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Systemic lupus erythematosus: a behavioural medicine perspective

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Systemic lupus erythematosus: a behavioural medicine perspective

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CHAPTER 1

GENERAL INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, rheumatic autoimmune disease in which pathogenic autoantibodies can cause inflammation throughout the whole body. Immunosuppressive drugs are often necessary to suppress this inflammation and to prevent tissue damage. Although immunosuppression is generally effective in controlling disease activity, these drugs can have numerous unpleasant and serious side effects. In addition, frequent exacerbations are characteristic of SLE, so that continuous treatment may be necessary. Although developments in immunosuppressive treatment have improved survival rates[1], SLE remains a burdensome disease.

An important contributor to the improved survival rates are advances in the treatment of one of the most serious and prevalent organ involvements of SLE, i.e., lupus nephritis.[2] Although multiple pharmacological treatment regimens for lupus nephritis have been investigated over the last few decades, which treatment results in optimal renal outcome and the least side effects is still a matter of debate. Type and intensity of treatment are based on the results of renal biopsy[3], which is a burdensome procedure for patients and gives risk of haemorrhages and infections.[4] Therefore, it would be desirable to be able to keep the frequency of biopsies to a minimum. However, there is an ongoing discussion on whether repeat renal biopsies are necessary in the case of recurrent episodes of lupus nephritis.

Studies investigating the preferred frequency of renal biopsies and optimal treatment for lupus nephritis focus on the effects on renal outcome. The impact of diagnosis and treatment on patients´ well-being has been given less attention. Quality of life (QoL) of SLE patients has been shown to be low[5] and whether treatments that result in better renal outcome also lead to a better QoL is seldom investigated. In addition, even if there is a positive effect of improved renal outcome on QoL, this plausible relationship is not likely to be a unidirectional, straightforward cause-and-effect relationship. Besides disease and treatment characteristics, QoL of patients with a chronic illness is influenced by many other factors, such as demographics (e.g. age, culture) and psychological factors (e.g. emotions, coping). In addition, a patient's level of QoL may in turn influence disease management through its effect on psychological determinants of treatment outcome, such as treatment adherence.[6] The notion that the relationship between disease

characteristics and patients' well-being is reciprocal and multifactorial and that therefore the patient and not the disease should be the centre of focus, is the key concept of the biopsychosocial model as proposed by Engel.[7] This thesis reports on several studies aimed to describe a part of this complex interaction between disease- and patient-related factors from a biopsychosocial point of view. Hence, these studies do not only describe the results of optimization of diagnosis and treatment of lupus nephritis on renal outcome, but also the impact on patients' well-being and its determinants. The theoretical background of the biopsychosocial and associated models will be discussed in the corresponding paragraphs.

Repeat renal biopsies

At the first signs of lupus nephritis, a renal biopsy is necessary to define the classification of lupus nephritis. Lupus nephritis is divided into six different classes of varying severity and prognosis[8], with an additional important distinction between proliferative and non-proliferative classes. Between 27% and 66% of patients who have once been treated for lupus nephritis experience a renal flare.[9] In addition, third, fourth and fifth episodes of lupus nephritis have been reported. The role of a repeat renal biopsy in recurrent episodes of lupus nephritis has been subject of discussion. Several studies have proposed to perform repeat renal biopsies in the case of a lupus nephritis flare[10-15], because a switch to another classification has been found in the majority of patients.[16] However the majority of these studies are based on protocol renal biopsies, whereas in clinical practice biopsies are performed on account of a clinical manifestation of a lupus nephritis flare. In addition, most earlier studies applied the old WHO classification for lupus nephritis. Because of this the clinical significance of the reported switches can be questioned, but also because the most frequent transformation occurred from one proliferative class to another, which has no consequences for type or intensity of treatment. Therefore, it has also been suggested that the choice for repeated biopsy should be based on the type of nephritis in the initial biopsy.[9;17] The indication for a repeat biopsy could therefore be limited to cases where there is a reasonable chance to detect an important class switch. This would mean a great reduction in the number of repeated

biopsies, which will clearly lower discomfort and complication risk for patients. This thesis will report on a study which investigated how often a clinically relevant switch occurred when repeat biopsies were performed in the face of a renal flare.

Therapeutic drug monitoring in lupus nephritis

The proliferative classes of lupus nephritis are the most prevalent (40 to 60% of lupus nephritis cases)[18] and there is much debate on the optimal treatment. Treatment for proliferative lupus nephritis is divided in an induction and maintenance phase. The cornerstone of both phases is a chemotherapeutic drug in combination with glucocorticosteroids. There are three main immunosuppressive drugs in the treatment of lupus nephritis, i.e., cyclophosphamide (CYC), azathioprine (AZA), and mycophenolate mofetil (MMF). CYC has long been the golden standard for both induction and maintenance treatment of proliferative lupus nephritis[19], but concerns about toxicity and varying results on renal outcome have led to comparisons with alternative treatments including AZA or MMF.[19-21] Although AZA and MMF have not shown to be superior to CYC as induction treatment in terms of renal outcome and side effects[20;22], preference for one or the other may exist because of ethnicity, disease severity or the need to avoid certain side effects (i.e., risk for ovarian failure after CYC treatment).[22-24] In maintenance treatment, AZA and MMF do appear to be superior to CYC in terms of survival, relapse and side effects[25], but results on the difference between MMF and AZA have been conflicting.[26-28] It has been suggested that AZA would be most suitable as alternative if MMF is not tolerated or when women in remission on maintenance therapy have a desire to become pregnant[24], as MMF has been associated with a higher risk for congenital malformations and spontaneous abortion.[29]

An additional issue that arises on choosing MMF in the treatment of proliferative lupus nephritis is that it is a relatively new drug, which in the Netherlands is officially only registered for the use in patients with a kidney, heart or liver transplantation. Hence, formal dosage recommendations for MMF in the treatment of lupus nephritis are unavailable and therapeutic regimens are based on the results with renal transplantation patients. However, MMF has been shown to have complex pharmacokinetic and

pharmacodynamic characteristics with high inter- and intra-individual variability.[30;31] The intra-individual variability in mycophenolic acid (MPA; the active metabolite of MMF) exposure in SLE patients with lupus nephritis has been shown to be influenced by renal function and serum albumin levels.[32-34] In addition, MMF dose does not show a relationship with exposure[35] or with measures of renal outcome.[35;36] Instead, MPA exposure did show strong associations with therapeutic response[35], disease recurrence[36], and side effects.[36]

Because of these characteristics of MPA exposure and its associations with clinical outcomes, therapeutic drug monitoring of MMF has been advised to improve management of patients with lupus nephritis.[33-37] Therapeutic drug monitoring allows the detection and adjustment of too low or too high levels of MPA at an earlier phase in treatment. In this way, the beneficial effects on renal outcome may be optimized and the occurrence of side effects may be reduced to a minimum. However, studies on the implementation of therapeutic drug monitoring in patients with SLE and its influence on MPA exposure and renal outcome are still missing. This thesis will report on a study that investigated optimized dosing of MMF in maintenance treatment for proliferative lupus nephritis.

Health-related quality of life

Quality of life (QoL) is defined in various ways, reflecting differences in theoretical background. One definition is `an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[38] This definition reflects a complex interaction between a person's physical health, psychological state, level of independence, social relationships, personal beliefs, and the relationship to salient features of the environment.[38] Health-related quality of life (HRQoL) reflects the extent to which an illness and its treatment influences a patient's life, as perceived by that patient. There are many factors that influence HRQoL, including demographics (e.g., age, culture), the condition itself, treatment, and psychological and social factors (e.g., emotions, coping, support). To illustrate the relationships between these factors and level of HRQoL, Leventhal and

Colman (1997) have proposed a process model in which a distinction has been made between the determinants of HRQoL and patients' judgments of HRQoL (Figure 1).[39] In their model, six different determinants of quality of life are distinguished: physical function, symptoms, psychological function, mood, economic status, and social relationships. HRQoL is influenced by patients' perceptions of these various domains of their life as well as by the importance they attach to their perceptions. Changes in any of the determinants may influence patients' perceptions of these determinants and in turn result in a new level of HRQoL. In addition, determinants can be interpreted by one patient to have a negative impact on HRQoL, while another patient may view them as having a positive influence on HRQoL.

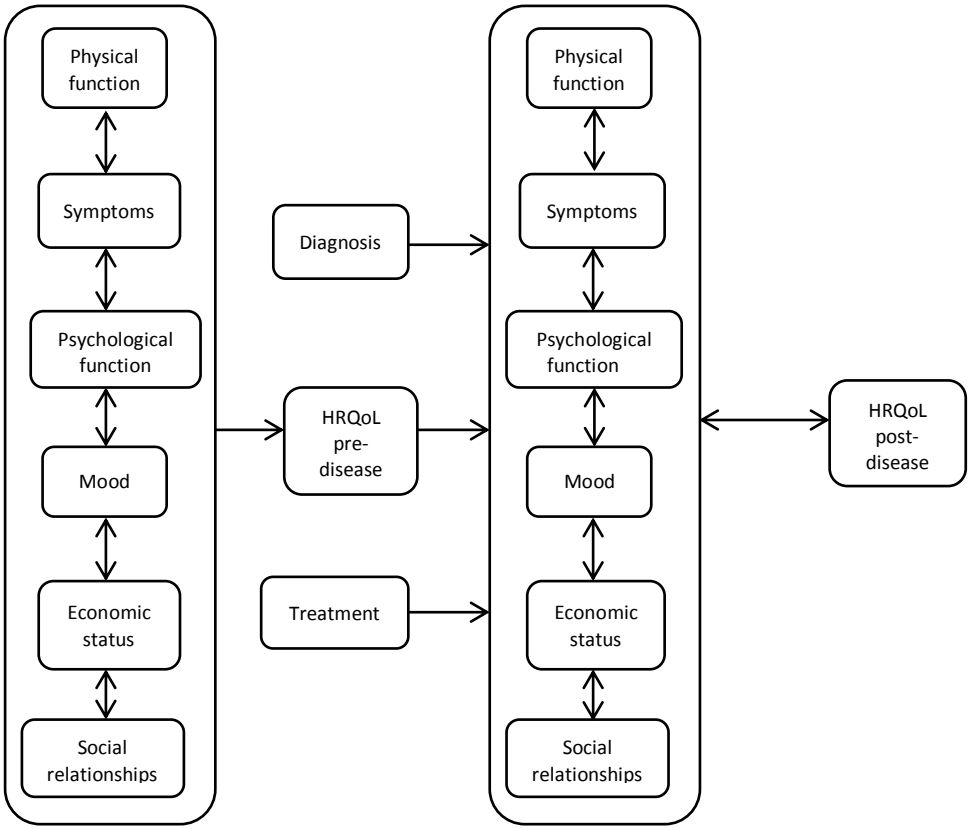

Figure 1. Process model of HRQoL by Leventhal & Collman (1997).[39]

Research into HRQoL in SLE patients has been scant until the late nineties, but has been rapidly increasing over the last decade. The need for HRQoL assessment has become more apparent as several studies have reported a discrepancy between physicians' and patients' perceptions of disease activity and global health.[40] In addition, it has been proposed that behavioural outcomes such as HRQoL should obtain a central role in studies of health care and medicine because they are more important predictors of health outcome than biological variables.[41] Studies of HRQoL in SLE patients have shown it to be significantly reduced compared with the general population.[5;42] Assessment with the Medical Outcomes Study Short Form 36 (SF-36) has shown an impact across all eight domains of HRQoL (i.e., physical functioning, vitality, bodily pain, mental health, physical role functioning, social role functioning, emotional role functioning, and general health).[40;43] HRQoL in SLE patients has been found to be less affected when compared with fibromyalgia patients, but worse in comparison with patients with Wegener's granulomatosis[44], diabetes, hypertension, congestive heart failure, and myocardial infarction.[45]

Studies investigating factors affecting HRQoL in SLE patients have largely focused on socio-demographic factors (e.g., age and educational status) and measures of disease activity. However, the attention for the relationship with psychological and social factors, such as emotions and support, has been increasing. Although studies on the relationship between disease activity and damage and HRQoL do not always use the same measure of disease activity, HRQoL does not seem to be correlated to disease activity or damage in SLE patients.[5;46] Age appears one of the strongest socio-demographic determinants of HRQoL and especially seems to effect physical health.[5] Important psychological and social factors that have been associated with reductions in HRQoL in SLE patients are social support[47;48] and coping.[49] Patients with SLE reported lower levels of HRQoL when they experienced little social support[47;48] or when coping efforts were more task-oriented instead of emotion-oriented during active disease.[49]

Treatment is another important determinant of HRQoL, which has not been widely studied in SLE patients. Especially with the rapid increase in new biological therapies for lupus, it will become more important to determine the impact of therapy not

only on disease activity but also on HRQoL. Previous studies have found a negative effect of glucocorticosteroids, immunosuppressants, and antimalarials on HRQoL in cohorts of SLE patients with varying levels of disease activity.[50-52] Although SLE patients in general require some form of maintenance therapy, the intensity of therapeutic regimens is greatest during severe organ involvements of which lupus nephritis is one of the most common and serious. However, the effect of treatment for lupus nephritis on HRQoL has only been addressed by two studies.[53;54] This thesis will report on a study that compared HRQoL in SLE patients with lupus nephritis who were treated with either a low or high dose CYC induction treatment.

Sexual functioning

Sexual functioning is one of the subdomains of HRQoL and has been shown to be important for SLE patients.[5] Patients with SLE report a higher rate of problems with sexual functioning compared with healthy controls.[55] Sexual functioning is a complex process which not only depends on physiological systems (neurologic, vascular, endocrine), but is also influenced by numerous psychological and social factors, such as self-esteem, body image and the relationship with the sexual partner.[56] Chronic medical illnesses may influence every stage of the sexual response cycle.[57]

Despite the significance of sexual functioning in SLE patients, it has not been frequently studied[58] and findings have been inconclusive. The reported incidence rates of sexual problems among SLE patients range from 4% to 52.5%.[59;60] The few previous studies that have investigated possible determinants of reductions in sexual functioning have focused on its associations with medical factors. Apart from the relation with symptoms of depression[55;61;62], the association with other emotions or psychological parameters such as illness perceptions has not been investigated. Research in patients with other chronic medical illnesses has suggested that such psychological parameters may be more important determinants of sexual functioning than medical factors.[63] This thesis includes a study on sexual functioning in SLE patients to define the problem and to investigate additional psychological associations that could be addressed to improve sexual function.

Illness perceptions

The influence of medical conditions and their symptoms on HRQoL depends on how patients interpret these medical conditions and symptoms.[39] In addition, these interpretations of disease and symptoms are guided by patients' illness perceptions.[64] Illness perceptions are cognitive and emotional representations of one's illness and are composed of one's own implicit common-sense beliefs about illness.[64] These illness beliefs can be grouped into nine different dimensions, i.e. identity (illness name and symptoms), causes, duration, consequences, personal control, the effectiveness of treatment, understanding, concerns, and emotional responses.[65] Illness perceptions not only play a role in how patients make sense of their symptoms and illness, but they also guide behaviour to manage the illness. This process by which patients make sense and respond to illness is described by the self-regulatory model (SRM), also known as the Common Sense Model of self-regulation.[65] The SRM states that patients create mental representations of their illness based on three sources of information: 1) the current experience with the illness, 2) the external social environment, and 3) previous experiences and cultural norms. Patients process this information to form illness perceptions and these perceptions elicit a coping response. When coping efforts result in an unsuccessful outcome, the coping strategy or the initial representation of the illness may be revised. The resulting feedback loop from coping to representations and back again makes this model self-regulatory and enables responsiveness to changes and thus maximizes the likelihood of a positive outcome (Figure 2).[65]

Research has demonstrated the importance of illness perceptions in patients' illness behaviour across various patient populations. Patients' illness perceptions have been shown to be related to important health outcomes, including functioning, health care utilization, adherence, and mortality.[66] For instance, a long-term study of patients with end-stage renal disease requiring hemodialysis showed that patients' perceptions of treatment control predicted survival independently of survival risk factor.[67] In addition, an increasing number of studies have reported a beneficial effect of illness perception interventions on health outcomes and treatment adherence. For instance, a text-messaging intervention to increase adherence in patients with asthma resulted in

significant changes in beliefs about time line, personal control, and medication necessity and treatment adherence.[68]

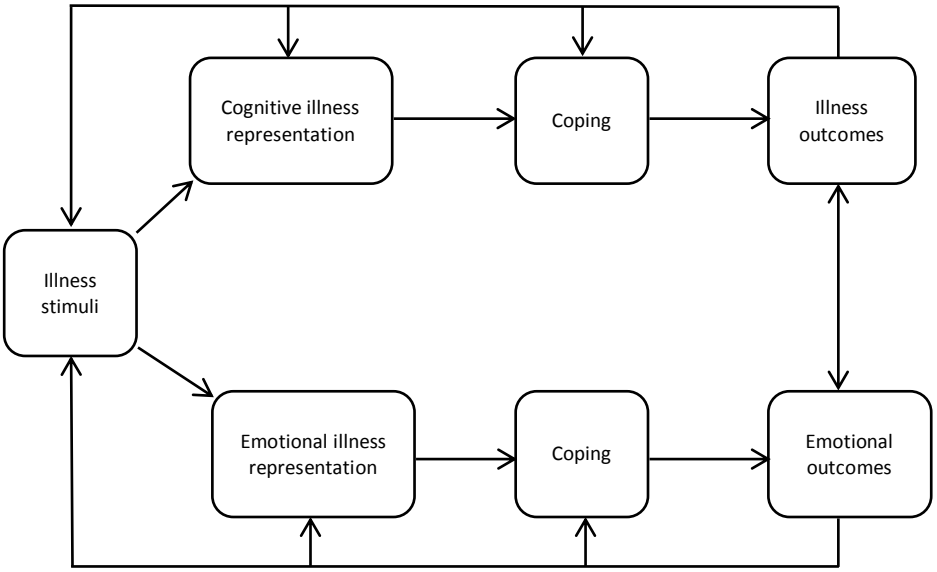

Figure 2. Leventhal's Self-Regulation Model (adapted from Hagger & Orbell, 2003).[65]

Studies investigating illness perceptions in SLE patients are scarce and the applicability is limited because their results are based on different interview techniques. However, general findings are that patients hold negative perceptions.[69-73] One important study used a reliable measure of illness perceptions (e.g., the Illness Perception Questionnaire Revised) and showed a positive effect of a cognitive behavioural intervention on patients' perceptions of treatment control and on the effect of SLE on their emotions.[74] In addition, psychological distress and perceived stress were reduced in the intervention group. A new approach in the assessment of illness perceptions is the use of drawings to improve clinicians understanding of patients' psychological status.[75] However, how patients' drawings relate to standard measures of illness perceptions or to outcome measures has not been investigated in patients with SLE. Hence, there is a need for research into illness perceptions and its association with well-being in SLE patients.

Treatment adherence

Treatment adherence is defined as the extent to which the amount of medical care patients use, corresponds with agreed recommendations from a health care provider.[76] Treatment adherence does not only include taking medications, but also following-up on appointments, dietary or lifestyle advice and so on. Research into treatment adherence has shown that non-adherence (i.e., not following agreed recommendations) is very common, especially in patients with a chronic illness.[77] With regard to medication intake, up to 50% of patients with a chronic medical condition do not take their medications as recommended.[76] Treatment non-adherence has not only been found to be related to poorer health outcomes, but also to increased health care costs.[78]

Treatment non-adherence rates in SLE patients have been found to range from 17% up to 68%[79-83] and has been associated with poor health outcomes, including a higher morbidity, hospitalization, and poor renal outcome.[13;16] Hence, interventions aimed at improving adherence could contribute to better health in SLE patients. These interventions should be directed at the determinants of non-adherence in SLE patients.

Treatment non-adherence can be divided in intentional and unintentional non-adherence. Unintentional non-adherence is thought to be the result of a passive process[78] and is associated with factors such as marital status[79;84], education[80], side effects[85;86], financial costs[86], and doctor-patient communication.[84;85] In the case of intentional non-adherence, patients actively choose not to follow agreed treatment recommendations. An extension of the Common Sense Model proposes that illness perceptions and treatment beliefs play a major role in this decision to non-adhere (Figure 3).[87] Although the majority of patients with varying illnesses believe that the prescribed medication is necessary for their health, this belief is weighed against concerns about potential side effects. Stronger concerns about possible adverse effects were associated with lower reported adherence. Hence, patients will be more motivated to use their medication as agreed if their belief in its necessity outweighs their concerns about taking it.[6;87]

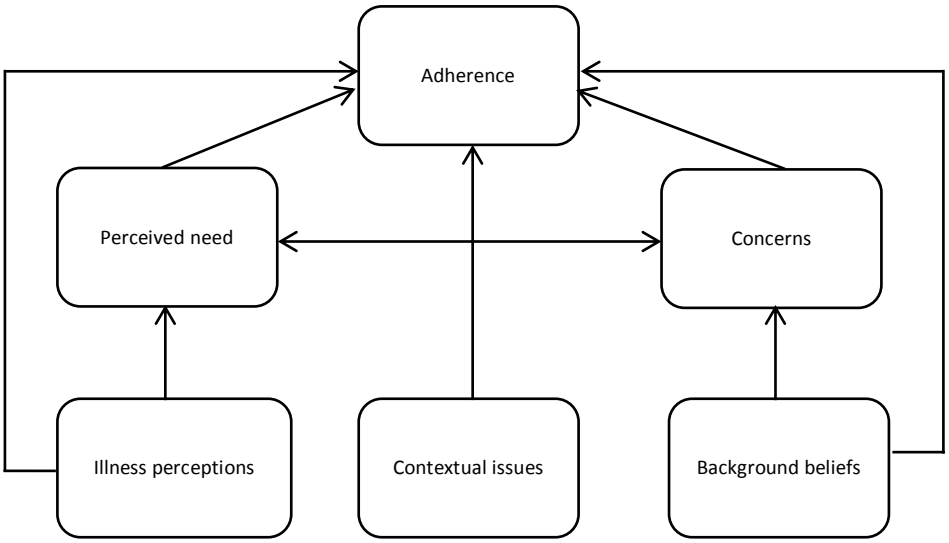

Figure 3. Extension of the Common Sense Model by Horne (2006).[87]

The majority of studies on treatment non-adherence in SLE patients do not distinguish between intentional and unintentional non-adherence. In addition, the focus has been on the determinants of unintentional non-adherence. Only one previous study made a distinction between intentional and unintentional non-adherence, but possible determinants of intentional non-adherence, such as patients' beliefs about their illness and treatment, were not investigated.[80] Hence, there is a need for a comprehensive assessment of treatment non-adherence in which intentional and unintentional non-adherence are discerned and relationships with both medical and psychological factors are investigated.

Aim of this thesis

By investigating both clinical care for patients with SLE and psychological factors, this thesis aims to give a behavioural medicine perspective on SLE. This perspective is in line with the biopsychosocial model which states that the patients' experience and behaviour is the central point through which the associations between physical condition and well-being interact. Hence, this thesis not only addresses on-going questions about

optimization of diagnosis and treatment, but also the underexposed role of psychological determinants in disease outcome.

Thesis outline

Chapter 2 presents the results of a retrospective study on the clinical relevance of repeat renal biopsies in lupus nephritis. The aim of the study was to show that switches from proliferative to non-proliferative classes and vice versa are rare and that repeat biopsies are unnecessary in many cases.

Chapter 3 provides the results of an individualized dosing regimen of MMF through concentration controlled treatment on MPA exposure in patients with proliferative lupus nephritis. This study aimed to examine the effect of therapeutic drug monitoring on renal outcome and the occurrence of side effects.

The influence of two different treatment regimens for proliferative lupus nephritis on HRQoL is presented in chapter 4. The aim of the study was to investigate the effect of high versus low dose immunosuppressive treatment on HRQoL.

In chapter 5 sexual functioning in SLE patients is investigated. This study aimed to assess the influence of SLE on sexual functioning and its associations with illness perceptions and medical and socio-demographic characteristics.

Chapter 6 presents the results of a study on the assessment of illness perceptions of SLE patients. In addition, this study investigated whether perceptions were influenced by type of treatment for proliferative lupus nephritis.

Treatment non-adherence and its associations with psychological and medical parameters are described in chapter 7. The aim of this study was to investigate the determinants of non-adherence in SLE patients.

Chapter 8 provides a general discussion in which the results of these six studies are reviewed and integrated.

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CHAPTER 2

THE CLINICAL RELEVANCE OF REPEAT BIOPSY IN LUPUS NEPHRITIS FLARES

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ABSTRACT

Background The clinical utility of performing repeat biopsies during lupus nephritis flares is questionable and data pointing towards frequent class switches are based on the old WHO classification. This retrospective study investigated the hypothesis that clinically relevant switches from proliferative to non-proliferative lesions and vice versa as determined by the new ISN/RPS classification are a rare event and that repeat biopsies are unnecessary in many cases. *Methods* Thirty-five patients with lupus nephritis and one or more repeat renal biopsies were included. Eighty-four biopsies were blindly reassessed according to the ISN/RPS classification. *Results* Twenty-five patients had one repeat biopsy, six patients had two and four patients had three repeat biopsies. Forty-nine comparisons between reference and repeat biopsies could be made. In 25 cases (54.3%) there was no shift in ISN/RPS class on repeat biopsies. In 41 instances, paired biopsies showed proliferative lesions both on reference and repeated biopsy, whereas five of six cases with non-proliferative lesions on reference biopsy switched to proliferative lesions on repeated biopsy. Clinically significant class switches during lupus nephritis flares were more frequent in patients with non-proliferative lesions in their reference biopsy ($p < 0.001$). *Conclusion* The results show that patients with proliferative lesions in the original biopsy rarely switch to a pure non-proliferative nephritis during a flare. Therefore, a repeat biopsy during a lupus nephritis flare is frequently not necessary if proliferative lesions were found in the reference biopsy. However, in the case of a non-proliferative lesion in the reference biopsy, class switches are frequently found and repeat biopsies are advisable.

INTRODUCTION

Renal biopsy is a pivotal step in determining the nature of renal involvement in patients with lupus nephritis. Up to 60% of patients with SLE develop lupus nephritis.[1] Six classes of lupus nephritis are distinguished in the current classification of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS). Classification and treatment decisions strongly depend on the findings in the renal biopsy. The diagnosis lupus nephritis cannot be based on clinical features alone (e.g. proteinuria, rising serum creatinine, active sediment), since the clinical features do not permit a reliable prediction of the type of SLE nephritis.[2;3] Kidney diseases due to other causes than lupus nephritis may also need to be excluded as a cause of renal damage.[1]

Relapses occur frequently in patients with lupus nephritis, even after an initial complete remission.[4] To determine the most effective treatment in the case of a lupus nephritis flare, a number of authors advise to perform repeat biopsies.[1;5-8] Based on such findings it has been hospital policy at the Leiden University Medical Centre (LUMC) for over 25 years to perform a biopsy before treating renal flares. However, others have suggested that the need for repeat biopsies in renal flares may depend on the type of lupus nephritis in the original biopsy.[4] Conversion from one proliferative form to another (e.g. class III to IV) will usually not influence the choice of current therapeutic regimens. Recent studies investigating the optimal therapy for proliferative lupus nephritis include class III and IV nephritis together in the treatment arms.[9-13] Moreover, treatment guidelines usually do not differentiate between class III and IV nephritis. Therefore, transitions between proliferative classes have no additive value on treatment decisions. Similarly, the addition or disappearance of class V lesions on a second biopsy next to persisting proliferative lesions should not be of great influence on treatment choices, since the prognosis is largely determined by the associated proliferative lesions.[14] Thus only a switch from proliferative to non-proliferative lesions (e.g. class III to V) or vice versa will have clear therapeutic consequences and a reasonable chance to detect such a switch will justify performing a repeat biopsy.

To determine the role of repeat biopsies, this study investigated how often a clinically relevant switch occurred when repeat biopsies were performed for renal flares. Based on the concept that the presence or absence of proliferative lesions determines therapy in lupus nephritis, it was hypothesized that repeat biopsies would only be helpful if switches between purely non-proliferative to proliferative or vice versa were detected. Since haemorrhage remains a concern in the face of renal biopsies, with major complications requiring blood transfusion or invasive intervention in 0-6.4% of biopsies[1], it is desirable only to perform biopsies that will influence treatment. In addition, the discomfort for the patient and the costs of renal biopsies are important factors.

First and successive biopsies were compared for classification according to the new ISN/RPS revision, therapy regimen, and clinical manifestation (e.g. proteinuria and serum creatinine).

METHODS

Study Population

Patients were selected from the electronic database of the patient registration at the LUMC. Inclusion criteria were a diagnosis of SLE and two or more renal biopsies. Thirty-eight patients were included on the basis of these criteria. Thirty patients are under treatment at LUMC for their SLE, four are currently treated elsewhere and four patients are deceased (one male and three females).

Materials and Procedure

Ninety-four biopsies were retrieved from the archive and blindly reassessed by two renal pathologists (IMB and NNTG) by light microscopy. The Renal Biopsy Scoring Form of the Dutch Lupus Nephritis Study[11] was used to record ISN/RPS-classification, activity index and chronicity index. After reassessment, the new classifications were compared with those in the old pathology reports. In the case of notable deviations between the former and new assessment (e.g. a class III on original diagnosis and a class IV on reassessment), the assessment was repeated. Hence, these second assessments

were not blinded. If important electron microscopy (EM) or immunofluorescence (IF) findings were mentioned in the reports, these were added to the classification.

ISN/RPS-classification between first and second biopsy were compared. If patients had more than two biopsies, the second and third and third and fourth biopsies were paired. Thus, the last biopsy performed before the repeat biopsy served as the reference biopsy.

Paper files and the electronic database were consulted to register clinical parameters. Serum creatinine and proteinuria at the time of biopsy were recorded. Hospital correspondence retrieved from the paper files and the electronic database were used to collect date of diagnosis and medical regime following biopsy.

Statistical analysis

Data were analysed using SPSS Version 15.0 software. A Fisher's Exact Test for categorical variables was applied to determine if class switch occurred more often in patients with non-proliferative versus proliferative lesions. Two-sided *P*-values of less than .05 were considered statistically significant.

RESULTS

Ten biopsies were excluded from the study after reassessment. Four biopsy specimens contained no useful material (e.g. solely renal medulla) or inadequate material so that judgement was not possible. Two repeat biopsies were performed as protocol biopsies in the setting of a clinical trial and were excluded. One biopsy performed in a hospital other than the LUMC could not be traced. As a result, three patients and their original biopsies were excluded. The 84 remaining biopsies were included in the analysis.

Material from three biopsies could not be recovered from the archives. Classification of these biopsies was based on careful examination of the old pathology reports. In six cases, IF results, as mentioned in the pathology reports, led to the addition of a class V to the classification. Four specimens were assessed a second time as important discrepancies with the original pathology reports were found. After comparing the results from the biopsy evaluations of the two pathologists with the original reports,

discrepancies were found in only four cases. These only involved minor issues, which were solved by plenary discussion in order to reach a final scoring.

The patient group consisted of 26 females and nine males. The mean age of the total group was 41.5 (*SD* = 10.9). Patients were on average 26.0 years (*SD* = 9.6) when SLE was diagnosed and the mean disease duration at the moment of reassessment of biopsies was 15.5 (*SD* = 6.0) years. Twenty-five patients had one repeat biopsy, six patients had two and four patients had three repeat biopsies. The mean time period between reference and repeated biopsy was 4.1 years (*SD* = 3.6).

Table 1 shows the ISN/RPS classification in the 84 biopsies that were reassessed. Forty-nine comparisons between reference and repeat biopsies could be made. In 25 instances (51.0%), there was no shift in ISN/RPS class on repeated biopsy. This concerned 19 cases of class IV (35.7%), three of class III+V (7.1%), one of class III (2.4%), one class of VI (2.4%), and one of class IV+V (2.4%). The most frequent transitions occurred between class IV and III (54.2%), with five transitions in both directions, two shifts of class III + V to class IV, and one from class IV+ V to class III.

Table 1. ISN/RPS classifications on repeated biopsy

	Reference Biopsy								
	I	II	III	IV	V	VI	II+V	III+V	IV+V
Repeat Biopsy									
I	0	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0	0
III	0	0	1	5	0	0	0	0	1
IV	0	1	5	19	2	0	0	2	0
V	0	0	0	1	0	0	0	0	0
VI	0	0	0	0	0	1	0	0	0
II+V	0	0	0	0	0	0	0	0	0
III+V	0	0	0	2	1	0	1	3	0
IV+V	0	0	0	2	0	0	0	0	1
Other	0	0	0	1	0	0	0	0	0

Table 2 shows the changes from proliferative to non-proliferative lesions and vice versa between the reference and repeated biopsies. In 41 instances (84%), the reference biopsy as well as the repeated biopsy showed proliferative lesions. One patient with proliferative lesions in the reference biopsy showed extensive glomerular amyloid depositions in the repeat biopsy.

Table 2. Proliferative versus non-proliferative

	Reference Biopsy	
	Proliferative	Non-proliferative
Repeat biopsy		
Proliferative	41	5
Non-proliferative	1	1
Glomerulosclerosis	1	0

$p < .001$.

Figure 1 illustrates the presence of proliferative lesions in three successive biopsies from a representative patient. Five cases (10%) with pure non-proliferative lesions on reference biopsy switched to proliferative lesions on repeated biopsy. This indicates that clinically relevant class switches were more frequent in patients with non-proliferative lesions in the reference biopsy ($p < .001$).

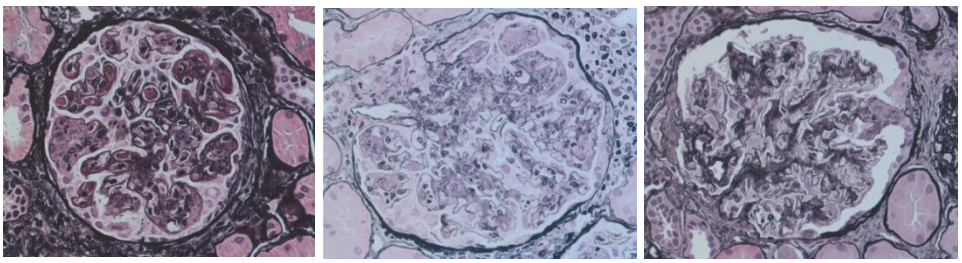

Figure 1. Example of a patient with proliferative lesions in three successive biopsies (class IV, IV and III respectively).

The mean renal activity index on first biopsy was 6.18 (*SD* = 4.43) and 5.27 (*SD* = 3.84) on repeated biopsy ($p = .315$). The mean chronicity index for the first biopsy was 2.62 (*SD* = 2.53) and 4.20 (*SD* = 2.39) for the repeated biopsy ($p < .001$).

Data on serum creatinine and proteinuria at the time of biopsy could be retrieved for 45 out of the 49 instances of reference as well as repeat biopsy. Because of the missing values, the presence of a high creatinine and/or the extent of proteinuria could be determined in 43 instances of reference biopsy and in 42 cases of the repeat biopsy. The most frequent clinical manifestation of nephritis at the time of biopsy consisted of nephrotic range proteinuria in combination with a progression of renal failure, in 20 instances (46.5%) at the time of reference biopsy and in 19 cases (45.2%) of repeat biopsy (Table 3).

Forty-one comparisons of clinical presentation on reference versus repeat biopsy could be made. In 24 instances (58.5%) a change in presentation was seen, whereas in 17 (41.5%) cases the clinical manifestation at repeat biopsy had not changed.

Table 3. Clinical manifestation at the time of reference versus repeated biopsy

	Reference biopsy	Repeat biopsy
Proteinuria > 3.5 g/24hrs	10	7
Proteinuria > 3.5 g/24hrs + serum creatinine > 106 umol/L	20	19
Proteinuria < 3.5 g/24hrs	10	7
Proteinuria < 3.5 g/24hrs + serum creatinine > 106 umol/L	4	9
Total	43	42

Data on therapy could not be retrieved for six patients before biopsy, in three cases of reference biopsy and in eight instances of repeat biopsy. As a result, comparison of treatment regimen before and after reference biopsy and on reference versus repeat biopsy could not be made in seven and nine cases, respectively.

Nineteen patients received an increase in immunosuppression after reference biopsy (Table 4). In three instances therapy remained unchanged and in one case immunosuppressive therapy was decreased or stopped. After repeated biopsy, a comparable number of patients received an increase in immunosuppression, but immunosuppression was decreased or stopped more often than after reference biopsy.

Table 4. Alterations in immunosuppressive therapy after biopsy

	After reference biopsy	After repeat biopsy
Increased immunosuppression	19	21
Decreased/stopped immunosuppression	1	8
No change	3	8
Other	5	3
Unknown	7	9
Total	35	49

A clear shift from single steroid use before biopsy (55.2%) to a combination of steroids and immunosuppression after reference biopsy (80.4%) was found (Table 5). In two instances of reference biopsy and in two cases of repeat biopsy no immunosuppressive therapy was initiated on the basis of the biopsy results. As for the reference biopsies this comprised two cases of class III. A repeat biopsy that was reassessed as a class IV in the present study was originally misdiagnosed as a lupus nephritis in remission. The second repeat biopsy that did not result in therapy concerned a class VI nephritis.

Table 5. Treatment regimens

	Pre-biopsy	After reference biopsy	After repeat biopsy
Steroids alone	16 (55.2%)	5 (10.9%)	3 (7.3%)
Steroids + immunosuppression	5 (17.2%)	37 (80.4%)	33 (80.5%)
Steroids + AZA	3 (10.3%)	25 (54.3%)	15 (36.6%)
Steroids + AZA + Other	1 (3.4%)	2 (4.3%)	1 (2.4%)
Steroids + Other	1 (3.4%)	1 (2.2%)	0 (0)
Steroids + CYC	0 (0)	8 (17.4%)	10 (24.4%)
Steroids + MMF	0 (0)	0 (0)	3 (7.3%)
Steroids + CYC + MMF	0 (0)	1 (0)	4 (9.8%)
Other	6 (20.7%)	1 (2.2%)	3 (7.3%)
None	2 (6.9%)	3 (6.5%)	2 (4.9%)
Total	29	46	41

DISCUSSION

This retrospective study investigated the hypothesis that clinically relevant switches in lupus nephritis from proliferative to non-proliferative lesions and vice versa as determined by the new ISN/RPS classification are a rare event and that repeated biopsies during flares are unnecessary in many cases. The results show that patients with proliferative lesions on their original biopsy rarely switch to a pure non-proliferative nephritis during a flare. However, in the case of a non-proliferative lesion in the reference biopsy, class switches are frequently found.

A number of studies report a high degree of transformation from one WHO class to another on repeated biopsy.[5-8;15-20] Class switch is thought to be a characteristic of lupus nephritis.[4] Studies that assessed biopsy specimens according to the old WHO-classification showed class switch in 26% to 50% of repeated renal biopsies.[8] The present study used the new ISN/RPS classification in the assessment of the renal biopsies, but similar results were found with class switch in 49% of instances. A switch between class III and IV (with or without an additional class V) was the most frequent (54.2%). A predominance of transitions between class III and IV (with or without an additional class V) has been reported in several studies.[8;15;17] In a study by Moroni et al. (1999)[8] 42.9% of transitions occurred between class III and IV. Another study found 4 transitions from class III to IV, which comprised 36.4% of all shifts.[15]

Transitions in WHO class in other studies on repeat biopsies is variable, but the direction of the majority of transitions in five studies is remarkable. Two studies found the most frequent switches from class IV to a class II or V, in 50%[16] and 65.2%[6] of cases, and two other studies showed the most shifts from class III or IV to a class II or V (60.7%[7] and 61.1%).[19] In a fifth study with only class IV on first biopsy, 56% of patients had switched to a class III on repeated biopsy.[20] The high frequency of transitions from a class III or IV to a class II or III could be the result of the fact that repeat biopsies were not performed for clinical reasons but according to protocol[6;7;19;20] or postmortem.[16] As the present study only pertains to repeat biopsies on account of a clinical manifestation of a lupus nephritis

flare, we cannot address the role of protocol biopsies in the management of patients with lupus nephritis.

Numerous authors advise serial renal biopsy in the management of lupus nephritis.[5-8] Bajaj et al. (2000)[5] reported that all therapeutic decisions were influenced by the repeated biopsy results, with no change in therapy in 23% of patients and either an increase or decrease in therapy in the remaining 77% of patients. However, repeat biopsies are performed because of the presence of the clinical manifestation of a lupus nephritis flare. Without a repeat biopsy, patients may have been treated on clinical grounds alone. The biopsy results could only help to choose or confirm therapy choice. Therapy change itself after biopsy does not prove that the therapy would not have been changed without a biopsy.

Eighty-four percent of transitions in this study consisted of a switch from one proliferative form to another. The detection of these transformations within the proliferative group does not have clear therapeutic consequences and does not justify the performance of repeat biopsy during a flare. The application of similar therapeutic schedules for all proliferative forms of lupus nephritis is justified by recent studies investigating the efficacy of therapy in proliferative lupus nephritis. In these studies, no distinction between the different proliferative classes is made.[9-13] In addition, the recent lupus nephritis European consensus statement does not differentiate in the treatment of class III and IV lupus nephritis.[21] Moreover, it has been proposed that transitions from focal to diffuse proliferative nephritis might indicate a progression of the same type of nephritis rather than a true transition.[15;17;22;23] Additionally, since the difference between class III and IV lupus nephritis is defined as less or more than 50% of the glomeruli having proliferative lesions, a class switch may also be explained by sampling error in borderline cases. Clearly more studies are necessary to define whether significant pathophysiological and clinical differences between class III and IV lupus nephritis exist.

If the majority of patients who flare remain in the same proliferative class or switch to another proliferative form and assuming that proliferative lesions are treated alike, no difference between therapy regimen after initial biopsy and after successive biopsy would be expected. However, in 77.5% of cases, treatment schedule differed after reference versus repeat biopsy in the present study. The mean time between initial and repeated biopsy was 4.1 years, which can explain the lack of consistency in treatment policy in the case of successive proliferative lesions. Pharmaceutical developments could have led to new insights in treatment strategy and new alternatives. Therapy schedules were often difficult to recover, accounting for the amount of missing data (nine comparisons could not be made) and could have resulted in incomplete data.

Interestingly, only one case of class II nephritis was diagnosed in our group of patients who had repeat biopsies. This is probably the result of a conservative biopsy policy at LUMC. Since some mesangial abnormality is present in all patients with SLE[7;15;16], the earlier in the course of lupus nephritis the biopsy is taken the more cases of class II nephritis will be found.

Although the immediate clinical relevance of serial renal biopsy may be limited, repeat biopsies could have a prognostic value.[6;8;11;24;25] One study allocated a good predictive power to systematic repeat biopsies at six months after the start of treatment for proliferative lupus nephritis since they provided a measure of the response to therapy.[24] Patients who did not respond fully to treatment, as reflected by continuing inflammatory lesions at six months, were more likely to show a worse response on treatment for a lupus nephritis flare and showed more accumulation of chronic damage. Esdaile et al. (1993)[6] state that the amount of electron-dense deposits, especially subendothelial deposits, at protocolized repeat biopsy two years after the start of treatment for all classes of lupus nephritis is the best predictor of renal outcome as well as mortality. In addition, a prognostic association of the chronicity index (CI) and mortality was found.

In contrast, a randomized controlled trial found that repeat biopsies were not predictive of outcome.[11] Although the CI was significantly increased on repeat protocolized biopsy 2 years after initiating treatment for proliferative lupus nephritis, it could not predict outcome. The authors suggest that clinical parameters in patients with lupus nephritis are more informative than are findings on repeat renal biopsy.

Only two known studies investigated the prognostic value of repeat biopsies in the face of a flare and both report a predictive association of high CI scores and poor renal outcome.[8;25] Moroni et al. (1999)[8] found an association between a CI of 5 or greater and a doubling plasma creatinine level in the long term. In addition, they state that the presence of extracapillary proliferation demands aggressive treatment to prevent irreversible renal failure.

Whether repeat renal biopsies have prognostic value was not addressed in the present study. The two known studies do indicate an association, especially with regard to the CI, but data are too scarce to make a definite conclusion. Moreover, the application of the CI as a measure of outcome seems questionable, since the reproducibility of the CI remains moderate.[26-28]

The most frequently mentioned and most important reason to perform a repeat biopsy is to decide on a treatment strategy in the case of a lupus nephritis flare. However, if evaluation of the biopsy specimen will show transition to another proliferative form in the majority of cases and if these forms receive the same treatment, repeated biopsy becomes unnecessary in these instances. This study did find a significant class switch to proliferative forms in patients with non-proliferative lesions in their reference biopsy. Based on these results, it seems that patients with a class V nephritis should be followed closely. If these patients flare or show a progression in renal failure a re-biopsy may be indicated to exclude the development of proliferative lesions.

On choosing a policy in which repeat biopsies are only performed in patients who flare and had non-proliferative lesions on initial biopsy, it remains uncertain what strategy to follow in the case of prolonged mild deviations. When a patient maintains mild but substantial proteinuria, which does not improve on therapy, it can be difficult to uncover

whether this reflects chronic damage or activity. In these selected cases a renal biopsy should be considered. Although pure sclerotic lesions were only found in one repeat biopsy in our series, it may be difficult to clinically distinguish a mild flare from proteinuria and worsening renal function due to glomerulosclerosis in some patients. In these cases a biopsy will be necessary to guide appropriate treatment and prevent inappropriate immunosuppression. Similarly, a biopsy may be helpful in patients with very poor renal function where severe chronic damage may contribute to the decision to withhold aggressive treatment.

It should be noted that the results of this study might not be applicable to every patient group. The participant group in this study consisted mostly of individuals of Caucasian descent. It is well known that patients with SLE of African descent have a more aggressive course of disease and poorer outcomes.[29] A similar study with this patient group should be performed before a recommendation about biopsy policy can be given.

In conclusion, the clinical relevance of repeat biopsy in lupus nephritis seems to be limited. In the case of non-proliferative lesions on reference biopsy, repeated biopsy is advisable in the presence of clinical deterioration since a switch to more proliferative lesions is often found. If a patient with proliferative lesions on a previous biopsy presents with a renal flare, appropriate induction treatment can be initiated without additional biopsies, since repeated biopsy will show similar lesions in most cases.

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CHAPTER 3

CONCENTRATION CONTROLLED TREATMENT OF LUPUS NEPHRITIS WITH MYCOPHENOLATE MOFETIL

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ABSTRACT

Background Mycophenolate mofetil (MMF) has recently been established as a potent drug in maintenance treatment for lupus nephritis. However, there is no consensus on the optimal dosing regimen due to a high inter-individual variability of mycophenolic acid (MPA), the active metabolite of MMF. This retrospective study aimed to investigate the effect of an individualized dosing regimen through concentration controlled treatment on MPA exposure and renal outcome in patients with lupus nephritis. *Methods* Sixteen patients with lupus nephritis and treatment with low dose intravenous cyclophosphamide followed by MMF were included. MPA area under the plasma concentration-time curve from 0 to 12 hours (MPA-AUC_{0-12}) was assessed within a month after MMF initiation. After determination of MPA-AUC_{0-12}, MMF doses were titrated to achieve a target MPA-AUC_{0-12} of 60-90 mg*h/l. After on average six months, MPA-AUC_{0-12} measures were repeated to assess the effect of dose adjustment. *Results* One month after introducing MMF, MPA-AUC_{0-12} was low and showed a high inter-individual variability. Dose adjustment with a target MPA-AUC_{0-12} of 60-90 mg*h/l resulted in individualized MMF dosing, significantly higher MPA-AUC_{0-12} levels and a non-significant reduction in variability of MPA-AUC_{0-12}. Adverse effects were reported by 37.5% of patients, which resulted in a switch to azathioprine in two patients. There was no significant relationship between the occurrence of adverse effects and MPA-AUC_{0-12}. At 12 months of follow-up 87.5% of patients had achieved either partial (18.7%) or complete (68.8%) remission. *Conclusion* Concentration controlled dose adjustments with a target MPA-AUC_{0-12} of 60-90 mg*h/l was associated with optimized MPA exposure and an excellent renal outcome at 12 months of follow-up in a small sample of SLE patients with lupus nephritis.

INTRODUCTION

Lupus nephritis is a prevalent organ involvement in systemic lupus erythematosus (SLE) and affects up to 60% of patients.[1] Renal involvement is strongly related to a high morbidity and mortality in SLE, but early and intensive treatment can greatly improve renal outcome.[2] For decades the first choice of treatment for severe lupus nephritis consisted of high doses intravenous cyclophosphamide (IVC) in combination with corticosteroids, known as the NIH regimen.[3] This regimen with high IVC doses has shown variable results as a remission induction and maintenance therapy in proliferative lupus nephritis.[4-6] In addition, the high incidence and severity of IVC related adverse effects[4] has resulted in a search for less toxic alternative therapies. Among these alternatives, the Euro-Lupus regimen with low dose IVC as remission induction followed by azathioprine (AZA) as maintenance therapy has been shown to be an equally effective and safe therapy.[7] Also at a 10 years follow-up, the Euro-Lupus regimen did not differ from the NIH regimen in terms of clinical outcomes.[8]

Another frequently studied drug for treatment of lupus nephritis is mycophenolate mofetil (MMF). MMF as remission induction treatment has shown to be at least equivalent in terms of efficacy and safety compared to high dose IVC.[9] In addition, some studies have reported better clinical outcome and less drug related adverse events with MMF.[10] Although both MMF and AZA have been established as effective maintenance treatments, contradictory results have been published on the optimal maintenance regimen. One recent study found MMF to be superior to AZA in preventing renal flares in patients with a good response after 6 months induction treatment with either MMF or IVC.[11] However, the MAINTAIN trail in which maintenance treatment with MMF was compared to AZA after induction treatment with low dose IVC showed no difference in the incidence of renal flares.[12]

The inconsistent findings in the differences in clinical outcome between MMF and AZA maintenance therapy may be influenced by the fact that the optimal MMF dose in lupus nephritis is unknown and different dosing regimens have been applied. Although MMF has become an important drug in the management of SLE, it is not officially

registered for treatment of lupus nephritis and formal dosage recommendations are unavailable. As a result, dosages have been based on experience in the renal transplantation setting. In kidney transplantation patients, doses below 1 g/d have been associated with a higher risk of graft rejection[13], while doses above 3 g/d have been related to an increased occurrence of drug related adverse effects.[14] Therefore, MMF trials for lupus nephritis have applied dosages between 1 to 3 g/d and adjustments were made based on therapeutic response and side effects.[15] In current clinical practice of maintenance therapy for lupus nephritis, MMF is generally administrated at a fixed starting dose of 2 g/d. However, studies in renal transplantation patients have also shown that the pharmacokinetics of mycophenolic acid (MPA), the active metabolite of MMF, exhibit a considerable variability between individuals and over time.[16;17] A high inter-patient variability of MPA has also been found in patients with autoimmune diseases, including SLE[18;19], and more specifically in SLE patients with lupus nephritis.[20;21]

Because of these characteristics of MPA exposure and its associations with clinical outcomes, establishing individualized dosing regimens by means of therapeutic drug monitoring (TDM) is considered essential in MMF treatment in SLE patients.[18;19;21-23] In addition, therapeutic target levels of MPA area under the plasma concentration time curve (MPA-AUC) above 35 and 45 mg*h/l have been recommended to achieve good response based on retrospective data.[21;24] To our knowledge, no study has reported on the actual implementation of such therapeutic target ranges and its influence on MPA exposure and treatment outcome. Therefore, the aim of the present study was to report our experience with optimized dosing of MMF with a target MPA-AUC_{0-12} of 60-90 mg*h/l after induction treatment with low dose IVC according to a modified version of the Euro-Lupus protocol in SLE patients with proliferative lupus nephritis.

METHODS

Patients

From 2005 onwards the patients presenting with proliferative lupus nephritis to the nephrology and rheumatology departments at the Leiden University Medical Centre (LUMC) were treated with low dose IVC (six pulses of 500 mg in three months) followed by MMF with a starting dose of 2 g per day. As part of local hospital policy, after determination of MPA-$AUC_{0\text{-}12}$, MMF doses were titrated to achieve a target MPA-$AUC_{0\text{-}12}$ of 60-90 mg*h/l. All included patients had SLE according to the revised American College of Rheumatology criteria.[25] For this retrospective cohort study 16 patients were identified with a total of 28 registered MPA measurements. The majority of patients were of Caucasian descent (75%).

Pharmacokinetic analyses

MPA concentration measures were derived from blood samples that have been taken for therapeutic drug monitoring (TDM) purposes. Prior to sampling, patients had held a 12-hour overnight fast. Blood samples were taken before the administration of MMF morning dose and one, two, and three hours after intake.

Samples were analyzed for MPA by high performance liquid chromatography (HPLC). TDM was performed on the basis of the limited sampling strategy and Bayesian estimation of the MPA clearance using MW/Pharm version 3.5 (Mediware, Groningen, The Netherlands) as previously described.[26] MPA oral clearance was used to calculate MPA-$AUC_{0\text{-}12}$. Therapeutic dose adjustments based on MPA-$AUC_{0\text{-}12}$ measurements were also recorded.

Outcome measures

The following disease activity parameters were recorded at the time of MPA exposure measurement: hemoglobuline (Hb), serum and urinary creatinine levels, serum albumin levels, proteinuria, and glomerular filtration rate according to the Modification of Diet in Renal Disease (MDRD) study equations. In addition, serum creatinine, serum

albumin and proteinuria were registered three months prior to initiation of MMF treatment, and 0, three, six, nine, and 12 months after the start of treatment.

Treatment response was assessed at six and 12 months. The following three response categories were defined: 1) complete response: proteinuria below 0.5 g/day and stable serum creatinine levels or less than 25% higher than at the start of treatment, 2) partial response: more than 50% reduction in proteinuria and no increase in serum creatinine levels, and 3) failure: not reaching the criteria for partial response.

Statistical analyses

Data were analysed using SPSS software version 17. Descriptive statistics and frequencies were obtained for the patient characteristics. Independent t-tests were used to investigate differences in MPA exposure between first and second measurements and to assess changes in disease activity parameters. Associations between MPA-AUC_{0-12} and disease activity parameters were explored with Pearson correlation coefficients. ANOVA was used to test differences in MPA-AUC_{0-12} between treatment response groups. An alpha level of .05 was used for all statistical tests.

RESULTS

Patient characteristics

All 16 patients were treated with low dose IVC followed by MMF for an episode of proliferative lupus nephritis. Five patients were diagnosed with a class III, 11 with a class IV. This was the first episode of proliferative lupus nephritis for 10 patients and six patients experienced a renal flare. Previous episodes of lupus nephritis had been treated with IVC and corticosteroids (two), IVC and azathioprine (one), MMF and corticosteroids (one), or azathioprine and corticosteroids (two). 93,7% of patients used one or more anti-hypertensive drugs at time of treatment for lupus nephritis: 73.3% ACE inhibitors, 40.0% AT-II antagonists, 20.0% calcium antagonists, 20.0% diuretics, and 13.3% beta blockers.

Twelve patients had two or more measurements of MPA blood concentrations. The first measurement before dose adjustment was performed on average 32.6 (*SD* = 27.7) days after the start of MMF maintenance treatment. The second MPA levels that

were assessed after dose adjustment took place on average 6.6 (*SD* = 7.2) months after the first measurement. Patient characteristics before dose adjustment are shown in Table 1.

Table 1. Patient characteristics at first MPA-AUC_{0-12} (before dose adjustment) (N = 16)

Male (N, %)	1 (6.3%)
Age in years (SD)	33.2 (12.1)
Weight in kg (SD)	67.0 (11.5)
Serum albumin (SD)	39.2 (5.7)
Serum creatinine (SD)	98.6 (55.0)
Hemoglobin (SD)	7.1 (.99)
Proteinuria (SD)	1.3 (1.3)
MDRD (SD)	78.3 (36.8)
MMF dose g/day (SD)	1.9 (.29)

Before the start of MMF, four patients (25.0%) had already reached complete remission, four patients (25.0%) showed partial remission and eight patients (50.0%) were labeled as failures. After six months of MMF treatment, 10 patients (62.5%) had completely responded, four patients (25.0%) showed a partial response, and two patients (12.5%) were classified as non-responders. At 12 months, one patient had switched from a partial to a complete response.

Pharmacokinetics

On the basis of the first MPA-AUC_{0-12} measurement, dose adjustments were made in 13 of 16 patients (81.3%). In two patients MMF dose was reduced and 11 patients received a dose increase. MMF dose was on average 1.9 g (*SD* = .29) before and 2.6 (*SD* = .82) after first MPA-AUC_{0-12} measurement. Figure 1 depicts the dose adjustments in the 12 patients who had repeated MPA-AUC_{0-12} determinations. The dose range was 1-2 g/24h before the first MPA-AUC_{0-12} and 1.5-4 g/24h before the second MPA-AUC_{0-12}.

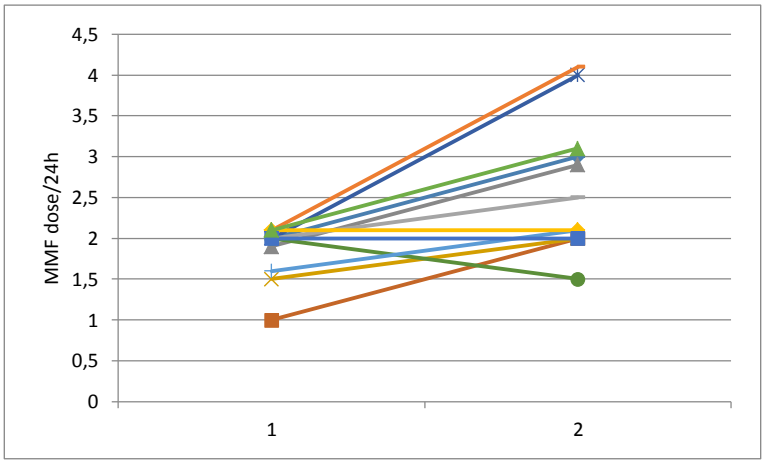

Figure 1. MMF dose/24h at first (1) and second (2) MPA-$AUC_{0\text{-}12}$ (N = 12).

Figure 2a shows the mean MPA levels before and after dose adjustment for four different time points after MMF administration in the 12 patients who had at least two MPA-$AUC_{0\text{-}12}$ measurements. Mean MPA level after dose adjustment was significantly higher one hour after MMF intake (p = .023).

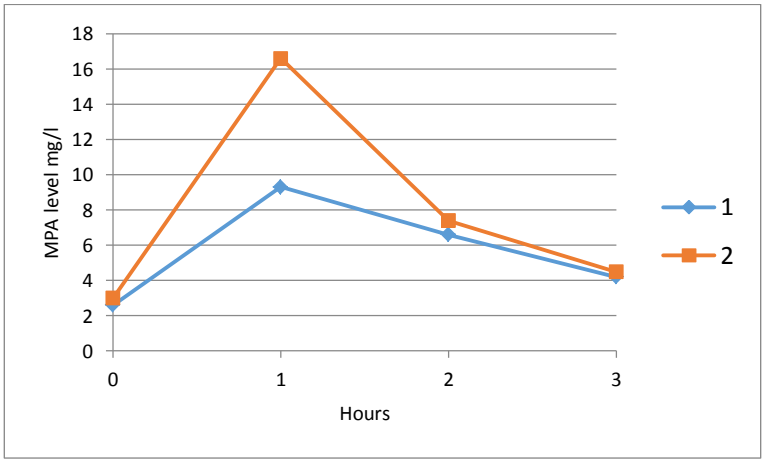

Figure 2a. MPA level (mg/l) before (1) and after (2) dose adjustment.

The mean MPA-AUC_{0-12} levels before and after dose adjustment are depicted in Figure 2b. Mean MPA-AUC_{0-12} before dose adjustment was significantly lower than after dose adjustment (*M* = 46.5, *SD* = 24.3 vs. *M* = 69.3, *SD* = 19.4; *p* = .018). In addition, MPA-AUC_{0-12} levels tended to be less variable after dose adjustment (*SD* = 24.3 versus *SD* = 19.4), although the difference in variances was not significant (*p* = .456).

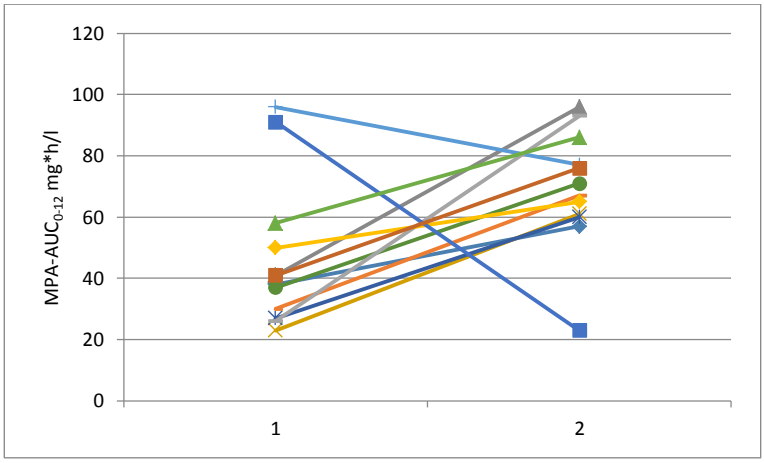

Figure 2b. MPA-AUC_{0-12} before (1) and after (2) dose adjustment (N = 12).

MPA-AUC_{0-12} was significantly correlated with levels at 0, one, two, and three hours after MMF administration (*r* = .79, .62, .60, .52, all *p* < .001). There was no significant relationship between MPA-AUC_{0-12} and serum albumin (*r* = .270, *p* = .212), proteinuria (*r* = -.18, *p* = .468), or creatinine clearance (*r* = -.275, *p* = .174).

Renal outcome

The efficacy of MMF therapy was evaluated by the follow-up of proteinuria, serum creatinine, and serum albumin levels. Twelve months after the start of MMF treatment proteinuria levels had significantly decreased (*M* = 2.18 g/day, *SD* = 1.60 vs. *M* = .72 g/day, *SD* = .95; *p* = .007) (Figure 3). Serum creatinine remained stable over time (*M* = 92.38 µmol/l, *SD* = 68.32 vs. *M* = 92.00 µmol/l, *SD* = 50.24; *p* = .986). Albumin levels showed a marked increase from a mean value of 38 g/l (*SD* = 5.31) to 43.0 g/l (*SD* = 3. 82; *p* = .008).

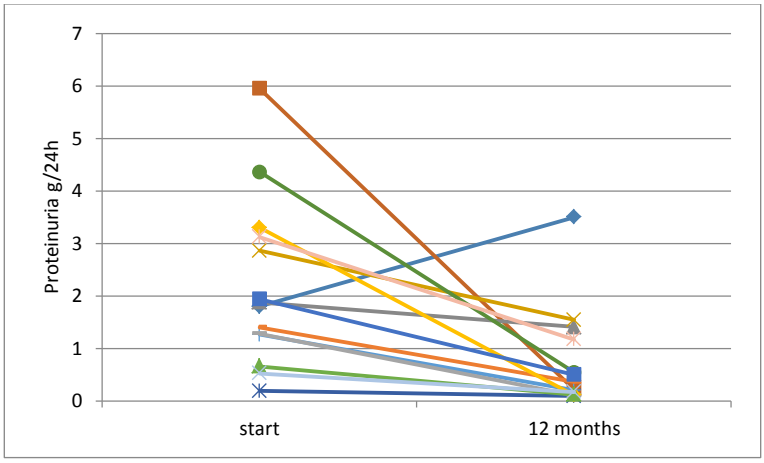

Figure 3. Proteinuria (g/24h) at start of MMF treatment and at twelve months follow-up.

Adverse events

Adverse effects were reported by six patients (37.5%). One patient (16.7%) ended MMF treatment after three weeks because of ongoing nausea and vomiting and switched to AZA as maintenance therapy. Two patients (33.4%) also experienced gastrointestinal complaints such as nausea, cramps and diarrhea, but no dose adjustments were made. One patient (16.7%) switched to AZA after two years because of recurrent episodes of sinusitis. Recurrent infections were experienced by three other patients (50%) as well. Sleeping disturbances were reported by one patient (16.7%).

There was no significant relationship between the occurrence of adverse effects and MPA-$AUC_{0\text{-}12}$ (p = .293).

DISCUSSION

This is the first study to report on the effect of MPA concentration controlled treatment on MPA exposure and renal outcome in a cohort of SLE patients with proliferative lupus nephritis. The findings indicate that adjusting MMF dose aimed at a target MPA-$AUC_{0\text{-}12}$ of 60-90 mg*h/l results in individualized MMF dosing with increased MPA exposure and decreased inter-individual variability. In addition, this individualized dosing regimen of MMF in the context of a modified version of the Euro-Lupus protocol was associated with a good renal outcome with 87.5% of patients showing partial or complete response after 12 months of MMF treatment.

MMF has recently been established as an effective drug in both the induction and maintenance treatment of lupus nephritis.[12;27;28] However, it remains unclear whether it is superior to alternative therapies such as high dose IVC or the Euro-Lupus regimen with low dose IVC followed by AZA. In the present study, patients were treated according to a modified version of the Euro-Lupus regimen with low dose IVC followed by MMF instead of AZA. A recently published long-term study of the ALMS group found MMF to be superior to AZA in maintaining renal response to treatment and in preventing renal relapse.[11] In addition, fewer patients in the MMF group withdrew due to adverse effects.[11] However, most previous studies failed to find differences in efficacy or adverse events between MMF and AZA maintenance therapy.[12;27;29] Among these studies is the long-term MAINTAIN Nephritis Trial, which did find fewer renal flares in the MMF group (19% vs. 25%), but this difference was not significant.[12]

Studies investigating the difference in clinical outcome between MMF and AZA maintenance therapy administrated MMF at a fixed dose. However, studies into the pharmacokinetics of MMF have suggested that results with MMF may be further improved through concentration controlled treatment.[19;21] Because exposure to MPA, the active metabolite of MMF, has been found to have a high inter-individual variability, concentration controlled treatment is considered to have a pivotal role in MMF therapy**.** This high inter-individual variability has been reported across various patient groups

including renal transplantation[30], autoimmune disease in general[18;22], and SLE[19;24] and lupus nephritis in particular.[20;21] Guidelines for therapeutic target ranges for MMF therapy in SLE patients have been proposed for MPA-AUC_{0-12}[21;31] and trough levels.[19;22] MPA-AUC_{0-12} levels above 45 mg*h/l have been shown to precisely distinguish responders from non-responders in lupus nephritis patients who were treated with MMF and prednisone.[21] In addition, a more precise differentiation of MPA-AUC_{0-12} levels was associated with response rates of 60 and 100% for MPA-AUC_{0-12} levels of 30-60 mg*h/l and > 60 mg*h/l, respectively.[21]

Although pharmacokinetic monitoring based on MPA-AUC_{0-12} levels is considered to be the golden standard to measure MPA exposure, the application in real life is impractical because of the numerous blood samplings. Limited sampling strategies up to three hours after MMF administration[32] and even single point trough levels have been shown to be good alternatives in patients with SLE.[19;22]

The present study used sampling times up to three hours after MMF intake to calculate MPA-AUC_{0-12} and showed that concentration controlled treatment with a target MPA-AUC_{0-12} of 60-90 mg*h/l resulted in exposure within the target range. Although MPA-AUC_{0-12} levels were low with a mean of 46.5 mg*h/l before dose adjustment, MPA-AUC_{0-12} levels increased to an average of 69.3 mg*h/l after dose adjustment. In addition, inter-individual variability in MPA exposure tended to be lower on second measurement of MPA-AUC_{0-12} levels. But also levels at 0, one, two, and three hours after MMF administration showed significant associations with MPA-AUC_{0-12} levels. Hence, both limited sampling strategies in combination with population pharmacokinetics as well as single point trough levels are potential alternatives to the extensive MPA-AUC_{0-12} measurements. The choice for one method over the other could be based on the availability of resources and/or personal preference of the patient or treating physician.

Another alternative for TDM that has not been addressed in the present study, is the use of inosine 5'monophosphate dehydrogenase (IMPDH). IMPDH is a rate-limiting enzyme and inhibition by MPA results in a decreased proliferation and recruitment of monocytes and lymphocytes to areas of inflammation.[33] IMPDH has been suggested as a

promising biomarker of MPA pharmacodynamic activity in renal transplant patients and childhood-onset SLE patients, with an additional role in determining MMF starting dose in the SLE group.[34] However, studies with less specific cohorts of SLE patients have not been performed and no standardized analytical protocol exists to determine IMPDH.[35] Hence, more studies are needed to validate the use of IMPDH in TDM in SLE patients with lupus nephritis.

Previous studies have indicated that the variability in MPA exposure between SLE patients cannot be explained by differences in MMF dose.[18;19;21] Instead, associations have been found for creatinine clearance[18;24], albumin levels[24], and immunological markers (i.e., anti-dsDNA and complement).[19;24] Although comparable determinants of variability have been reported in renal transplantation patients, the most important influence in this group has been ascribed to the use of concomitant medications.[30] Especially the administration of calcineurin inhibitors next to MMF has been shown to influence MPA exposure. In lupus nephritis, MMF treatment is often combined with the use of prednisone. However, there does not seem to be a relationship between glucocorticoid dose and MPA-$AUC_{0\text{-}12}$.[36]

Associations between MPA-$AUC_{0\text{-}12}$ and disease parameters were also investigated in the present study, but the previously reported associations of MPA-$AUC_{0\text{-}12}$ with serum albumin and creatinine clearance could not be confirmed. It should be noted that the findings of previous studies are partly based on a cohort of SLE and ANCA-associated small vessel vasculitis patients together.[18] In addition, it is not the first time that these findings could not be replicated in a group of SLE patients only.[19] This may suggest that there are other variables that influence MPA variability in SLE patients, such as the aforementioned immunological markers[19] or genetic factors which have been reported in renal transplantation patients.[37] Studies with larger cohorts are needed to assess the determinants of variability in MPA exposure in patients with lupus nephritis.

Pharmacokinetic monitoring in MMF therapy has not only been recommended because of the high inter-patient variability in MPA exposure, but also because MPA exposure has been related to clinical outcomes. In patients with autoimmune diseases (including SLE), higher exposure has been associated with lower disease activity[24] and better protection from recurrence of active disease.[22] One study has even suggested that MPA-AUC_{0-12} is a better predictor of renal outcome than clinical or standard laboratory measures in patients with lupus nephritis.[21] In the present study, an individualized dosing regimen with a target MPA-AUC_{0-12} of 60-90 mg*h/l was associated with a good renal outcome after six and 12 months of treatment. The majority of patients were either partial or complete responders and only two patients (12.5%) failed to respond to MMF therapy.

Although pharmacokinetic studies in renal transplantation patients have shown a relationship between high MPA concentrations and the occurrence of adverse events[14], previous studies which have focused solely on SLE patients did not find a similar association.[19;21] Also in the present study, adverse events were not related to MPA-AUC_{0-12} levels. Two patients discontinued MMF treatment because of side effects, but one patient only switched after two years of treatment in which complete remission had been achieved. In general, the percentage of patients with adverse effects was low and side effects were well tolerable. This favorable outcome appears to be an additional positive effect of concentration controlled treatment.

Limitations of the present study are the small sample size and the lack of a control group. However, our patient population was homogenous in duration of MMF treatment and the circumstances of MMF initiation (i.e., after six pulses of low dose IVC). This makes the results relevant for SLE patients with proliferative lupus nephritis who are treated with low dose IVC followed by MMF. Of course a randomized controlled trial comparing fixed dose to concentration controlled treatment would be necessary to determine the clinical superiority of an optimized dosing regimen in patients with lupus nephritis with certainty. In addition, the study did not include patients with membranous

lupus nephritis, so that the results only pertain to patients with pure proliferative lupus nephritis.

In conclusion, concentration controlled dose adjustments with a target MPA-AUC_{0-12} of 60-90 mg*h/l resulted in optimized MPA exposure and decreased variability. Moreover, in the context of a modified version of the Euro-Lupus protocol this individualized dosing regimen was associated with an excellent renal outcome at 12 months of follow-up. An optimized dosing regimen through concentration controlled treatment appears to result in a better efficacy and safety profile in lupus nephritis.

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CHAPTER 4

HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND PROLIFERATIVE LUPUS NEPHRITIS

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ABSTRACT

Background The present study investigated the influence of two different treatments for a kidney inflammation (i.e., proliferative lupus nephritis) on health-related quality of life (HRQoL) in patients with the chronic, autoimmune disease systemic lupus erythematosus (SLE). One treatment protocol, the National Institutes of Health (NIH) protocol, was characterized by a high dose of cyclophosphamide (CYC; an immunosuppressive drug), and the second treatment, the Euro-Lupus protocol, involved a low dose CYC. *Methods* Thirty-two SLE patients were included based on a received treatment for an episode of proliferative lupus nephritis according to either the Euro-Lupus or NIH protocol. The two groups were compared on HRQoL as measured by the Medical Outcomes Study Short Form 36 (SF-36) and the SLE Symptom Checklist (SSC). *Results* The Euro-Lupus group (N = 16) tended to show a higher HRQoL than the NIH group (N = 16) on four of seven scales of the SF-36. In addition, the Euro-Lupus group experienced less burden of the symptom nausea/vomiting than the NIH group as assessed by the SSC. Fatigue was the most disturbing symptom in both groups. The most burdensome aspects of treatment were related to chemotherapy (55.2%) and prednisone use (34.5%). Patients with a low HRQoL and high levels of fatigue were more likely to have low levels of serum complement C4 (i.e., elevated immune activity). *Conclusion* Patients who are treated according to the Euro-Lupus protocol may experience a higher HRQoL than patients who receive the NIH treatment. However, chemotherapy remains burdensome in the low dose treatment regimen. Potential interventions to further enhance HRQoL in SLE patients with proliferative lupus nephritis are discussed.

INTRODUCTION

Few studies have investigated the effect of treatment on health-related quality of life (HRQoL) in patients with the chronic, autoimmune disease systemic lupus erythematosus (SLE). This could be due to a lack of valid and reliable disease-specific HRQoL measurements for SLE patients. However, over the last few years several attempts to develop such measurements have shown good results.[1,2,3] The present study used one of those newly validated instruments to assess HRQoL in SLE patients with proliferative lupus nephritis.

In SLE, the immune system attacks the body's own cells, which can result in inflammation of multiple organ systems at the same time. SLE is most prevalent among women in their reproductive years with usual disease onset between ages 15 and 40.[4] The worldwide prevalence is estimated to be about one per 1000 and the female to male ratio is 10:1.[5] Most patients present with vague and varying symptoms including marked malaise, extreme fatigue and fever. Also sun over-sensitivity, painful joints, oral ulcers, and on the psychosocial level mild depression, are frequently reported. The course of disease of SLE is characterized by alternating periods of either relatively stable disease or high disease activity. In the face of active disease, patients may need to take high doses of strong immunosuppressive agents. But also when the disease is relatively stable, maintenance doses are often required to preserve low activity and patients are closely monitored for signs of flare-ups.

Lupus nephritis is the most prevalent organ involvement in SLE that affects up to 60% of patients[6] and results in a substantial increase in morbidity and mortality.[7] A renal biopsy is required to confirm a diagnosis of lupus nephritis. Six different classes of lupus nephritis can be distinguished.[8] Most importantly, a subdivision between proliferative and non-proliferative lesions can be made which guides the choice of treatment regimen.[9] This study will only relate to the treatment of patients with proliferative lesions in their biopsy.

Up to 2004, the National Institutes of Health (NIH) regimen was the standard treatment for proliferative lupus nephritis at Leiden University Medical Centre (LUMC) and involved high doses of cyclophosphamide (CYC) and corticosteroids for two years. Although this therapy regimen results in a complete or partial remission in more than 80% of patients[10], it also has many severe side effects. Immediate side effects include nausea, vomiting, fatigue, and hair loss. In the long term cytopenias (i.e., a reduction in the number of blood cells), infections, infertility, and malignancy can occur.[11] Since 2004, a modified version of the Euro-Lupus protocol has been introduced as an alternative treatment because it involves lower doses of CYC and corticosteroids and a large portion of the CYC is substituted by mycophenolate mofetil (MMF). An important advantage of MMF is that it can be taken orally, whereas CYC had to be given intravenously. The efficacy of MMF has been shown to be at least equivalent or even superior to CYC, while MMF has fewer side effects.[11]

There are many factors that influence the impact of illness on quality of life, such as demographics, the condition itself, treatment, and psychosocial factors. It would be expected that less toxic treatments with fewer side effects will enhance patients' HRQoL significantly. Two previous studies have investigated the effect of treatment for lupus nephritis on HRQoL. The first study showed that a MMF-based induction treatment for proliferative lupus nephritis was associated with better HRQoL than CYC.[13] The second study found a higher self-reported treatment burden and worse mental HRQoL in a for proliferative lupus nephritis CYC treated patient group compared with a group treated with corticosteroids and azathioprine.[14]

The present study aimed to assess HRQoL in two different treatment groups for proliferative lupus nephritis and to examine the associations of HRQoL with socio-demographic and clinical characteristics. In addition, HRQoL of SLE patients was compared with HRQoL of patients with other chronic illnesses and with HRQoL of a reference population of healthy respondents. It was expected that HRQoL would be higher in patients who received the less toxic Euro-Lupus treatment and that HRQoL of SLE patients

would be lower than HRQoL of patients with other chronic illnesses and of a reference population of healthy respondents.

METHODS

Participants

Patients were selected from the electronic patient registration at Leiden University Medical Centre (LUMC). Inclusion criteria were a diagnosis of proliferative lupus nephritis and a received treatment according to either the NIH or the Euro-Lupus protocol. Thirty-seven patients who fulfilled the inclusion criteria were approached to participate in the study. One patient refused to join the study without knowing its aim, two patients could not be contacted and two patients decided not to participate on personal grounds. Hence, the final participant group consisted of 32 patients (86.5% participation rate), with 16 patients in each treatment group.

Participants completed two self-administered paper-and-pencil questionnaires in a private room at LUMC. Participants filled out the questionnaires on the basis of recall about the first half year of treatment. Prior to the assessment, participants provided informed consent. The study was approved by the Committee on Medical Ethics LUMC.

Materials

Research in the area of quality of life has shown that combining generic and disease-specific HRQoL assessments in SLE patients results in the optimal measurements.[15] Therefore, the Medical Outcomes Study Short Form 36 (SF-36) was used as a generic measurement of HRQoL.[16] The questions about mood were excluded because memory for emotions has been shown to be especially subjective to bias from subsequent experiences.[17] As a result, two of the nine scales (i.e. vitality and mental health) of the SF-36 were not included in this study.

The SLE Symptom Checklist (SSC) was included to assess disease-specific HRQoL.[1] The questions about mood were again excluded and because of this, one of the five components of the SSC was not assessed. The remaining four components of the SSC

include: (1) socio-demographic characteristics; (2) presence and burden of 38 symptoms; (3) influence on daily life and (4) treatment burden.

Besides assessing HRQoL, disease activity was recorded according to the following parameters: proteinuria (i.e., the amount of protein in the urine), serum albumin (i.e., an important plasma protein), serum creatinine (i.e., a measure of kidney function), serum complement C3 and C4 (i.e., a measure of immune activity) and haematuria (i.e., the amount of blood in the urine). These parameters were registered at the start of the treatment, at every monthly follow-up up to six months, and at the time of assessment.

Design and Procedure

Data were analysed using SPSS Version 16.0 software. Means on measures of HRQoL were compared between the two patient groups with an independent t-test. One sample t-tests were performed to investigate differences in HRQoL between the two treatment groups and a reference population of healthy respondents and patients with other chronic illnesses (copied from Aaronson et al., 1998).[18] Associations among the HRQoL measures, socio-demographic characteristics, and disease parameters were examined with Spearman's rho correlations. Effect sizes were classified using Cohen's d. G-Power 3.1.2 was used to compute post-hoc power analyses.

RESULTS

Participants

Table 1 gives an overview of the socio-demographic characteristics. The mean age of the total participant group was 35.3 (*SD* = 10.4). Patients had been diagnosed with SLE on average 11.1 (*SD* = 5.0) years ago. The majority of patients were of Dutch origin (65.6%). The time since the start of treatment for patients in the NIH group was longer than for patients in the Euro-Lupus group ($t = 4.30$, df = 16.5, $p = .001$).

Table 1. Socio-demographic characteristics for the NIH, Euro-Lupus and total patient group

	NIH[a] (N = 16)	Euro-Lupus[b] (N = 16)	Total (N = 32)
Female to male ratio	10:6	14:2	24:8
Age mean (SD)	36.8 (10.3)	33.8 (10.7)	35.3 (10.4)
Age at diagnosis of SLE mean (SD)	25.2 (7.0)	25.3 (10.3)	25.3 (8.7)
Disease duration mean (SD)	12.4 (4.9)	9.8 (4.8)	11.1 (5.0)
Years since start of treatment mean (SD)	8.5 (3.7)	4.5 (.82)**	6.5 (3.4)
Origin			
Dutch	11 (34.4%)	10 (31.3%)	21 (65.6%)
Surinam	3 (9.4%)	4 (12.5%)	7 (21.9%)
Other	2 (6.3%)	2 (6.3%)	4 (12.5%)
Marital status			
Living alone	7 (21.9%)	4 (12.5%)	11 (34.4%)
Married/cohabitating	9 (25.0%)	12 (34.4%)	21 (59.4%)
Higher education:			
Vocational	9 (28.1%)	10 (31.3%)	19 (59.4%)
University	3 (9.4%)	1 (3.1%)	4 (12.5%)
Work status:			
Student	1 (3.1%)	4 (12.5%)	5 (15.6%)
Employed	8 (25.0%)	7 (21.9%)	15 (46.8%)
Unemployed	7 (21.9%)	5 (15.6%)	11 (34.4%)

[a]Treatment for proliferative lupus nephritis consisted of high dose cyclophosphamide.

[b]Treatment for proliferative lupus nephritis consisted of low dose cyclophosphamide and mycophenolate mofetil.

**$p < .01$.

Disease activity parameters at the start of treatment show that the two treatment groups only differed in proteinuria values and level of hypoalbuminemia (see Table 2). Both groups showed good improvements at six months follow-up and were comparable on all disease parameters. Patients in general showed stable disease at the time of assessment.

Table 2. Disease activity parameters at the start of treatment, after six months and at time of assessment between the NIH and Euro-Lupus group

	NIH	Euro-Lupus	Reference
Serum creatinin (μmol/L)			max. 106
Start of treatment (N = 32)	143.8 (97.5)	139.3 (133.0)	
After six months (N = 32)	117.1 (26.6)	97.9 (59.3)	
Assessment (N = 32)	108.4 (57.4)	85.6 (44.7)	
Proteinuria (g/24hrs)			0 – 0.15
Start of treatment (N = 28)	4.7 (3.0)	2.6 (1.5)*	
After six months (N = 21)	1.1 (1.2)	1.0 (.91)	
Assessment (N = 17)	.38 (.50)	.75 (1.4)	
Serum albumin (g/L)			40 – 50
Start of treatment (N = 28)	24.4 (6.3)	30.2 (6.5)*	
After six months (N = 24)	40.9 (6.1)	41.3 (3.8)	
Assessment (N = 16)	42.4 (7.1)	42.7 (3.7)	
Hematuria[a]			0
Start of treatment (N = 30)	4.0 (1.3)	3.6 (1.3)	
After six months (N = 22)	2.4 (2.0)	1.8 (1.4)	
Assessment (N = 27)	1.1 (1.6)	.79 (1.3)	
Serum C3[b] (N= 21)	31.6 (13.4)	28.3 (15.3)	47 – 80
Serum C4[b] (N = 22)	11.5 (6.2)	9.3 (11.5)	13 – 39
Serum C1Q[b] (N = 20)	10.9 (4.3)	12.11 (7.9)	9 – 14

[a]Hematuria was scored as follows: 1 = trace, 2 = few, 3 = several, 4 = many, 5 = full. [b]Values only for the start of treatment.

*$p < .05$.

Medical Outcomes Study Short Form-36 (SF-36)

The NIH and Euro-Lupus did not show significant differences on the seven HRQoL scales, but effect sizes were moderate for the scales physical functioning, social functioning, change in health and role limitations emotional (see Table 3). Post-hoc power analysis suggests moderate to high power to detect differences for these four scales and low power for the scales pain, general health, and role limitations physical. Hence, it is likely that the two treatment groups differ on several HRQoL scales but that the sample size was too small to detect differences.

Table 3. Mean scores (SD) on the SF-36 for the Euro-Lupus, NIH, and total patient group in comparison with a reference population of healthy respondents (asterisks indicate significant differences with the reference population, no significant differences between the Euro-Lupus and NIH group were found)

Scale	Reference population	SLE	Euro-Lupus	NIH	Cohen's d[a]	Power[a]
Physical Functioning	81.9 (23.2)	55.3 (25.6)***	61.0 (20.8)**	50.0 (29.1)**	0.44	76.5%
Social Functioning	86.9 (20.5)	44.9 (27.7)***	50.8 (27.2)***	39.1 (27.7)***	0.43	74.1%
Role Limitations	79.4 (35.5)	55.5 (42.0)**	57.8 (42.5)	53.1 (42.7)*	0.11	9.3%
Role Limitations	84.1 (32.3)	51.0 (44.8)***	58.3 (47.9)*	43.8 (41.7)**	0.32	45.6%
Pain	79.5 (25.6)	67.2 (23.8)**	67.9 (25.8)	66.6 (22.4)*	0.05	5.9%
General Health	72.7 (22.7)	41.4 (22.0)***	41.3 (23.1)***	41.6 (21.7)***	0.01	5.0%
Change in Health	52.7 (19.4)	81.2 (26.9)***	87.5 (20.4)**	75.0 (31.6)*	0.47	83.0%

*$p < .05$. **$p < .01$. ***$p < .001$.

[a]Cohen's d and power were calculated for scores between the Euro-Lupus and NIH group.

The NIH group showed a lower HRQoL than a reference population of healthy respondents on six scales, whereas the Euro-Lupus group had a lower functioning than this population on four scales. In addition, the NIH group differed at a more conservative significance level from the reference population than the Euro-Lupus group on the scale role limitations emotional. Hence, HRQoL of the NIH group could have been more affected by treatment as it was less comparable with that of a reference population than HRQoL of the Euro-Lupus Group. When HRQoL of the two treatment groups together were compared with HRQoL of the reference population, SLE patients showed a lower HRQoL on all scales, except for the scale change in health.

To investigate whether HRQoL of SLE patients differed from that of patients with other chronic illnesses, the scores of the two treatment groups together were compared with scores for patients with migraine and cancer (derived from Aaronson et al., 1998)[18]. Table 4 shows the scores for all three groups. In general, SLE patients had a lower HRQoL than patients with migraine and cancer. The three patient groups did report a comparable level of pain and cancer patients showed a lower HRQoL on the scale role limitations physical than SLE patients.

Table 4. Mean scores (SD) on the SF-36 for SLE patients compared with migraine and cancer patients

	SLE (N = 32)	Migraine[a] (N =)	Cancer[a] (N =)
Physical Functioning	55.3 (25.6)	82.4 (21.3)***	63.6 (25.1)
Social Functioning	44.9 (27.7)	76.2 (20.9)***	73.9 (24.1)***
Role Limitations Physical	55.5 (42.0)	62.2 (40.8)	35.0 (40.3)*
Role Limitations Emotional	51.0 (44.8)	74.5 (37.8)**	58.4 (43.6)
Pain	67.2 (23.8)	64.9 (22.4)	69.3 (26.6)
General Health	41.4 (22.0)	67.5 (20.5)***	52.5 (21.4)**

[a]Values copied from Table 4 from Aaronson et al. (1998).[18]

*p < .05. **p < .01. ***p < .001.

SLE Symptom Checklist (SSC)

Of the 38 symptoms on the SSC, nausea/vomiting was the only symptom for which patients in the NIH group reported a higher burden than patients in the Euro-Lupus group (t = 3.39, df = 30, p = .002). Almost all patients (96.6%) mentioned the symptoms "fatigue" and "rounding of face". Fatigue caused the highest burden in both treatment groups.

Patients in the NIH and Euro-Lupus group reported a comparable level of influence of treatment on their daily lives. Physical activities were most influenced and especially riding the bike. As for the non-physical activities, the influence on work and study was the greatest.

Level of treatment burden did not differ between the two treatment groups. Sixteen patients (55.2%) reported chemotherapy and/or adverse effects of chemotherapy as the most burdensome aspect(s) of treatment. Frequently mentioned adverse effects of chemotherapy were fatigue (17.3%), nausea (13.8%), hospital stay (13.8%) and hair loss (6.9%). Ten patients (34.5%) experienced prednisone and/or adverse effects of prednisone as the most disturbing effect(s) of treatment. Weight gain and joint involvement were stated as adverse effects of prednisone by three (10.3%) and two (6.9%) patients, respectively. All mentioned aspects did not show a relationship with type of treatment.

Correlations

Table 5 gives an overview of the correlations between HRQoL measures, disease activity parameters and socio-demographic characteristics. Patients with a low HRQoL on the scales physical functioning, pain, and role limitations emotional of the SF-36 tended to report high levels of fatigue. A high HRQoL on social functioning was associated with high serum levels of C4 (i.e., low immune activity).

Patients who experienced a high influence of treatment on daily life, as measured by the SSC, tended to be younger, to have lower serum levels of C4 (i.e., elevated immune activity), to have a higher proteinuria (i.e., a large amount of protein in the urine) and to report a higher level of fatigue. High levels of fatigue were also associated with a high self-reported treatment burden.

Because fatigue was experienced as the most burdensome symptom by both groups, its association with disease activity was investigated. Patients who had low levels of serum C4 (i.e., elevated immune activity) were more likely to report high levels of fatigue. The severity of fatigue was not related to the extent to which treatment influenced sleeping habit.

Table 5. Correlations between health-related quality of life measures and age, proteinuria, serum C4, albumin and fatigue

	Age	Fatigue	Proteinuria[a]	Albumin[b]	Serum C4[c]	Physical Functioning	Social Functioning	Role Limitations	Role Limitations	Pain	General Health	Change Health	Total Complaints	Total Distress	Treatment Burden	Mean influence Daily	Physical	Emotional
Age	1.000																	
Fatigue	-.195	1.000																
Proteinuria[a]	-.287	.148	1.000															
Albumin[b]	.107	-.225	**-.421***	1.000														
Serum C4[c]	**.610****	**-.430***	.020	.177	1.000													
Physical Functioning	.201	**-.411***	**-.405***	.123	.097	1.000												
Social Functioning	.257	-.284	-.325	.139	**.469***	**.606****	1.000											
Role Limitations Physical	-.147	-.005	.064	.222	-.099	-.156	-.145	1.000										
Role Limitations Emotional	.206	**-.458****	-.047	**.410***	.347	.178	.047	**.495****	1.000									
Pain	.085	**-.498****	-.276	.208	.253	**.465****	.343	**-.432***	-.015	1.000								
General Health	.110	-.037	-.327	-.255	.177	.218	.345	-.067	-.246	.200	1.000							
Change in Health	-.182	**.434***	-.037	-.152	-.054	-.291	-.177	.011	-.142	-.273	.272	1.000						
Total Complaints	.166	.133	.050	.158	.205	**-.389***	-.069	.149	.137	**-.437***	**-.378***	.099	1.000					
Total Distress Level	.124	.294	.090	.068	-.009	**-.509****	-.193	.213	.043	**-.610****	-.320	.305	**.867****	1.000				
Treatment Burden	-.157	.299	.236	-.244	-.291	**-.424***	**-.388***	-.010	-.089	**-.551****	-.268	.278	.224	**.445***	1.000			
Mean Influence Daily Life	**-.439***	**.422***	**.451***	-.090	**-.544****	**-.687****	**-.660****	.184	-.121	**-.354***	**-.531****	.164	.340	**.417***	**.378***	1.000		
Physical	-.331	**.409***	.198	-.089	-.367	**-.589****	-.347	.069	-.179	-.337	**-.394***	.254	.332	**.497****	**.376***	**.774****	1.000	
Emotional	.169	.174	.087	.241	.012	-.299	**-.552****	-.118	-.014	-.112	-.229	.143	.175	.111	.123	**.368***	.116	1.000

[a]The amount of protein in the urine. [b]An important plasma protein. [c]An index of immune activity.

*$p < .05$. **$p < .01$.

DISCUSSION

The present study aimed to assess HRQoL in SLE patients who were treated for proliferative lupus nephritis according to one of two treatment protocols, and to examine associations of HRQoL with socio-demographic and disease characteristics. The results seem to support the prediction that patients who were treated according to the Euro-Lupus protocol showed a better physical and psychological functioning than patients from the NIH group. However, a manifest better HRQoL was not demonstrated. Chemotherapy remained burdensome in low dose and also prednisone use contributed to a worse HRQoL in both groups. All patients rated fatigue as the most disturbing symptom, which was frequently perceived as an adverse effect of chemotherapy. Worse HRQoL and high levels of fatigue were associated with low levels of serum C4 (i.e., elevated immune activity).

Few studies have investigated the effect of different treatments on HRQoL in patients with proliferative lupus nephritis.[13,14] One retrospective between-subjects study assessed HRQoL in 12 patients who had experienced two episodes of lupus nephritis for which they were treated with either CYC and prednisone or MMF and prednisone.[13] Although scores on the SF-36 did not show many significant differences, they did tend to be higher overall in the MMF group.

In contrast, a randomized controlled trial (RCT) found no substantial differences in HRQoL as measured by the SF-36.[14] Patients who were treated for proliferative lupus nephritis with either CYC pulses or with azathioprine (AZA) and methylprednisolone tablets were compared on HRQoL measures at the start of treatment and at a follow-up of 12 and 24 months. The AZA group did show a significantly lower treatment burden as measured by the SSC. Such an effect was not found in the present study, which could be explained by the low dose CYC in the Euro-Lupus group while the AZA group in the RCT was completely deprived of CYC. Surprisingly, the AZA group did not report less burden of nausea/vomiting, whereas in the present study the Euro-Lupus group reported a significantly lower burden. However, it appears that the questionnaire in the RCT study referred to a period in which no CYC pulses were given[14], which can explain the different findings. It seems that a low dose CYC does reduce the disturbance of a symptom like

nausea/vomiting, but that treatment burden as a whole may decrease only if CYC is totally abandoned.

The finding that fatigue was the most disturbing symptom is in line with results from previous studies.[14,19] The few studies that have investigated the relationship between fatigue and HRQoL, also support the finding that high levels of fatigue are associated with worse HRQoL.[21,21]

The association between fatigue and disease activity has been examined more extensively, but results are inconsistent. Although SLE Disease Activity Index (SLEDAI) scores have not shown a relationship with fatigue[20,21], physician's ratings of disease activity have been associated with fatigue levels.[22] In addition, comparable to the association between fatigue and serum C4 levels in the present study, low serum C3 levels and high lymphocyte counts have been related to high levels of fatigue.[19]

Many studies have investigated the relation between HRQoL and disease activity, and although results from these studies are inconsistent, in general, HRQoL is not well correlated with disease activity.[23] The present study did find moderate correlations for serum C4, proteinuria and serum albumin with some measures of HRQoL. The association of serum C4 with both HRQoL and fatigue suggests an important role of serum C4 level in physical and psychological functioning. A focus on improvements in serum level of C4 may contribute to an enhancement in HRQoL and a reduction in fatigue.

In line with a previous study, the results showed that SLE patients have a significantly lower HRQoL than patients with other common chronic illnesses.[24] Interventions other than reductions in CYC and prednisone dose seem desirable to enhance HRQoL. A range of psychological interventions, such as self-management interventions, cognitive behavioral therapy, and coping skills training, have been successful in enhancing HRQoL and fatigue in patients with diabetes, COPD, cancer and cardiovascular disease.[25] Only one known study has addressed the effect of a psychological intervention in SLE patients.[26] This study investigated the application of

cognitive behaviour therapy to alter illness perceptions and also looked at the effects of therapy on psychological well-being. The beneficial effects on psychological functioning were limited, but levels of psychological distress did show significant reductions.[26] Psychological interventions aimed at enhancing HRQoL are expected to be beneficial for SLE patients and future research should address the implementation of the available range of interventions.

One important limitation of the present study is the retrospective reporting of quality of life. Patents' reports may have been influenced by recall bias and subsequent experiences. In addition, the time interval between treatment and time of assessment varied between the two treatment groups, as patients in the NIH group were mostly treated before 2004 and those in the Euro-Lupus group only from or after 2004. However, measuring HRQoL on the basis of recall with varying time intervals between patients is common, as reflected in the number of studies that apply such a method.[13,27,28] Moreover, a response shift, the re-evaluation of HRQoL in response to changing health, occurs as soon as six days after an event[29] and time period is one of many factors that may influence recall bias.[30] Other limitations of the present study include the small sample size and the non-random allocation of patients to treatment groups, which limits its power and generalizability. Finally, the patient group consisted mainly of patients of Dutch (Caucasian) origin.

In conclusion, the Euro-Lupus protocol tends to result in better HRQoL outcomes than the NIH protocol. However, SLE patients with lupus nephritis remain having a lower HRQoL compared to patients with other common chronic illnesses. Chemotherapy remains burdensome in low dose and also prednisone use may contribute to a low HRQoL in both groups. Psychological interventions could be beneficial to further enhance HRQoL, but research is needed to find out which interventions will be the most effective.

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CHAPTER 5

THE IMPACT OF ILLNESS PERCEPTIONS ON SEXUAL FUNCTIONING IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Background Sexual problems are common in patients with chronic illnesses. However, few studies have investigated problems with sexual functioning in patients with systemic lupus erythematosus (SLE). The present cross-sectional study assessed the influence of SLE on sexual functioning and its associations with illness perceptions and medical and socio-demographic characteristics. *Methods* The study included 106 SLE patients who used at least one immunosuppressive agent to control their SLE. Sexual functioning was measured using the Physical Disability Sexual and Body Esteem and the Medical Impact Scale from the Sexual Functioning Questionnaire. Patients' illness perceptions were assessed using the Brief Illness Perception Questionnaire. *Results* 49.1% of patients agreed that their SLE had a negative influence on their sexual functioning. In addition, treatment for SLE seemed to play an important role in the negative impact on sexual functioning. Patients' illness perceptions were more important predictors of sexual functioning than medical and socio-demographic characteristics. SLE patients appear to report a lower sexual functioning than patients with other chronic illnesses. *Conclusion* SLE in general and immunosuppressive treatment for SLE specifically have a negative influence on sexual functioning. Patients' illness perceptions appear to play a more important role in the negative impact on sexual functioning than medical characteristics such as disease activity. The high prevalence of sexual problems highlights the need to more frequently address and aim to improve sexual functioning in patients with SLE. Patients may benefit from methods such as illness perception modification and coping style interventions to reduce their sexual problems.

INTRODUCTION

The impact of the chronic, rheumatic, autoimmune disease systemic lupus erythematosus (SLE) on health-related quality of life (HRQoL) has been addressed by several studies.[1-3] HRQoL aims to assess both the extent to which illness and its treatment influences functioning on several domains (e.g., physical, mental, social, and role) and patients' emotional responses to these influences.[4] The effect of SLE on the domain of sexual functioning specifically has been less studied.[5;6] There is no universal definition of sexual functioning and it is used interchangeably with other terms such as sexual well-being and sexual satisfaction.[7] In the present study, sexual functioning will refer to the extent to which illness interferes with one's sexual identity (e.g., feelings of sexual attractiveness, sexual expression, preferences) and sex life (e.g., arousal, orgasm, intercourse) and patients' emotional responses to these interferences. Sexual functioning may be disturbed by a variety of factors, including pain, fatigue, stiffness, functional impairment, depression, anxiety, negative body image, reduced libido, hormonal imbalance, and drug treatment.[6]

Several disease characteristics specific for SLE may have a negative impact on sexual functioning. First, disease onset is commonly in the adolescent years, which is an important period for the development of body-image and sexual identity.[8] Second, the clinical manifestations of SLE (e.g., skin rashes, vitiligo, painful joints) may have an adverse effect on interest, desire, and body image. Third, common side effects of immunosuppressive agents such as weight gain, hair loss, and infertility, may also negatively affect body image. Fourth, active SLE is associated with an increased likelihood of adverse pregnancy outcomes[9], which could have an additional negative impact on sexual functioning.

Although few previous studies have investigated sexual functioning in SLE patients, the results in general indicate a negative impact.[10-15] In comparison with healthy women, SLE patients report lower sexual functioning and poorer body image.[11] Among SLE patients a lower sexual functioning has been found to be associated with high levels of

fatigue[12], depressive symptoms[12], disease activity or severity[14], menstrual cycle disturbances[15], and the presence of vascular disease (i.e., coronary or peripheral artery disease).[15]

Apart from the association between sexual functioning and medical and a few psychosocial factors, no research with SLE patients has investigated the relationship with psychological constructs such as illness perceptions**.** Illness perceptions consist of emotional and cognitive responses to illness and can be grouped into different dimensions: perceived identity (illness name and symptoms), illness cause, timeline, consequences, how much personal control the patient has, how much treatment can help, how much the illness makes sense to the patient (coherence), whether the illness concerns the patient, and emotional responses.[16]

Research with other chronic illness patients has suggested that such psychological parameters may be more important determinants of sexual functioning than medical factors.[17] Therefore, the purpose of the present study was not only to expand the knowledge of the influence of SLE on sexual functioning, but also to investigate whether sexuality in these patients was more strongly associated with patients' illness perceptions than medical or socio-demographic characteristics. In addition, SLE patients were compared with patients with other chronic illnesses on measures of sexual functioning to assess the presence of a disease specific influence.

METHODS

This cross-sectional study was conducted at Auckland City Hospital, Auckland, New Zealand and was approved by the Northern X Ethics Committee.

Participants

Patients were recruited from the rheumatology clinic at Greenlane Clinical Centre (the outpatient clinic of Auckland City Hospital) and from two lupus patients' associations in New Zealand. This study was coupled with one investigating the association between treatment non-adherence and psychosocial and medical characteristics.[18] Therefore, inclusion criteria were not only a diagnosis of SLE according to the revised American

College Rheumatology (ACR) criteria for SLE[19], but also current treatment with corticosteroids and/or another immunosuppressive agent. Two weeks after sending out invitation letters to potential participants, patients were contacted by telephone. Out of the 141 patients who were approached, 106 patients were willing to participate (75% participation rate). Twenty-two patients showed no interest in joining the study, four patients did not attend the scheduled appointment, and nine patients stated that they were too busy or didn't want to participate because of language barriers.

Participants provided informed consent and completed four self-administered, paper-and-pencil questionnaires. After completion of the questionnaires, the principal investigator (GMND, MD and MSc in psychology) assessed disease activity according to the SLE Disease Activity Index (SLEDAI).[20] The assessment took place in a private room at the clinical centre or at the patient's home if that was more convenient for the patient.

Instruments

Socio-demographic and medical characteristics were recorded through a separate questionnaire and included the following parameters: age, gender, ethnic group, marital status, number of children (no distinction between biological or adopted) employment status, highest educational level achieved, religion, year of diagnosis of SLE, past and present organ involvement(s), and current medication use.

Sexual functioning was measured using the Physical Disability and Sexual and Body Esteem scale (PDSBE)[21] and the Medical Impact Scale of the Sexual Functioning Questionnaire (SFQ).[22] Because there is no questionnaire specifically developed to measure sexual functioning in SLE patients, these two scales were chosen because of their good psychometric characteristics and because they were developed for or tested in several patient groups with diverse medical conditions.[21;22] Both questionnaires measure level of sexual functioning at the time of assessment. The PDSBE has been shown to be a psychometrically sound instrument to assess body esteem and sexual esteem in patients with physical disabilities.[21] The questionnaire consists of 10 items that are rated on a 5-point scale from strongly disagree to strongly agree. The items can be subdivided in three subscales: 1) attractiveness, 2) sexual esteem and 3) body esteem. Examples of items of

the PDSBE are “I feel that my illness interferes with my sexual enjoyment” (subscale Sexual Esteem), “I feel that people are not sexually interested in me because of my illness” (subscale Attractiveness) and “I envy people with ‘normal’ bodies”(subscale Body Esteem). Mean scores are calculated for the three subscales separately and all together. In addition, sum scores of the three subscales were dichotomized at the scale midpoint to assess the strength of patients’ body and sexual esteem and feelings of attractiveness.

The Sexual Functioning Questionnaire (SFQ) was originally developed to assess sexual functioning in patients with cancer, but is thought to result in equally reliable and valid outcome measures in patients with other medical conditions as well.[22] The Medical Impact Scale assesses the impact of treatment on sexual functioning and contains five items: one rating scale item and four 5-point scale items. The rating scale item asks patients to rate how well they think they have adjusted to changes in their sex life since their treatment for SLE. An example of a 5-point scale item is “What impact has your treatment had on your interest or desire for sex?”. A total score is calculated as the mean score on all five items.

The Brief Illness Perception Questionnaire (B-IPQ) was used to measure illness perceptions. The B-IPQ contains eight items scored on a scale from 0 to 10 and one open-ended question where the participants state what they think are the three most important causes of their disease. The scale items measure patients’ cognitive and emotional representations of their illness and correspond to eight different domains: identity, consequences, timeline, personal control, treatment control, coherence, concern, and emotion. The reported causes in the open-ended question were grouped into categories on the basis of common themes. The B-IPQ has been shown to be a valid and reliable measure to assess illness perceptions in ill populations.[23]

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to measure disease activity at the time of assessment.[20] The SLEDAI is a reliable, valid and widely used instrument to assess disease activity in patients with SLE.[24-26] Disease activity scores can range from 0 to 105. Five activity categories have been defined: 1) no activity (SLEDAI = 0), 2) mild activity (SLEDAI = 1-5), 3) moderate activity (SLEDAI = 6-10), 4) high activity (SLEDAI = 11-19), and 5) very high activity (SLEDAI ≥ 20).

Statistical analysis

Data were analysed using SPSS 17.0 software. Descriptive statistics and frequencies were obtained for the socio-demographic and disease related characteristics. One sample t-tests were used to test differences in PDSBE scores between SLE patients and patients with other chronic illnesses (derived from Kedde & Berlo, 2006)[27] and to assess whether scores on the Medical Impact Scale were significantly different from 0. Scores on the Medical Impact Scale for the SLE group were compared with those for a group of cancer patients (derived from Syrjala et al., 2000).[22]

Associations between sexual functioning and socio-demographic and disease related characteristics and illness perceptions were explored with correlational analysis. Significant relationships were investigated with multiple linear regression analyses to further explore the predictive associations between variables, while controlling for socio-demographic characteristics and SLEDAI scores. In these analyses, the involved socio-demographic characteristics were scored as follows: religion as a dichotomous variable (0 = no religion, 1 = religion), education as an ordinal variable with five categories (1 = primary education, 2 = secondary education, 3 = bachelor's degree, 4 = master's degree, and 5 = doctoral degree). Five separate analyses were performed for sexual functioning in general (i.e., total score on the PDSBE), the three subscales of the PDSBE (i.e., sexual esteem, body esteem, and attractiveness), and the impact of treatment on sexual functioning. The stepwise method was used to select the most important predictor variables. An alpha level of .05 was used for all statistical tests.

RESULTS

Participants

The mean age of the patients was 43.34 years (SD = 14.96). 94.3% of the patients were female, which can be explained by the higher prevalence of SLE in females. The largest ethnic group consisted of New Zealand Europeans (39.6%). Table 1 gives an overview of socio-demographic characteristics.

Table 1. Socio-demographic variables of the total participant group (N = 106)

Female to male ratio	100:6
Age mean (SD)	43.34 (14.96)
Ethnicity	
New Zealand European	42 (39.6%)
Pacific Islands	15 (14.2%)
Maori	13 (12.3%)
Middle Eastern/Latin American/African	3 (7.5%)
Other	3 (6.6%)
Employment	
Fulltime	34 (32.1%)
Part time	23 (21.7%)
Sickness benefit	20 (18.9%)
Housewife	9 (8.5%)
Retired	9 (8.5%)
Student	8 (7.5%)
Unemployed	7 (6.6%)
Marital Status	
Unmarried	31 (31.2%)
Married or living together	55 (51.9%)
Divorced	11 (10.4%)
Widow/widower	7 (6.6%)
Education	
Primary education	5 (4.7%)
Secondary education	63 (59.4%)
Bachelor's degree	31 (29.2%)
Master's degree	5 (4.7%)
Doctoral degree	2 (1.9%)
Children (one or more)	65 (61.3%)
Religion	
None	60 (56.6%)
Christianity	37 (34.9%)
Other	9 (8.5%)

The patients had a mean disease duration of 10.2 years (SD = 9.1). Half of the patients (54.7%) had experienced one or more organ involvements. Nearly three quarters of patients (71.7%) had one or more comorbidities. An overview of disease characteristics is provided in Table 2.

Table 2. Disease characteristics of total participant group (N = 106)

Disease duration, mean (SD) in years	10.2 (9.1)
SLEDAI[a] score, mean (SD) (range 0-105)	10.2 (6.2)
Organ involvement	
None	48 (45.3%)
Lupus nephritis	31 (29.2%)
NPSLE[a]	17 (16.0%)
Pleuritis	13 (12.3%)
Pericarditis	10 (9.4%)
Hepatitis	7 (6.6%)
Eyes	8 (7.5%)
Co-morbidity	
None	30 (28.3%)
Other autoimmune diseases	18 (17.0%)
Hypertension	18 (17.0%)
Fibromyalgia	12 (11.3%)
Antiphospholipid antibody syndrome	12 (11.3%)
Secondary Sjögren's syndrome	11 (10.4%)
Dyslipidemia	10 (9.4%)
Medication	
Hydroxychloroquine	89 (84.0%)
Prednisone	56 (52.8%)
Azathioprine	42 (39.6%)
Other immunosuppressants	15 (14.2%)
Psychopharmaceuticals	26 (24.5%)
Analgesics	30 (28.3%)

[a]Systemic lupus erythematosus disease activity index. [b]Neuropsychiatric systemic lupus erythematosus.

Physical Disability and Sexual and Body Esteem (PDSBE)

A hundred and one patients completed the PDSBE. Two patients did not want to complete the questionnaires, one patient had never been sexually active, and two patients thought the majority of the questions were not applicable to their situation. 49.1% of the patients agreed that having SLE had a negative influence on their sexual functioning. This influence consisted of a lower sexual esteem and body esteem for 38.4% and 46.1% of the patients, respectively, and feelings of a lower attractiveness for 25.8% of the patients. In comparison with patients with other chronic illnesses[27], SLE patients appear to have a lower sexual esteem (M = 10.11, SD = 3.91 vs. M = 12.58, SD = 4.25; t = -6.28, df = 98, p < .001) and feel less attractive (M = 7.25, SD = 3.0 vs. M = 9.63, SD = 3.2; t = -7.33, df = 92, p < .001) .

Medical Impact Scale (MIS)

The impact of treatment on sexual functioning was assessed for 87 patients. Nineteen patients could not complete the questionnaire because they were either not sexually active at the time of assessment or they had not had sexual contact yet before they were diagnosed with SLE. The mean score on the SFQ Medical Impact Scale (M = 2.27, SD = .97) differed significantly from 0, i.e., there is no effect of treatment on sexual functioning (t = 21.8, df = 86, p < .001). SLE patients appear to report a greater negative influence of treatment on their sexual functioning than patients who have been treated with bone marrow transplantation for different types of cancer (M = 2.27, SD = .97 vs. M = 2.92, SD = .96; t = -4.97, df = 86, p < .001).[22] In conclusion, SLE patients' sexual functioning was negatively affected by their treatment.

Brief Illness Perception Questionnaire (B-IPQ)

Patients' illness perception scores in general clustered around the midrange of the items (see Table 3). Two exceptions are the items timeline with the highest mean score (M = 8.43, SD = 2.53) and treatment control with the lowest mean score (M = 2.71, SD = 2.23) This indicates that patients held chronic perceptions of their SLE and felt that treatment could not help them much. The first most important reported causes were

grouped into 5 broad categories: psychosocial causes (33.3%), genetics (32.0%), environmental causes (10.7%), previous bacterial or viral infections (13.3%), and pregnancy (10.7%). Causal perceptions showed no relationship with measures of sexual functioning.

Table 3. Means and standard deviations for the Brief Illness Perception Questionnaire (B-IPQ)

	SLE patients (*N* = 106)
Identity	6.14 (2.58)
Consequences	5.45 (2.71)
Timeline	8.44 (2.49)
Personal control	4.88 (3.00)
Treatment Control	2.71 (2.23)
Coherence	3.29 (2.47)
Emotion	5.50 (3.03)
Concern	6.90 (2.83)

Regression analyses

Table 4 summarizes the results for the five separate regression analyses. With sexual functioning in general as the dependent variable, a significant model emerged in which emotion and religion explained 16.7% of the variance (F (2, 100) = 11.20, $p < .001$). emotion was the strongest predictor accounting for 11.3% of the explained variance. Religion added a further 5.4% to the proportion of explained variance. The subscale attractiveness was best predicted by emotion (Adjusted $R^2 = 0.95$) and coherence (Adjusted $R^2 = 0.73$), which together explained 16.8% of the variance (F (2, 90) = 10.32, $p < .001$). A model with sexual esteem as the dependent variable explained 14.2% of the variance and included the variables emotion (Adjusted $R^2 = 0.11$) and identity (Adjusted $R^2 = 0.32$; F (2, 94) = 8.94, $p < .001$). The variables personal control, emotion, religion, and education were important predictors of body esteem and explained 22.3% of the variance (F (4, 97) = 8.24, $p < .001$). Personal control was the strongest predictor accounting for 8.2% of the explained variance. Emotion, religion, and education added a further 6.4%, 4.7%, and 3.2% to the proportion of the explained variance, respectively. With the impact

of treatment on sexual functioning as dependent variable, a significant model emerged with consequences, coherence, SLEDAI, and treatment control as significant predictors (F (5, 92) = 4.97, p < .000). The model explained 31.3% of the variance in sexual functioning. Coherence was the strongest predictor accounting for 12.6% of the explained variance. Consequences, treatment control, and SLEDAI added a further 10.8%, 4.3%, and 3.6% to the proportion of explained variance, respectively.

Altogether these analyses suggest that illness perceptions are stronger predictors of sexual functioning than medical or socio-demographic characteristics.

Table 4. Summary of regression analyses to predict sexual functioning (Physical Disability Sexual and Body Esteem (PDSBE) overall score, subscales and the Medical Impact Scale)

	PDSBE Total		Sexual Esteem		Body Esteem		Attractiveness		Medical Impact Scale	
Predictor variables	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
Socio-demographic										
Religion[a]	-.249	.007	N/A		-.245	.008	N/A		N/A	
Education	N/A		N/A		-.198	.028	N/A		N/A	
Disease-related										
SLEDAI	N/A		N/A		N/A		N/A		.239	.015
Illness perceptions										
Emotion	.362	.000	.251	.019	.252	.006	.333	.001	N/A	
Coherence	N/A		N/A		N/A		.286	.003	.326	.001
Treatment Control	N/A		N/A		N/A		N/A		.225	.016
Consequences	N/A		N/A		N/A		N/A		.321	.001
Identity	N/A		.222	.037	N/A		N/A		N/A	
Personal control	N/A		N/A		.232	.012	N/A		N/A	

High scores correspond with low sexual functioning. [a]Religion was coded as 0 = not religious, 1 = religious.

DISCUSSION

The present study assessed the influence of SLE and its treatment on patients' sexual functioning. The results showed that half of the patients experienced negative effects of SLE in general on their sexual functioning, especially on their sexual esteem and body esteem. In addition, treatment for SLE specifically seemed to play an important role in the negative influence on sexual functioning. Patients' illness perceptions were more

important predictors of sexual functioning than socio-demographic and medical characteristics. The influence of SLE on sexual functioning appears to be disease specific as SLE patients seem to report a lower sexual functioning than patients with other chronic illnesses.

Problems with sexual functioning are common among patients with chronic illnesses.[28] Between one and two thirds of patients with rheumatic diseases experience sexual problems.[5] However, sexual functioning in rheumatic patients, and specifically in patients with SLE, has not been frequently studied.[5] The few previous studies that have addressed sexual functioning in SLE patients, in general, found a negative effect.[10-15] This was also demonstrated in the present study, with nearly 50% of patients reporting a lower sexual functioning because of their SLE. The high prevalence of sexual problems in SLE patients highlights the need to address this subject during regular check-ups. Patients may feel reluctant to introduce the topic themselves, but if the physician inquires about sexual functioning this will make it more likely that patients will report problems at that time and in the future.[29]

Previous studies have found medical and socio-demographic factors to be important predictors of sexual functioning in SLE patients.[12;14;15] Although the present study also found an association between sexual functioning and disease activity, religion, and education, patients' illness perceptions were stronger predictors of sexual functioning than medical and socio-demographic characteristics. In particular, patients who were more emotionally affected by their SLE reported a lower sexual functioning. In addition, patients reported a lower sexual functioning when they perceived that SLE had a large impact on their lives, felt they did not understand their SLE, and believed that treatment could not help them much. Of interest is the finding that patients' emotional representations were associated with the PDSBE subscales attractiveness, body esteem, and sexual esteem, whereas patients' cognitive perceptions showed a relationship with the influence of treatment on SLE as measured by the Medical Impact Scale. Hence, in assessing sexual functioning in SLE patients it is important to differentiate between what

patients feel and think because the impact on sexual functioning may differ. Sexual functioning may be enhanced by interventions that are directed towards illness perception modification. Previous research with SLE patients has shown positive changes in the perceptions of identity, treatment control, and emotion and related improvements in distress after a onetime two-hour cognitive behavior therapy.[30]

Although patients' illness perceptions appear to be important predictors of the influence of illness on sexual functioning, the results suggest that other factors not included in the present study also play a role. For instance, it is likely that coping strategies are involved since coping acts as a mediator between illness perceptions and outcomes, as described by self-regulation theory.[16] In addition, a recent model of coping with sexual dysfunction in chronic illness claims that flexibility in coping with sexual dysfunction can be increased by enhancing the flexibility in patients' definitions of sexual functioning within their self-concept.[31] A preliminary application of the model in cancer survivors with sexual problems has shown good results.[32] The effectiveness of such an intervention to improve sexual functioning in SLE patients should be explored.

Determinants of problems with sexual functioning have been shown to be multifactorial and disease specific.[5] The present study illustrates this disease specificity by showing that SLE patients appear to experience a lower sexual functioning in general and as a result of treatment, compared with patients with other chronic illnesses. These comparison groups were derived from two separate studies. One study investigated sexual satisfaction and sexual self-image among men (N = 95) and women (N = 65) with one of seven different chronic medical conditions (e.g., arthritis related conditions, muscular illnesses, neurological related illnesses).[27] The second study looked at sexual problems in 161 women and 118 men who have been successfully treated with blood or bone marrow transplants for leukemia or other types of cancer.[22] Patients from both studies were comparable on socio-demographic characteristics such as age, education and marital status. The difference in sexual functioning between SLE patients and patients with other chronic illnesses could indicate that SLE has a greater impact on sexual functioning

than other illnesses, which would be in line with the finding that HRQoL is lower in SLE patients than in patients with other chronic illnesses.[1;2] Sexual functioning is one of the domains of quality of life and because research has shown that disease specific measures are essential for an optimal measure of HRQoL in SLE patients[33], future studies should be dedicated to the development of disease specific measures of sexual functioning in SLE patients.

An important limitation of the present study is that it was cross-sectional and correlational, which limit interpretations about causality. In addition, regression analyses indicated that important factors in the prediction of sexual functioning were not included in the present study. Apart from a possible association with coping behavior, previous research has shown that sexual functioning was strongly related to premorbid sexual adjustment and relationship quality.[14] These psychosocial characteristics were not assessed in the present study.

In conclusion, SLE in general and treatment for SLE specifically have a negative influence on sexual functioning. Patients' illness perceptions appear to play a more important role in the negative impact on sexual functioning than medical characteristics such as disease activity. SLE patients with sexual problems could benefit from methods such as illness perception modification and coping style interventions to reduce their sexual problems. The high prevalence of sexual problems highlights the need to more frequently address and aim to improve sexual functioning in SLE patients.

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CHAPTER 6

ILLNESS PERCEPTIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND PROLIFERATIVE LUPUS NEPHRITIS

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ABSTRACT

Background This study investigated the illness perceptions of patients with systemic lupus erythematosus (SLE) and whether perceptions are influenced by type of treatment for proliferative lupus nephritis. In addition, the illness perceptions of SLE patients were compared with those of patients with other chronic illnesses. *Methods* Thirty-two patients who had experienced at least one episode of proliferative lupus nephritis were included. Patients were treated with either a high or low dose cyclophosphamide (CYC) regimen (National Institutes of Health (NIH) vs. Euro-Lupus protocol). Illness perceptions were measured with the Brief Illness Perception Questionnaire (B-IPQ) and a drawing assignment. *Results* The low dose CYC group perceived their treatment as more helpful than the high dose CYC group. In comparison with patients with asthma, SLE patients showed more negative illness perceptions on five of the eight illness perception domains. Drawings of the kidney provided additional information about perceptions of treatment effectiveness, kidney function and patients' understanding of their illness. Drawing characteristics showed associations with perceptions of consequences, identity, concern and personal control. *Conclusion* These findings suggest that the type of treatment SLE patients with proliferative lupus nephritis receive may influence perceptions of treatment effectiveness. In addition, patients' drawings reveal perceptions of damage caused by lupus nephritis to the kidneys and the extent of relief provided by treatment. The finding that SLE is experienced as a more severe illness than other chronic illnesses supports the need to more frequently assess and aim to improve psychological functioning in SLE patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a severe chronic illness with major effects on not only patients' physical functioning, but also on patients' psychological well-being. The importance of this latter effect is exemplified by the finding that health-related quality of life (HRQoL) tends to be lower in SLE patients than in patients with other chronic illnesses.[1] Despite the acknowledgement that SLE is a severe disease with substantial impact on the patient's life, few studies have assessed psychological functioning in SLE patients. The present study contributes to the need to map out psychological functioning in SLE patients by assessing illness perceptions and its associations with socio-demographic and disease characteristics. In addition, the study investigated the effect of two different treatments for proliferative lupus nephritis on patients' illness perceptions.

Lupus nephritis is the most prevalent organ involvement in SLE. It affects up to 60% of patients[2] and results in a substantial increase in morbidity and mortality.[3] Six different classes of lupus nephritis can be distinguished.[4] Most importantly, a subdivision between proliferative and non-proliferative lupus nephritis can be made, which guides the choice of treatment regimen. At present, treatment for proliferative lupus nephritis in Leiden University Medical Center (LUMC) usually follows a modified version of the Euro-Lupus protocol.[5] Up to 2004, the older NIH regimen was the standard treatment which involved higher doses of cyclophosphamide (CYC).[5] Because of the lower doses of CYC and substitution of a part of the CYC by mycophenolate mofetil (MMF), the modified version of the Euro-Lupus protocol is thought to result in less toxic side-effects.[6] In addition, it would be expected that treatments with fewer side effects will not only form a lesser burden for physical health but also for psychological well-being.

There are many factors that influence the impact of illness on psychological and physical functioning, such as demographics, the condition itself, treatment and psychosocial factors.[7] In the realm of psychosocial factors, illness perceptions play an important role. Leventhal's self-regulatory model proposes that patients are active problem solvers who seek to make sense of illness and form mental representations that

influence coping strategies.[8] These mental representations of illness (or illness perceptions) are composed of cognitions about its identity (the name of the illness and its associated symptoms), its consequences, timeline, causes, personal control over the illness and the effectiveness of its treatment, as well as overall understanding. How individuals respond to illness is partly determined by these perceptions as well as their emotional responses.[9]

Although the role of illness perceptions in the impact of illness is broadly recognized, only five studies have looked at illness perceptions in patients with SLE. In addition, comparison of these studies is limited because of the use of solely qualitative measures, such as interviews, to assess perceptions. Another important limitation is that no study included male patients. Three studies used semi-structured interviews based on Leventhal's self-regulatory model.[10-12] The first study could not support a relationship between illness perceptions and disease characteristics, such as disease activity and disease duration.[11] The most important finding of the second study was that every patient holds unique illness perceptions[12], which is also reported by two other studies.[11;13] However, such a result could be expected in studies with small sample sizes and uncontrolled measures, such as interviews, where the findings depend on what comes to mind at the time of assessment. The third study found that the illness perceptions of SLE patients are consistent with the self-regulatory model and that patients' perceptions change over time.[10] The fourth study is the only study which used a validated and reliable questionnaire, i.e., the Illness Perception Questionnaire Revised (IPQ-R), to investigate whether a cognitive behaviour therapy (CBT) intervention would influence patients' illness perceptions.[14] The results showed that CBT indeed had influenced patients' perceptions of treatment control and the effect of SLE on their emotions. The fifth study used a relatively new way to measure patients' illness perceptions by asking patients to draw their disease and providing comments on their drawings.[13] The author states that drawings may not only make the individual experience more tangible and comprehensible, but it may also enhance patients' feelings of understanding. However, these results were based on the author's interpretation only and drawings were not analyzed to derive scores or other

quantitative measures. A more extensive use of drawings to assess illness perceptions has been applied with patients with other chronic illnesses. In these studies, quantitative analysis of drawings has allowed measurement of underlying perceptions in patients with heart disease and headache.[15-19]

The present study aimed to assess illness perceptions in SLE patients and to examine their associations with socio-demographic and disease characteristics. It was hypothesized that type of treatment for lupus nephritis (i.e., NIH or Euro-Lupus) would influence patients' illness perceptions and that the perceptions of SLE patients would be different from those of patients with other chronic illnesses. Specifically, we expected to find a beneficial effect of the Euro-Lupus treatment on illness perceptions and that SLE patients would perceive their illness as more negative than patients with other chronic illnesses.

METHODS

Participants

Patients were selected from the electronic patient registration at Leiden University Medical Center (LUMC). This study was coupled with one investigating the effect of two different treatments for proliferative lupus nephritis on health-related quality of life (HRQoL). Therefore, inclusion criteria were a previous diagnosis of proliferative lupus nephritis and a received treatment according to one out of two protocols (i.e., either the NIH or Euro-Lupus regimen). Patients were approached by telephone and received an information letter when they showed interest in the study. Ten days after sending the information letter, patients were contacted again by telephone to determine their willingness to participate in the study.

Thirty-seven patients fulfilled the criteria and were approached to participate in the study. One patient refused to join the study without knowing the objective, two patients could not be contacted and two patients decided not to participate on personal grounds. Hence, the final participant group consisted of 32 patients (86.5% participation rate), with 16 patients in each treatment group. One patient was excluded from the

analysis of the B-IPQ because this patient developed a chemotherapy induced SLE and proliferative lupus nephritis, which completely resolved after completion of the chemotherapeutic treatment.

Materials

The Brief Illness Perception Questionnaire (B-IPQ)[20] and patients' drawing of their kidneys were used to assess illness perceptions. The B-IPQ contains eight items to score on a scale from 0 to 10 and one open-ended question where the participants have to state the three most important causes for their disease. A mean score is calculated for every scale and the reported causes can be grouped into categories on the basis of common themes. The B-IPQ has been shown to be a valid and reliable measure to assess illness perceptions in ill populations, including patients with renal disease[20], but no validation for patients with SLE has been done. The Dutch version of the B-IPQ has been used in several studies with varying chronic patient populations.[21-24]

In the drawing assignment, participants were asked to make two drawings: 1) a drawing of their kidneys at the time of the diagnosis of lupus nephritis and 2) a drawing of their kidneys after the treatment for lupus nephritis. It was stressed that the drawing should represent what they thought their kidneys looked like. Participants were ensured that the assignment had no purpose of judging their drawing abilities according to the drawing instructions protocol.[18]

Besides assessing illness perceptions, parameters of kidney function were retrieved from the electronic patient registration at LUMC to assess the effect of both treatments on renal outcome. The following parameters were recorded: proteinuria, serum creatinine, serum albumin, and hematuria. These parameters were registered at the start of treatment, at six months follow-up, and at the time of assessment.

Participants completed the B-IPQ and drawing assignment in a private room at LUMC in the presence of the principal investigator (GMND). Because this assessment was combined with another questionnaire based study, time between completion of the first and second drawing could be stretched out with 20 up to 30 minutes. So, patients started with the first drawing, continued with several questionnaires including the B-IPQ, and

finished with the second drawing. Prior to the assessment, participants provided informed consent. The study was approved by the Committee on Medical Ethics LUMC.

Design and Procedure

Data were analysed using SPSS Version 16.0 software. An alpha level of .05 was used for all statistical tests. Descriptive statistics and frequencies were obtained for the socio-demographic and disease characteristics and kidney function parameters. An independent t-test was used to test differences in illness perceptions and measures of kidney function between the two treatment groups. Percent reductions in serum levels of proteinuria and creatinine and percent increases in serum albumin levels between the start of treatment and six months follow-up were calculated and compared between the two groups with independent t-tests. One sample t-tests were performed to compare the illness perceptions of patients with SLE with those of patients with asthma. Scores for the latter group were derived from the study of Broadbent et al. (2006).[20] Associations between illness perceptions and kidney function, and socio-demographic, disease and drawing characteristics were examined with Pearson's *r* or Spearman's *rho* correlations.

The drawings were analysed by means of ImageJ software.[25] The drawings were analysed for the area of the kidneys, the way in which infection or damage was represented in the drawing, and the location in the kidney of the representation of infection or damage. Moreover, the drawings were rated for the patients' perceived efficacy of treatment and kidney function. Patients' perceived efficacy was assessed by comparing the drawing before treatment with the drawing after treatment. For instance, when the first drawing contained many dots to represent damage and the second drawing contained no dots, this was regarded as indicating a high perceived efficacy of treatment. Patients' perceived kidney function was assessed on the basis of the second drawing of the kidney after treatment. For instance, if the kidney in the second drawing contained no representations of damage, this was seen as demonstrating good perceived kidney function.

RESULTS

Participants

The participant group consisted of 24 females and eight males. The majority of patients (62.5%) were of Dutch origin. Patients in the NIH group began their treatment for proliferative lupus nephritis on average 8.6 (*SD* = 3.7) years ago, whereas the time since the start of treatment for patients in the Euro-Lupus group was on average 4.5 (*SD* = .82) years ago (t = 4.30, df = 16.5, p = .001). There were no other significant differences on socio-demographic or disease characteristics between the two treatment groups (see Table 1).

Table 2 shows kidney function parameters for the two treatment groups at the start of treatment, at six months follow-up and at the time of assessment. At the start of treatment, patients from the NIH group showed higher levels of proteinuria (t = 2.48, df = 21.4, p = .022) and lower serum albumin levels (t = -2.47, df = 25, p = .021) than Euro-Lupus patients. Both groups showed good improvements at six months follow-up and were comparable on all disease parameters. With regard to percent reductions or increases between start of treatment and six months follow-up, only the percent increase in serum albumin was greater in the NIH group than in the Euro-Lupus group, 41.6% and 22.6%, respectively (t = 2.07, df = 18, p = .053). Patients in general showed stable disease at the time of assessment. Hence, even though patients from the NIH group showed a worse protein loss at the start of treatment, renal outcome in general was comparable between both treatment groups.

Table 1. Socio-demographic and disease characteristics for the NIH and Euro-Lupus group

	NIH[1] (N = 16)	Euro-Lupus[2] (N = 16)	Total (N = 32)
Percentage females	62.5%	87.5%	75.0%
Age mean (SD)	36.8 (10.3)	33.8 (10.7)	35.3 (10.4)
Age at diagnosis of SLE mean (SD)	25.2 (7.0)	25.3 (10.3)	25.3 (8.7)
Disease duration mean (SD)	12.4 (4.9)	9.8 (4.8)	11.1 (5.0)
Years since start of treatment mean (SD)	8.5 (3.7)	4.5 (.82)**	6.5 (3.4)
Number of lupus nephritis episodes:			
First episode	11	9	20
Second or third episode	5	7	12
Ethnicity:			
Dutch	11 (34.4%)	10 (31.3%)	21 (65.6%)
Surinam	3 (9.4%)	4 (12.5%)	7 (21.9%)
Other	2 (6.3%)	2 (6.3%)	4 (12.5%)
Marital status:			
Living alone	7 (21.9%)	4 (12.5%)	11 (34.4%)
Married/cohabitating	9 (25.0%)	12 (34.4%)	21 (59.4%)
Higher education:			
Vocational	9 (28.1%)	10 (31.3%)	19 (59.4%)
University	3 (9.4%)	1 (3.1%)	4 (12.5%)
Work status:			
Student	1 (3.1%)	4 (12.5%)	5 (15.6%)
Employed	8 (25.0%)	7 (21.9%)	15 (46.8%)
Unemployed	7 (21.9%)	5 (15.6%)	12(37.5%)

[1]Treatment for proliferative lupus nephritis consisted of high dose cyclophosphamide.

[2]Treatment for proliferative lupus nephritis consisted of low dose cyclophosphamide and mycophenolate mofetil.

**$p < .01$.

Table 2. Kidney function parameters at the start of treatment, after six months, and at time of assessment

	NIH Mean (SD)	Euro-Lupus Mean (SD)	Reference ranges
Serum creatinine (µmol/L)			max. 106
Start of treatment (N = 32)	143.8 (97.5)	139.3 (133.0)	
After six months (N = 32)	117.1 (26.6)	97.9 (59.3)	
Assessment (N= 32)	108.4 (57.4)	85.6 (44.7)	
Proteinuria (g/24hrs)			0 – 0.15
Start of treatment (N = 28)	4.7 (3.0)	2.6 (1.5)*	
After six months (N = 21)	1.1 (1.2)	1.0 (.91)	
Assessment (N = 17)	.38 (.50)	.75 (1.4)	
Serum albumin (g/L)			40 – 50
Start of treatment (N = 28)	24.4 (6.3)	30.2 (6.5)*	
After six months (N = 24)	40.9 (6.1)	41.3 (3.8)	
Assessment (N = 16)	42.4 (7.1)	42.7 (3.7)	
Hematuria[a]			0
Start of treatment (N = 30)	4.0 (1.3)	3.6 (1.3)	
After six months (N = 22)	2.4 (2.0)	1.8 (1.4)	
Assessment (N = 27)	1.1 (1.6)	.79 (1.3)	

[a]Hematuria was scored as follows: 1 = trace, 2 = few, 3 = several, 4 = many, 5 = full.

*$p < .05$.

Brief Illness Perception Questionnaire (B-IPQ)

Table 3 shows the mean scores on the eight B-IPQ items for the total patient group. Patients held the strongest perceptions about timeline and treatment control. Hence, they perceived their illness as chronic and experienced benefits from their treatment. The other illness perception scores clustered around the midrange of the items. Patients' perceptions about the most important cause for their SLE were grouped in five categories: stressful events (28.9%), no idea (20.0%), genetics (17.8%), immune system defaults (11.1%), environment (11.1%), and bad luck (11.1%).

The two treatment groups only differed in their perception of treatment control. Patients from the Euro-Lupus group thought that treatment had helped them more than patients from the NIH group (t = -2.26, df = 29, p = .035).

Table 3. Mean scores (SD) on the B-IPQ dimensions of SLE patients versus patients with asthma

Dimension	SLE (N = 31)	Asthma[1] (N = 309)
Consequences[2]	6.5 (2.3)	3.5 (2.3)***
Timeline	9.2 (1.8)	8.8 (2.2)
Personal control	5.6 (2.7)	6.7 (2.4)*
Treatment control	8.4 (1.6)	7.9 (2.0)
Identity[2]	6.0 (2.6)	4.5 (2.3)**
Concern[2]	5.8 (2.7)	4.6 (2.8)*
Understanding	6.8 (1.9)	6.5 (2.6)
Emotional response[2]	5.8 (2.7)	3.3 (2.9)***

[1]Values from Broadbent et al. (2006).

[2]Higher scores indicate more negative perceptions.

*p < .05. **p < .01. ***p < .001.

To investigate whether the illness perceptions of SLE patients differed from the perceptions of patients with another chronic illness, the scores of the total patient group were compared with scores of patients with asthma (scores were derived from Broadbent et al. (2006).[20] This sample of asthma patients from the UK had a mean age of 39.8 (*SD* = 10.1) and 58.9% of patients was female. Table 3 shows that the illness perceptions of SLE patients were more negative on five of the eight items in comparison with asthma patients.

Associations between illness perceptions, kidney function and socio-demographic and disease characteristics

None of the kidney function parameters were associated with illness perceptions, but several socio-demographic and disease characteristics did show an association with illness perceptions. Patients' illness perceptions of emotion and identity showed a relationship with ethnicity and employment status, respectively. Emotional responses to SLE were higher for patients from Surinam than for patients of Dutch origin (F = 4.40, df = 2, p = .021). Patients who were unemployed or received sick benefit reported more symptoms than patients with a job or students (t = 2.28, df = 24, p = .032).

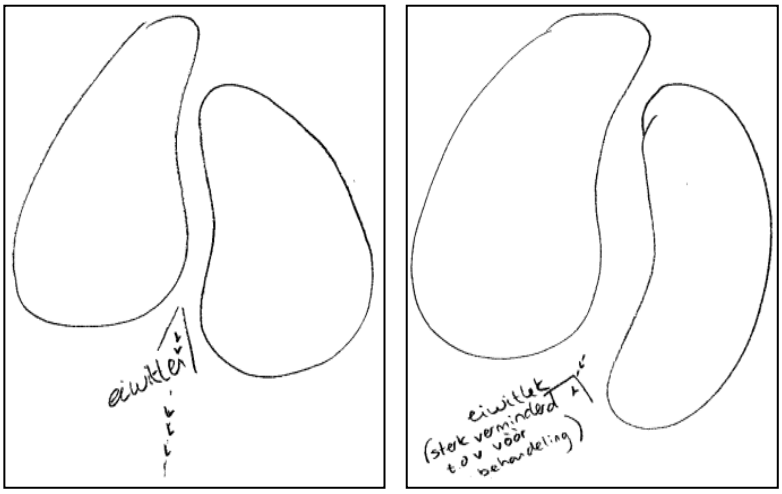
Two disease characteristics were associated with the illness perception concern. Patients with longer disease durations tended to be less concerned about their SLE (r = -.55, p = .001). In addition, patients who have had two or more episodes of lupus nephritis were less concerned than patients with just one experienced episode (t = 3.58, df = 29, p = .001).

Drawing assignment

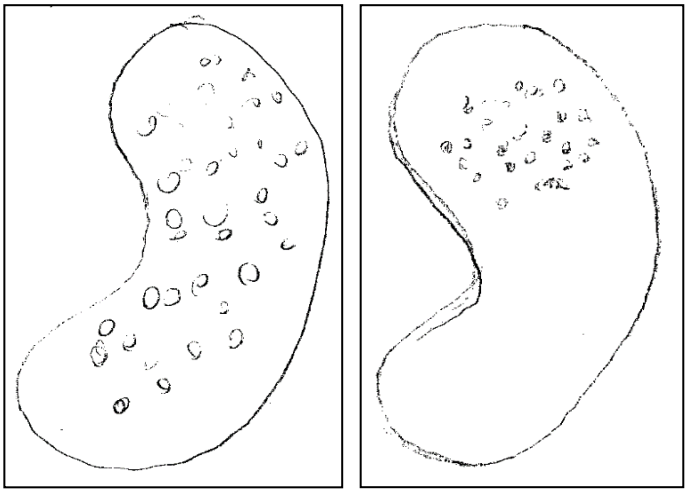
Thirty patients fulfilled the drawing assignment (see Figure 1 for examples of drawings from three patients). Twenty-one patients (70.0%) drew two kidneys and nine patients (30.0%) drew just one kidney. The area of the kidneys did not differ between the time of diagnosis and after treatment.

Twenty-two patients (73.3%) showed a clear difference between their drawings at diagnosis and after treatment. This difference could consist of 1) a change in the amount of damage that was drawn on the kidney, 2) a change in the distribution of this damage across the kidney, or 3) a change in the meaning of the drawn damage.

A



B



C

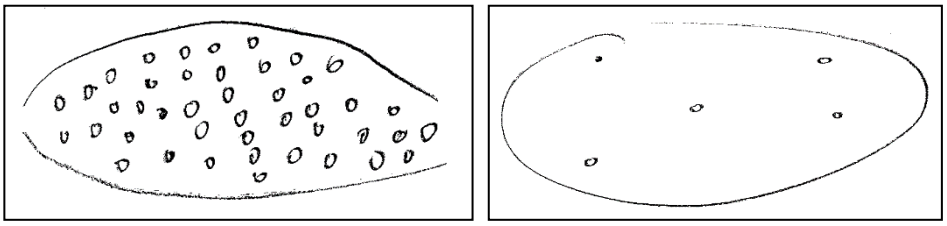


Figure 1. Drawings of three patients representing their kidneys at the start of treatment and after treatment. A. Word in the left drawing means “proteins” and in the right drawing “proteins (highly decreased compared to before treatment)”.

Amount of drawn damage

Sixteen patients (53.3%) used dots to represent damage to the kidney. The number of dots that were drawn at diagnosis was larger than the number drawn after treatment (t = 3.66, df = 15, p = .002). Six patients (20.0%) represented damage by colouring parts of the kidney. 83.3% of the second drawings of these patients showed less colouring. Seven patients (23.3%) left their kidneys blank both before and after treatment.

Distribution of damage

In some cases, another noticeable difference between two drawings was the position of the damage, which changed in seven occasions (31.8%). For instance, the first drawing showed dots globally distributed over the kidney and the second drawing located the dots in a circumscribed portion of the kidney (e.g., Figure 1B).

Meaning of the drawn damage

Fifteen patients (50.0%) wrote down the meaning of the depicted damage, which changed in four instances (26.7%) in the second drawing. The most frequently mentioned representations were infection, protein leakage and holes.

Perceived efficacy of treatment

The sets of drawings were categorized into three groups based on the patients' perceived efficacy of treatment. Group 1 was defined as "no change to kidneys", group 2 as "kidneys better" and group 3 as "kidneys much better". For instance, a patient's drawings were put into group 3 when the first drawing contained many dots to represent damage and the second drawing contained no dots. According to this classification, eight patients (26.7%) believed that their kidneys had not improved after treatment, eleven patients (36.7%) thought that their kidneys were better, and another eleven patients (36.7%) depicted their kidneys as much better after treatment.

Perceived current kidney function

The after-treatment drawings were assessed for the patient's depiction of the kidneys' current function. Three groups were distinguished: 1) poor function, 2) moderate function, and 3) good function. For instance, a second drawing with many dots or colouring was categorized as group 1. Two patients (6.7%) viewed their kidney function as poor, 14 patients (46.7%) as moderate, and 14 patients (46.7%) as good.

Associations between drawing characteristics, illness perceptions, kidney function and socio-demographic and disease characteristics

None of the socio-demographic characteristics and kidney function measures were related to the drawing characteristics, but several drawing characteristics did show associations with illness perceptions and disease characteristics.

The illness perception identity was associated with the number of kidneys that were drawn. Patients who drew two kidneys experienced more physical symptoms than patients who drew just one kidney (t = -3.12, df = 27, p = .004).

Reporting the meaning of the drawn damage on the kidneys was associated with the illness perceptions concern and personal control. Patients who stated the meaning of the dots or colouring in their drawings tended to be more concerned than patients who did not explain their drawing (t = 2.11, df = 27, p = .044). In addition, patients who wrote down the meaning also experienced less control over their illness than patients who did not write down the meaning (t = -2.38, df = 27, p = .025).

There was also a relationship between reporting the meaning of damage and the number of experienced episodes of lupus nephritis. Within the group of patients who had experienced one episode of lupus nephritis, the majority (80%) stated the meaning of their drawings, whereas in the group of patients who have experienced two or more episodes, only a minority (20%) explained what they had drawn (X^2(1, N = 30) = 5.0, p = .025).

Perceived efficacy of treatment was associated with the illness perceptions identity and consequences. Patients who depicted their kidneys as much better after treatment experienced fewer physical symptoms and a smaller influence of SLE on their lives than patients who depicted their kidneys unchanged after treatment (F = 7.50, df = 2, p = .003; F = 6.45, df = 2, p = .005).

DISCUSSION

The present study assessed illness perceptions in SLE patients and its associations with socio-demographic and disease characteristics. In addition, the study investigated the influence of two different treatments for proliferative lupus nephritis on illness perceptions and differences in illness perceptions between SLE patients and patients with another chronic illness. Patients who were treated with the less aggressive Euro-Lupus regimen rated their treatment as more helpful than patients who had received the heavier NIH treatment. SLE patients perceived their illness more negatively than patients with asthma on most illness perception dimensions. Patients with longer disease duration or those who had experienced more than one episode of lupus nephritis, reported lower concern about their condition. Patients' drawings of their kidneys provided additional information on patients' perceptions of damage to their kidneys due to lupus nephritis and the extent of improvement due to treatment.

The finding that the two treatment groups differed in their perception of treatment effectiveness is consistent with self-regulation theory. Self-regulation theory states that patients are active problem solvers who form mental models about their treatment based on their experiences.[8] That patients see the Euro-Lupus treatment as more effective suggests that this regimen may have more positive effects for patients.

The more negative illness perceptions of SLE patients compared with patients with another chronic illness may indicate that SLE is a more severe illness, which has been suggested previously.[1] This higher impact of SLE stresses the necessity to investigate patients' psychological functioning more fully and to develop methods to improve it when desirable.

The notion that illness perceptions are susceptible to change, was demonstrated by an effect of time and illness experience on the extent to which patients were concerned about their SLE. The longer patients had lived with SLE and the more episodes of lupus nephritis they had experienced, the less concern they expressed. One of the previous studies on illness perceptions in SLE patients also found beneficial changes in

illness perceptions over time.[10] However, these changes were self-reported and no associations with socio-demographic or disease characteristics were investigated.

In addition to these naturally occurring changes, previous work has shown positive changes in the perceptions of identity, treatment control, and emotional representations after an onetime CBT intervention of two hours.[14] The study does show some important limitations (small sample size (N = 22), self-selection of treatment condition, and participant differences across conditions), which may explain that the effects were rather small. However, the positive results suggest that it would be worthwhile to perform randomized controlled studies with larger samples and varying types of interventions.

Two previous semi-structured interview studies found that patients' illness perceptions often conflicted with medical information and recommendations.[11;12] A comparable finding in the present study is that few patients named autoimmunity as an important causational mechanism of their SLE symptoms. Instead, the most frequently stated causal factors were related to experiencing stress. In addition, a considerable percentage of patients had no idea what played a role in the origin of their SLE symptoms. This finding does not really support the presence of perceptions that conflict medical information, but rather a lack of adequate medical knowledge. Improving patients' understanding of the mechanisms of SLE may contribute to a better adjustment to living with their illness.

Few studies have used drawings as a research method for assessing illness perceptions.[13;15-18] Among these studies is one that asked 38 SLE patients to draw their disease and comment on what they had drawn.[13] The author recommends the use of drawings in clinical practice to improve clinicians' understanding of patients' psychological status. However, information from the drawings could not be extended beyond the individual patient and there were no attempts to investigate associations with other measures of illness perceptions or disease parameters. Previous work with cardiac patients has shown that drawing characteristics are associated with outcome

measures.[15;16;18] For instance, myocardial infarction (MI) patients who drew a larger amount of damage at discharge[18] and a bigger heart at 3 months follow-up[15] showed a slower recovery and more heart-focused anxiety.

In the present study, all patients were surprised by the drawing assignment and many patients showed some initial reluctance. Many patients reported that they had never thought about what their kidneys looked like and that they had never seen their kidneys. However, after a moment of reflection almost every patient successfully completed both drawings. Several patients who gave explanations for their drawings named protein leakage or some kind of filters that were leaking. Thus, some patients were aware of at least one of the most important clinical manifestations of lupus nephritis and could represent it in a drawing. The observation that the majority of patients (70%) drew less damage in their second drawing, seems to indicate that patients perceived an improvement in their kidney function because of treatment, but recovery was not complete or without damage. More detailed drawings and the inclusion of comments were associated with poorer perceptions, and these drawing features may indicate greater cognitive focus on the illness. Patients' drawings added important information to the questionnaire assessment, showing details about how patients understood the illness, their perceptions of its effects on the kidneys, the effects of treatment, as well as their perception of how well their kidneys were currently functioning.

Although the influence of type of treatment on patients' illness perceptions was small, the possible effects on perceptions of treatment effectiveness may have important implications. For instance, patients are more likely to adhere to treatment that is perceived as effective. In addition, when aggressive treatments are necessary any adjustment that can reduce the burden of treatment is worth considering.

The more positive illness perceptions reported by patients with longer disease duration and those who had experienced more episodes of lupus nephritis, suggests that patients in the early phases of their SLE may especially benefit from interventions aimed

to modify patients' illness perceptions. A combination of questionnaire and visual based assessment is likely to capture the broadest range of patients' perceptions.

Some limitations of the present study include the small sample size, the non-random allocation of patients to treatment groups, and the lack of ethnic diversity in the sample, which limits its power and generalizability. In addition, the study was cross-sectional, which limits its ability to draw conclusions about changes in perceptions over time. Finally, it should be mentioned that the sample of SLE patients was not matched for age and sex with the referent sample of asthma patients.

In conclusion, SLE may have a higher impact on the patients' life than other chronic illnesses and the level of impact may be influenced by type of treatment. Patients' drawings provide additional information on the physical and psychological burden of SLE.

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CHAPTER 7

INTENTIONAL AND UNINTENTIONAL TREATMENT NON-ADHERENCE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Background Patients may be defined as non-adherent if they don't take their medications as prescribed by their physicians. Determinants of non-adherence may vary between and within patient groups. This study investigated the extent to which patients with systemic lupus erythematosus (SLE) show intentional and unintentional non-adherence, and the associations of non-adherence with psychological and medical parameters. *Methods* The study included 106 patients who were on at least one immunosuppressive agent to control their SLE. Level of self-reported adherence and a measure of both intentional and unintentional non-adherence were obtained. Questionnaires were completed to assess associations between adherence and problems with cognitive functioning, beliefs about medicines, illness perceptions, emotional health, and disease characteristics. *Results* The mean self-reported adherence rate for the total patient group was 86.7%. At least occasional intentional non-adherence was reported by 46.2% of patients and 58.5% of patients were at least occasionally unintentionally non-adherent. Problems with cognitive functioning, concerns about adverse effects of medication and younger age were the strongest predictors of (non-)adherence. Patients who were emotionally affected by their SLE were more likely to report low adherence, but this was not a significant predictor after accounting for other variables. Disease characteristics showed no relationship with measures of adherence. *Conclusion* Although SLE patients reported high levels of adherence on average, they commonly reported intentional and unintentional non-adherence. Adherence was associated with both cognitions and emotions. Non-adherence may be reduced by targeting emotional and cognitive functioning and by fine-tuning doctor-patient communication to address patients' individual concerns about their medications.

INTRODUCTION

Treatment adherence in patients with systemic lupus erythematosus (SLE) has been shown to be low, with around 30% never failing to take their medications[1-3], between 20% and 40% stopping their medication on their own[2] and between 14.0% and 42.6% missing one or more clinic visits.[1;4-6] Non-adherence may pose a severe problem as it has been associated with higher morbidity[5], hospitalization[6] and poor renal outcome.[7] Few studies have investigated treatment adherence in SLE patients and generalization of the results is often limited because rheumatic arthritis (RA) and SLE patients were treated as one patient group[2;8;9] or differences between specific ethnic groups were investigated.[1;2;8-10] Moreover, psychosocial factors that may predict treatment adherence in SLE patients have not been sufficiently investigated.[11] The present study aimed at assessing treatment adherence in a representative cohort of SLE patients and investigating associations with psychosocial and medical factors.

SLE is an autoimmune disease that can result in inflammation of multiple organ systems at the same time. The worldwide prevalence is estimated to be about 1 per 1000 and the female to male ratio is 10:1.[12] The course of disease is characterized by alternating periods of either relatively stable disease or high disease activity. In the face of an exacerbation, patients may need to take high doses of immunosuppressive agents. But also when the disease is relatively stable, maintenance doses are often required to preserve low activity and patients are closely monitored for signs of flare-ups. Hence, treatment adherence is important to control the course of disease.

A comprehensive assessment of treatment non-adherence should involve both intentional and unintentional non-adherence.[13] In the case of intentional non-adherence, patients actively choose not to follow treatment recommendations. A social cognition model that aims to explain intentional non-adherent behavior was developed by Horne (1997)[14] and is based on the Health Belief Model (HBM)[15] and the illness perceptions model.[16] According to Horne's model, adherence to medication is based on a combination of a range of beliefs concerning perceived severity, susceptibility, benefits and barriers

and patients' illness perceptions, i.e., their understandings of the nature of the illness, its severity, cause, timeframe, likely prognosis and treatability.

In contrast to intentional non-adherence, unintentional non-adherence is thought to be the result of a passive process which is less strongly associated with individuals' beliefs and perceptions.[13] Factors associated with unintentional non-adherence can be categorized according to the following three groups: 1) patient factors (e.g., age), 2) treatment factors (e.g., side effects), and 3) patient-health care provider factors (e.g., doctor-patient interaction).[13]

Problems with cognitive functioning are frequently reported in SLE patients. The prevalence of cognitive dysfunctions is not only high (i.e., 27-52%) in patients with past or present neuropsychiatric manifestations of SLE, but also 20-42% of patients without neuropsychiatric lupus show cognitive impairments.[17] Two previous studies have looked at the association between medication adherence and cognitive functioning in SLE patients.[1;3] In both studies, the assessment of cognitive impairments was based on patients' performance on ability tests: reading ability and short-term memory in one study[1] and verbal learning and memory in the second study.[3] Poor performance on short-term memory was associated with low adherence in African-American patients, but not in White patients.[1] However, the authors propose that this difference between ethnic groups is a result of socioeconomic disparity and it may not reflect a real barrier to adherence. Problems with verbal learning and memory did show a relation with poor adherence, but were not important predictors after accounting for other variables.[3] Contrary to measuring performance, the present study aimed to assess patients' self-reported problems in doing several cognitive functions and activities of daily life. From a clinical perspective, it is more informative to know which problems patients actually experience and how these real problems relate to non-adherent behavior.

The present study assessed intentional and unintentional treatment non-adherence in SLE patients. Moreover, we examined the associations between treatment non-adherence and socio-demographic and disease characteristics, cognitive functioning

and several psychosocial factors, including beliefs about medicines, illness perceptions, and emotional well-being.

METHODS

Participants

Patients were recruited from the rheumatology clinic at Greenlane Clinical Centre (i.e., the outpatient clinic of Auckland City Hospital) and from two lupus patients' associations. Patients were included when a diagnosis of SLE according to the revised American College Rheumatology (ACR) criteria for SLE[18] was well documented in the electronic patient records, and when they received a current treatment with prednisone and/or another immunosuppressive agent. Two weeks after sending out invitation letters to potential participants, patients were contacted by telephone. Out of 141 patients who were approached, 106 patients participated (75% participation rate). Twenty-two patients indicated no interest in joining the study, four patients did not attend their scheduled study appointment, and nine patients stated they were either too busy or did not want to participate due to language barriers.

Participants provided informed consent prior to the assessment and completed six self-administered, paper-and-pencil questionnaires. After completion of the questionnaires, the principal investigator (GMND) assessed disease activity according to the SLE Disease Activity Index (SLEDAI).[19] Assessment took place in a private room at Greenlane Clinical Center or at the patient's home. The study was approved by the Northern X Ethics Committee (Auckland region, New Zealand).

Materials

Treatment adherence was measured using part A of the Medication Adherence Self-Report Inventory (MASRI).[20] Part A of the MASRI has been shown to be a reliable (Cronbach's α = .70 and ICC = .93) and valid ($r_s \geq .55$) measure of medication adherence in SLE patients. Part A of the MASRI is 87% sensitive and 86% specific for identifying patients who were non-adherent.[21] Part A consists of five 4-point scale items and one visual analogue scale (VAS) item.

As a measure of adherence to clinic visits, hospital records were consulted to determine the number of visits that were missed in the past 12 months as a percentage of the total scheduled appointments in that period.

The distinction between intentional and unintentional non-adherence was made using the Medication Adherence Report Scale (MARS).[22] This self-report scale consists of one statement to measure unintentional non-adherence and four statements to obtain a measure of intentional non-adherence. Two different variables were derived for both non-adherence measures: a continuous variable (mean score) and a dummy variable (mean score 1 is never unintentionally or intentionally non-adherent; mean score > 1 is at least occasionally unintentional or intentionally non-adherent).

The Cognitive Symptoms Inventory (CSI) was used to measure cognitive functioning.[23] The CSI has been demonstrated to be a good screening measure of cognitive impairment in SLE patients in research settings.[24] The CSI contains 21 questions to assess difficulties in daily activities that relate to: 1) concentration, 2) recognition/planning, 3) intermediate memory, and 4) executive function.

The Beliefs about Medicines Questionnaire (BMQ) was used as a measure of commonly-held beliefs about medicine.[25] The BMQ consists of 18 items divided over four scales: 1) the Specific Necessity scale assesses the perceived necessity of the prescribed medication, 2) the Specific Concern scale addresses concerns about the potential adverse effects of prescribed medication, 3) the General Harm scale measures the perceived level of harm and addiction caused by medications in general, and 4) the General Overuse scale assesses beliefs about the use of medicines by doctors. An extended version of the BMQ also contains four single items about complementary or alternative medication use.

The Brief Illness Perception Questionnaire (B-IPQ) was used to measure illness perceptions.[26] The B-IPQ contains eight items to score on a scale from 0 to 10 and one open-ended question where the participants have to state the three most important causes for their disease. The reported causes were grouped into categories on the basis of common themes.

The subscale emotional health of the LupusQol was used as a measure of the emotional domain of health-related quality of life (HRQoL).[27] The LupusQol is a validated

SLE-specific HRQoL instrument. The subscale emotional health consists of six items with a 5-point scale response format.

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to measure disease activity at the time of assessment.[19] The SLEDAI is a reliable, valid and widely used instrument to assess disease activity in SLE patients.[28-30]

Design and procedure

Data were analysed using SPSS 17.0 software. Descriptive statistics and frequencies were obtained for the socio-demographic and disease characteristics. Associations between measures of adherence and other variables were explored with Pearson's *r* or Spearman's *rho* correlation coefficients. In the presence of significant correlations, regression analyses were performed to further study the predictive associations between variables. Independent t-tests or Chi-square tests were used to test differences on predictor variables between patients who were at least occasionally non-adherent and patients who were never non-adherent (i.e., dichotomized intentional and unintentional adherence variables). In the case of not normally distributed data, non-parametric t-tests (Mann-Whitney U tests) were performed. To test differences in adherence levels between more than two groups (e.g., ethnicity), ANOVA or non-parametric ANOVA (Kruskal-Wallis test) with Bonferroni correction were used. An alpha level of .05 was used for all statistical tests.

RESULTS

Patients

The participant group consisted of 100 females and six males, and had a mean age of 43.4 (*SD* = 15.0). New Zealand Europeans formed the largest ethnic group (39.6%). The distribution of ethnicities in the current sample is a good representation of the general Auckland population.[31] Table 1 gives an overview of socio-demographic characteristics.

Table 1. Demographic variables (N = 106)

Female:male	100:6
Age mean (SD)	43.34 (14.96)
Ethnicity	
New Zealand European	42 (39.6%)
Pacific Islands	15 (14.2%)
Maori	13 (12.3%)
Indian	11 (10.4%)
Asian	14 (7.5%)
Other	11 (6.6%)
Employment	
Fulltime	34 (32.1%)
Part time	23 (21.7%)
Sickness benefit	20 (18.9%)
Housewife	9 (8.5%)
Retired	9 (8.5%)
Student	8 (7.5%)
Unemployed	7 (6.6%)
Marital Status	
Unmarried	31 (31.2%)
Married or living together	55 (51.9%)
Divorced	11 (10.4%)
Widow/widower	7 (6.6%)
Education	
Primary education	5 (4.7%)
Secondary education	63 (59.4%)
Bachelor degree	31 (29.2%)
Master degree	5 (4.7%)
Doctoral degree	2 (1.9%)
Children (one or more)	65 (61.3%)
Religion	
None	60 (56.6%)
Christianity	37 (34.9%)
Other	9 (8.5%)

Two-thirds of patients were on two or more immunosuppressive agents (62.3%). The majority of patients (54.7%) had experienced one or more organ involvements. Nearly three quarters of patients (71.7%) had one or more comorbidities. An overview of disease characteristics is provided in Table 2.

Table 2. Disease characteristics (N = 106)

Disease duration mean (SD) in years	10.2 (9.1)
SLEDAI[a] score (range 0-105)	10.2 (6.2)
Organ involvement	
None	48 (45.3%)
Lupus nephritis	31 (29.2%)
NPSLE	17 (16.0%)
Pleuritis	13 (12.3%)
Pericarditis	10 (9.4%)
Hepatitis	7 (6.6%)
Eyes	8 (7.5%)
Co-morbidity	
None	30 (28.3%)
Other autoimmune disease	18 (17.0%)
Hypertension	18 (17.0%)
Fibromyalgia	12 (11.3%)
Antiphospholipid antibody syndrome	12 (11.3%)
Secondary Sjögren's syndrome	11 (10.4%)
Dyslipidemia	10 (9.4%)
Medication	
Hydroxychloroquine	89 (84.0%)
Prednisone	56 (52.8%)
Azathioprine	42 (39.6%)
Other immunosuppressants	15 (14.2%)
Psychopharmaceuticals	26 (24.5%)
Analgesics	30 (28.3%)

[a]Systemic lupus erythematosus disease activity index.

Adherence measures

The mean self-reported adherence rate for the total patient group was 86.7%. Hence, on average patients reported they had taken 86.7% of their medication in the past month. The dichotomous distinction between intentional and unintentional non-adherence showed that 46.2% of patients were at least occasionally intentionally non-adherent, 58.5% of patients were at least occasionally unintentionally non-adherent, and 25.5% of patients stated never to be either intentionally or unintentionally non-adherent. Unintentional non-adherence was significantly more common than intentional non-adherence (t = 7.47, df = 105, $p < .001$). The most common form of intentional non-adherence was altering the dose of the medications (35.8%).

Twenty-three patients (22.8%) did not attend one or more clinic visits in the past year. On average, 5.2% of scheduled visits were not attended. The more visits patients did not attend, the lower the self-reported adherence levels (r = -.28, p = .004). In addition, patients who reported frequent unintentional non-adherence tended to miss more clinic visits (r_s= .24, p = .018).

Associations between adherence measures and socio-demographic characteristics

Adherence measures were associated with some socio-demographic characteristics. Older patients were more likely to report high adherence levels (r = .23, p = .017) and unintentional non-adherers were younger than patients who were never unintentionally non-adherent (Z = -2.68, p = .007). Ethnicity showed a relationship with self-reported adherence level, non-attendance at clinic visits and unintentional non-adherence. Patients from the Pacific Islands missed out on more clinic visits than patients from all other ethnicities (X^2 = 10.02, df = 4, p = .040, two-sided) and reported lower adherence levels than patients from Asian countries (X^2 = 10.15, df = 4, p = .038, two-sided). Patients from the Pacific showed more unintentional non-adherence than patients from New Zealand European or Asian ethnicity (X^2 = 16.72, df = 4, p = .002, two-sided).

Disease characteristics (e.g., SLEDAI scores, disease duration, number of comorbidities, number of organ involvements, number of medications) showed no relationship with measures of (non-)adherence.

Associations between adherence measures and cognitive functioning

Patients who reported low adherence rates were more likely to experience problems with cognitive functioning in general (r_s = -.24, p = .013) and specifically with concentration (r_s = -.24, p = .014) and recognition/planning (r_s = -.30, p = .002). Problems in these three domains were more common in unintentional non-adherers than in patients who did not show unintentional non-adherence (see Table 3). There was no effect for intentional non-adherence. Age was not associated with problems with cognitive functioning.

Table 3. Means and standard deviations for the Cognitive Symptoms Inventory (CSI) for the total patient group and for unintentional versus never unintentional non-adherers

	Total patient group (N = 106)	Unintentional non-adherent (N= 62)	Never unintentional non-adherent (N=44)	*P*
Concentration	14.3 (4.2)	15.2 (4.3)	13.0 (3.6)	.005**
Recognition/Planning	4.9 (1.3)	5.2 (1.5)	4.5 (.90)	<.001***
Intermediate Memory	3.4 (1.3)	3.5 (1.2)	3.2 (1.3)	.181
Executive Function	2.6 (1.0)	2.5 (.80)	2.7 (1.3)	.785
Total CSI score	30.9 (8.0)	32.2 (8.3)	28.9 (7.2)	.017*

*p < .05. **p < .01. ***p < .001.

Relations between adherence measures and psychological variables

Beliefs about Medicines Questionnaire (BMQ)

80.2% of patients supported the necessity of taking SLE medications to maintain good health. However, the majority of patients (63.2%) also expressed concerns about the possible negative effects of SLE medications.

The extent to which patients expressed concerns about their SLE medications was associated with all measures of adherence. The more concerned patients were about taking SLE medications, the lower their mean self-reported adherence rate (r_s = -.23, p = .019). Table 4 shows the scores on all 4 subscales for patients who reported intentional or unintentional non-adherence versus those who did not. Intentional and unintentional

non-adherers were more concerned about the possible side effects of their medications than patients who reported no intentional or unintentional non-adherence.

With regard to medicines in general, 24.5% of patients regarded them as harmful and 40.6% of patients thought doctors overuse medicines. Intentional non-adherers held stronger beliefs about overuse than patients who were not intentionally non-adherent (see Table 4).

Alternative or complementary medicines were used by 50.9% of patients to relieve symptoms, but only a minority of patients agreed that these medicines could control their lupus between acute episodes (36.8%). The belief that alternative medicines were more natural and less damaging was supported by 24.5% of patients and one-third of patients agreed that Western medicines should be substituted by alternative medicines. Beliefs about alternative or complementary medicines were not associated with adherence measures.

Table 4. Mean scores on the Beliefs about Medicines Questionnaire (BMQ) for intentional versus never intentional non-adherers and unintentional versus never unintentional non-adherers

	Intentional non-adherent (N = 49)	Never intentional non-adherent (N = 57)	*p*	Unintentional non-adherent (N = 62)	Never unintentional non-adherent (N = 44)	*p*
Necessity	20.1 (4.1)	19.5 (3.9)	.389	20.1 (3.9)	19.3 (4.0)	.192
Concern	18.0 (3.5)	15.2 (3.9)	.001***	17.5 (3.4)	14.2 (4.2)	.003**
Harm	10.7 (3.2)	10.6 (2.9)	.896	10.8 (2.9)	10.4 (3.1)	.439
Overuse	12.6 (2.8)	11.4(2.7)	.023*	12.3 (2.9)	11.5 (2.0)	.145

*p < .05. **p < .01. ***p < .001.

Brief Illness Perception Questionnaire (B-IPQ)

Patients' illness perception scores in general clustered around the midrange of the items. An exception is the item timeline with the highest mean score (M = 8.43, SD = 2.53). This indicates that patients held chronic perceptions of their SLE. Patients who experienced strong emotional effects from their SLE showed lower self-reported adherence levels (r_s = -.25, p = .012). The first most important reported causes were grouped into 5 broad categories: psychosocial causes (33.3%), genetics (32.0%),

environmental causes (10.7%), previous bacterial or viral infections (13.3%), and pregnancy (10.7%). There were no associations with adherence measures.

LupusQol

Emotional Health for the total patient group was moderate (M = 72.2, SD = 2.2; range 0-100). Patients who were at least occasionally intentionally non-adherent showed a worse emotional health than patients who were never intentionally non-adherent (M = 66.6, SD = 25.3 vs. M = 77, SD = 18.1; Z = -2.09, p = .036). There was no effect for unintentional non-adherence.

Regression analyses

Stepwise linear regression analysis was used to test whether problems with cognitive functioning, concerns about medication (i.e., concern), and emotions were stronger predictors of self-reported adherence level than demographic variables (age and ethnicity). A significant model emerged in which recognition/planning and age explained 35.9% of the variance in self-reported adherence levels (F (3, 101) = 20.45, p < .001). Recognition/planning was the strongest predictor, accounting for 18.8% of the explained variance. Age added a further 8.3% to the proportion of explained variance. Table 5 shows the regression coefficients.

Table 5. Summary of regression analyses to predict treatment non-adherence

	VAS level[a]		Unintentional non-adherence		Intentional non-adherence	
Predictor variables	Beta	*P*	B	*P*	B	*P*
Cognitive Functioning						
Recognition/Planning	-1.342	.001***	.632	.015*	N/A	
Concentration	-.003	.976	.069	.332	N/A	
Beliefs about Medicines						
Concern	-.046	.631	.173	.006**	.204	.001**
Overuse	-.005	.959	.035	.696	.063	.463
Socio-demographic						
Age	-1.089	.001***	-.039	.014*	N/A	
Ethnicity	-.043	.627	N/A		N/A	
Religion	N/A		N/A		.130	.694
Psychosocial						
Emotional Health	N/A		N/A		-.012	.240
B-IPQ[b] Emotions	-.050	.592	N/A		N/A	

[a]VAS = Visual analogue scale. [b]B-IPQ = Brief Illness Perception Questionnaire.

*p < .05. **p < .01. ***p < .001.

Logistic regression analyses were performed to assess the strongest predictors of intentional and unintentional non-adherence as dummy variables. The Forward:LR method was used to test whether intentional non-adherence could be predicted by concern, beliefs about medication overuse, and emotional health. A significant model emerged with concern as the only significant predictor of intentional non-adherence (omnibus X^2 = 13.56, df = 1, p < .001). The model accounted for between 12.0% and 16.0% of the variance in intentional non-adherence (see Table 5). Using a similar analysis to predict unintentional non-adherence, showed that a model with the predictors recognition/planning, age, and concern was significant (omnibus X^2 = 24.56, df = 3, p < .001). The model accounted for between 20.7% and 27.8% of the variance in unintentional non-adherence (see Table 5).

In conclusion, regression analyses showed that problems with recognition/planning, concerns about medication use, and age were the strongest predictors of non-adherence.

DISCUSSION

This study assessed the prevalence and predictors of intentional and unintentional treatment non-adherence in SLE patients. The high mean self-reported adherence level indicates good adherence, but patients also commonly report intentional or unintentional non-adherence. Unintentional non-adherence was more common than intentional non-adherence and was associated with non-attendance of clinic visits. Problems with cognitive functioning, concerns about potential adverse effects of medication, and age were the best predictors of non-adherence.

Treatment non-adherence has been identified as a substantial problem in patients with chronic inflammatory rheumatic diseases.[32] However, few studies have focused on treatment non-adherence in SLE patients specifically and no prior studies have included self-report adherence questionnaires that have been validated for use in SLE patients. Previous studies that have assessed adherence in SLE patients report levels between 69.1% and 83%.[2;6;10;33;34] Even though every study used a different measure to assess adherence, the mean adherence level of 86.7% found in the present study seems to lie at the high end of the range. This may be partly explained by a difference in the regulation of the healthcare system. Three of the previous studies have been conducted in the United States or Mexico where costs for medication may be a barrier to adherence.[2;6;33] This is less likely to be a problem for patients in New Zealand due to the publicly funded health care system. Health care costs have indeed been identified as potential threats to adherence for SLE patients in the United States and developing countries.[8;35] Higher health care costs may also explain the difference in percentage of missed clinic visits: 5.2% in the present study versus rates between 14% and 42.6% in previous studies.[1;4-6]

Only one known study, in which RA and SLE patients were assessed together, has made the distinction between intentional and unintentional non-adherence.[2] Two third of patients reported forgetting their medication at least occasionally and between 20% and 40% of patients said they intentionally did not take their medication at least occasionally.[2]

These results are comparable to the findings in the present study that both intentional and unintentional non-adherence were frequently reported and unintentional non-adherence seems to be more common.

Problems with cognitive functioning, more specifically with recognition/planning, were the strongest predictors of self-reported adherence level and unintentional non-adherence. Activities that pertain to recognition/planning are managing money and paying bills, remembering to take medication and recognizing people. As mentioned before, two previous studies have looked at the association of cognitive functioning with adherence measures in SLE patients[1;3] and both could not support a predictive effect of cognitive impairments. A study that looked at the relationship between adherence and cognitive impairments in three different patient groups does propose that cognitive dysfunctions may identify patients at risk of poor adherence regardless of diagnosis or regimen.[36]

Concern about potential adverse effects of medication was the second most important predictor of unintentional non-adherence and the only predictor of intentional non-adherence. Although most studies on treatment adherence in SLE patients have also looked at associations with socio-demographic and psychological factors, only few have used validated questionnaires to measure these variables.[1;2;33] Despite this limitation, fear of side effects of medication was an important barrier to adherence in five out of six studies.[1;2;8;10;35]

Age was a third significant predictor of self-reported adherence level and unintentional non-adherence. One other study has examined the relationship between age and adherence in SLE and found a non-significant tendency for adherent patients to be older than non-adherent patients.[33] A similar effect of age on adherence has been reported in a study investigating predictors of adherence in four chronic illnesses.[37]

Adherence measures did tend to differ between ethnic groups, with patients from the Pacific Islands reporting lower adherence and missing more clinic visits than patients from the other ethnicities. However, ethnicity was not a significant predictor on the basis of regression analyses. Previous studies have reported mixed results on the relationship between ethnicity and adherence levels and comparison with the present study is limited because prior research involved different ethnic groups. Three studies report a lower self-reported adherence in African-Americans compared with Whites[2;5;33], but one study used a physician's assessment of adherence[5] and another study only found an effect for hydroxychloroquine, and not for prednisone or other immunosuppressants.[33] Studies that involved the same ethnic groups as the present study, but looked at medication adherence in diabetes patients, support a poorer medication self-care[38] and lower adherence rates[39] in Pacific Islanders compared with Europeans.

Although three previous studies have found a relationship between adherence and education[2;33;34] and two between adherence and marital status[2;33], the present study could not confirm these results. Similarly, none of the disease characteristics (disease activity, disease duration, number of comorbidities, number of organ involvements, number of medications) were related to measures of adherence. However, the disease activity index that was used in the present study, the SLEDAI, may have failed to detect a relationship with adherence because of a lack of the inclusion of subjective symptoms. For instance, the assessment of fatigue is not part of the SLEDAI but has been identified as a highly prevalent and disturbing symptom.[40] Other indices, such as the European Consensus Lupus Activity Management (ECLAM)[41], do include these subjective measures and may be better correlated with adherence measures.

The high prevalence of unintentional non-adherence and its association with missing clinic visits, suggests that a primary focus on reducing unintentional non-adherence would greatly improve treatment adherence. This approach is supported by findings from a previous study that the main self-reported barriers to adherence among SLE patients were examples of unintentional non-adherence (e.g., "just having forgotten"

or "being busy at work").[33] In addition, suggestions by these patients on how to improve adherence all referred to actions that are related to preventing unintentional non-adherence (e.g., pill boxes or task lists). Apart from these direct methods to reduce unintentional non-adherence, adherence can be further improved indirectly by resolving problems with cognitive functioning and concerns about adverse effects of medication. A recent study found a significant improvement in cognitive functioning of SLE patients after an eight-week psycho-educational intervention.[42] With regard to concerns about possible side effects, addressing a patient's specific concerns may not only reduce fear of adverse effects and thereby improve adherence, but it may also improve the doctor-patient relationship. Problems with communication and trust have been identified as important barriers to adherence in SLE patients.[1;8;10;33]

A limitation of this study is that it was cross-sectional and correlational, which limits interpretations about causality. In addition, several potential barriers to adherence were not investigated. For instance, assessment of the patient-doctor relationship[1;10;33], perceived costs and evaluation of the healthcare system[8;10], and frequent dosing of medication[8;33] have been identified as a threat to adherence but were not assessed in the present study. Lastly, the majority of patients were of New Zealand European origin, which limits comparisons between different ethnic groups. A substantial proportion of SLE patients of Asian origin could not be included in the study because of language barriers.

In conclusion, intentional and unintentional non-adherence are common in SLE patients. Adherence measures were associated with age, cognitive functioning, and illness-related emotions. Non-adherence may be reduced by targeting cognitive functioning and by fine-tuning doctor-patient communication to address patients' individual concerns about their medications.

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CHAPTER 8

GENERAL DISCUSSION

The overall aim of this thesis was to provide a behavioural medicine perspective on SLE by investigating both clinical care for patients with SLE and their well-being. Therefore, this thesis included studies which described optimization of SLE diagnosis and treatment and studies investigating the impact of SLE on patients' psychological functioning. The five main results of this thesis are:

1. Repeat renal biopsies during a lupus nephritis flare are only advisable in the case of a non-proliferative lesion in the original biopsy (chapter 2). The majority of patients with proliferative lesions in the reference biopsy have proliferative lesions in a repeat biopsy of either the same or a closely related class, which has no therapeutic consequences and frequently makes repeat biopsies unnecessary.
2. Concentration controlled dose adjustments with a target MPA-$AUC_{0\text{-}12}$ of 60-90 mg*h/l appears to result in optimized drug exposure and an optimal renal outcome in patients with proliferative lupus nephritis (chapter 3).
3. Type of treatment for proliferative lupus nephritis may not only influence HRQoL (chapter 4), but also patients' perceptions of treatment effectiveness (chapter 6). In addition, SLE in general and immunosuppressive treatment for SLE specifically have a negative influence on sexual functioning (chapter 5).
4. Specific illness-related cognitions and emotions which are not assessed by questionnaires may be revealed by patients' drawings (chapter 6).
5. Intentional and unintentional non-adherence is common in SLE patients and associated with both cognitions and emotions (chapter 7).

These main results show that a selective repeat renal biopsy policy and therapeutic drug monitoring do not hamper renal outcome and may even reduce treatment burden. However, also low dose immunosuppressive treatment remains burdensome. This burden is reflected by a lowered HRQoL and lowered sexual functioning. In view of limitations in the extent to which immunosuppressive treatment can be further lowered, patients' illness perceptions may be targeted to enhance psychological functioning. In addition, treatment outcome may benefit from illness

perception modification through a beneficial effect of positive (i.e. more adaptive) treatment perceptions on level of treatment adherence.

Disease outcome is generally regarded as an important determinant of good patient care. One could argue that the correct diagnosis and treatment are essential steps in achieving a good disease outcome and therefore important for good patient care. In the case of SLE patients with lupus nephritis, classification of lupus nephritis and the subsequent treatment are indeed important parameters of disease outcome and good patient care. However, good patient care includes more than the management of disease parameters. It also comprises consideration of the patient's management of the illness itself and how illness influences everyday functioning and feelings of well-being. In addition, there is a reciprocal relationship between disease characteristics and patients' well-being. This perspective is in line with the biopsychosocial model which states that the relationship between disease characteristics and patients' well-being is reciprocal and multifactorial and that therefore the patient and not the disease should be the centre of focus.[1] The studies included in this thesis aimed to derive at a patient centered perspective on SLE.

Repeat renal biopsies in the classification of lupus nephritis

Although a renal biopsy can be necessary to decide on the optimal treatment for lupus nephritis, this procedure is risky and burdensome for patients. Hence, it would be desirable to keep the number of biopsies to a minimum. However, numerous authors advise serial renal biopsy in the management of lupus nephritis.[2-6] This advice is based on the finding that transformations from one WHO class to another are frequent, i.e. between 26-75%.[2-7] **Chapter 2** reports on a study that also found a frequent class switch of 49%. However, 84% consisted of a switch from one proliferative form to another. A switch between class III and IV (with or without an additional class V) was the most frequent (54.2%). A predominance of transitions between class III and IV (with or without an additional class V) has been reported in several studies.[3;4;8;9] The detection of these transformations within the proliferative group does not have clear therapeutic

consequences and does not justify the performance of repeat biopsy during a flare. On the contrary, this thesis does report a significant class switch to proliferative forms in patients with non-proliferative lesions in their reference biopsy. Hence, repeat renal biopsy may be preserved for patients with non-proliferative lesions in their original biopsy. In these cases it remains uncertain which treatment strategy to follow and a biopsy should be considered.

Therapeutic drug monitoring in lupus nephritis

Several treatments have been shown to be effective in achieving a good renal outcome in lupus nephritis, but treatment for lupus nephritis in general is burdensome because of frequent and serious side effects. Mycophenolate mofetil (MMF) has recently been established as an effective drug in both the induction and maintenance treatment of lupus nephritis.[10-12] However, studies into the pharmacokinetics of MMF have suggested that results with MMF may be further improved through therapeutic drug monitoring.[13;14] Although several studies have proposed guidelines for therapeutic target ranges for MMF therapy in SLE patients[13-16], no study reports on the application of these guidelines in a concentration controlled treatment. **Chapter 3** describes a study where concentration controlled treatment with a target MPA-AUC_{0-12} of 60-90 mg*h/l resulted in exposure within the target range in a sample of SLE patient with proliferative lupus nephritis. Although MPA-AUC_{0-12} levels were low with a mean of 46.5 mg*h/l before dose adjustment, MPA-AUC_{0-12} levels increased to an average of 69.3 mg*h/l after dose adjustment. In addition, the individualized dosing regimen was associated with a good renal outcome with 87.5% of patients showing a partial or complete response after 12 months of treatment.

Health-related quality of life (HRQoL)

A negative effect of pharmacological therapy for SLE on HRQoL has been reported previously, but mostly for medication groups only (e.g., immunosuppressants or glucocorticosteroids).[17-19] Differences between certain variants within medication groups or differences in treatment schedules have only been investigated by two previous

studies.[20;21] Comparison of CYC with MMF[20] and CYC with AZA[22] showed a lower physical and social functioning and higher treatment burden in the CYC groups. **Chapter 4** shows that patients who were treated according to a low dose CYC and MMF protocol showed a non-significant improvement in physical and psychological functioning compared with patients in a high dose CYC only group. Hence, with regard to immunosuppressants CYC appears to have a more negative effect on HRQoL than other cytotoxic drugs and remains burdensome when low dosages are given.

Sexual functioning

Sexual functioning is a subdomain of HRQoL that has been shown to be important for patients with SLE, but which has been studied infrequently. **Chapter 5** shows that nearly 50% of SLE patients reported a lower sexual functioning because of their SLE. This is consistent with a general negative effect found in previous studies that have addressed sexual functioning in SLE patients.[23-29] The focus in previous studies with regard to predictors of sexual functioning has been on medical and socio-demographic factors, which have been shown to have associations with sexual functioning in patients with SLE.[23;26;28] However, this thesis showed that when also psychological factors are included, patients' illness perceptions appear to play a more important role in the negative impact on sexual functioning than disease or socio-demographic characteristics. This is consistent with comparable research in patients with other chronic medical illnesses[30], strengthening the relevance of Engel's biopsychosocial model[1] which forms the theoretical basis of this thesis.

Illness perceptions

The findings in **chapter 6** suggest that type of treatment for proliferative lupus nephritis influences perceptions of treatment effectiveness. Patients who were treated with low dose CYC rated their treatment as more helpful than patients with a high dose CYC treatment. An effect of treatment on illness perceptions has not been studied previously in patients with SLE. Moreover, illness perception assessment in SLE patients in general has been scarce. Although previous studies are difficult to compare because of the

use of non-standardized measures, general findings are that patients hold negative perceptions[31-35] and that their perceptions are susceptible to change.[36;37] The results of this thesis are in line with these previous findings.

Drawings

Patients' drawings of their illness have been shown to uncover additional information on illness perceptions in various patient populations[38-40], including patients with SLE.[41] More importantly, drawing characteristics have been shown to predict physical recovery better than medical parameters (e.g. recovery after myocardial infarction).[42] Also in this thesis, SLE patients' drawings of their kidneys provided additional information on their perceptions of damage to their kidneys due to lupus nephritis and the extent of improvement due to treatment. Drawing characteristics were not associated with measures of renal outcome.

Treatment adherence

Adherence to treatment is an important factor in achieving successful treatment outcomes. Although the mean self-reported adherence level in **chapter 7** of 86.7% implies good adherence, patients' also reported frequent intentional and unintentional non-adherence. Non-adherence has been reported frequently in studies with SLE patients[43-49], but a distinction between intentional and unintentional non-adherence has been only made once.[43] The previous finding that unintentional non-adherence was more common than intentional non-adherence[43] is also supported by the findings in **chapter 7**. In contrast to the earlier study[43], this thesis also investigated predictors of unintentional non-adherence. Problems with cognitive functioning, concerns about potential side effects and age were the best predictors of unintentional non-adherence.

Clinical implications and future research

In studies with patients with SLE, the focus has mainly been on improving disease characteristics such as renal outcome and disease activity. Although research into patients' well-being is increasing over the last few decades, this thesis also showed that

several aspects of psychological functioning for patients with SLE are only beginning to be uncovered. The studies included in this thesis aimed to give more insight in the reciprocal relationship between disease characteristics and well-being in patients with SLE. The results point in the direction of several recommendations to influence this relationship in a positive way and for the focus of future research.

First of all, a restrictive repeat renal biopsy policy may reduce the number of repeat renal biopsies and therefore reduce treatment burden. Current renal biopsy policies are often based on results from studies existing of protocol renal biopsies. However, in clinical practice biopsies are performed on account of a clinical manifestation of a lupus nephritis flare. **Chapter 2** describes one of the few studies that performed repeat biopsies based on clinical characteristics. Given this study's results and its implications, more such studies are needed to confirm the results. In addition, the participant group in **chapter 2** consisted mostly of individuals of Caucasian descent, so that a similar study with patients of other ethnicities should be performed. For example, patients with SLE of African descent have a more aggressive course of disease and poorer outcomes which may influence preferred biopsy policy.

Secondly, therapeutic drug monitoring allows making early adjustments in medication dosages in order to minimize the occurrence of adverse and toxic effects and to maximize renal outcome. Although therapeutic drug monitoring requires frequent blood sampling, the early detection of too high or too low drug concentrations may result in an overall reduction of treatment burden. Future studies are needed to investigate the actual effects on patient experience. In addition, randomized controlled trials comparing fixed dose to therapeutic drug monitoring would be necessary to confirm the superiority of an individualized dosing regimen.

Thirdly, the finding that SLE has a great impact on patients' HRQoL highlights the need to address this issue regularly. Patients may feel hesitant to introduce problems with psychological functioning themselves, especially when the focus is on medical aspects. Moreover, it has been shown that patients are more likely to report problems with sexual functioning if physicians inquire about such problems.[50] But besides making problems with psychological functioning open to discussion, disease specific measures of HRQoL can be

useful to assess the most important problems and their impact. Although several measures of HRQoL have been developed for use with SLE patients, cross-cultural validation is often missing and these measures in general do not include an adequate assessment of sexual functioning. Future studies are needed to address these issues.

Furthermore, besides discussing psychological problems, the results of this thesis highlight the importance of adequate doctor-patient communication. **Chapter 6** showed that patients with SLE in general hold negative illness perceptions. Such negative emotions and cognitions have been associated with poor outcomes, such as a lowered sexual functioning (**chapter 5**) and low adherence levels (**chapter 7**). Therefore, improving psychological functioning in patients with SLE starts with uncovering patients' specific emotional and cognitive perceptions about their illness. Besides the use of short questionnaires, drawings have been shown to be a successful tool to reveal patients' unique illness perceptions (**chapter 6**). Knowing these perceptions will enable doctors to fine-tune their communication to address patients' specific needs and concerns.

Lastly, this thesis showed a negative influence of treatment on both HRQoL and illness perceptions. Not only adjustments in pharmacological treatment should be sought to lower this burden, but also non-pharmacological methods to improve HRQoL and illness perceptions should be applied. Psychological interventions aimed at enhancing HRQoL have been shown to be successful in patients with different chronic diseases, but implementation in SLE patients and its effect on HRQoL have not been studied. A previous study did find a positive effect of cognitive behavioural therapy on patients' illness perceptions.[36] More positive illness perceptions may not only have a beneficial effect on psychological functioning, but also on treatment adherence. Illness perceptions modification in SLE patients should therefore be addressed in future studies.

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CHAPTER 9

SUMMARY

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which autoantibodies can cause inflammation throughout the whole body. Intensive immunosuppressive therapy is often necessary to suppress this inflammation and to prevent organ damage. The optimal treatment for one of the most serious and prevalent manifestations of SLE, lupus nephritis, is a matter of debate. Although several treatment regimens have been compared in many different studies, it is unclear which treatment regimen results in the best renal outcome and the least adverse effects. Type and intensity of treatment are based on the results of a kidney biopsy, which is a burdensome procedure for patients and gives risk of haemorrhages and infections. Therefore, it would be desirable to be able to keep the frequency of biopsies to a minimum. However, lupus nephritis tends to relapse, which results in the question whether repeated biopsies are necessary in recurrent episodes of lupus nephritis.

Previous studies investigating the relevance of repeated biopsies and optimal treatment for lupus nephritis have focused on the effects on renal outcome. The impact of diagnosis and treatment on patients' well-being has been given less attention. Engel's biopsychosocial model describes the relationship between disease characteristics and patients' well-being. This model states that there is a reciprocal relationship between disease and well-being and many factors can influence this relationship. This thesis aimed to produce a biopsychosocial perspective on SLE by investigating both medical care and psychological functioning in patients with SLE. Therefore, the studies included in this thesis did not only look at the diagnosis and treatment of lupus nephritis, but also at the influence of psychological factors on disease outcome.

Chapter 1 provides a general introduction on the studies in this thesis and outlines the theoretical background of the biopsychosocial perspective. This chapter describes Leventhal's process model of quality of life, the Self-Regulatory Model and Horne's extension of the Common Sense Model. The concepts of quality of life, illness perceptions and treatment adherence are defined and reviewed in relation to previous research.

Chapter 2 describes the relevance of repeated biopsies in the choice of treatment for lupus nephritis flares. This retrospective study included 35 patients with lupus nephritis and one or more repeat renal biopsies. A total of 84 biopsies were blindly reassessed by two pathologists according to the new ISN/RPS criteria. The results showed that patients with proliferative lesions in their original biopsy rarely switch to a pure non-proliferative nephritis during a flare. Therefore, a repeat renal biopsy during a lupus nephritis flare appears not to be necessary if proliferative lesions were found in the reference biopsy. However, transformation to another class of lupus nephritis during a flare was frequently found in patients with a non-proliferative lesion in the original biopsy. For these patients, a repeat renal biopsy during a recurrent episode of lupus nephritis is advisable.

Chapter 3 presents a retrospective study on the effect of an individualized dosing regimen of mycophenolate mofetil (MMF) on the concentration of the active metabolite of MMF (mycophenolic acid, i.e. MPA) and renal outcome. A total of 16 patients with proliferative lupus nephritis were treated with low dose intravenous cyclophosphamide followed by MMF. MPA area under the plasma concentration-time curve (AUC) was assessed within one month after the start of MMF therapy. After the determination of MPA-AUC, MMF dosages were adjusted to reach a target MPA-AUC of 60-90 mg*h/l. One month after the start of MMF treatment mean MPA-AUC was low and showed a high inter-individual variability. Dose adjustments of MMF to reach a target MPA-AUC of 60-90 mg*h/l resulted in a significant higher MPA-AUC and a non-significant reduction in variability. At 12 months of follow-up 87.5% of patients had a good renal outcome. An individualized dosing regimen appears to result in optimal MPA concentrations, which may result in the best renal outcome and least adverse effects.

In **chapter 4**, the effect of two different treatments for proliferative lupus nephritis on quality of life is discussed. The study consisted of 32 patients with proliferative lupus nephritis who were treated with cyclophosphamide in a low or high dose, the Euro-Lupus and National Institutes of Health (NIH) group, respectively. The two

treatment groups were compared on health-related quality of life (HRQoL), as measured by the SF-36 and the SLE Symptom Checklist (SSC). Patients in the Euro-Lupus group reported a higher HRQoL than patients in the NIH group. The most burdensome aspects of treatment were related to chemotherapy and corticosteroids. Hence, also low dose treatment for proliferative lupus nephritis remains burdensome. The application of psychological interventions, such as self-management and coping skills training, seem desirable to try to improve HRQoL in patients with SLE.

Chapter 5 describes the extent to which sexual functioning of patients with SLE is influenced by their illness. The Physical Disability Sexual and Body Esteem (PDSBE) and the Medical Impact Scale of the Sexual Functioning Questionnaire were used to assess sexual functioning in 106 patients who were treated with at least one immunosuppressive drug. In addition, patients' illness perceptions were measured with the Brief Illness Perception Questionnaire (B-IPQ). The results showed that 49.1% of patients experienced a negative influence of SLE on their sexual functioning. In addition, treatment for SLE seemed to play an important role in this negative impact. Patients' illness perceptions were more important predictors of sexual functioning than medical or socio-demographic characteristics. The high prevalence of sexual problems highlights the need to more frequently address this subject. Illness perception modification and coping style interventions may be beneficial in improving sexual functioning.

Chapter 6 discusses the illness perceptions of patients with SLE and the influence of pharmacological treatment for SLE on these perceptions. The patient group consisted of 32 patients who were treated for lupus nephritis with cyclophosphamide in a low or high dose, the Euro-Lupus and NIH group, respectively. Illness perceptions were assessed with the Brief Illness Perception Questionnaire (B-IPQ) and a drawing assignment. Patients in the Euro-Lupus group perceived their treatment as more helpful than patients in the NIH group. Patients' drawings of the kidney provided additional information about perceptions of treatment effectiveness, kidney function and patients' understanding of their illness. The results indicate that type of treatment may influence perceptions of treatment

effectiveness. In addition to the use of questionnaires, a drawing assignment can provide an important contribution to an extensive assessment of patients' illness perceptions.

In **chapter 7**, intentional and unintentional treatment non-adherence in patients with SLE is investigated. Self-reported adherence and a measure of intentional and unintentional non-adherence were assessed for 106 SLE patients who were treated with at least one immunosuppressive drug. In addition, patients completed questionnaires to measure cognitive functioning, beliefs about medication, illness perceptions, and emotional health. This study investigated whether these psychological factors and medical parameters had a relationship with the extent to which patients were non-adherent. Although the mean self-reported adherence was high (86.7%), patients also reported to be regularly intentional and unintentional non-adherent, 46.2% versus 58.5%. Problems with cognitive functioning, concerns about side effects and younger age were the strongest predictors of non-adherence, whereas no relationship with medical parameters was found. Non-adherence may be reduced by targeting problems with cognitive functioning and by addressing patients' individual concerns.

Chapter 8 presents the main conclusions of this thesis. In addition, several implications for clinical practice and suggestions for future research are given. A selective biopsy policy and individualized treatment regimen do not have a negative influence on renal outcome and may even result in a reduction of treatment burden. However, even low dose immunosuppressive treatment for SLE remains burdensome, as reflected in a lowered quality of life and sexual functioning in patients with SLE. Although there are limits to the extent to which immunosuppressive medication can be further adjusted, illness perceptions modification may help in improving psychological functioning. In addition, renal outcome can benefit from this modification because of a positive effect of more favourable perceptions about treatment on level of adherence. In conclusion, the assessment, and if necessary adjustment of patients' perceptions about their illness, is an essential step in achieving a good psychological and medical treatment outcome.

CHAPTER 10

NEDERLANDSE SAMENVATTING

Systemische lupus erythematosus (SLE) is een chronische auto-immuunziekte waarbij auto-antilichamen een ontstekingsreactie door het gehele lichaam kunnen veroorzaken. Intensieve immunosuppressieve therapie is vaak nodig om deze ontsteking te onderdrukken en schade aan organen te voorkomen. De optimale behandeling van een van de meest voorkomende manifestaties van SLE, lupus nefritis, is onderwerp van discussie. Alhoewel verschillende behandelschema's in veel studies met elkaar zijn vergeleken, blijft het onduidelijk welke behandeling de beste uitkomst en de minste bijwerkingen geeft. Het type en de intensiteit van de behandeling worden gebaseerd op de uitkomst van een nierbiopt, een voor de patiënt belastend onderzoek dat risico's geeft op bloedingen en infecties. Gezien de belasting van het onderzoek, is het wenselijk om zo min mogelijk biopsieën te verrichten. Lupus nefritis heeft echter veelal een recidiverend karakter, waardoor de vraag bestaat of herhaalde biopten noodzakelijk zijn bij terugkerende episodes van lupus nefritis.

Eerdere studies naar het nut van herhaald biopteren en de optimale behandeling van lupus nefritis, hebben zich gefocust op het effect hiervan op de nierfunctie. De impact van diagnose en behandeling op het welzijn van patiënten komt veel minder vaak aan bod. Het biopsychosociale model van Engel beschrijft de relatie tussen ziektekenmerken en het welzijn van patiënten. Volgens dit model is er sprake van een wisselwerking tussen de ziekte en welzijn en zijn er velerlei factoren die deze wisselwerking beïnvloeden. Door zowel de medische zorg als het psychologisch functioneren van patiënten met SLE te onderzoeken beoogde dit proefschrift om een biopsychosociaal perspectief op SLE te verwezenlijken. De studies in dit proefschrift hebben dan ook niet alleen gekeken naar het optimaliseren van de diagnose en behandeling van lupus nefritis, maar ook naar de rol van psychologische factoren hierin.

Hoofdstuk 1 geeft een algemene introductie op dit proefschrift en schetst de theoretische achtergrond van het biopsychosociale perspectief. In dit hoofdstuk komen Leventhal's process model of quality of life, het Self-Regulatory Model en Horne's uitbreiding van het Common Sense Model aan de orde. De begrippen kwaliteit van leven,

ziektepercepties en therapietrouw worden geïntroduceerd en beschreven aan de hand van eerder onderzoek.

Hoofdstuk 2 beschrijft de relevantie van herhaald biopteren in de keuze voor behandeling van recidiverende lupus nefritis. Deze retrospectieve studie bevatte 35 patiënten met lupus nefritis waarvan één of meer herhalingsbiopten beschikbaar waren. In totaal werden 84 biopten opnieuw beoordeeld door twee pathologen volgens de nieuwe ISN/RPS criteria. Uit de resultaten blijkt dat patiënten bij wie in het originele biopt een proliferatieve lupus nefritis werd vastgesteld, zelden een overgang naar een niet-proliferatieve lupus nefritis vertoonden. Herhalingsbiopten lijken dus niet noodzakelijk bij een recidiverende nefritis als er sprake was van proliferatieve laesies in het voorafgaande biopt. Echter, bij patiënten met een niet-proliferatieve nefritis in het eerste biopt, bleek bij een recidiverende nefritis vaak sprake te zijn van een overgang naar een andere klasse nefritis. Voor deze groep patiënten wordt geadviseerd om bij een recidief wel opnieuw een nierbiopt uit te voeren.

Hoofdstuk 3 behandelt een retrospectieve studie naar het effect van een geïndividualiseerde behandeling met mycofenolaatmofetil (MMF) op de concentratie van de werkzame stof van MMF (mycofenolzuur) en de nierfunctie. In totaal werden 16 patiënten met proliferatieve lupus nefritis behandeld met een lage dosis intraveneuze cyclofosfamide gevolgd door MMF oraal. Binnen één maand na de start van MMF werd bij alle patiënten de concentratie onder de curve (AUC) van mycofenolzuur gemeten. Op basis van de gemeten AUC werd de MMF dosis aangepast opdat een streef AUC van 60-90 mg*h/l zou worden bereikt. De resultaten van deze studie toonden dat de gemiddelde AUC van mycofenolzuur één maand na de start van de behandeling met MMF laag was en dat er sprake was van een hoge interindividuele variabiliteit. Dosisaanpassingen van MMF om een streef AUC van 60-90 mg*h/l te bereiken resulteerde na 6 maanden in een significant hogere AUC en een niet-significante afname in de variabiliteit. Na 12 maanden behandeling met MMF had 87.5% van de patiënten een goede uitkomst met betrekking tot de nierfunctie. Met een geïndividualiseerde

behandeling van MMF lijkt het dus mogelijk om een optimale concentratie te bereiken, waardoor het optreden van bijwerkingen zo beperkt mogelijk blijft en de behandeluitkomst zo optimaal mogelijk gemaakt kan worden.

In **hoofdstuk 4** wordt gekeken naar het effect van twee verschillende behandelingen voor proliferatieve lupus nefritis op kwaliteit van leven. De studie omvatte 32 patiënten met proliferatieve lupus nefritis die waren behandeld met cyclofosfamide in een lage of hoge dosis, respectievelijk de Euro-Lupus en National Institutes of Health (NIH) groep. De twee behandelingsgroepen werden met elkaar vergeleken op ziekte gerelateerd kwaliteit van leven, gemeten met de Medical Outcomes Study Short Form 36 en SLE Symptom Checklist (SSC). Patiënten in de Euro-Lupus groep rapporteerden een hogere kwaliteit van leven dan patiënten in de National Institutes of Health (NIH) groep. De meest belastende aspecten van de behandeling waren gerelateerd aan chemotherapie en het gebruik van corticosteroïden. Dus ook in lage dosis blijft de behandeling voor proliferatieve lupus nefritis belastend. Het introduceren van psychologische interventies voor patiënten met SLE, zoals zelfmanagement of coping vaardigheden training, is wenselijk om de kwaliteit van leven te kunnen verbeteren.

Hoofdstuk 5 beschrijft de mate waarin het seksueel functioneren van patiënten met SLE beïnvloed wordt door hun ziekte. Bij 106 patiënten die tenminste één immunosuppressivum gebruikten werd seksueel functioneren gemeten met de Physical Disability Sexual and Body Esteem (PDSBE) en de Medical Impact Scale van de Sexual Functioning Questionnaire. Ook ziektepercepties werden gemeten met de Brief Illness Perception Questionnaire (B-IPQ). De resultaten lieten zien dat de 49.1% van de patiënten een negatieve invloed ervoer van SLE op hun seksueel functioneren, waarin de invloed van de behandeling voor SLE een belangrijke rol speelde. De ziektepercepties van patiënten waren belangrijkere voorspellers van hun seksueel functioneren dan medische en sociaal demografische kenmerken. De hoge prevalentie van seksuele problemen benadrukt het belang om dit thema bespreekbaar te maken. Het aanpassen van ziektepercepties en

copingstijl interventies lijken goede methoden om te proberen het seksueel functioneren te verbeteren.

Hoofdstuk 6 behandelt de ziektepercepties van patiënten met SLE en de invloed van medicamenteuze behandeling voor SLE op de aard van deze percepties. De patiëntengroep bestond uit 32 patiënten die waren behandeld voor lupus nefritis met een lage of hoge dosis cyclofosfamide, respectievelijk de Euro-Lupus en NIH groep. De ziektepercepties werden gemeten met de B-IPQ en een tekenopdracht. Patiënten uit de Euro-Lupus groep beschouwden hun behandeling als meer behulpzaam dan patiënten uit de NIH groep. Tekeningen die patiënten maakten van hun nieren leverden extra informatie op over hoe patiënten dachten over de effectiviteit van hun behandeling, de functie van de nieren en het begrip van hun ziekte. De resultaten geven aan dat type behandeling kan bepalen hoe patiënten de werkzaamheid van hun behandeling beoordelen. Naast het invullen van vragenlijsten lijkt het maken van een tekening een belangrijke bijdrage te leveren aan een zorgvuldige beoordeling van de ziektepercepties van patiënten.

In **hoofdstuk 7** wordt beschreven in hoeverre patiënten met SLE therapieadviezen bewust en onbewust niet opvolgen. Van 106 SLE patiënten die tenminste één immunosuppressivum gebruikten werd de zelf gerapporteerde therapietrouw en een meting van bewuste en onbewuste therapieontrouw vastgelegd. Daarnaast vulden alle patiënten vragenlijsten in voor het meten van cognitief functioneren, opvattingen over medicatie, ziektepercepties en emotionele gezondheid. Er werd gekeken of deze psychologische metingen en medische parameters een relatie hadden met de mate waarin patiënten therapieontrouw waren. Alhoewel de gemiddelde zelf-gerapporteerde therapietrouw hoog was (86.7%), gaven patiënten ook aan regelmatig bewust en onbewust therapieontrouw te zijn, 46.2% versus 58.5%. Problemen met cognitief functioneren, zorgen over medicatiebijwerkingen en een jonge leeftijd waren de sterkste voorspellers van therapieontrouw, terwijl er geen relatie met medische parameters werd gevonden. Om therapieontrouw te kunnen verminderen, is het nodig

om mogelijke problemen met cognitief functioneren aan te pakken en om de specifieke zorgen van de patiënt bespreekbaar te maken.

In **hoofdstuk 8** worden de belangrijkste conclusies van dit proefschrift besproken. Daarnaast worden enkele implicaties voor de klinische praktijk en suggesties voor toekomstig onderzoek gegeven. Een beleid van selectief herhaald biopteren en geïndividualiseerde behandeling hebben geen nadelige invloed op de uitkomst voor de nierfunctie en kunnen zelfs tot een vermindering van de therapielast zorgen. Maar immunosuppressieve therapie blijft ook in lage doseringen belastend, wat blijkt uit een verminderde kwaliteit van leven en seksueel functioneren bij patiënten met SLE. Alhoewel er een grens is aan de mate waarin immunosuppressieve medicatie verder verlaagd kan worden, lijkt het aanpassen van de ziektepercepties van patiënten een manier om het psychologisch functioneren te verbeteren. De uitkomst voor de nierfunctie kan hiervan profiteren vanwege een positief effect van gunstige percepties over de behandeling op therapietrouw. Concluderend, het achterhalen en zo nodig aanpassen van de percepties van patiënten over hun ziekte is een essentiële stap in het bereiken van een goede psychologische én medische behandeluitkomst.

SUPPLEMENT 1

DANKWOORD

Vele mooie, maar gevoelsmatig soms ook lange jaren, heeft het voltooien van mijn proefschrift in beslag genomen. Het ene jaar maakte ik grote sprongen vooruit, het andere jaar lag het project nagenoeg stil. Ik vond het niet altijd makkelijk om naast studie en werk door te gaan met mijn proefschrift. De hulp en steun van onderstaande personen hebben me in staat gesteld om het tot een mooi resultaat te volbrengen!

Mijn eerste kennismaking met het wetenschappelijk onderzoek verliep via dr. Ingeborg Bajema. Zij heeft mij geïntroduceerd in haar onderzoeksgroep waar ik me zeer welkom voelde en veel inspiratie heb opgedaan. Ik ben haar dankbaar voor de mogelijkheden die ze me geboden heeft om kennis te maken met het wetenschappelijk onderzoek en haar deelnemers, waaronder in het bijzonder mijn co-promotor, dr. Stefan Berger.

Stefan Berger heeft mij geïntroduceerd in de wereld van de SLE en lupus nefritis. Ik was plezierig verrast door de vanzelfsprekendheid en het vertrouwen waarmee hij me in zijn onderzoek betrok. Ik heb van hem veel geleerd over SLE, lupus nefritis en het wetenschappelijk onderzoek. Ik ben hem zeer dankbaar voor de deuren die hij voor me geopend heeft om mijn onderzoeken zo goed mogelijk uit te kunnen voeren. Daarnaast waardeer ik het zeer dat hij heeft willen meedenken en het mede mogelijk heeft gemaakt om mijn onderzoek uit te bouwen tot een proefschrift.

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I am grateful for all the help from the colleagues from the departments of Nephrology and Pathology from the LUMC, Rheumatology of Auckland City Hospital and Psychological Medicine from the University of Auckland with patient recruitment and data collection. In particular, I would like to thank dr. Elizabeth Broadbent. I am very thankful for the opportunities she has given me to do my research in New Zealand. The preceding discussions and team work have given me much inspiration and job satisfaction. Her hospitality and professional support have meant a lot to me.

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SUPPLEMENT 2

CURRICULUM VITAE

Gabriëlle Daleboudt was born on October 17th 1983 in Delft. She completed secondary education at the Erasmiaans Gymnasium in Rotterdam in June 2002 and in September of that same year she started studying Psychology at Leiden University. In 2004 she decided to switch her full-time studies to medical school, also at Leiden University. She completed Psychology in the following years in part-time. Her first research activities in 2006 at the departments of Pathology and Nephrology at LUMC were supervised by Ingeborg Bajema and Stefan Berger. She contacted Ad Kaptein in 2007 for guidance of the psychological aspects of her research. She completed part of her research in Auckland, New Zealand, where she worked for 6 months under supervision of Elizabeth Broadbent. In 2010, she obtained her master's degree in Psychology and in 2012 she received her Medical Degree. In March 2013 she started her training as a general physician at the department of Public Health and Eerstelijnsgeneeskunde at LUMC. At the annual patient conference of the NVLE and Lupus Nederland in May 2014, Gabriëlle received the Lupus Award for her PhD research.

Gabriëlle Daleboudt werd op 17 oktober 1983 geboren te Delft. Zij behaalde haar eindexamen VWO aan het Erasmiaans Gymnasium te Rotterdam in juni 2002 en in september van dat jaar begon zij met de studie Psychologie aan de Universiteit Leiden. In 2004 besloot zij over te stappen naar de voltijd opleiding Geneeskunde aan de Universiteit Leiden. Haar studie Psychologie heeft zij in de daarop volgende jaren in deeltijd afgerond. Haar eerste onderzoeksactiviteiten vonden plaats in 2006 op de afdelingen Pathologie en Nefrologie van het LUMC onder begeleiding van Ingeborg Bajema en Stefan Berger. In 2007 benaderde zij Ad Kaptein voor begeleiding van het psychologische deel van haar onderzoek. Een deel van haar onderzoek voltooide ze in Auckland, Nieuw Zeeland, waar zij 6 maanden verbleef en werd begeleid door Elizabeth Broadbent. In 2010 behaalde ze haar doctoraal Psychologie en in 2012 deed ze haar artsexamen. Sinds maart 2013 is zij bezig met de huisartsenopleiding op de afdeling Public Health en Eerstelijnsgeneeskunde in het LUMC. Op het jaarlijkse patiënten congres van de NVLE en Lupus Nederland in mei 2014 ontving Gabriëlle de Lupus Award voor haar promotieonderzoek.

SUPPLEMENT 3

LIST OF PUBLICATIONS

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