingdom; [3]Norwich Medical School, University of East Anglia, Norwich, United Kingdom; [4]Department of Medicine, Imperial College London, London, United Kingdom; [5]Internal Medicine Department, University Hospital Complex of Pontevedra, Pontevedra, Spain; and [6]Centre for Nephrology, University College London, London, United Kingdom

Objectives: Poor adherence to immunosuppressive treatment is common in patients with systemic lupus erythematosus and may identify those with lupus nephritis (LN) who have a poorer prognosis. Non-adherence has also been reported to be a potential adverse outcome predictor in renal transplantation (rTp). We investigated whether non-adherence is associated with increased rTp graft rejection and/or failure in patients with LN. Methods: Patients with LN undergoing rTp in two major London hospitals were retrospectively included. Medical and electronic records were reviewed for documented concerns of non-adherence as well as laboratory biochemical drug levels. The role of non-adherence and other potential predictors of graft rejection/failure including demographics, comorbidities, age at systemic lupus erythematosus and LN diagnosis, type of LN, time on dialysis prior to rTp and medication use were investigated using logistic regression. Results: Out of 361 patients with LN, 40 had rTp. During a median follow-up of 8.7 years, 17/40 (42.5%) of these patients had evidence of non-adherence. A total of 12 (30.0%) patients experienced graft rejection or failure or both.
In the adherent group 2/23 (8.7%) had graft rejection, whilst in the non-adherent this rose to 5/17 (29.4%, $p=0.11$). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group ($p=0.89$). Non-adherent patients had a trend towards increased graft rejection, hazard ratio 4.38, 95% confidence interval=0.73–26.12, $p=0.11$. Patients who spent more time on dialysis prior to rTp were more likely to be adherent to medication, $p = 0.01$. Conclusion: Poor adherence to immunosuppressive therapy is common and has been shown to associate with a trend towards increased graft failure in patients with LN requiring rTp. This is the first paper to report that shorter periods on dialysis prior to transplantation might lead to increased non-adherence in lupus patients. *Lupus* (2019) 28, 651–657.

Key words: Lupus nephritis; adherence to treatment; renal transplant; graft rejection; graft failure; systemic lupus erythematosus

Introduction

[redacted]

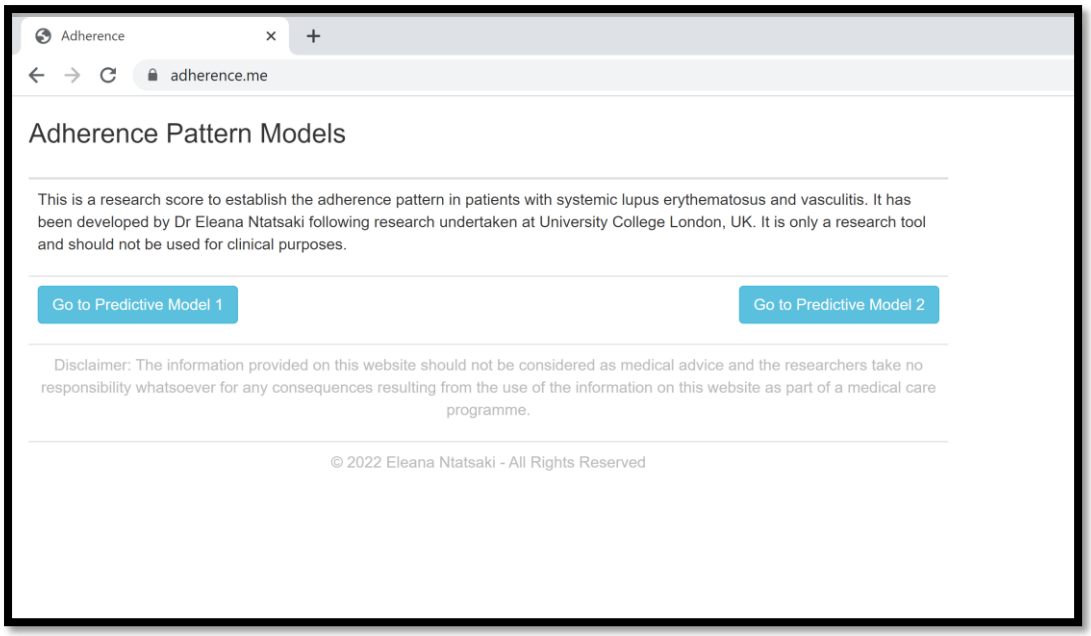
Correspondence to: Eleana Ntatsaki, Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom.
Email: ntatsakie@doctors.org.uk
Received 15 October 2018; accepted 14 March 2019

[redacted]

Appendix 10

Adherence Tool on Line calculator

Screenshots of *www.adherence.me* website with on line calculation tool based on Adherence Prediction Models 1 and 2


Adherence
adherence.me
Adherence Pattern Models
This is a research score to establish the adherence pattern in patients with systemic lupus erythematosus and vasculitis. It has been developed by Dr Eleana Ntatsaki following research undertaken at University College London, UK. It is only a research tool and should not be used for clinical purposes.
Go to Predictive Model 1
Go to Predictive Model 2
Disclaimer: The information provided on this website should not be considered as medical advice and the researchers take no responsibility whatsoever for any consequences resulting from the use of the information on this website as part of a medical care programme.
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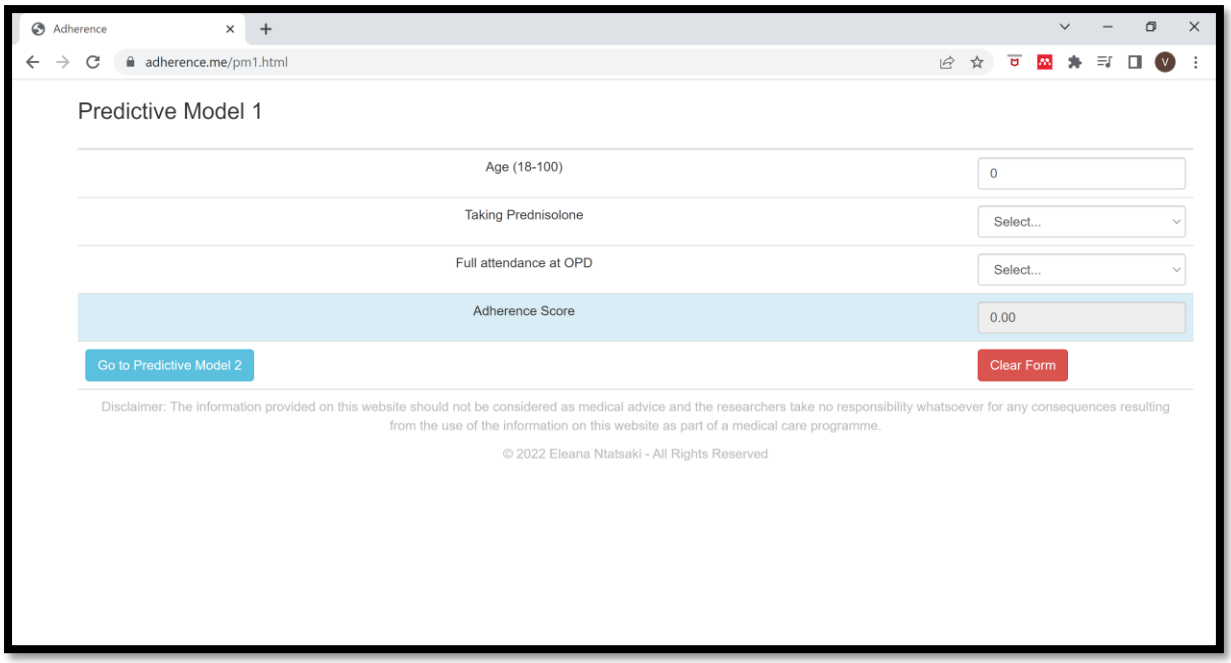
Adherence
adherence.me/pm1.html
Predictive Model 1
Age (18-100)
0
Taking Prednisolone
Select...
Full attendance at OPD
Select...
Adherence Score
0.00
Go to Predictive Model 2
Clear Form
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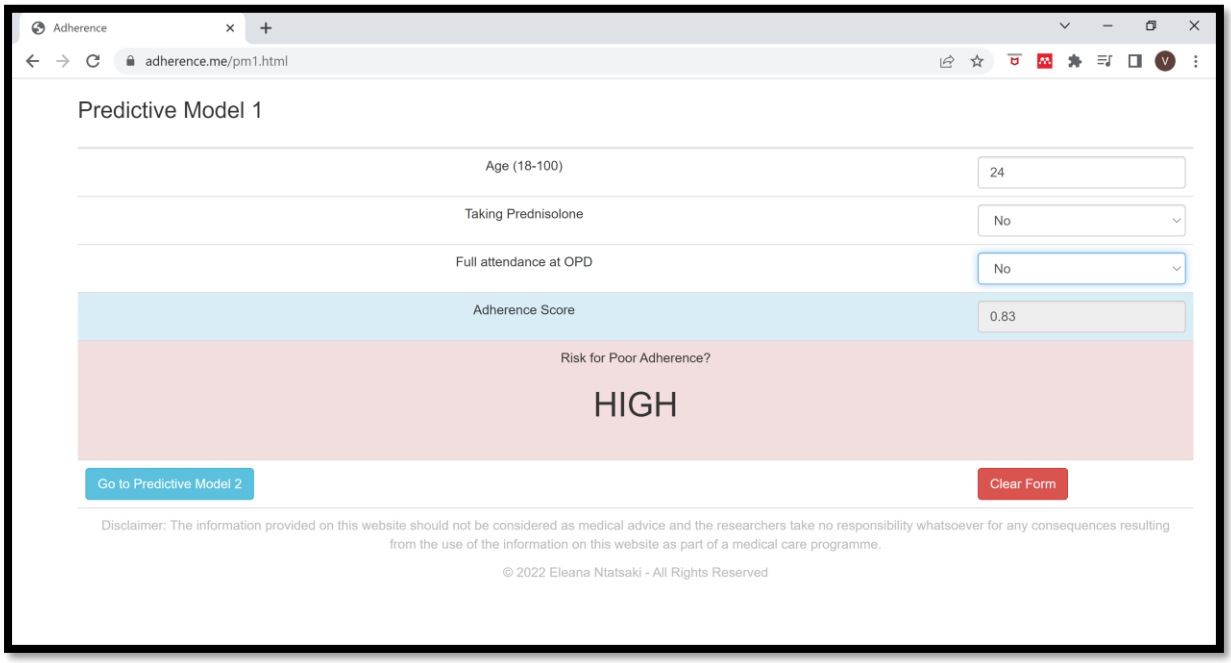
Adherence
adherence.me/pm1.html
Predictive Model 1
Age (18-100)
24
Taking Prednisolone
No
Full attendance at OPD
No
Adherence Score
0.83
Risk for Poor Adherence?
HIGH
Go to Predictive Model 2
Clear Form
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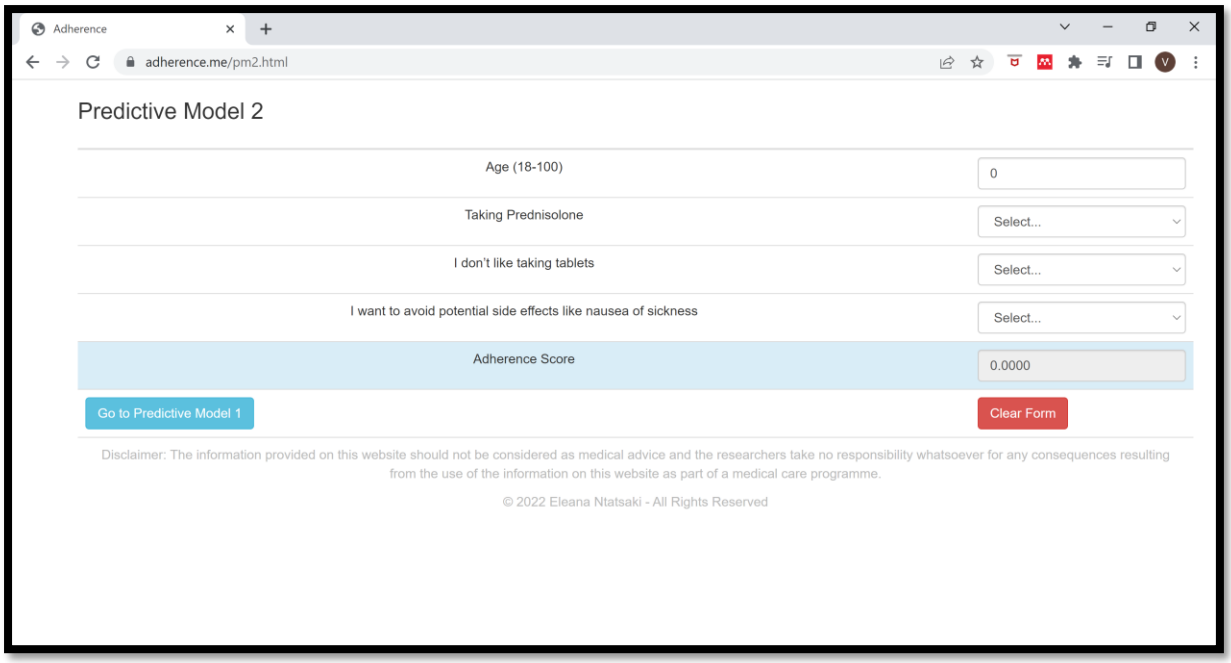
Adherence
adherence.me/pm2.html
Predictive Model 2
Age (18-100)
0
Taking Prednisolone
Select...
I don't like taking tablets
Select...
I want to avoid potential side effects like nausea of sickness
Select...
Adherence Score
0.0000
Go to Predictive Model 1
Clear Form
Disclaimer: The information provided on this website should not be considered as medical advice and the researchers take no responsibility whatsoever for any consequences resulting from the use of the information on this website as part of a medical care programme.
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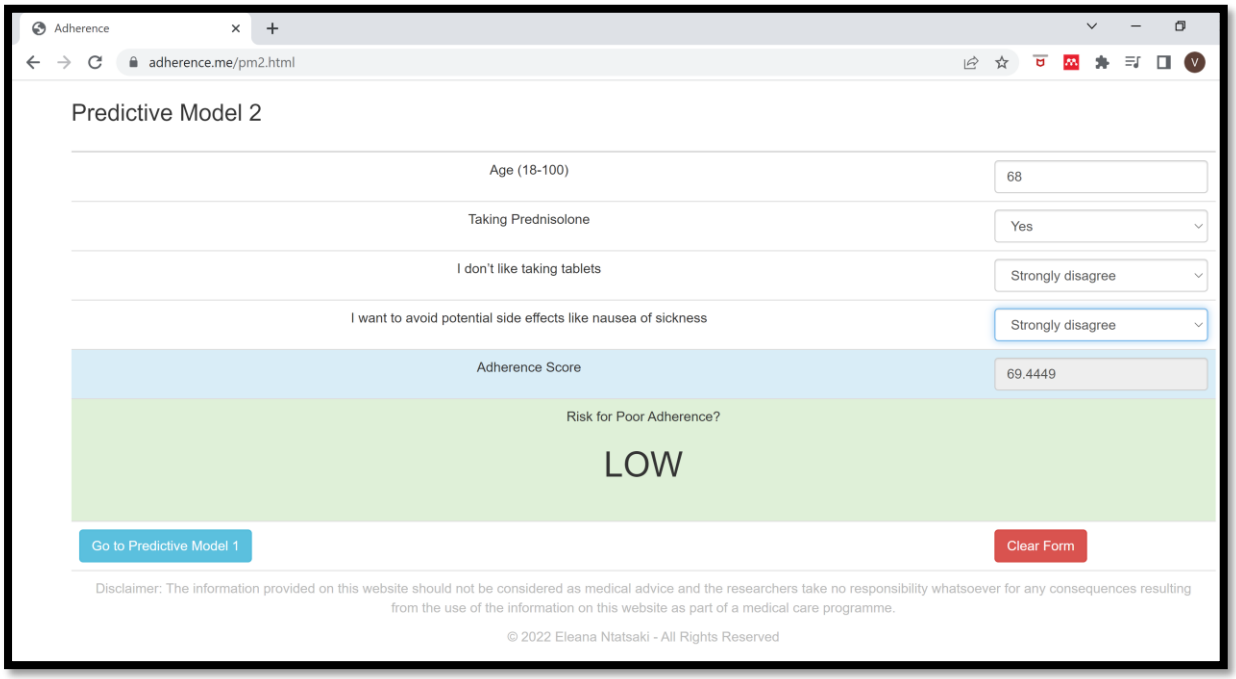
Adherence
adherence.me/pm2.html
Predictive Model 2
Age (18-100)
68
Taking Prednisolone
Yes
I don't like taking tablets
Strongly disagree
I want to avoid potential side effects like nausea of sickness
Strongly disagree
Adherence Score
69.4449
Risk for Poor Adherence?
LOW
Go to Predictive Model 1
Clear Form
Disclaimer: The information provided on this website should not be considered as medical advice and the researchers take no responsibility whatsoever for any consequences resulting from the use of the information on this website as part of a medical care programme.
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