A COHORT STUDY OF EXPOSURE

CONTROLLED MYCOPHENOLIC ACID IN CLASS III

AND IV LUPUS NEPHRITIS IN A TERTIARY CARE

CENTRE IN SOUTH INDIA

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A Dissertation submitted in part fulfillment of **D.M. Branch II**

(Nephrology) examination of the **Tamilnadu**

Dr.M.G.R. Medical University, Chennai to be held in

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BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**A COHORT STUDY OF EXPOSURE CONTROLLED MYCOPENOLIC ACID IN CLASS III AND CLASS IV LUPUS NEPHRITIS IN A TERTIARY CARE CENTRE IN SOUTH INDIA"** done towards fulfillment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–II) (Nephrology) exams to be conducted in July/August 2010, is a bonafide work of the candidate Dr. Suceena Alexander, Senior Post graduate student in the Department of Nephrology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

Dr. V. Tamilarasi, B.A, M.D. D.M.

Professor and Acting Head, Department of Nephrology,

Christian Medical College,

Vellore – 632004

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INTRODUCTION

A prevalence study of systemic lupus erythematosus (SLE) in India showed a crude incidence rate of 4 per 100,000 population per year[1]. Lupus nephritis occurs in about half of SLE patients (range: 35%-73%) in India [2-7]. Most patients with SLE do not present initially with renal disease[1]; only 25% of patients have this as their initial presenting feature. In 5% of these cases, usually in men older than 40 years, it can be several years before other lupus criteria or serological abnormalities develop[8].

Although the survival of SLE patients have improved in the west with modern treatment to the tune of 80% at 10 years after diagnosis[9], among Indians the figures are not so good (50%-60% survival at 10 years) as shown by Murali et al in a study of 98 patients between 1981 and 1993[10,11]. Renal involvement in SLE is a therapeutic challenge for all involved in the care of SLE, since early intervention can dramatically change the disease course. Thirty or more years ago, few patients with severe grade IV nephritis survived more than a year or two, and half of those with less severe form of nephritis used to die within 5 years[12]. After the introduction of Cyclophosphamide into the therapeutic armamentarium of lupus nephritis 20 years later, renal involvement no longer affects the survival rates of these patients[13]. However, long-term treatment with cyclophosphamide for patients with proliferative lupus nephritis is associated with adverse effects, including an increased risk of infection (10–18% per year) [14]. Cumulative doses of cyclophosphamide over 9 g, particularly in women over the age of 32 years, are associated with ovarian failure[15, 16]. The aim of treatment therefore, is to induce and maintain remission of active nephritis with minimum toxicity. A major advance in

achieving the goal of identifying new therapies for the treatment of severe lupus nephritis occurred in 2000, with the report by Chan et al. of the first prospective controlled study comparing the efficacy and toxicity of Mycophenolate Mofetil (MMF) to oral Cyclophosphamide in patients with diffuse proliferative lupus nephritis [17]. Also for maintenance therapy in lupus nephritis MMF seems to be a good alternative to azathioprine[18].

Mycophenolate mofetil (MMF) has become the most frequently used immunosuppressive drug in kidney transplant recipients. Initially, in patients with lupus nephritis MMF doses of up to 2 g daily were used. Subsequent dosing regimens started with 1 g MMF/day and titrated on a weekly basis up to a maximum of 3 g/day[19]. It is questionable whether standard dose therapy is the best way to treat a patient, given the large inter-individual variability in pharmacokinetics[20]. Since patients with autoimmune diseases are regularly treated with only one or two immunosuppressive drugs, an adequate Mycophenolic Acid (MPA) exposure may be even more important compared to renal transplant recipients receiving multiple immunosuppressive drugs. Also, in patients treated for autoimmune diseases MPA has highly variable pharmacokinetics, and dose is a poor predictor for MPA exposure [21]. If in patients with autoimmune diseases MPA exposure can be shown to correlate with either efficacy or toxicity, then therapeutic drug monitoring could contribute to optimum patient care.

Hence we undertook to study the outcomes of exposure controlled MPA in proliferative lupus nephritis patients.

AIM

To evaluate the Outcomes of Exposure-controlled Mycophenolic Acid as Induction and Maintenance therapy in Class III and IV Lupus Nephritis.

OBJECTIVES

1. To study the effect of Exposure-controlled Mycophenolic Acid on Inducing and Maintaining remission in Class III and Class IV Lupus Nephritis patients.

2. To study the side effect profile and complications of Mycophenolic Acid therapy in Lupus Nephritis

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LITERATURE REVIEW

Epidemiology

A prevalence study in India (carried out in a rural population near Delhi) by Malaviya et al published in 1993 surveyed a population of 91,888 and found a point prevalence of 3 per 100,000 (95%CI= 0-6.86 per 100,000)[22]. This is a much lower figure than reported from the west (varying from 12.5 per100, 000 adults in England[23] to 39 per 100,000 in Finland[24] and 124 per 100,000 in USA)[25]. However, a fair number of cases of SLE are encountered in any large hospital in India. The Copcord Bhigwan study (an ongoing, prospective population study from Pune) found a crude incidence rate of 1 per 25,000 person years i.e. 4 per 100,000 population per year[1].

Among children, SLE occurs three times more commonly in females than in males. In the 60% of SLE patients who experience onset of their disease between puberty and the fourth decade of life the female to male ratio is 9:1. Thereafter, the female preponderance again falls to that observed in prepubescent[26].

The ethnic group at greatest risk is African Caribbean blacks. The annual incidence of SLE ranges from 6 to 35 new cases per 100,000 population in relatively low-risk to high-risk groups[26].

Renal involvement in systemic lupus erythematosus (SLE) is a common disease manifestation and a strong predictor of poor outcome. The prevalence of renal disease in eight large cohort studies consisting of 2649 SLE patients varied from 31 to 65%[9]. A recent study analyzed the annual incidence of nephritis in 384 lupus patients followed at the Johns Hopkins Medical Center from 1992-94. The one year incidence of acute renal

disease was 10%[27]. Lupus nephritis occurs in about half of SLE patients (range 35%-73%) in India[1].

In a recent retrospective study, male sex, young age (<33years), and non-European ancestry were found to be determinants of earlier renal involvement in SLE patients[13].

Etiology

The etiology of SLE remains unknown. A genetic predisposition, sex hormones, and environmental trigger(s) likely result in the disordered immune response that typifies the disease[26].

HLA antigens have been associated with an increased risk of developing nephritis and the HLA-DR2 and HLA-B8 are more associated with the development of lupus renal disease [28-30]. Polymorphisms of Fc receptors for IgG (FcgammaR) were recently identified as a risk factor, implicating defective handling of circulating immune complexes in the development of renal disease[31]. The role for heredity is further supported by the concordance for this illness among monozygotic twins. The polygenic nature, however, of this genetic predisposition as well as the contribution of environmental factors is suggested by the only moderate concordance rate which is reported to be between 25 and 60%[26].

Immunopathogenesis of lupus nephritis

There are at least three potentially overlapping, immuno-pathogenic mechanisms supported by experimental data. First, circulating immune complexes consisting chiefly of DNA and anti-DNA are deposited in the kidney. Resulting complement activation and

chemotaxis of neutrophils leads to a local inflammatory process. Accumulating data suggest that Nucleosomes are the target and mediators of antibody-related glomerular immune-complex deposition[32]. The nucleosome is the fundamental unit of chromatin released by internucleosomal cleavage by endonucleases activated during cell apoptosis. It consists of a core composed of an octamer of two copies each of Histones H2A, H2B, H3 and H4, around which is wrapped a stretch of helical DNA, approximately 150bp in length[32] (figure 1). Adjacent nucleosome particles are linked like beads on a string by histone-free linker DNA of about 60bp in length, and a molecule of histone H1 is located at the point where DNA enters and exits the nucleosome. Antibodies reactive to nucleosomes have been detected both in patients with lupus and murine models even prior to the development of anti-dsDNA and anti-histone antibodies[32]. These antibodies are IgG in isotype and usually are of IgG2a and IgG2b in subclass consistent with a T-cell mediated antigen driven response[32].

Second, in situ formation of antigen and antibody complexes may similarly lead to complement activation and leucocyte-mediated injury. Third, antibodies against specific cellular targets may produce renal injury (figure 2). For example, antibodies, such as anti-ribosomal P, may bind to cytoplasmic antigens that have been translocated to the cell membrane with subsequent penetration and disruption of cellular function.

An additional mechanism is observed in SLE patients with the antiphospholipid antibody syndrome. Glomerular thrombosis can result from the hypercoagulability that accompanies antibodies directed against negatively charged phospholipid-protein complexes (e.g. biologic false positive VDRL, anticardiolipin antibodies, and lupus anticoagulant)[32].
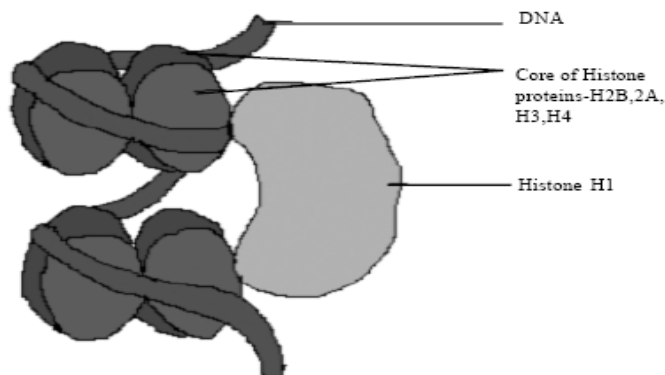
Nucleosome Structure

Figure 1 : Structure of a nucleosome

Schemabc representation of role of Apoptosis and nucleosomes in pathogenesis of SLE.
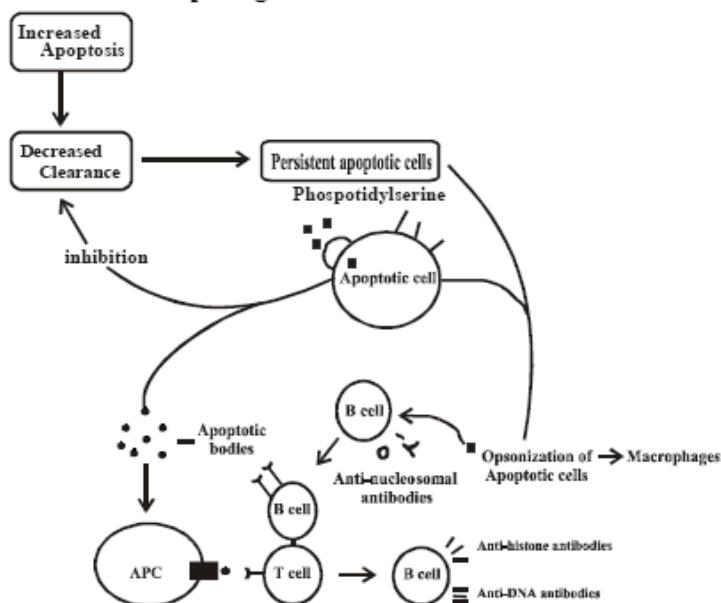
Figure 2 : Schemabc representation of role of Apoptosis and nucleosomes in pathogenesis of SLE.

Presenting Signs and Symptoms

80% of patients with SLE present with involvement of the skin or joints. However, patients may present with fever accompanied by single organ involvement, such as inflammatory serositis, glomerulonephritis, neuropsychiatric disturbance or hematological disorder (i.e. autoimmune hemolytic anemia or thrombocytopenia). Rarely,

patients present with severe, generalized acute lupus crisis with multiorgan involvement [26].

Clinical features reported by workers from different parts of India show some interesting regional variations[2-7]. Raynaud's phenomenon is conspicuous by its absence in patient from southern India where lymphadenopathy tends to be a presenting feature more often[2-7]. Low frequency of neuropsychiatric manifestations at onset in northern India emerges as another significant difference. When patients are followed up for several years, significant differences can still be made out. These include lower frequency of photosensitivity and neuropsychiatric manifestations in western India, lower frequency of nephritis in central India in comparison to other parts of the country. But these studies are hospital based studies and hence may not reflect the true prevalence in the general population[2-7].

Diagnosis Of SLE

The American College of Rheumatology has a criteria for the classification of patients as having SLE[33]. If a patient has, at any time in his or her medical history, 4 of the 11 criteria listed, the diagnosis of SLE can be made with about 95% specificity and 85% sensitivity. These criteria are actually meant for epidemiological purposes (to ensure that SLE patients reported in the literature do in fact have the disease) and not for bedside diagnosis of an individual patient. The diagnosis of SLE is based on clinical judgement. SLE can be suspected whenever 2 or more organ systems listed in ARA criteria are involved. Thus, a lady with nephritis and presence of ANA and anti-dSDNA meets only 3 criteria but can be treated as "Probable SLE"[1].

Evaluation of disease activity and severity

A number of validated indices are available for quantifying disease activity. The more popular indices include BILAG [34], SLEDAI [35], SLAM [36] and LAI [37]. These help in formulating the overall treatment plan and assessment of prognosis. The details of SLEDAI activity index are shown in Annexure A. A valid measure of damage in patients with lupus is the SLICC/ ACR Damage Index (DI)[38].

Laboratory Procedures

In 90-95% of patients with SLE the serum ANA will be positive typically with a speckled, diffuse, or peripheral pattern[26]. When the ANA is negative but the diagnosis is still strongly suspected a test for anti-Ro (SS-A) and anti-La (SS-B) antibodies can be used to identify the rare patient with ANA negative, Ro lupus. Additionally, a total hemolytic complement or CH50 can be helpful. A CH50 of zero is consistent with the unusual patient who has a homozygous early complement component deficiency (e.g. C1q, C2, C4), is at risk for developing a SLE-like illness, but is ANA negative[26]. 30-70% of patients with SLE will be anti-DNA positive. 30% of patients with SLE will be anti-Sm positive. The presence of anti-double stranded DNA antibodies and hypocomplementemia strongly suggests the diagnosis of lupus and identifies the patient at increase risk for glomerulonephritis[26].

In patients with a history of recurrent thrombosis or recurrent fetal wastage, the presence of the antiphopholipid antibody syndrome is evaluated by a VDRL, PTT, sensitive assay for lupus anticoagulant such as the dilute Russell viper venom time, and anti-cardiolipin antibodies[26].

Assessment of Renal Disease

Assessment of urine and renal function- Urinary abnormalities of microscopic haematuria, proteinuria or pyuria (persistent white cells not due to infection) are usually the first indication of nephritis. It is essential that all patients with known SLE have regular urinalysis, even when extra-renal disease is thought to be controlled or minimal. Normal-range serum creatinine does not indicate normal renal function, particularly in patients with SLE, and calculation of creatinine clearance is advised.

Cockcroft–Gault formula

In men:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (in kg)}}{(72 \times \text{serum creatinine})}$$

In women:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (in kg)}}{(72 \times \text{serum creatinine})} \times 0.85$$

The Cockcroft–Gault formula can overestimate GFR, particularly in patients with impaired renal function. In these patients the MDRD equation, which was derived from the Modification of Diet in Renal Disease Study Group data, is recommended[39]. The advantages of this method are that no weight and height measurements are required but that ethnicity, which is an important factor in the development of end-stage renal disease (ESRD), is taken into account.

$$\text{MDRD} - \text{GFR(ml/min/1.73 m}^2) = 170 \times [\text{PCr}]^{-0.999} \times [\text{age}]^{-0.176}$$
$$\times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [\text{SUN}]^{-0.170} \times [\text{Alb}]^{0.318}$$

Newer methods such as measurement of serum cystatin C are being introduced and have been found to be a more sensitive marker for changes in glomerular filtration rate (GFR) than serum creatinine[40].

Assessment by renal biopsy- Although clinicians vary in their opinion, the strongest argument for a renal biopsy is likelihood that the pathologic findings will influence initiation, selection or discontinuation of therapeutic agents. In determining the role of renal biopsy in lupus renal disease several points are relevant. Transitions from one WHO Classification to another is not uncommon and occurs in as many as 20% of the patients, especially Class III. Although it is possible to infer the WHO class of renal disease by evaluating the urinalysis, 24 hour urine protein excretion, and serologies, this is not inviolate. There is data correlating WHO Classification and National Institute of Health activity and chronicity indices with prognosis and these can be discerned reliably only by biopsy. Another consideration is that membranous lupus nephritis has a different prognosis and treatment than proliferative disease[41].

A renal biopsy may be indicated when the clinical findings are indeterminate and objective evidence of active lupus nephritis is required prior to initiating treatment. More commonly, a biopsy may be required to determine whether aggressive (i.e. cytotoxic) therapy is warranted. Finally, in the setting of rising serum creatinine and loss of renal function, a biopsy may help distinguish a patient with a high activity but low to moderate chronicity index, an excellent candidate for therapy, from a patient with moderate to high chronicity in whom the likelihood of reversibility is too small to justify further immunosuppressive therapy[42].

Indications for a renal biopsy in SLE patients include:[42]

Hematuria and proteinuria;

Renal dysfunction;

Hypertension;

Low levels of the complement factor C3;

The presence of chronic renal lesions; and modifications in

therapy: initiation, changes, or discontinuation.

Renal biopsy can provide 3 mainstays of the final diagnosis: classification, extent of reversibility and chronicity of the renal disease, and outcome prediction. Limitations are represented by the need to obtain renal cortical tissue and to collect adequate specimens, as well as the evaluation of focal lesions with limited sampling of highly heterogeneous glomerular involvement[42]. Also proliferative disease may occasionally be present with no clinical and lab parameters suggestive of renal involvement.

Classification of lupus nephritis

Different classification systems for lupus nephritis have been suggested but the WHO classification, published in 1982 and subsequently revised in 1995, has in the past been the most widely used. The WHO system classifies glomerular involvement according to the extent and pattern of immune deposits and inflammation, which are detected by immunohistochemistry on light microscopy. The finding of positive staining for immunoglobulin (Ig)G, IgM and IgA, together with staining for C1q, C3 and C4, is known as 'full house' and is present in up to 25% of patients with lupus nephritis and almost never in patients with non-lupus disease. The WHO system does not assess glomerular activity, involvement of the renal tubules, blood vessels or chronicity of

interstitial damage. The limitations of the WHO system have led to modifications recently being suggested by the International Society of Nephrology/Renal Pathology Society (ISN/RPS)[43]. The ISN/RPS classification is summarised in Table 2.

Activity and Chronicity indices (Table 1) are being provided to the clinician for LN patients, as they represent predictors, although weak, of long-term prognosis. Such a weakness may be related to the still-lingering interobserver and intraobserver variations. A value of 1+ corresponds to an involvement of < 25%, 2+ to 25% to 50%, and 3+ to > 50%. As reported by different investigators, negative prognostic indices include crescents in more than 30% of the glomeruli, a chronicity index > 5, male sex, and a higher lesion activity in the glomeruli[36].

Repeat renal biopsy

Repeat biopsy at times of deteriorating renal function, new microscopic haematuria or proteinuria provides useful information and can be useful in helping to determine renal prognosis[44]. It can help:

- to confirm the presence of a clinically suspected renal flare

- in the assessment of chronic damage and progression

- in guidance of treatment duration, and to assess whether proteinuria is due to ongoing disease activity or chronic damage.

- to document class switching.

The new classification is expected to simplify diagnosis, reporting, therapy, and followup, although some challenges still need to be tackled, including the high heterogeneity of LN and the limited classification of tubular lesions. The association of LN with antiphospholipid antibodies also has a significant effect on prognosis because it

leads more frequently to irreversible organ damage, with destruction of most renal findings, hence, the lack of association with a specific LN class. The addition of gene microarray results may lead to further improvements and refinements of this interim, working classification[45].

TABLE 1: NIH RENAL PATHOLOGY SYSTEM[36]

ACTIVITY INDEX	CHRONICITY INDEX
Glomerular abnormalities	
1. Cellular proliferation	1. Glomerular sclerosis
2. Fibrinoid necrosis, karyorrhexis	2. Fibrous crescents
3. Cellular crescents	
4. Hyaline thrombi, wire loops	
5. Leukocyte infiltration	
Tubulointerstitial abnormalities	
1. Mononuclear cell infiltrates	1. Interstitial fibrosis
	2. Tubular atrophy

Severity of each index quantitated as 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Fibrinoid necrosis and cellular crescents are weighted by a factor of 2. Maximum activity index is 24 and that of chronicity index 12.

Table 2. International society of nephrology/renal pathology society classification of lupus nephritis (2003).

Class	Description
Class I	Minimal mesangial lupus nephritis Normal at light microscopy Mesangial deposits on immunofluorescence
Class II	Mesangial proliferative lupus nephritis Mesangial hypercellularity or expansion with mesangial immune deposits Some subepithelial or subendothelial deposits on immunofluorescence by electron microscopy
Class III	Focal lupus nephritis Involves <50% glomeruli. Active or inactive lesions typically with subendothelial deposits A: Active lesions; focal proliferative lupus nephritis A/C: Active and chronic lesions; focal proliferative and sclerosing lupus nephritis C: Chronic inactive lesions with glomerular scars; focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis Involves >50% glomeruli. Active or inactive diffuse, segmental or global endo- or extracapillary glomerulomephritis. Typically with subendothelial deposits. Divided into diffuse segmental (S) when >50% of involved glomeruli have segmental lesions and diffuse global when >50% of involved glomeruli have global lesions S(A): Active lesions; diffuse segmental proliferative lupus nephritis G(A): Active lesions; diffuse global proliferative lupus nephritis S(A/C): Active and chronic lesions; diffuse segmental proliferative and sclerosing lupus nephritis G(A/C): Active and chronic lesions; diffuse global proliferative and sclerosing lupus nephritis S(C): Chronic inactive lesions with scars; diffuse segmental sclerosing lupus nephritis G(C): Chronic inactive lesions with scars; diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits by light microscopy and immuno-fluorescence or electron microscopy, with or without mesangial changes Class V lupus nephritis can occur in combination with class III or class IV disease in which case both are diagnosed Class V disease can show advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis >90% of glomeruli globally sclerosed without residual activity

Management

     The management of lupus renal disease ultimately should be based on risk stratification and the prognostic information available clinically or by renal biopsy.

WHO CLASS I

     Class I nephritis which is defined by normal histologic findings requires no specific therapy[7, 12, 46]. Here, therapy depends on extent of extra renal involvement.

WHO CLASS II-MESANGIAL

     Class II-A mesangial lupus nephritis with mesangial deposition of immunoglobulin if unaccompanied by proteinuria and active urinary sediment does not require treatment. Class II-B mesangial lupus nephritis when accompanied by significant proteinuria (e.g.: greater than 1 gram per day) usually requires treatment with steroids, especially if accompanied by hematuria, leukocyturia, other evidence of active urinary sediment, elevated anti-double stranded DNA, or low C3[7]. These patients may be treated with between .5 and 1 mg/kg of prednisone or equivalent per day for from four to twelve weeks. Subsequently, steroids are tapered by 5-10 mg. increments every 1-3 weeks[7].

WHO CLASS III and IV(PROLIFERATIVE)

     A recently published 2004 Cochrane systematic review analysed all published therapeutic trials for proliferative lupus nephritis and found that 25 of 920 articles were eligible for consideration, with a total of 909 patients across all therapeutic

combinations[47]. The review found that the use of cyclophosphamide with steroids

reduced the risk of doubling serum creatinine, compared with steroids alone, but had

no impact on overall mortality. The risk of ovarian failure was significantly increased

with the use of cyclophosphamide. Azathioprine with steroids reduced the risk of death

but had no effect on renal outcomes compared with steroids alone. As trials from 1971 to

2002 were included, interpretation of the review is limited by the variable range of drug

doses used over this time period. Routine dosages of steroids have been significantly

reduced during this time. Trials using both oral cyclophosphamide and intravenous

cyclophosphamide regimens were pooled, with large variations in cumulative doses of

cyclophosphamide administered. Despite these provisos, the use of cyclophosphamide

with steroids to preserve renal function in patients with diffuse, proliferative, lupus

nephritis was recommended.

Long-term treatment with cyclophosphamide for patients with proliferative lupus

nephritis is associated with adverse effects, including an increased risk of infection (10–

18% per year). Oral cyclophosphamide is associated with an increased risk of herpes of

19%, compared with 9% for intravenous cyclophosphamide regimens, and with an

increased risk of ammenorrhoea in 50% compared with 29% for intravenous

cyclophosphamide therapy[14]. Cumulative doses of cyclophosphamide over 9 g,

particularly in women over the age of 32 years, are associated with ovarian failure[15, 16].

Reversible alopecia can occur in 20% of patients treated with cyclophosphamide[48].

Bladder toxicity (in 14–17%) is well reported particularly with the older treatment

regimes but now occurs less frequently, particularly with the use of pre-treatment

hydration[13, 48]. The aim of treatment therefore, is to induce and maintain remission of active nephritis with minimum toxicity.

Therapeutic regimens to treat proliferative lupus nephritis can be divided into those therapies aiming to induce remission of renal disease and those maintaining the renal remission achieved.

Induction therapy

The aim of treatment is to achieve a rapid clinical renal remission, as this is associated with an improved long-term renal prognosis.

Cyclophosphamide

Cyclophosphamide, as outlined above, can be used for this phase of treatment. Most units now use intravenous regimens because this reduces the cumulative dose administered. The later lupus nephritis trials at the National Institutes of Health (NIH) used pulsed intravenous cyclophosphamide at 0.5–1 g/m^2 given monthly for 6 months, then every 3 months for a further 2 years[38]. This regimen was subsequently used by many for the treatment of active proliferative lupus nephritis. Recently, dosing regimens have been adjusted by many units with 6–12 months of therapy using 6–8 pulses of cyclophosphamide now commonly being used, assuming renal remission is achieved during this time[49].

In the Euro-Lupus trial of 90 patients, a shorter course of cyclophosphamide therapy of 0.5 g fortnightly for six doses was compared with the 20-month intravenous cyclophosphamide regime. After a median follow-up period of 73 months, no difference was found between the two groups for the end-points of ESRD or doubling of serum creatinine. All patients included in this trial had proliferative glomerulonephritis but only

22% of them presented with renal impairment, and 28% with nephrotic syndrome. Also few Black or Afro-Caribbean patients, whose prognosis is poorer, were included in the study[49].

Cyclophosphamide is an effective induction agent in the majority of cases but 22% of patients might have disease refractory to cyclophosphamide[50]. Adverse effects of cyclophosphamide, particularly infertility, are of concern as most patients with lupus nephritis are of child-bearing age. There is, therefore a need for alternative agents for disease induction or for cases refractory to cyclophosphamide.

Mycophenolate mofetil (MMF)

MMF is an immunosuppressant that is successfully used in solid organ transplantation and has been used to good effect in the treatment of lupus nephritis and other immunemediated glomerular disorders[51]. MMF has been used for induction therapy in newly diagnosed active lupus nephritis and also for those patients with lupus nephritis refractory to cyclophosphamide therapy. Prospective trials for remission induction in lupus nephritis are summarised in Table 4[52-59]. MMF is teratogenic in animal studies and is therefore contraindicated during pregnancy but there is no current consensus on preconception advice for women on MMF wanting to become pregnant.

Table 4. Prospective trials in lupus nephritis using mycophenolate mofetil[52-59].

Trial (ref. no.) and no. patients	Treatment regimen	Endpoints	Adverse effects MMF	Follow-up results
Chan et al 2000(39, 40) 51 patients	MMF 2 g/day for 6 months then 1 g/day for 6 months versus oral CYC (2.5 mg/day) for 6 months then AZA for 6 months Steroid doses equal in both limbs	CR: 81% MMF, 76% CYC, PR: 14% MMF, 14% CYC at 12 months	1 GI upset, 11 infection	At 3 years: relapse rate: 46% MMF, 17% CYC, significantly lower infection rate in MMF group
Kingdon et al 2001 (41) 13 patients	MMF 1 g/day for 25 months	69% serological improvement, 23% withdrawn, 8% relapse	23% infections	
Karim et al 2002 (42) 21 patients	MMF 2 g/day for 14 months	Proteinuria decreased ($P=0.02$)	2 infections	
Li et al 2002 (43) 75 patients	0.5–2 g MMF/day for at least 6 months	Proteinuria decreased at 6 months ($P<0.01$) improvement in serum creatinine	16% infection, 10% GI	
Appel et al 2003 (44) 140 patients	MMF 1–3 g/day for 6 months versus, IV CYC 0.5–1 g/m²	CR: 22% MMF, 5.8% CYC, PR: MMF=CYC	GI upset: 20% MMF, 3%CYC, Infection: MMF=CYC, 3 deaths CYC	
Kapitsinou et al 2004 (45) 18 patients	MMF 2 g/day + steroids for 15 months	CR: 55%, PR: 22%	11% GI upset, 1 infectious meningitis	
Cross et al 2005 (46) 24 patients	MMF 2 g/day for 12 months	CR: 83%, PR: refractory disease 8.5%, withdrawn 21%	10 infections	At 35 months: 5% relapse

AZA, azathioprine; CR, complete remission; CYC, cyclophosphamide; GI, gastrointestinal; IV, intravenous; MMF, mycophenolate mofetil; PR, partial remission.

Asperva Lupus Management Study[60] reported the comparison of MMF and intravenous Cyclophosphamide (IVC) as induction treatment for active lupus nephritis in a multinational, two-phase (induction and maintenance) study. 370 patients were randomly assigned with classes III through V lupus nephritis to open-label MMF (target dosage 3 g/d) or IVC (0.5 to 1.0g/m2 in monthly pulses) in a 24-wk induction study. Both groups received prednisone, tapered from a maximum starting dosage of 60 mg/d. The primary end point was a prespecified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. Secondary end points included complete renal remission, systemic disease activity and damage, and safety. Overall, they did not detect a significantly different response rate between the two groups: 104 (56.2%) of 185 patients responded to MMF compared with 98 (53.0%) of 185 to IVC. Secondary end points were also similar between treatment groups. There were nine deaths in the MMF group and five in the IVC group. They did not detect significant differences

between the MMF and IVC groups with regard to rates of adverse events, serious adverse events, or infections. MMF was at least equivalent to IVC in inducing remission. Although most patients in both treatment groups experienced clinical improvement, the study did not meet its primary objective of showing that MMF was superior to IVC as induction treatment for lupus nephritis[60].

Maintenance Therapy

The aim of this phase in treatment is to maintain renal remission without compromising patient long-term morbidity. Renal flare or relapse is associated with a worse longer term renal outcome. Optimum duration of maintenance therapy is unclear.

Azathioprine

Azathioprine is the most commonly used drug for maintenance therapy in lupus nephritis. The recent systematic review by Flanc et al reported found that azathioprine with steroids did not improve renal outcome compared with steroids alone in the treatment of diffuse proliferative lupus nephritis[47]. A prospective trial comparing azathioprine with cyclophosphamide is underway in the Netherlands[61]. A European trial (EULAR) randomised 32 patients with diffuse proliferative lupus nephritis to either pulse intravenous cyclophosphamide with methylprednisolone for 24 months compared with daily oral Cyclophosphamide followed by azathioprine. Two patients in the azathioprine group reached ESRD and required dialysis; none in the pulsed cyclophosphamide group reached this stage. Three deaths occurred in the continuous cyclophosphamide group and one in the azathioprine group. No statistically significant differences between the two regimens were found[62].

Mycophenolate mofetil (MMF)

Azathioprine has well-documented adverse effects and 10% of patients can produce a hypersensitivity reaction or be intolerant. MMF has therefore been used as an alternative maintenance agent. Contreras et al reported a comparison of MMF, azathioprine and pulsed intravenous quarterly cyclophosphamide as maintenance therapy in proliferative lupus nephritis[63]. All 59 patients received monthly pulsed intravenous cyclophosphamide for a maximum of 7 months before being randomised to receive the maintenance therapies. During treatment, four patients in the Cyclophosphamide group and one in the MMF group died. ESRD developed in three of the cyclophosphamide group and in one each in the azathioprine and MMF groups. Interestingly, the relapse-free survival was higher in the MMF group than the cyclophosphamide group (P= 0.02) and the number of infections was lower in the MMF and azathioprine groups[63].

The European Working Party on Systemic Lupus Erythematosus has recently concluded a new trial, MAINTAIN, to compare MMF with azathioprine as remission maintaining treatment in diffuse, proliferative, lupus nephritis. A 3-month course of the low-dose cyclophosphamide regime was administered initially[18]. The study showed equivalent efficacy for MMF and Azathioprine.

Cyclosporine

This agent has been used to treat membranous nephropathy associated with lupus (class V) and found to induce remission in all of the 24 patients over a 24-month period. High relapse rates on withdrawal of the cyclosporine were noted[64]. Cyclosporine as an adjunctive therapy in three patients with proliferative lupus nephritis, resistant to

intravenous cyclophosphamide, with favourable outcome have been reported[65].Concerns as to nephrotoxicity have limited its routine use.

Mizoribine

This drug has the same mechanism of action as MMF. It was developed in Japan and has been used in some patients with flares of proliferative lupus nephritis; it significantly reduced proteinuria and anti-dsDNA levels. Repeat biopsies in these patients documented histological improvement. At present its use is limited to Japan[66].

WHO CLASS V-MEMBRANOUS

Class V membranous lupus nephritis is often treated at the outset with 1 mg/kg per day of prednisone or equivalent for six to twelve weeks. Regardless of a response, steroids are usually then discontinued. Cyclophosphamide is generally reserved for those patients who have a concurrent proliferative component with their lupus membranous nephritis and continue to have clinical features of activity which typically requires not only proteinuria but either an active urinary sediment, persistent high anti-DNA, or hypocomplementemia. Therefore, patients with lupus membranous nephropathy and persistent nephrotic syndrome who have a component of proliferative nephritis are considered for cytotoxic therapy. Patients with pure membranous nephritis and incessant nephrotic syndrome are candidates for therapy with cyclosporin[67]. The dose typically is 3.5 mg to 5 mg/kg per day with close monitoring of the blood pressure and for a paradoxical effect on the serum creatinine reflective of the nephrotoxic effects of this agent. An additional mechanism of injury in patients with lupus nephritis relates to the hypercoagulability that accompanies the anti-phospholipid antibody syndrome. These

patients may develop hypertension, proteinuria, urinary sediment and abnormal renal function. These patients are candidates for therapy with anticoagulation or anti-platelet agents.

WHO CLASS VI-GLOMERULOSCLEROSIS

Improvement in this class, has been attributed to a number of different factors including the more judicious use of corticosteroids, refinements in immunosuppressive therapy, more effective treatment of hypertension and cardiovascular disease, and greater availability of dialysis and renal transplantation[68].

In the routine management of lupus renal disease, the addition of plasmapheresis to steroids and cyclophosphamide compared to steroids and cyclophosphamide alone, proved of no benefit[69]. Plasmapheresis is most useful in lupus patients with thrombotic microangiopathic hemolytic anemia or secondary thrombocytopenic purpura (TTP). The renal disease that accompanies this syndrome is clearly responsive to plasmapheresis with plasma exchange. Synchronized plasmapheresis based on the theory of "stimulation depletion" was initially reported to be of benefit[47]. Synergism between pheresis and cytotoxic treatment was predicated on the concept that plasmapheresis is followed by a period of accelerated B cell proliferation such that synchronized doses of cyclophosphamide would have the greatest cytolytic effect on autoreactive anti-DNA producing clones of lymphocytes. However, a more recent study suggested that synchronization was of no greater benefit than standard cyclophosphamide and low dose prednisone treatment yet associated with greater toxicity[70, 71].

Intravenous immunoglobulin is a relatively less toxic, although expensive approach to the treatment of lupus and lupus renal disease. However, save for scattered case reports, there is no convincing data to state with any certainty its benefits. Intravenous immunoglobulins can be associated, albeit rarely, with acute renal failure; presumably on the basis of tubular injury related to the infused immunoglobulin and the vehicle used.

Novel Immunotherapies

Rituximab

Rituximab is an mouse/human anti-CD20L antibody and is used in the treatment of lymphoma. CD20 is a 33–37 kDa, non-glycosylated phosphoprotein expressed on the surface of almost all normal and malignant B cells but not on plasma cells. B-cell depletion is producing promising results in preliminary studies of SLE, including refractory diffuse, proliferative, lupus nephritis. Typical regimens have employed four infusions of rituximab (375 mg/m2) weekly for four weeks with intravenous pulsed cyclophosphamide[72]. Regimen used in this study by Fra GP et al was consolidation phase with 1.Cyclophosphamide 20mg/kg i.v. every 28 days for 3 cycles, 2.Rituximab 375mg/m^2 i.v. weekly for four weeks, and 3.slow maintenance treatment with methotrexate, cyclosporine and low dose prednisolone[72]. Phase I/II trials of rituximab in SLE have shown it to be well tolerated and safe, with B-cell depletion being profound in the majority of patients. This was associated with an improvement in disease activity scores[73].

The moderate sized phase II/III trials EXPLORER and LUNAR that tested Rituximab, an anti-CD 20 monocloal antibody, for treatment of non-renal and renal lupus, disappointed many investigators with anecdotal success in refractory patients. These rituximab trials were intended to detect a large clinical effect in patients with very active disease and this was not found. However, additional studies in targeted populations or with a change in design to detect smaller or longer term effect is warranted[74, 75].

Anti-BLys therapy

B-lymphocyte stimulator (BLyS) is a protein discovered by Human Genome Sciences. It is required for the development of B-lymphocyte cells into mature plasma B cells. LymphoStat, a human monoclonal aAnti-BLyS antibody, specifically recognizes and inhibits the biological activity of BLyS. Dysregulation of BLyS over extended periods of time is common in patients with SLE[76]. Phase I trials in SLE have documented a reduction in B cells and anti-dsDNA levels without toxicity. The most promising studies were BLISS 52 and BLISS 76, large phase III studies that demonstrated measurable efficacy for Belimumab, a monoclonal antibody against B cell activating factor (BAFF)[75].

Table 5. Novel immunosuppressive/modulatory therapies for SLE[77]

B cell targeted therapies

    B cell depletion

        Anti CD 20 mAb

        Anti CD 22 mAb- Epratuzumab

B cell survival factors

    Anti BLyS mAb

    TACI Ig

    Anti BLyS and APRIL mAb- Atacicept

Tolerogen

    LJP 394

Co stimulatory blockade

    CTLA4-Ig

    Anit CD 40 ligand mAb

Anti cytokine therapies

    Anti IL10 mAb

    Anti TNF α

Anti complement therapy

    Anti C5b-9 mAb

Non specific immunotherapy

    Intravenous immunoglobulin

    Bone marrow transplantation

Fig 3. Mechanisms of current immunotherapies.
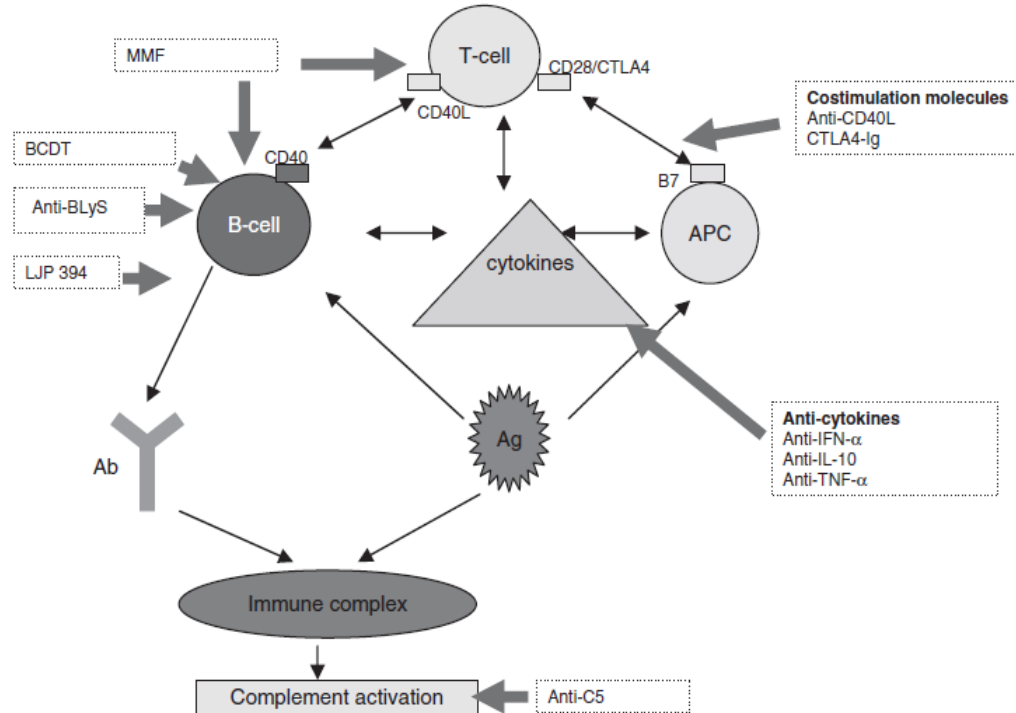
Therapeutic drug monitoring for mycophenolic acid in SLE

Mycophenolate mofetil (MMF) has become the most frequently used immunosuppressive drug in kidney transplant recipients. Since its approval for the prevention of acute rejection after kidney transplantation in 1995 in the USA and in 1996 in Europe, the use of azathioprine has been rapidly diminishing, giving way to the use of MMF. A second formulation of mycophenolic acid (MPA), the active metabolite of MMF, has become available as enteric-coated mycophenolate sodium (EC-MPS). Randomized clinical trials have shown that EC-MPS 720 mg b.i.d. is therapeutically equivalent to MMF 1000 mg b.i.d. with a comparable safety profile. These equimolar doses of EC-MPS and MMF produce equivalent MPA exposure. The delayed release formulation, EC-MPS, exhibits more variable pre-dose MPA concentrations and more variable peak concentrations[78].

Optimal Dosing

Initially, in patients with lupus nephritis MMF doses of up to 2 g daily were used.

Subsequent dosing regimens started with 1 g MMF/day and titrated on a weekly basis up

to a maximum of 3 g/day[19]. A similar dose escalation is used in the ALMS trial. It is

questionable whether standard dose therapy is the best way to treat a patient, given the

large inter-individual variability in pharmacokinetics[20]. In renal transplant patients,

monitoring of MPA exposure to optimize MMF treatment is a heavily debated topic [79-

82].Several studies have shown a correlation between MPA exposure and efficacy [83]. This

is remarkable, as most renal transplant patients are being treated with three or sometimes

four immunosuppressive drugs in the first months after transplantation. Apparently

exposure to only one (MPA) of these three or four drugs is so important that it affects the

incidence of acute rejection in these patients. Recently, a French study showed a reduced

incidence of acute rejection in concentration-controlled MMF-treated renal transplant

recipients compared to treatment with a fixed dose regimen [84]. Since patients with

autoimmune diseases are regularly treated with only one or two immunosuppressive

drugs, an adequate MPA exposure may be more important compared to renal transplant

recipients receiving multiple immunosuppressive drugs. Also, in patients treated for

autoimmune diseases MPA has highly variable pharmacokinetics, and dose is a poor

predictor for MPA exposure [21]. Factors affecting the inter individual variability of MPA

have been extensively investigated in transplant patients and are likely the same for lupus

patients, as they are drug related [85, 86]. Patients with a poor renal function (creatinine

clearance<25 mL/min) and patients with low albumin (<32 g/L) are known to have lower

MPA exposure. This is explained by the fact that the clearance of MPA depends on its

non-protein bound fraction [87]. Hypoalbuminaemia, as well as renal insufficiency, results in a higher free fraction of MPA, and this higher free fraction results in a higher MPA clearance. Other factors influencing MPA pharmacokinetics are listed in Table 6. If in patients with autoimmune diseases MPA exposure can be shown to correlate with either efficacy or toxicity, then therapeutic drug monitoring could contribute to optimize patient care.

Correlating MPA exposure to clinical outcome

Neumann *et al*. reported on the value of measuring MPA plasma concentrations in patients with autoimmune diseases [88]. The study consisted of two parts. In the first part of the study the correlation between 12-h trough MPA concentrations and full area under the concentration–time curve (AUC) of MPA was investigated. Despite a rather weak correlation between trough and AUC the authors decided to longitudinally monitor a cohort of patients in the second part of the study, collecting serial trough values, which were linked to the occurrence of adverse events and to disease recurrence. Optimal efficacy, i.e. prevention of recurrence to active disease, was associated with higher MPA trough concentrations (> 3.0 mg/L). A remarkable finding is the observation that in this study adverse events were clustered in patients with a high MPA exposure. This is in contrast with studies in renal transplant patients, in whom tolerability was poorly correlated with MPA concentrations. The authors defined the upper threshold of the therapeutic window based on toxicity. In renal transplant patients, the upper threshold of the therapeutic window is not based on increased toxicity, but merely on a lack of further improvement of efficacy above a certain exposure.

Table 6. Factors affecting MPA pharmacokinetics[87]

Factor	Mechanism
Creatinine clearance <25 mL/min	Increased MPA clearance (through higher free fraction)
Plasma albumin concentration (<32 g/L)	Increased MPA clearance (through higher free fraction)
Sex (male gender)	Increased MPA clearance (more glucuronidation activity)
Aluminium/magnesium containing antacids	Lower MPA bioavailability
Sevelamer co-therapy	Lower MPA bioavailability
Glucocorticoid co-therapy	Mechanism unknown, possibly lower MPA bioavailability
Cyclosporine co-therapy	Lower MPA exposure due to interruption of enterohepatic recirculation
Colestyramine co-therapy	Lower MPA exposure due to interruption of enterohepatic recirculation
Rifampicin co-therapy	Mechanism unknown, possibly due to faster glucuronidation of MPA
Antibiotic co-therapy	Lower MPA exposure due to interruption of enterohepatic recirculation
Polymorphisms in metabolizing enzymes	Increased MPA clearance (more glucuronidation activity)

When C12h values were subject to regression analysis, a significant association with AUC0–12h was observed (r = 0.545, P < 0.001). The corresponding regression line is shown in Figure 4. If those patients were counted who achieved an MPA exposure within 40–75 hmg/L (i.e.close to the range of 30–60 mgh/L recommended for transplant recipients), then 24/38 patients (63.2%) met this AUC range, whereas 5 (13.1%) and 9 (23.7%) were below and above this target, respectively. Hence, an MPA12-h trough level of ~3mg/L was considered an appropriate surrogate for providing autoimmune disease patients with an adequate MPA exposure and was chosen for monitoring immunosuppression in subsequent 12-h trough levelstudies.

The association of MPA trough levels with reoccurrence of disease and MPA toxicity is displayed in Table 7. Of the 13 SLE patients, 8(62%) experienced one or more flares; all were of minor severity (new B score according to the BILAG index) comprising arthralgia/arthritis and/or myalgia and cutaneous manifestations (some with ulcers). Generally, lower MPA trough levels were associated with disease recurrence.

Remission persisted in all patients with 12-h MPA trough levels ≥3.5mg/L. An MPA

level of 4.5 mg/mL best discriminated between patients with and without adverse events.

Fig 4. Relationship between mycophenolic acid (MPA) plasma concentration at 12 h

(C12 h) andAUC0–12 h for MMF following an oral dose of 1 g in patients with

autoimmune disease[88].
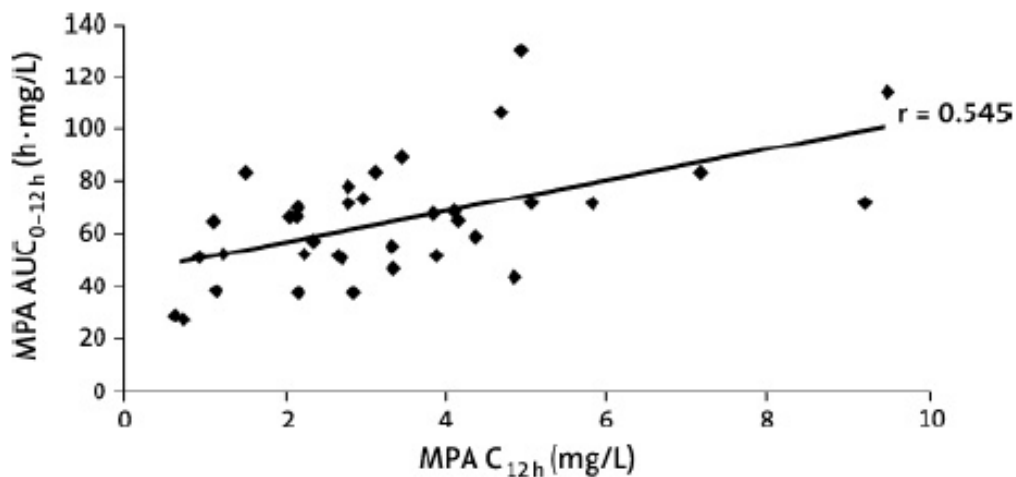
There was no relationship apparent between MMF dose and clinical end points.

Likewise, the amount of MMF necessary to achieve MPA levels close to the targeted

trough (around3mg/L), showed a wide range as depicted in Table 8[88].

Unanswered questions

Neumann *et al*. are careful in the interpretation of their data. They acknowledge

that this is an exploratory study. The therapeutic window of MPA concentrations between

3.5 and 4.5 mg/L may serve as a starting point for prospective studies, but is subject to

change. Prospective studies should be adequately powered to deal with other patient or

disease characteristics influencing the propensity to relapse. Although homogeneous

patient populations would be preferred for establishing correlations between drug

Table 7. Relationship between mycophenolic acid (MPA) 12-h trough levels and clinical outcome in patients with SLE ($N = 13$)[88]

MPA trough range (mg/L)	SLE		
	n	Active disease, n (%)	Adverse event, n
<1	8	4 (50)	1
1.0–<1.5	13	7 (54)	0
1.5–<2.0	20	6 (30)	1
2.0–<2.5	25	7 (28)	1
2.5–<3.0	22	4 (18)	2
3.0–<3.5	24	2 (8)	1
3.5–<4.0	12	0	0
4.0–<4.5	8	0	0
4.5–<5.0	6	0	1
5.0–<6.0	5	0	2
>6.0	6	0	0

Table 9. Relationship between mycophenolic acid (MPA) 12-h trough levels and MMF dose administered in patients with autoimmune disease ($N = 39$)[88]

MMF dosage (g/day)	n	Mean MPA 12-h trough concentration (mg/L)
<1	4	3.0 ± 2.4
1	59	2.6 ± 1.5
1.5	58	3.6 ± 2.2
2	125	3.7 ± 2.0
2.5	20	2.6 ± 0.9
3	28	3.3 ± 1.2

n = number of trough samples; N = number of patients.

exposure and clinical outcome, in reality patients with lupus nephritis form rather heterogeneous populations, and we want to get a better idea of optimal target levels in patients with a lower or higher risk of relapse. In the study by Neumann *et al.*, patients were not suffering from the more severe stages of autoimmune diseases. Obviously, this may have consequences for optimal target concentrations. For routine clinical practice, trough concentrations are more practical compared to obtaining a full AUC. Given the poor correlation between trough and AUC, for prospective trials it would be better to use a more robust measurement of MPA exposure than troughs only[89]. As an alternative to the latter abbreviated sampling strategies may be used to accurately estimate AUC[90].

What can we do now?

The data presented should not be considered strong evidence in favour of MPA monitoring. Nor should their predictions of a therapeutic window be looked upon as an established guidance for routine clinical practice. We need more pharmacokinetic/pharmacodynamic analyses to decide on the value of therapeutic drug monitoring for MPA in this patient population. For current patient care, however, even at this moment measurement of MPA plasma concentrations can be of some help. In patients with lupus nephritis in whom MMF is used as induction therapy, one would expect to see a clinical response within a period of 1 month in most patients. If, after 1 month of therapy, in non-responders MPA (trough) plasma concentrations are found to be low (say <2 mg/L), then a dose increase may have favourable effects on the likelihood of reaching remission. However, if in the same patient MPA trough is >4.0 mg/L already, then a further dose increase does not seem to be a good idea, as it may cause toxicity

without additional benefit in efficacy. In such patients switching to another agent may be the preferred way to go[89].

Outcomes for Clinical Trials in Lupus Nephritis

The most important requirement for lupus nephritis trials remains an adequate period of follow-up—ideally for 5–10 years. Design and reporting of trials in lupus has been criticised[90, 91]. For lupus nephritis trials, the following outcomes are commonly used:

- doubling of serum creatinine

- time to renal remission

- time to renal flare.

The definition of renal remission and flare varies between investigators but usually implies stable renal function, inactive urinary sediment with no haematuria or pyuria and proteinuria of less than 0.5 G/24 hours. Use of proteinuria as a separate endpoint is not recommended because of the difficulties in differentiating persistent proteinuria due to chronic damage from that due to persistent disease activity. Further outcome measures would include complication rates due to treatment, such as infections requiring hospitalisation and change in overall lupus disease activity.

Predictors of Outcome

Owing to the high heterogeneity of SLE among patients and the limited therapeutic resources available at present that may induce substantial toxic effects in the long term[92], it is important to identify those patients who may have a worse prognosis, and thus necessitate more-aggressive treatments to prevent or reduce complications and organ failures.

The predictors of outcome and long-term prognosis in patients with lupus nephritis are[93,94],

1. Disease severity, both in terms of clinical manifestations (serum creatinine and proteinuria) and histopathology;

2. Patients' characteristics: age and sex, race and ethnicity, socioeconomic status and access to healthcare;

3. Response to therapy; and

4. Specific treatment modalities.

Old data published by Estes and Christian[95] in the 1970s pointed to an estimated 5-year survival rate for patients with renal manifestations of about 50% vs. 75% for the whole SLE series analyzed. Such a rate was even lower for patients with severe kidney disease: about 68% for patients with focal proliferation, but only 28% for those with diffuse and membranous lesions. Patients in this series were being treated with 40 mg of prednisone, the conventional treatment at the time, as other immunosuppressive agents were not yet in use [95].

In a 1965-1998 series of 800 patients followed at SUNY/Brooklyn, the average survival rate of SLE patients with kidney disease was, overall, 60% to 65% at 300-350 months[96].

Of note, the effect of the inclusion of socioeconomically disadvantaged patients had a far less negative effect than reported in other series. It showed a trend, but it did not reach a significant difference. It is unclear whether the socioeconomic factors did not play such a significant role in this cohort or whether better care than average was provided to these patients.

Notwithstanding these successes, and the fact that SLE-related mortality has been significantly reduced with medical intervention in the past 20 years or so, there has been a 3-fold increase in morbidity, thus leading to an increase in the overall burden of disease.

A number of other factors have been shown to be of critical importance in predicting worse outcomes for patients with severe LN in a study of 65 patients[97]:

1. Initially high serum creatinine;

2. Lower hemoglobin/hematocrit;

3. Black race; and

4. The presence of interstitial fibrosis and crescents (which are a sign of chronicity and damage).

Role of Antiphospholipid syndrome (APS) in Lupus Nephritis

APS is characterized by recurrent arterial or venous thrombotic events and/or pregnancy morbidity along with the sustained presence of antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulant)[98]. Renal disease in antiphospholipid syndrome is characterized by interstitial tubular or glomerural injury due to obstruction of large, medium, or small-sized vessels[99]. In a recent study, Vlachoyiannopoulos et al studied renal involvement in a cohort of 248 patients with SLE and APS syndrome with positive titer of anticardiolipin antibodies, among which 40 % had evidence of renal involvement[100]. A renal biopsy was performed in 79 % of patients for diagnostic purposes. Patients with APS experienced high percentages of hypertension (59 %) compared to those without the syndrome, while increased levels of creatinine,

proteinuria, and hematuria with or without the presence of casts were similar in both groups. Renal biopsy analysis revealed that the main histopathologic finding in APS patients compared to controls was hyperplasia of intima (64 % vs. 19 %, p<0.001). Thrombi and atrophy of renal tubules were common but not pathognomic, since they were found in both groups. Renal biopsy findings determined further therapeutic approach to these patients. When findings are consistent with lupus nephritis, according to World Health Organization (WHO) classification, standard care with intravenous cyclophosphamide pulses and corticosteroids is recommended[101]. When thrombi and intimal hyperplasia predominate, the patient should be placed on long-term oral anticoagulant therapy.

LN: Therapy and Prognosis

The natural outcome of lupus nephritis is difficult to predict because many patients will have already received corticosteroids or other immunosuppressants. Long-term follow-up studies have demonstrated that, with treatment, patient survival is 72% at 10 years and 61% at 20 years. This compares with 5-year survival rates of 17% in the 1950s of patients with class IV disease[102]. Preservation of renal function is less encouraging, with reports of 5-year renal survival with treatment of 46–95%[93]. Retrospective studies have suggested prognostic factors at disease presentation to identify those patients at risk of development of ESRD. These factors can be divided into renal or non-renal.

In the decade from 1990 to 2000 there was significantly less proteinuria (46 v 17 g/l, p=0.008), significantly lower rates of renal failure (40% v 17%, p=0.02), and fewer histological signs of chronicity (33% v 10%, p=0.01) at the time of diagnosis of LN than

in the decade from 1980 to 1989[103]. The mean ± (SD) time from the first appearance of proteinuria until kidney biopsy was significantly shorter in the later decade [15.4 ± 15.6 vs. 3.9 ± 4.7 months]. Although treatment schedules were not significantly different, the outcome of the disease was significantly better in the patients who were diagnosed with LN between 1990 and 2000 (p=0.045)[103].

A number of factors have prognostic significance from a clinical point of view, as outlined by Dr. James Tumlin[104] of Emory University, Atlanta, Georgia, including persistent anemia, severity of the disease,[105, 106] time to treatment, and duration of remission. In patients treated with intravenous cyclophosphamide, an age at diagnosis of < 29 years was found associated with a higher risk of progression to LN in 5 years. Also, an advanced chronicity index (> 3) at biopsy and a delay to treatment of > 5 months were linked to worse outcomes[107].

Patients who did not have a flare-up of their disease had only a 25% risk of doubling their serum creatinine in 5 years vs. a 75% risk in patients who experienced flare-ups in the observation period. Austin and colleagues[97] reported in 1994 that the presence of focal necrosis, crescents, proteinuria, lower C3 (< 76 mg/dL) following therapy, female sex, age > 30 years, black race, and hematocrit of < 26% were associated with a worse outlook. The difference reported by the 2 groups in age significance has not been clarified. Treatment can critically improve the survival of SLE patients with renal disease. In a study by Laitman and colleagues[38], patients in group 1a (with relapsing/recurrent grades 2, 3, and 4 LN) had a survival of about 80% at 6 years vs. less than 5% for patients in group 1b who also had grades 2, 3, and 4 LN, but were refractory to medical treatment. Patients in group 2 (with grades 3 and 4 LN) with recurrent disease

had an intermediate survival rate.

If patients were treated within 5 months of diagnosis, they had a 25% chance of relapse of their renal disease at 7-10 years. Conversely, if they were treated only after 5 months from biopsy, their chances of relapse increased to 60%[107].

Use of renal biopsies is critical in the management of lupus patients in diagnostic, therapeutic, and prognostic terms[97]. The presence of cellular crescents and interstitial fibrosis was found associated, in addition to endocapillary proliferation, with an increased risk of progression (doubling of serum creatinine) in 40-50 months from 20% to 80% of cases. A global disease activity of < 1.73 was associated with progression (doubling of serum creatinine) at 4000 days in only 15% of cases vs. 80% in patients with a disease activity of > 1.73[108]. Persistent inflammation and positive findings at immunofluorescence are also predictive. Progression was seen in 75% of patients with karyorhexis vs. 26% in patients who were negative. Similarly, progression was seen in 69% of patients with crescents vs. 33% of control patients. Reinduction therapy with pulse steroids and intravenous cyclophosphamide in 12 refractory LN patients, however, achieved a reduction of progression risk from 34% to 10.5% in patients with crescents, and from 73% to 6.4% in patients with biopsies positive for endocapillary proliferation. Follow-up biopsies at 6 months were negative for cellular crescents, endocapillary proliferation, and karyorhexis. Thus, Dr. Tumlin[104] concluded that reinduction therapy was effective in salvaging LN patients who were otherwise refractory to treatment.

METHODOLOGY

Study Design   Cohort Study

Duration Of Study   August 2007 to December 2009

Inclusion Criteria

1. Diagnosis of ISN/RPN 2003 Class III/IV LN, with either active or active/chronic disease

2. 13-75 years of age

3. MPA as induction and/ or maintenance therapy

4. At least one follow up visit

5. MPA AUC available

Exclusion Criteria

1. Age </=12 years

Study Protocol

All consecutive patients diagnosed to have biopsy proven lupus nephritis were enrolled into the study. All patients were started empirically at 30mg/kg of Mycophenolate Mofetil (MMF). The equivalent dose for Mycophenolate sodium (MNS) is 720mg for every 1000mg of MMF[78]. After a minimum of 5 days of empiric therapy, all patients underwent therapeutic drug monitoring using abbreviated 6 hour MPA

(Mycophenolic Acid) Area Under the Curve (AUC). The therapeutic range considered adequate was 30-60 mg.h/L which has been extrapolated from the data in post renal transplant patients[83]. These patients also received oral steroids 1mg/kg/day for 2-4 weeks followed by 1mg/kg/alternate days tapered to 5-10mg per alternate days over next 4-6 weeks. They may or may not have received ACEIs/ARBs. Demographic, clinical and laboratory data was collected at entry and every follow up visit. Occurrence of flares, side effects, toxicities, infections, need for dialysis etc. was noted foe each patient.

The following specific data was collected at the time of enrolment into study through a Proforma (**Annexure B**):

1. Demography- Age, Sex, Region, Race

2. Clinical presentation of SLE

3. Clinical presentation of Lupus Nephritis

4. Biopsy findings of lupus nephritis

5. Laboratory parameters at enrolment

6. Co-morbidities

7. Treatment Details

8. MPA AUC

The following specific data was collected at each follow up visit through a Proforma (**Annexure B**).

1. Clinical and Laboratory parameters

2. Outcome Variables- Complete remission, Partial remission, No Remission, Relapse.

3. Flares, Side effects, Toxicities, Infections

4. Treatment details

1. **Primary outcome/s:**

1. Primary outcomes

Definition of outcome variables-

A. *Complete remission-* Inactive urinalysis (no cellular casts or hematuria with dysmorphic RBCs <10RBCs/hpf), reduction of proteinuria to less than <1g/24h, serum creatinine not more than 30% of the lowest during treatment[105, 109].

B. *Partial remission-* Stable serum creatinine not more than 50% of the lowest during treatment[105, 109].

C. *Relapse-* Renal flares can be classified as *nephritic* or *nephrotic*. In nephrotic (or proteinuric) *flares*, there is only increase in proteinuria (>2 g/day). Nephritic flares are further classified as mild, moderate or severe. A mild/moderate nephritic flare is characterized by active urine sediment (presence of cellular casts or hematuria with dysmorphic RBCs (10RBCs/hpf)), increase in proteinuria (<2 g/day for mild, >2g/day for moderate) but stable serum creatinine level. In severe nephritic flares there is active urine sediment and increase of plasma creatinine level >30% from baseline values, regardless of proteinuria[110].

D. *ESRD-* GFR <15ml/min/m^2 requiring dialysis or transplantation

2. *Secondary Outcome/s:*

1. Time to complete renal remission and partial remission

2. Change in anti dsDNA levels

4. Change in C3 and C4 levels

5. Change in Proteinuria, GFR, RBCs in urine

6. Side effects and complications of MPA

7. Proportion of patients achieving target MPA levels

8. Correlation of the side effects and complications of MPA with the drug levels attained

Statistical Analysis

The number of Lupus Nephritis patients who are newly diagnosed through biopsy each year in our department is approximately 40, and the proportion of patients with Class III and Class IV lupus nephritis is about 70% i.e., 28-30 patients per year. Out of the 30 patients, approximately one third i.e., about 10 patients per year choose to be on MPA considering the cost issues and side effect profile and agree to have therapeutic drug monitoring. Hence within a seven year study period we aimed to recruit 70 patients. With a 20% loss in at least one follow up, the final tally will be about 50-55 patients. Patients zero time corresponded to the time of Renal biopsy. It was a time based study. Our sample size is 52 patients. It compares well with the studies done on outcome in lupus nephritis. Study done in our centre by Abraham et al and published in '99 was done on 29 patients with class IV lupus with a follow up of 5 years[104]. Other single centre studies from the West[38,105, 111,112,113] had sample size ranging from 34-82.

Continuous data was presented as mean +/- SD unless otherwise specified. Comparison of continuous variables was by the t test or Mann whitney U test where approoriate. Pearson χ^2 test or Fisher exact test was used for comparison of categorical

variables. Relapse free survival will be analysed by actuarial survival and compard by log rank test.

Paired t Test (normal) and Wilcoxon Signed Rank Test (non normal) were performed to assess the significant improvement over time. Pearson Chi Square test were used for categorical variables. SPSS version 13 was used for the statistical analysis.

CONSORT DIAGRAM

68 CONSECUTIVE PATIENTS ENROLLED

| **52 patients with actuarial follow up at 3 months** | **16 patients were lost to follow up** |

CR =16   PR =33   NR =3   R =0   D =0
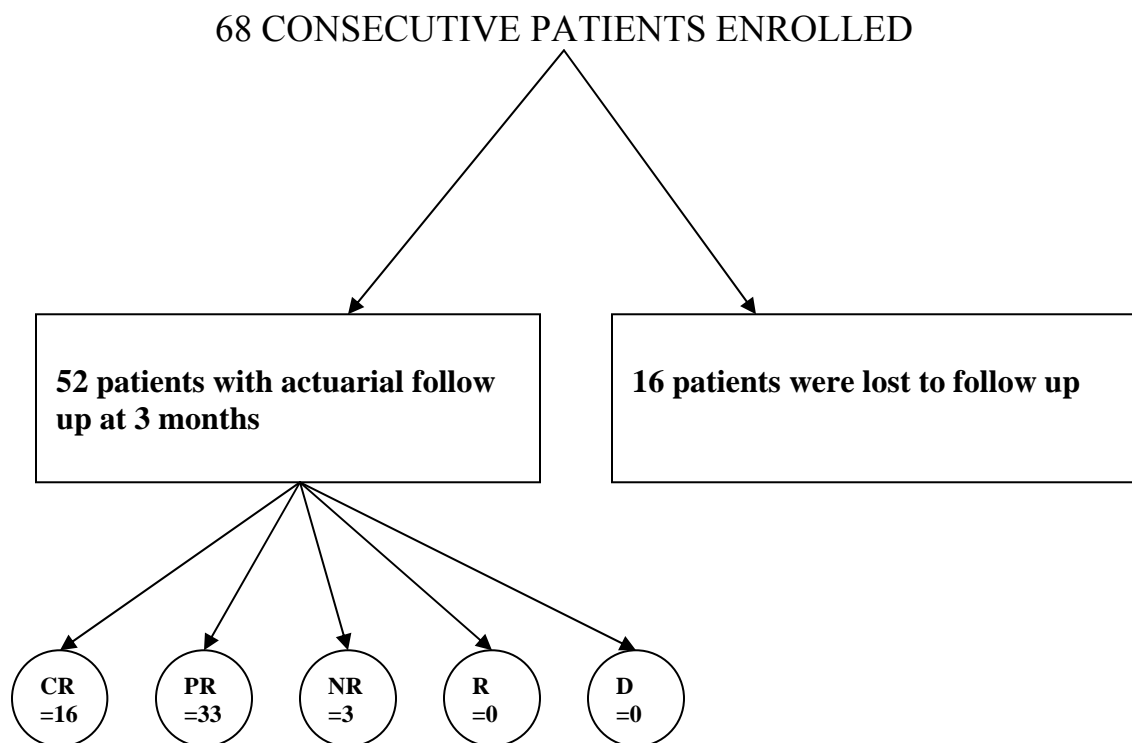
All patients had mean follow up of 17.1±13.3 months.

CR- Complete remission, PR- Partial remission,
NR- No remission, R- Relapse, D- Death

RESULTS

52 consecutive patients satisfied the inclusion criteria and were recruited prospectively into the study.

1. The following are the demographic characteristics of the study population.

Table A: Demographic Characteristics At Baseline

Age (yrs)	26.6 ±11.4 (11-65)
M:F(N)	3:49
Weight (kg)	51.8 ±9.6 (34-73)
SBP (mmHg)	129.6 ±15.5 (100-170)
DBP (mmHg)	82.6 ±7.7 (70-99)
Class III (n=52)	7 (13.5%)
Class IV (n=52)	45 (86.5%)

Figure A

Hypertension at onset

47%
53%
BP < 120/80
BP > 120/80
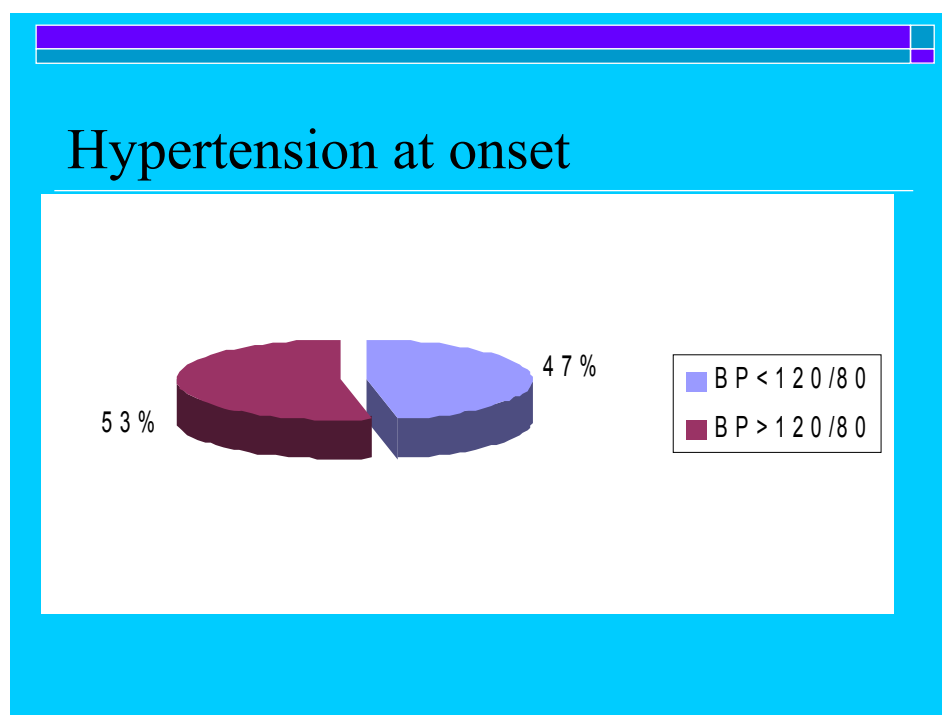
2. The following are the lab parameters of the study population.

Table B: Lab Parameters At Baseline

Proteinuria (mg/d)	3184.3 ±2720.3 (81-10100)
Urine RBCs /hpf	18.8±18 (2-60)
↓Comp (n=35)	31 (91.2%)
↑ dsDNA (n=49)	31 (63.3%)
S. Creat (mg/dl)	1.0 ±0.4 (0.9 - 4.3)
GFR (ml/min/1.73m2)	87.7 ±33.0 (29 - 174.9)
S. Albumin (mg/dl)	2.5±0.8 (0.9 - 4.3)

3. All patients were started empirically at 30mg/kg of Mycophenolate Mofetil (MMF). The equivalent dose for Mycophenolate sodium (MNS) is 720mg for every 1000mg of MMF[78]. After a minimum of 5 days of empiric dosing, all patients underwent therapeutic drug monitoring using abbreviated 6 hour MPA (Mycophenolic Acid) Area Under the Curve (AUC)[90]. The therapeutic range considered adequate was 30-60 mg.h/L which has been extrapolated from the data in post renal transplant patients[117]. After an empiric dosing schedule of 30mg per kg, 56% of patients had their MPA AUC below the therapeutic range of 30-60 mg.h/L and required modification of their drug dosages (Figure B). Very few patients had levels in the toxic range.

Figure B

MPA AUC Distribution
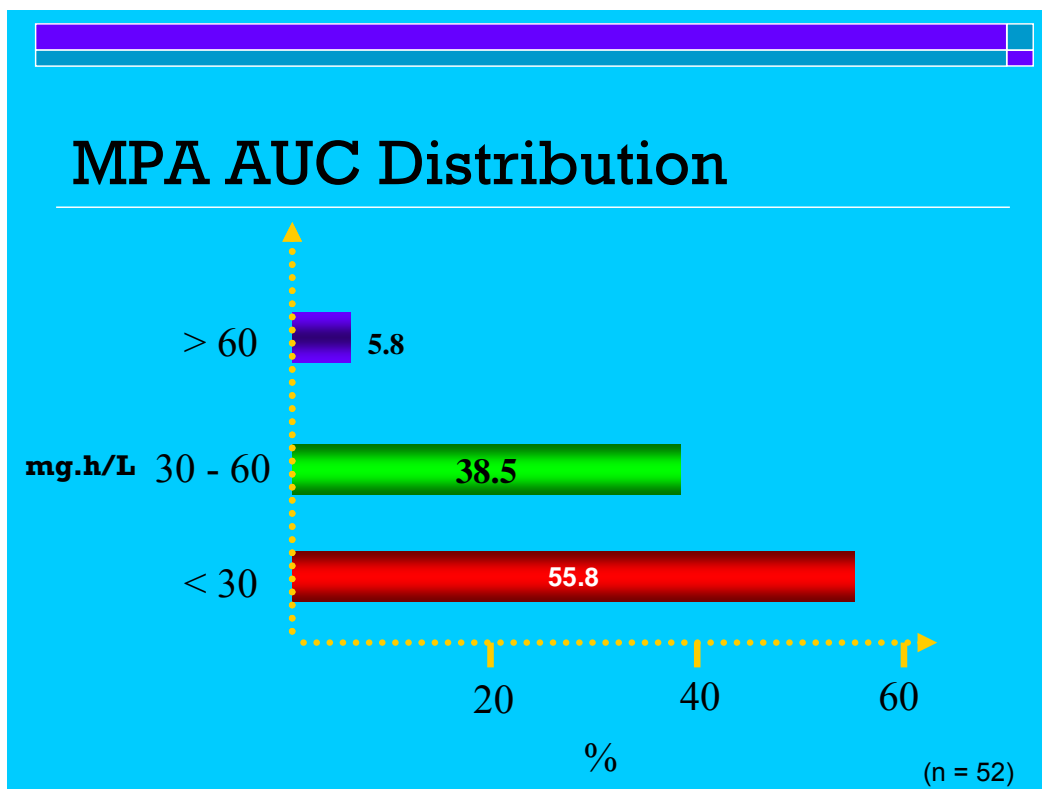
4. We plotted the MPA dose (mg/kg) before and after modification based on MPA AUC (Figure C). The scatter diagram to the left shows that with the empiric dosing schedule there was a wide variation of doses ranging from 1000 to 2000 mg per day. The scatter diagram to the right shows there is a significant escalation of the dose after the MPA AUC. Majority of them required 35mg per kg per day to reach the therapeutic MPA AUC of 30-60mg.h/L.

Figure C

Exposure Controlled MPA dose

P= 0.0

1394 ± (SE 50.6) mg/day
= 27.5 ± 1.0 mg/kg/day

1634 ± (SE 67.1) mg/day
= 32.2 ± 1.4 mg/kg/day

Weight (kg)

MPA dose at entry
(mg/day)

MPA dose modified after AUC
(mg/day)
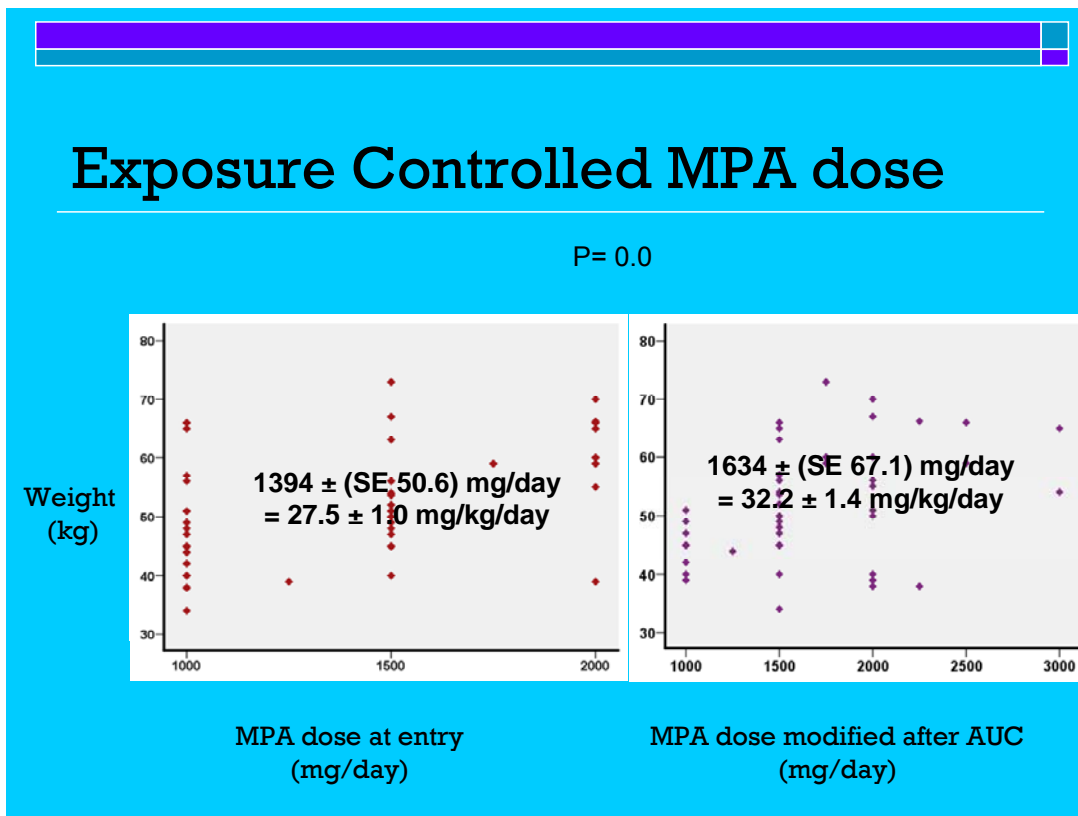
5. The mean change in GFR (glomerular filtration rate), proteinuria and S.Albumin over 2 years are plotted separately to show the magnitude of change (Figures D,E,F). There is a significant improvement in GFR within the 1st three months and the improvement is sustained at 24 months. Proteinuria declined steeply over the 1st 3 months and the steady declined continued during the maintenance phase. Albumin similarly improved significantly over the 1st three months with minimal improvement there after.

Figure D

Figure E

Figure F

Change in Albumin with time
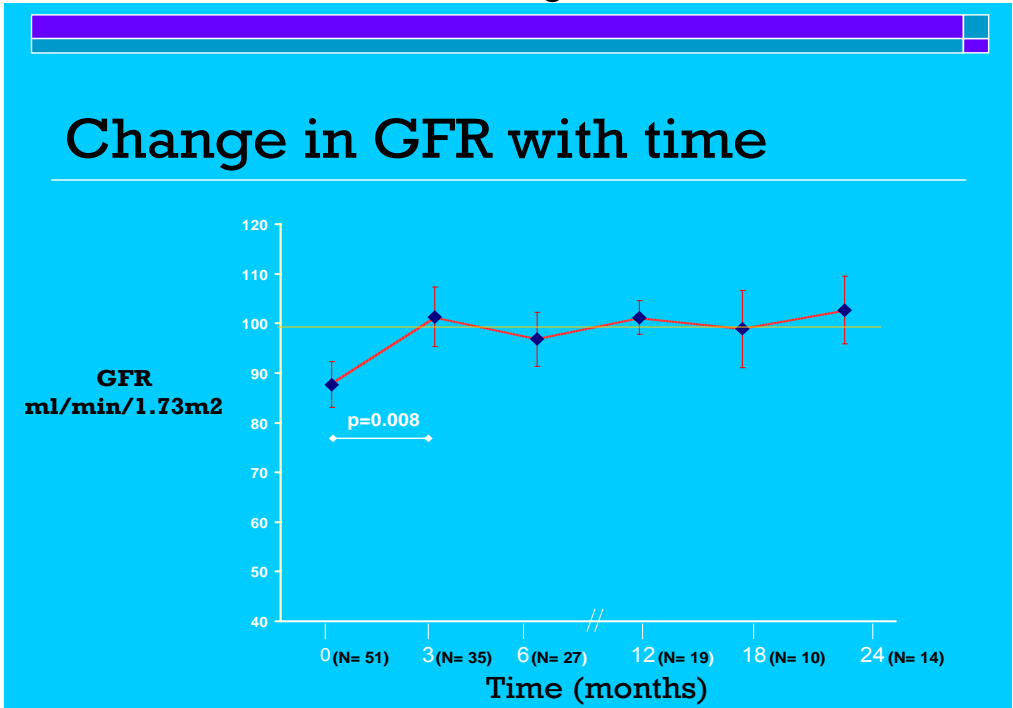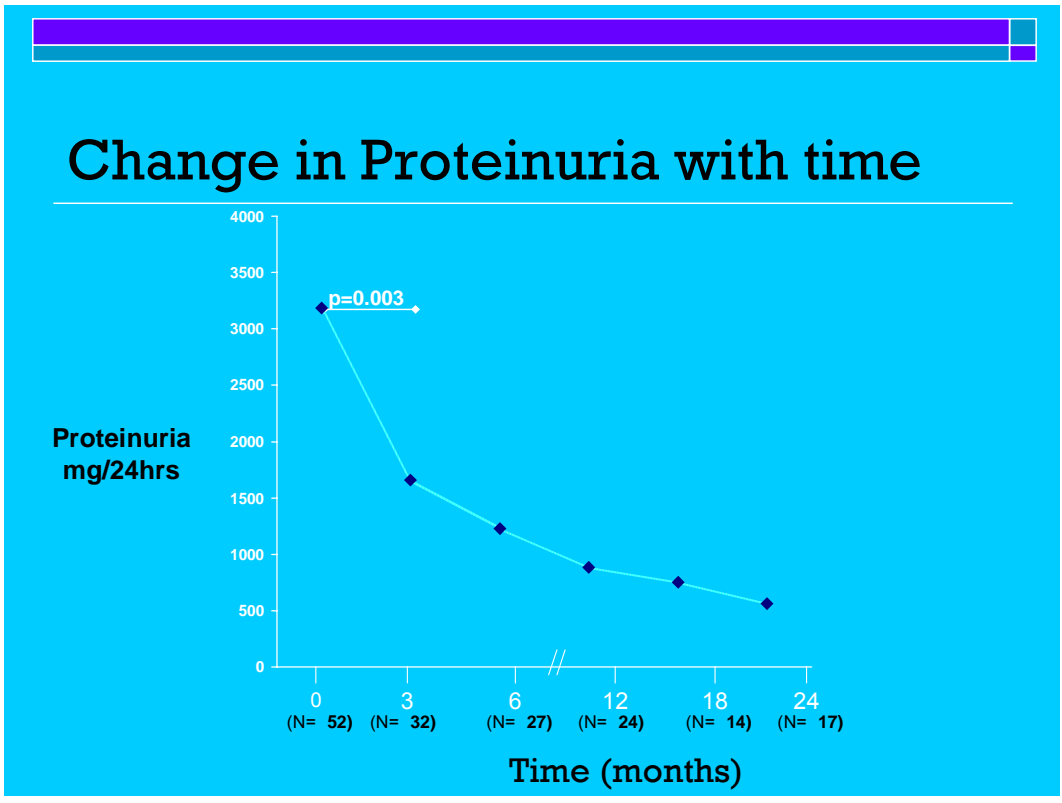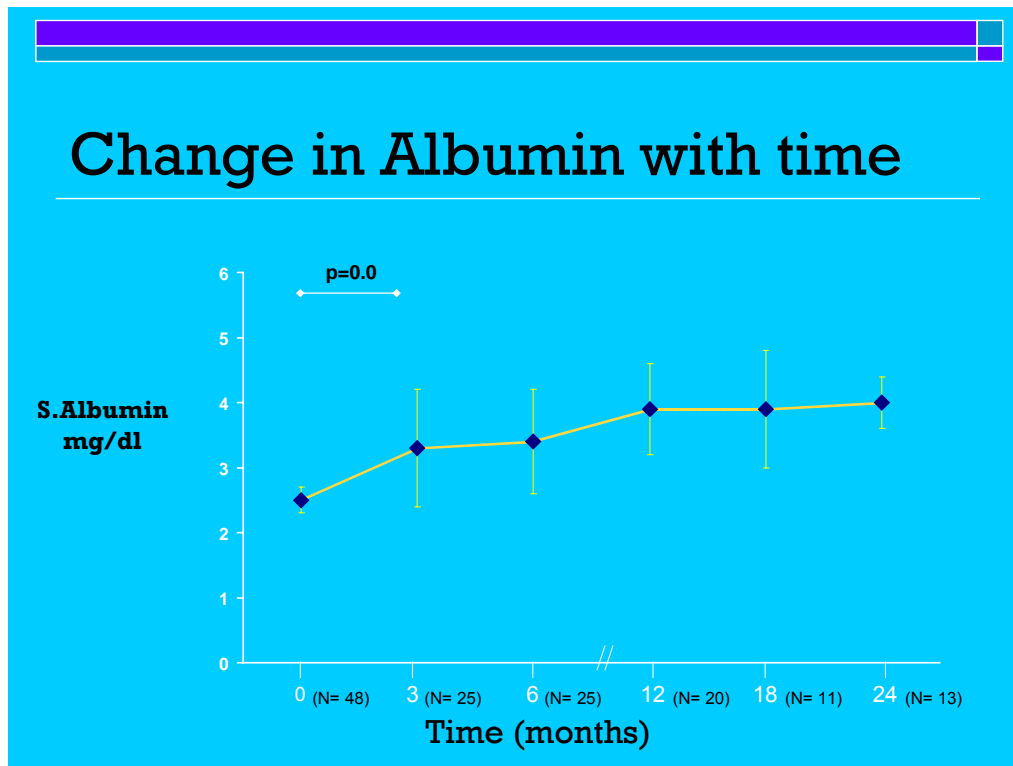
6. About one third went into complete remission by 3 months and it

progressively improved to 57% by 12 months (Figure G). The complete remission rates

improved through the maintenance phase to 88% at the end of two years.

Partial remission was seen in 50% of the patients at three months. Cumulative remission

which is the sum of complete and partial remission was seen in 94% at 3 months.

Figure G
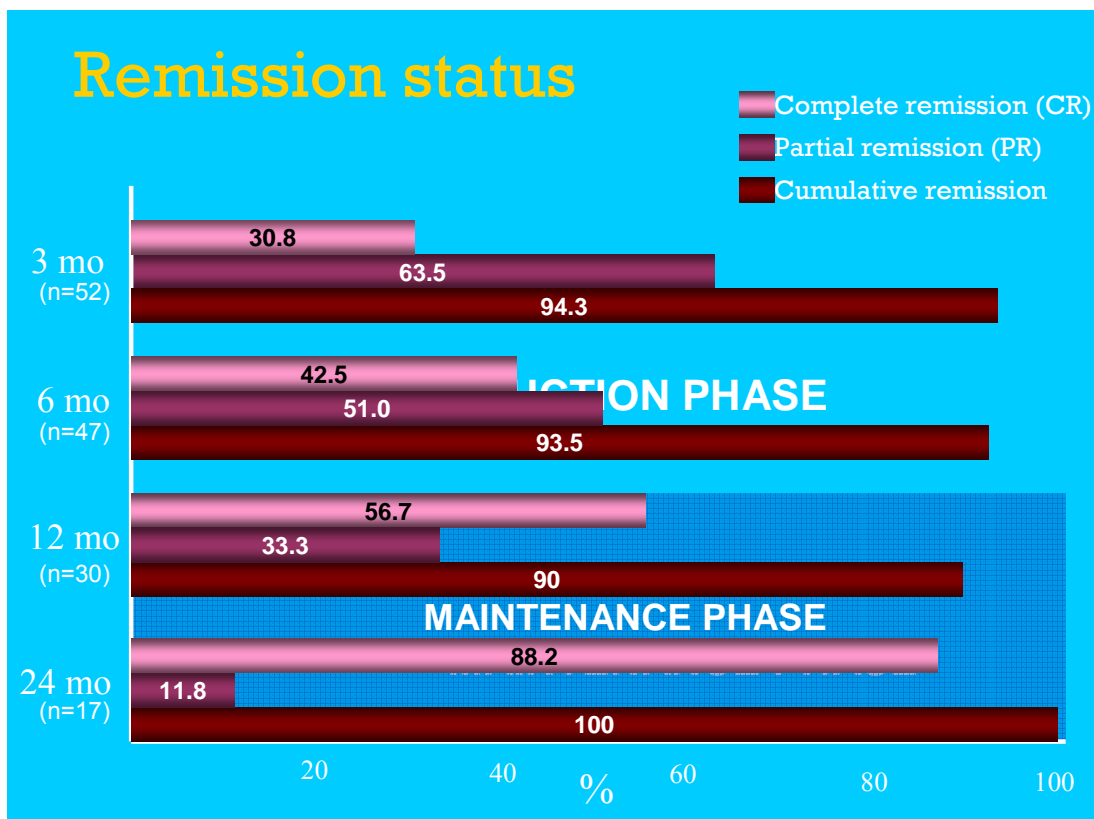
7. The median time to complete remission in this study was 11.1±1.3

months (Figure H). The earliest markers of remission were an improvement in GFR and

proteinuria to subneprotic range in 2-3 months. Anti dsDNA took a median time of 4

months for normalization. Among Complements C4 was more specific than C3 taking a

median time of 6 months for remission. Hence by 3-4 months we will know

approximately which patients are likely to respond to MPA therapy.

Figure H

Median time to remission
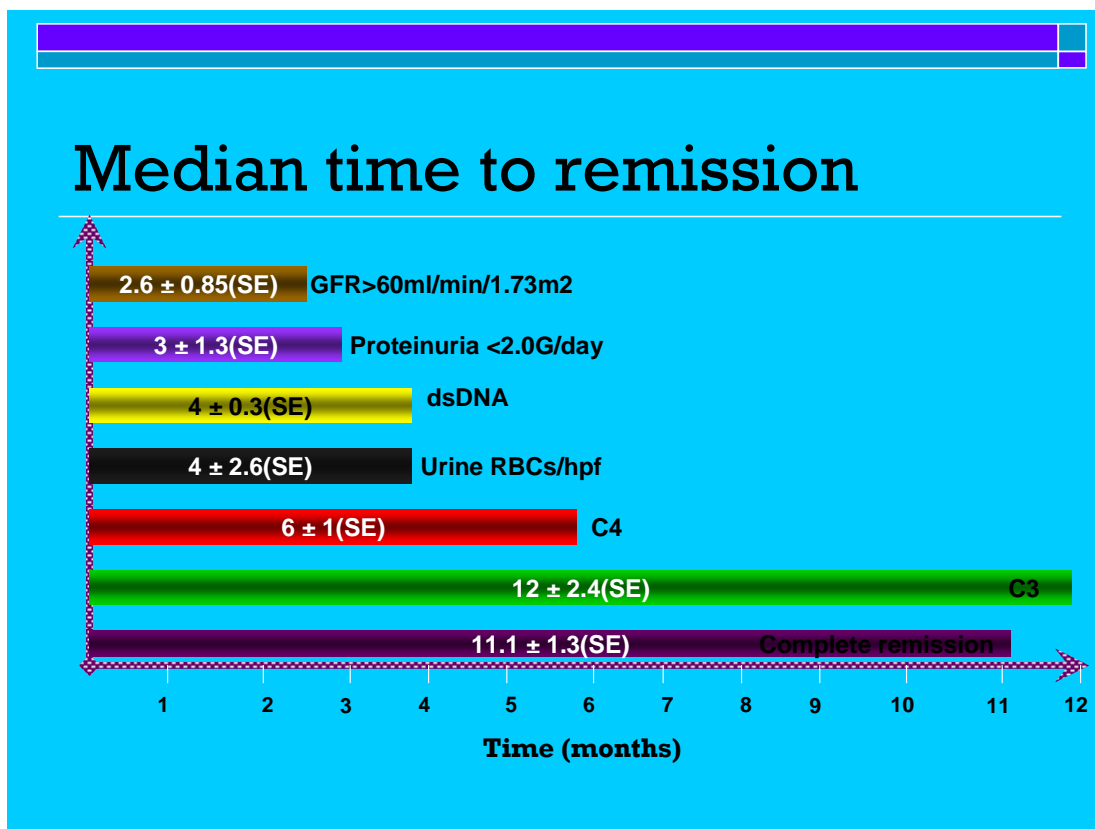
8. Contrary to the common belief that side effects are more likely with toxic levels (Figure I); neither leukopenia nor diarrhea had any correlation with the MPA AUC levels in this study.

Infections were present in 7 patients and again no strong correlation with MPA AUC could be demonstrated.

Figure I
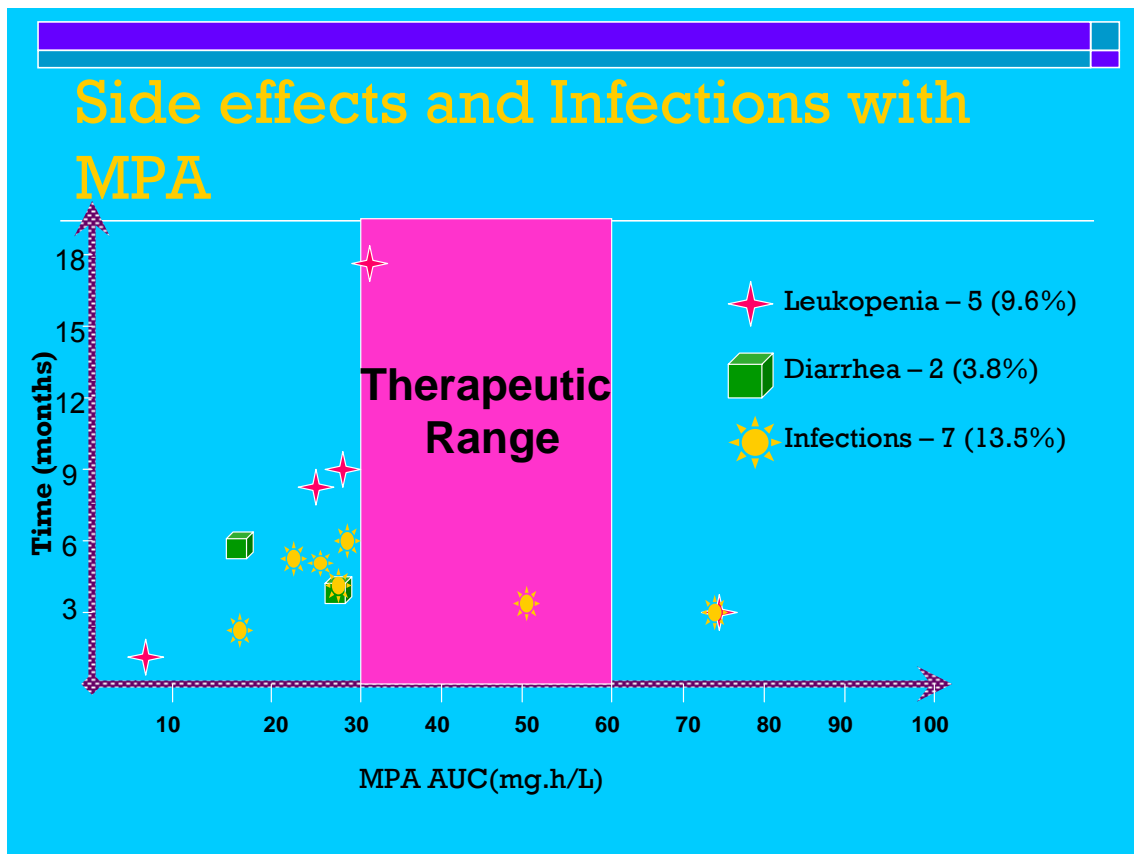
10. Flares were present in 7 patients (Figure J). But majority of them had mld

nephritic flares and all resolved without any modification of immunosuppression. There

was one death at 2 years to epsis well after stopping MMF therapy. Infections were

present in 17% of patients in this study.

Figure J

Complications

- Flares – 6 (11.5%)
    - Mild nephritic – 4
    - Severe nephritic – 1
    - Nephrotic – 1

- ESRD - 1(3.8%)

- Death – 1(0.02 %)

- **Infections**
  Episodes 9 (17.3%)
  Patients 7 (13.5%)
    - T.B – 1 (1.9%)
    - UTI – 3 (5.7%)
    - LRTI – 1 (1.9%)
    - Skin and mucosa – 4 (7.7%)
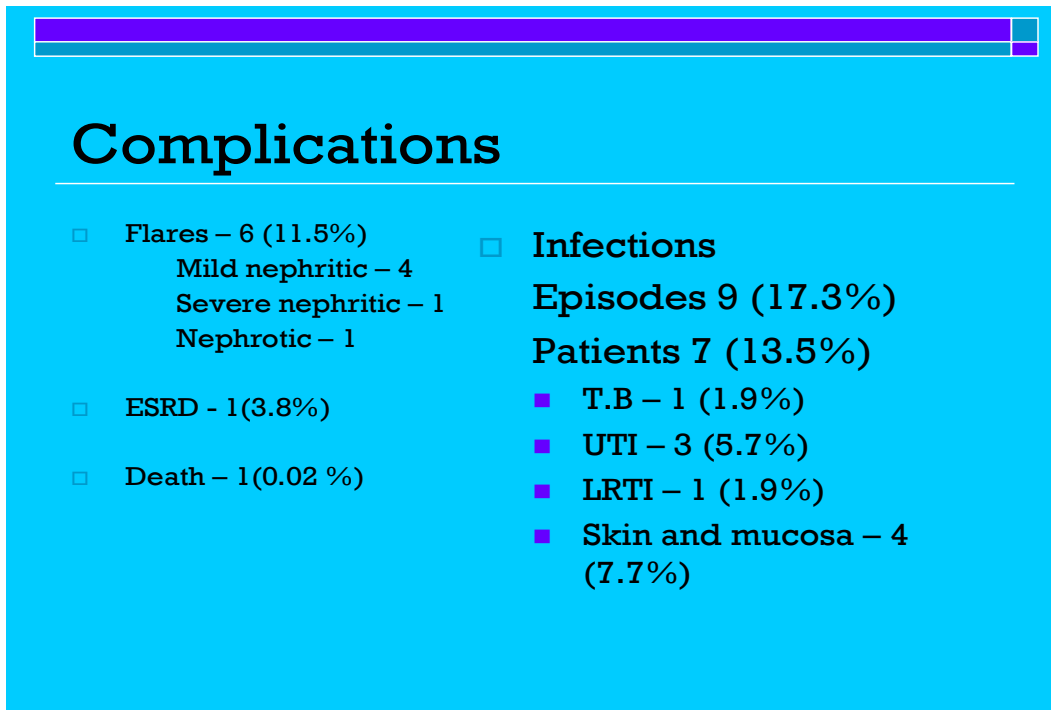
Discussion

52 consecutive patients satisfied the inclusion criteria and were recruited prospectively into the study. It compares well with the studies done on outcome in lupus nephritis. Study done in our centre by Abraham et al and published in '99 was done on 29 patients with class IV lupus with a follow up of 5 years [104]. Other single centre studies from the West [45, 114, 115] had sample size ranging from 34-82. Follow up was through outpatient visits to Nephrology Out patient Clinics.

The mean age in this study was 26.6 ±11.4 years with a range of 11-65 years. The various studies from India have reported the mean age as 24 years (range 4-55 years)[2], and 25.05 years (range 7-48 years)[3]. This is the reproductive age group in the vast majority of our population. The mean age in our study was in keeping with that found in literature.

The female to male ratio in this study is approximately 16:1 which is the higher than that reported in literature. Since this is not a prevalence study and has included only proliferative lupus nephritis treated with exposure controlled Mychophenolate, females may have been over represented. Malaviya et al in 1997 reported F: M ratio of 11:1 by among 1366 SLE patients from different regions of the country[6]. In the West the female: male ratio rises from 2:1 in prepubertal children up to 4.5:1 in adolescence to the 8 to 12:1 reported in series of adult onset patients, falling back to 2:1 in patients over 60 yr of age[12].

Mean systolic blood pressure is 129.6 ±15.5 mmHg and ranged from 100-170mmHg. Mean diastolic blood pressure is 82.6 ±7.7 mmHg and ranged from 70-99mmHg. 53% of the study population had blood pressures >120/80 mmHg.

Hypertension is found to be significant in multivariate analysis as a predictor of poor outcome and has been validated in several studies in India and the West. A study done by Fiehn et al in Germany published in 2003 among 56 patients showed that histological signs of chronicity and either arterial hypertension or renal insufficiency, or both, was predictive for terminal renal failure[116].

In this study, mean S albumin is 2.5±0.8 g/dl and range is 0.9 - 4.3g/dl. Hypoalbuminaemia reflects significant protein loss in urine and the underlying malnourished state and hence decreases the chance for a better outcome. This has been validated in several studies[70, 71, 93, 104]. Abraham et al in 1999 in a study of 29 patients from the same centre over a period of 5 years had shown that hypertension, nephrotic range proteinuria, and high activity Index were predictive of progression to end stage renal failure in patients with diffuse proliferative lupus nephritis[104].

The mean GFR calculated using the abbreviated MDRD formula is 87.7 ±33.0 ml/min/1.73m^2.

After an empiric dosing schedule of 30mg per kg, 56% of patients had their MPA AUC below the therapeutic range of 30-60 mg.h/L and required modification of their drug dosages. Very few patients had levels in the toxic range. Neumann *et al*. reported on the value of measuring MPA plasma concentrations in patients with autoimmune diseases [88]. Optimal efficacy, i.e. prevention of recurrence to active disease, was associated with higher MPA trough concentrations (> 3.0 mg/L). The authors defined the upper threshold of the therapeutic window based on toxicity. The therapeutic range 30-60mg.h/L of MPA AUC used in our study has been extrapolated from the renal transplant data[117]. In renal transplant patients, the upper threshold of the therapeutic window is not based on

increased toxicity, but merely on a lack of further improvement of efficacy above a certain exposure. Given the poor correlation between trough and AUC, for prospective trials it would be better to use a more robust measurement of MPA exposure than troughs only[89]. As an alternative to the latter, abbreviated sampling strategies may be used to accurately estimate AUC. 6 hour MPA AUC was used in this study.

About 64% of this study population required dose modification after the MPA AUC testing. Majority of them (55.8%) were under dosed and required upward titration of the daily divided dose. Few (5.8%) required their doses o be reduced from the toxic levels. It is realized that majority would require approximately 35mg per kg per day of empiric scheduling to reach the therapeutic MPA AUC of 30-60mg.h/L. For current patient care, however, even at this moment measurement of MPA plasma concentrations can be of some help. In patients with lupus nephritis in whom MMF is used as induction therapy, one would expect to see a clinical response within a period of 3 months in most patients as elaborated later. If, after 3 months of therapy, in non-responders MPA AUC plasma concentrations are found to be low (say <30mg.h/L), then a dose increase may have favourable effects on the likelihood of reaching remission. However, if in the same patient MPA AUC is >60.0 mg/L already, then a further dose increase does not seem to be a good idea, as it may cause toxicity without additional benefit in efficacy. In such patients switching to another agent may be the preferred option.

GFR (Glomerular filtration rate) improved maximally within the first three months in this study followed by steady levels. Proteinuria continued to decline throughout the induction and maintenance phase, though the steepest decrease was in the initial three months. Albumin improvement was also most noticeable in the first three

months of treatment. About one third went into complete remission by 3 months and it progressively improved to 57% by 12 months. The complete remission rates improved through the maintenance phase to 88% at the end of two years.

Partial remission was seen in 50% of the patients at three months. Cumulative remission which is the sum of complete and partial remission was seen in 94% at 3 months. In this study the remission rates were higher than that seen in similar studies described below in Asian population. Though this is encouraging in Asians where lupus nephritis is known to be severe; to categorically say whether the difference is due to exposure controlled MMF as opposed to fixed dose MMF will require randomized controlled trials.

In a study by Chan et al for the Hong Kong Nephrology Study Group, with a median follow up period of 63 months, twenty-four (72.7%) patients in the MMF group and 23 (74.2%) in the Cyclophosphamide- Azathioprine group had complete remission. Partial remission was attained by 24.2 and 22.6% of patients in the two groups, respectively. They had used more stringent criteria with complete remission being defined as a value for urinary protein excretion that was less than 0.3g per 24 hours, with normal urinary sediment, a normal serum albumin concentration, and values for serum creatinine and creatinine clearance that were no more than 15 percent above the base-line value and also the outcomes were analyzed at the end of one year[17]. The treatment response was similar between the two groups ($p= 0.878$). The time to reach complete remission was 15.3 ± 8.9 wk in the MMF group and 19.7 ± 11.2 wk in the CTX-AZA group ($p=0.851$). The incidence of complete remission was unrelated to baseline values of proteinuria, serum albumin, serum creatinine, anti-dsDNA antibodies, or C3[17]. A study done by Gan et al in National University Hospital in Singapore among fifty patients in

2002 showed lower rates of response as compared to our study. It showed 44% percent were in complete remission, 26% in partial remission, 34% had relapsed nephritis, 4% had chronic renal failure and 12% progressed to ESRD and there were five deaths over three years[118]. This further corroborates the fact that Asians have severe lupus nephritis compared to their western counterparts.

The median time to complete remission in this study is 11.1±1.3 months which is less than that reported by the Hong Kong Nephrology Study Group which used a fixed dose of MMF[17].

The earliest markers of remission were an improvement in GFR and proteinuria to subneprotic range in 2-3 months. Anti dsDNA took a median time of 4 months for normalization. Among the complement fractions, C4 was more specific than C3 taking a median time of 6 months for remission. Hence by 3-4 months we have an approximate knowldge of which patients are likely to respond to MPA therapy.

In this study neither leukopenia nor diarrhea had any correlation with the MPA AUC levels in this study. This contrasts to the study by Neumann et al where adverse events were clustered in patients with a high MPA trough exposure[88]. But since our numbers were small, no definite conclusions could be drawn. Infections were present in 7 patients (13.5%) and again no strong correlation with MPA AUC could be demonstrated.

In this study, flares occurred in 4 patients. But majority of them had mild nephritic flares and all resolved without any modification of immunosuppression. There were no deaths. Comparing this to the Chan et al study with fixed dose MMF[17]; disease relapse affected 11 patients in the MMF group with 9 of them showing clinically significant renal involvement.

In summary, Mycophenolate Mofetil is beneficial as both induction and maintenance therapy in lupus nephritis. Exposure controlled MPA does seem to have a role in follow up lupus nephritis patients. Since patients with autoimmune diseases are regularly treated with only one or two immunosuppressive drugs, an adequate MPA exposure may be even more important compared to renal transplant recipients receiving multiple immunosuppressive drugs. Also, in patients treated for autoimmune diseases MPA has highly variable pharmacokinetics, and dose is a poor predictor for MPA exposure. If in patients with autoimmune diseases MPA exposure can be shown to correlate with either efficacy or toxicity, then therapeutic drug monitoring could contribute to optimizing patient care. The least controversial area at present would be to help decide whether continuation of MMF therapy in a patient with suboptimal clinical and biochemical response is justified based on therapeutic drug levels.

LIMITATIONS

1. This study was done on a prospective cohort of patients followed up for maximum of 1 year. Though this gives us relevant information regarding short term outcomes, it would be appropriate to follow up this cohort for longer periods to assess the impact on clinical, lab parameters and treatment on a long term.

2. The heterogeneity of the treatment given, the genetic and geographic variations in the population studied would have been confounding variables in the assessment of outcomes.

3. The present cohort study needs to be compared to a similar cohort of Cyclophosphamide treated patients to assess differences in outcomes, side effects and infections.

4. In future a randomized controlled trial will need to be undertaken between patients receiving fixed dose MPA and exposure controlled MPA to assess the definite advantage of MPA AUC monitoring on clinical outcomes.

CONCLUSIONS

1. Mycophenolate Mofetil is beneficial as both induction an maintenance therapy in lupus nephritis.

2. With an empiric dosing schedule of 30mg/kg/day of Mycopheolate Mofetil (MMF), 55.8% of patients had 6 hour MPA AUC below the therapeutic range of 30-60mg.h/L and 5.8% of patients had 6 hour MPA AUC above the therapeutic range.

3. After dose adjustment, the average dose of MMF required to attain therapeutic range was 35mg/kg/day in our study population.

4. 57.6% had complete remission at 12 months in exposure controlled Mycophenolic Acid cohort and 50% had partial remission by 3 months. The complete remission rates improved through the maintenance phase to 88% at the end of two years. Partial remission was seen in 50% of the patients at three months. Cumulative remission which is the sum of complete and partial remission was seen in 94% at 3 months. This is comparable to studies on Cyclophosphamide as induction therapy and Azathioprine as maintenance therapy.

5. GFR was the earliest to improve with a median time of 2.6±0.85 months.

6. Proteinuria improved next at a median time of 3±1.3 months followed by Anti dsDNA at 4±0.3 months.C3 was the last to remit among the lab parameters at a median time of 12±2.4months.

7. There were four flares with majority being mild nephritic flares that did not require any modification of immunosuppression.

8. Infectious episodes were present 17.3% in the cohort.

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Annexures

A. SLEDAI Score

B. Proforma

C. SSPS data entry sheet

ANNEXURE A

SLE Disease Activity Index (SLEDAI)

Descriptor	Definition	Score
Seizure	Recent onset, exclude metabolic, infectious or drug causes	8
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, markedly loose associations, impoverished thought content, markedly illogical thinking, bizarre, disorganised or catatonic behaviour. Exclude uraemia and drug causes	
'Organic brain syndrome' or Acute confusional state	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, drug or infectious causes	8
Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudates/ haemorrhages in choroid or optic neuritis. Exclude hypertension, infection or drug causes	8
Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves	8
Lupus headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.	8
CVA	New onset of CVA. Exclude atherosclerosis.	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram evidence of vasculitis	8
Arthritis	≥ 2 joints with pain and signs of inflammation (tenderness, swelling or effusion)	4
Myositis	Proximal muscle aching/weakness, associated with elevated CPK/aldolase or EMG changes or biopsy evidence of myositis	4
Urinary casts	Haemoglobin, granular or RBC casts	4
Haematuria	> 5 RBC/HPF. Exclude stone, infection or other causes	4
Proteinuria	> 0.5 grams/24 hrs	4
Pyuria	> 5 WBCs/HPF. Exclude infection	4
Rash	Inflammatory type rash	2
Alopecia	Abnormal, patchy or diffuse loss of hair	2
Mucosal ulcers	Oral or nasal ulcerations	2
Pleurisy	Pleuritic chest pain with pleural rub/effusion/pleural thickening	2
Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or ECG or Echo confirmation	2
Low complement	Decrease in CH50, C3 or C4 below the normal limit of Lab	2
Increased DNA binding	Increased DNA binding using Farr assay	2
Fever	> 38 Deg C. Exclude infection	1
Thrombocytopaenia	< 100,000/cu mm, exclude drug causes	1
Leukopaenia	< 3000/cu mm, exclude drug causes	1

ANNEXURE B

Duration of SLE symptoms (mts from diagnosis of LN)

Duration of renal symptoms (mts from diagnosis of LN)

ARA Criteria-Malar rash	**Yes-1 / No-0**	**Others**	
Discoid rash	**Yes-1 / No-0**	**Arthralgia**	**Yes-1 / No-0**
Serositis	**Yes-1 / No-0**	**Alopecia**	**Yes-1 / No-0**
Oral ulcers	**Yes-1 / No-0**	**Raynauds**	**Yes-1 / No-0**
Arthritis	**Yes-1 / No-0**	**Scleroderma**	**Yes-1 / No-0**
Photosensitivity	**Yes-1 / No-0**	**Palp purpura**	**Yes-1 / No-0**
Hematological	**Yes-1 / No-0**	**Digital Gangr**	**Yes-1 / No-0**
Renal	**Yes-1 / No-0**	**Thrombosis**	**Yes-1 / No-0**
ANA	**Yes-1 / No-0**	**Abortion**	**Yes-1 / No-0**
Immunological	**Yes-1 / No-0**	**If yes, No.**	**Trimester**
Neurological	**Yes-1 / No-0**		

Renal symptoms-

Edema/Anasarca	**Yes-1 / No-0**
Haematuria	**Yes-1 / No-0**
Oliguria	**Yes-1 / No-0**
N&V	**Yes-1 / No-0**
Pruritis	**Yes-1 / No-0**
Altered sensorium	**Yes-1 / No-0**

Diabetes   **Yes-1 / No-0**

Hypertension   **No-0 / 1 / 2 / 3 / 4**

Prior Treatment Received   **Duration/ No of pulses   mg/dl**

Steroids	**Yes-1 / No-0**
Inj Cyclo	**Yes-1 / No-0**
Oral Cyclo	**Yes-1 / No-0**
Aza	**Yes-1 / No-0**
MMF	**Yes-1 / No-0**
Cyclosporine	**Yes-1 / No-0**

MMF used for Induction   **Yes-1 / No-0**   **Maintenance**   **Yes-1 / No-0**

Detail	Visit 1	2	3	4	5	6	7
Date							
Symptoms Improved – 2 / same -1/ worse-0							
BP							
No. of AntiHtn							
SLEDAI score							
Height (cm)							
Weight (kg)							
Hb							
WBC TC							
PLT							
Ur RBC							
Ur WBC							
S. Creat							
S. Urea							
S. Alb							
C3							
C4							
CH n-0 / low-1							
ANA +1/-0							
DsDNA +1/-0							
CANCA							
PANCA							
24HUP							
UP/UC							
DCT							
S.chol							
S.TG							

Detail	Visit 1	2	3	4	5	6	7
LDL							
HDL							
LA +1/-0							
ACLA +1/-0							
REMISSION No -0 /Partial -1 /Complete -2							
Relapse Yes -1 / No – 0							
Flare – no-0 / nephritic -1 / nephrotic -2/ ARF -3 / CRF - 4							
Reason non compliance -1 / Inadequate level -2/ Infection - 3 / Side effects – 4 / Unknown -5 / Others-9							
Biopsy outside1/CMC-2/Nil-3							
Biopsy No.							
Biopsy Date							
Biopsy Class							
No. of glomeruli seen							
IF C3							
IF C4							
IF C1q							
IF IgA							
IF IgM							
IF IgG							
Interstitial Fibrosis							
Tubular Atrophy							
Crescents-cellular1/fibrocellular2/fibrous3							
No of crescents							
Glomerulo Sclerosis No-0/ focal – 1/ diffuse – 2							

Detail	Visit 1	2	3	4	5	6	7
Vasculitis No – 0 / Yes – 1							
Thrombotic microangiopathy							
Podocytopathy							
Activity index							
Chronicity index							
Prednisolone dose							
Pred Dose increased -1 / tapered -2/ same -3/ stopped -0							
IV methyl pred doses							
IV Cyclophos Monthly – 1 / Quarterly – 2 / Stop - 3							
Oral Cyclophos Yes -1 / No – 0							
Aza Yes -1 / No – 0							
CsA Yes -1 / No – 0							
Keto Yes -1 / No – 0							
Tac Yes -1 / No – 0							
IVIG Yes -1/ No – 0							
ACEi/ARB Yes -1/No -0							
MMF No-0 / Cell – 1 / Myc -2/ Mofi-3 / Myfo-4 / Renf-5 / oth MMF – 8 / Oth MNA - 9							
Morn dose (mg)							
Eve dose (mg)							
6hr AUC							
Tmax							
Cmax							
C trough							
AUC low – 0 / normal – 1 / high - 2							
Why AUC not achieved? cost – 1 / poor abs –2/ side effects-3/ Non compliance - 4							
S/E diarhea Yes -1/No 0							

Detail	Visit 1	2	3	4	5	6	7
Leucopenia Yes -1/No–0							
S/E Others							
Compliance Yes – 1 / No - 0							
MMF Brand change No-0 / Cell – 1/ Myc -2/ Mofi-3 / Myfo-4 / Renf-5 / oth MMF – 8 / Oth MNA - 9							
Morn dose (mg)							
Eve dose (mg)							
6 hr AUC							
T max							
C max							
C trough							
MMF Drug Change No-0 / cost – 1 / poor abs –2/ side effects-3/ non response - 4 / flare – 5 / ARF – 6 / CRF – 7 / improved-9							
MMF Drug Changed to IV Cyphos 1 / Oral Cyphos -2 / CsA -3/ Tac -4/ Aza -5							
Non MMF drug change details							
Non MMF drug side effects							
Infections Bacteria isolated							
Viral							

Detail	Visit 1	2	3	4	5	6	7
Fungal							
TB							
Protozoal							
Parasitic							
Gen Urinary							
RS							
GI system							
Sepsis							
CNS							
CVS							
Skin n S/C							

Detail	Visit 1	2	3	4	5	6	7
Myositis							
Eye							
Others							
Lost to F/U No – 0 / Yes – 1							

Death: in CMC - 1/ In hospital -2/ at home – 3 / no info - 9
Cause of death-