Beyond immunosuppression – challenges in the clinical management of lupus nephritis

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Lupus nephritis remains the most common severe manifestation of systemic lupus erythematosus (SLE) with increased risk of death and end-stage renal disease. Although, recent research has focused on the choice of immunosuppressive in its treatment, other factors, including the quality and delivery of healthcare, the management of glucocorticoids and co-morbidity are probably of more importance. There has been significant progress in induction regimes with the successful use of mycophenolate mofetil, low dose intravenous cyclophosphamide and development of sequential regimes whereby cyclophosphamide is followed by an alternative immunosuppressive. However, the attention on the day-to-day management of lupus nephritis in the clinic has merited less attention. In this article, we aim to address more widely the major issues which are encountered regularly in the long-term management of these patients. The overall goals are the reduction of mortality and preservation of renal function. Lupus (2009) 18, 106–115.

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Introduction

Lupus nephritis remains the most common severe manifestation of systemic lupus erythematosus (SLE) with increased risk of death and end-stage renal disease (ESRD). Although, recent research has focused on the choice of immunosuppressive in its treatment, other factors, including the quality and delivery of healthcare, the management of glucocorticoids and co-morbidity are probably of more importance. Combination therapy with high dose glucocorticoids and an immunosuppressive is widely accepted therapy with an initial phase ‘induction’ aimed at controlling disease activity, and a longer follow-up phase, ‘maintenance’, aimed at preventing disease recurrence. There has been significant progress in induction regimes with the successful use of mycophenolate mofetil (MMF), low dose intravenous cyclophosphamide (IVC) and development of sequential regimes whereby cyclophosphamide is followed by an alternative immunosuppressive. These initiatives have challenged the previously recognised ‘standard of care’ of long-term IVC developed by the National Institutes of Health.1,2

Replacement of cyclophosphamide by either azathioprine or MMF at 6 months was successful in a small study by Contreras, et al. – the Eurolupus trial used azathioprine as the maintenance agent in its initial study. Direct comparison of azathioprine and MMF is being evaluated in the ongoing MAINTAIN study and the maintenance phase of the ALMS trial.3,4 However, the attention on the day-to-day management of lupus nephritis in the clinic has merited less attention. Few reviews on this subject have been published, and these have mainly focused on control of proteinuria, hypertension and hyperlipidaemia.5,6 In this article, we aim to address more widely the major issues which are encountered regularly in the long-term management of these patients. Table 1 summarises the major aims of care of lupus nephritis in the clinic. The overall goal in considering each of these targets is the reduction of mortality and preservation of renal function.

General principles

Systemic lupus erythematosus requires a multi-disciplinary approach to care and recognition of the
importance of co-ordinated management through
diagnosis, remission induction, remission mainte-
nance and long-term follow-up. This is particularly
true of lupus nephritis, where the involvement of a
nephrologist and the need for early detection of
nephritis is important often before clinical signs of
renal disease are apparent. Close monitoring of the
patient, with regular out-patient visits, and urine dip-
stick testing is vital. This approach is designed to pick
up renal flares early, and institute prompt and appro-
priate treatment.

The development of ESRD has reduced with the
introduction of immunosuppressive treatment.
However, varying degrees of chronic renal impair-
ment often develop, and ESRD in approximately
10–15% of lupus nephritis patients.7 Assessment by
the nephrologist is important not only in the initial
diagnosis and evaluation of nephritis but also in the
management of therapy in the context of renal disease
and, in a minority, the management of chronic renal
impairment, including preparation for transplantation
and dialysis.

Risk profiling

A number of studies have identified certain risk fac-
tors for the progression of lupus nephritis. These risk
factors include demographic, clinical, laboratory and
histopathological features,8–11 summarised in Table 2.

Dooley, et al.12 reported that the ESRD rate over a
5-year period in African-Americans in a study from
the Glomerular Disease Collaborative Network was
42%, compared with 5% in white patients. It is, there-
fore, important in patients who have high-risk features
to have a close eye on monitoring and compliance.

In the future, we may need to consider choice of
medication as part of the risk profiling assessment.
There is emerging data on reduced response rate to
IVC according to race seen in the recent ALMS induc-
tion trial compared with MMF.13 Of 370 patients, 100
(27.0%) were reported as ‘other’, mostly comprising
black (46 patients) and mixed-race (36 patients).
Response rates with MMF and IVC were similar for
Caucasian and Asian patients, but in the ‘other’ cate-
gory, 60.4% responded to MMF and 38.5% to IVC
\( (P = 0.033) \). The response rates among Hispanic
patients were 60.9% for MMF and 38.8% for IVC
\( (P = 0.011) \).

Features suggesting good response have been
reported in the Euro-Lupus Nephritis Trial, which
included patients with proliferative lupus nephritis,
randomised to high- and low-dose cyclophosphamide
regimes.14 Multivariate analysis showed that early
response to therapy at 6 months [decrease in serum
creatinine (SCr) level and proteinuria <1 g/24 h] was
the best predictor of good long-term renal outcome. In
this study, patients were predominantly Caucasian
(14/90 black or Asian), and hence this might not be
valid to extrapolate directly to other races.

Monitoring

Why monitor?
The early recognition of renal flare is important to
detect untreated renal inflammation and avoid conse-
quent loss of renal function. Relapses are relatively
frequent and early detection is associated with better
outcomes. The risk of ESRD is reported to be multi-
plied almost sevenfold in patients who experience
renal flares, and nephritic flares may carry poor
prognosis.11,15 Early detection may also impact on
treatment selection. Sensitive disease markers would
help optimise initiation and escalation of therapy at
the time of active or relapsing disease. In the long
term, such markers may limit the duration of immuno-
suppression by improving assessment of renal remis-
sion. Reasons for monitoring are summarised in
Table 3.

How to monitor?
A variety of techniques exist for the monitoring of
patients with lupus nephritis. These are summarised
in Table 4.
**Table 3** Why monitor in patients with lupus nephritis?

- Detection of renal remission in lupus nephritis
- Early detection of renal flare in known lupus nephritis
- Distinction between flare and chronic damage
- Assistance in assessing likely duration of immunosuppression
- Assessment of extra-renal SLE
- Detection of treatment-related toxicity

**Urine dipstick testing and urine cytology**

Simple urine dipstick testing in the clinic is useful to perform at each clinic visit. This can semi-quantitatively detect haematuria, proteinuria, pyuria, nitrite and glucose. Positive findings can prompt the requesting of further specific testing, such as urine cytology, urine protein quantification, urine culture and testing for diabetes (often steroid related).

Urine cytology (urinary sediment testing) can reveal the presence of dysmorphic red blood cells, and red cell casts associated with glomerulonephritis. Detection of isolated leucocytes may suggest interstitial nephritis or urinary tract infection. Urine cytology may also rarely identify clues to bladder malignancy in patients, who have been treated with cyclophosphamide.

Hebert, *et al.*\(^{16}\) reported on the use of urinary sediment testing in prediction of renal flare. 17 patients with class IV lupus nephritis were followed prospectively for 1129 patient-months. Semiquantitative urinalyses were performed at 2-month intervals during periods of low grade or absent SLE activity and more frequently during periods of increased SLE activity. They performed 877 semiquantitative urinalyses, and 43 renal relapses were observed in 14 patients (no flares in three patients). Red blood cell and/or white cell casts (cellular casts) were observed before or at the onset of 35 of the 43 renal relapses (sensitivity, 81%). The mean and median intervals between appearance of cellular casts and onset of renal relapse were 10 ± 2 weeks and 8 weeks respectively.

**Assessment of renal function**

Measurement of SCr, while a useful test, has many limitations which must be considered. Progressive glomerular injury may not initially lead to a rise in the SCr due to compensatory hypertrophy and hyperfiltration in normal or less-affected nephrons. It is estimated for the SCr to rise above the normal range that renal function may diminish by 50%. Normal ranges for SCr vary according to age, sex and race. This is important to note as lupus is nine times more common in women, and lupus nephritis is more common in patients of Afro-Carribean origin and Chinese origin, who have very different normal ranges for SCr.

A 24-h urine collection to determine the creatinine clearance (CrCl) is a widely used method for assessment of glomerular filtration rate (GFR) as it is more accurate than SCr alone. However 24-h urine collection is time consuming, inconvenient and difficult to perform. Patients often over- or under-collect urine leading to inaccurate results. It may be that tubular creatinine secretion is significantly elevated in patients with nephrotic syndrome, leading to a less accurate measurement.\(^{17}\)

Glomerular filtration rate estimating equations (eGFR) improve upon SCr alone by incorporating known demographic and clinical variables as observed surrogates for the unmeasured physiological factors other than GFR that affect SCr concentration. Examples include the Cockcroft-Gault (CG) equation, the Modification of Diet in Renal Disease (MDRD) study equation or the abbreviated MDRD (aMDRD) study equation. Kasitanon, *et al.*\(^{18}\) compared performance of CG and MDRD equations in 97 lupus nephritis patients in the Hopkins Lupus Cohort. They found that CG was more precise and more accurate than the MDRD, whereas Leung, *et al.*\(^{19}\) based in Hong Kong, found MDRD and aMDRD to be superior than CG. In our unit, we measure the nuclear medicine GFR in patients with SCr in the middle or upper normal range every 1–2 years, using chromium-51 ethylenediamine tetraacetic acid (EDTA-GFR). Godfrey, *et al.*\(^{20}\) found that EDTA-GFR was a more sensitive tool in detecting mild renal impairment in lupus nephritis, compared with calculated CrCl (CG formula).

**Estimation of proteinuria**

Proteinuria is an important marker of renal involvement in SLE, useful in diagnosis and in monitoring. Various techniques exist, including qualitative urine dipstick, 24-h urine collection, and more recently, spot urinary protein-creatinine ratio. The validity of qualitative urine dipstick vs. quantitative 24-h measurement of urinary protein/creatinine (P/C) ratio was assessed by Siedner, *et al.*\(^{21}\) They assessed three urine dipstick assays with varying results. None of the assays showed both high sensitivity and specificity. While the Atlas assay showed high sensitivity (97.7%) in detecting proteinuria (≥0.5 g), it had a low specificity in excluding proteinuria (62.2%). The
Clinitek assay showed the highest specificity (86.1%) in correctly excluding proteinuria <0.5 g.

The convenience of spot urinary protein-creatinine ratio has lead many units to adopt this technique in preference to 24-h collections. The evidence for this comes from general nephrology clinics, and there is some data in SLE. Lane et al. studied patients in a general nephrology clinic and reported a logarithmic relationship between spot urinary P/C ratio and 24-h urine protein excretion with a correlation of 0.92 ($P < 0.0001$). However, agreement between the actual and predicted 24 h urine protein and between spot and 24 h urine P/C ratios was suboptimal at higher levels of protein excretion. Leung, et al. studied 165 urinary samples in lupus nephritis, considered the spot urine P/C ratio to be useful in screening and monitoring proteinuria. They also added the caveat that this measure might not be so reliable at high levels of protein excretion. Birmingham, et al. reported that spot and 24-h urine P/C ratios in lupus nephritis showed good correlation over a range of values as well as reasonably strong concordance. However, over the range of most SLE glomerulonephritis flares, correlation was present but concordance was poor.

While one could advocate 24-h collection to confirm the results of patients who have elevated spot urine P/C ratio, the performance of the latter alone seems adequate. Ideally, further validation of the routine use of the spot urine P/C ratio should be undertaken in lupus nephritis, particularly in prospective longitudinal studies. To deal with the issue of poorer concordance at high levels of proteinuria, one could request 24-h collection in this subgroup. The counter argument is that at high levels of protein excretion, it may not be clinically essential to know the exact amount of proteinuria.

Autoimmune serology

Anti-dsDNA antibodies are more common in patients with lupus nephritis compared with non-renal lupus, but they are not specific for active renal disease. Several studies show the relationship of anti-dsDNA antibodies with SLE disease activity (reviewed in ter Borg, et al.25). In a meta-analysis, the mean positive likelihood ratio of anti-dsDNA antibodies as a marker of lupus activity was 4.14, indicative of low overall predictive value.26 We agree with Fernandez and Isenberg,27 who recommend increased vigilance of flare development in patients with rising anti-bodies to dsDNA, especially together with reducing C3 levels.

Anti-C1q antibodies seem to be more frequent in active lupus nephritis. Marto, et al.28 showed higher prevalence of anti-C1q antibodies in active lupus nephritis compared with non-renal SLE (74% vs. 32%, $P < 0.0001$), but no significant difference in anti-C1q prevalence between active and non-active nephritis (74% vs. 53%, $P = 0.06$). Patients with nephritis had higher anti-C1q levels than those without nephritis ($P < 0.001$). Sinico, et al.29 also showed that anti-C1q antibodies were more common in SLE with nephritis compared with non-renal SLE (60% vs. 14%, $P < 0.05$). However, they found that higher titres were present in active compared with inactive nephritis (89% vs. 0%).

Trendelenburg, et al.30 reported anti-C1q antibodies in 97.2% of patients with proliferative nephritis, 35% with inactive nephritis and 25% of non-renal lupus patients. Moroni, et al.31 showed anti-C1q antibodies correlated with renal disease activity (sensitivity 87%, specificity 92%), better than anti-dsDNA, anti-endothelial cell and antiphospholipid antibody–binding levels.

Estimation of complement components C3 and C4 does not directly reflect disease activity as their serum levels merely express the balance between synthesis and catabolism. Nevertheless measurement of C3 and C4 is a useful parameter to monitor,27 often reducing with the onset of increased disease activity, including nephritis. Measurement of complement degradation products is not routinely available, but could offer a more accurate measure of complement activation. Negi, et al.32 reported serum C3d to be comparable in patients with active renal and extra-renal SLE. However, urine C3d was highest in active lupus nephritis compared with patients with active extra-renal disease and inactive renal disease.

Repeat renal biopsy

Renal biopsy is the gold standard in baseline assessment of renal disease, by providing important information regarding the examination of morphology and inflammatory cell infiltration. However, as biopsy is invasive and associated with a significant risk, particularly in patients with associated antiphospholipid antibodies (aPL)/antiphospholipid syndrome (APS) who may be anticoagulated,33 the use of noninvasive measures to assess activity of nephritis is desirable. Nevertheless, there are situations in which re-evaluation of renal histology is desirable, for example in the presence of falling GFR. Moroni, et al.34 considered indications for repeat biopsy in three categories: improvement of renal disease, but persistence of non-nephrotic proteinuria; persistent or relapsing nephrotic syndrome and increase in plasma creatinine level of at least 50% compared with basal value. Bajaj, et al.35 reported that results of repeat biopsy frequently showed changes in histological class, although changes were often within a class. Changes between proliferative and non-proliferative classes were less common. In our experience, most patients who had a repeat renal biopsy...
underwent a treatment change (submitted for publication). Repeat renal biopsy has also been used following induction therapy to evaluate the response of histological activity and the progression of renal fibrosis. These studies have demonstrated ongoing histological activity despite normal urine analysis.

**Novel urinary markers**

The urine is an obvious potential source to study markers of active renal inflammation. Various biomarkers have been studied to date. Urinary monocyte chemotactant protein-1 (MCP-1) has been shown to be a useful correlate of lupus renal flare, with levels increasing 2–4 months before a flare. Urinary MCP-1 levels reduced in responders to treatment, but persisted in non-responders. The TNF superfamily cytokine TNF-related weak inducer of apoptosis (TWEAK) regulates secretion of MCP-1, Interferon-gamma-inducible 10 kD protein (IP-10) and regulated on activation, normal T expressed and secreted (RANTES), also known as CCL5. Schwartz, et al. showed that urinary TWEAK levels were higher in active nephritis and correlated with the renal SLE disease activity index.

Urinary lipocalin-2 levels have been found to be significantly higher in those with lupus nephritis those without nephritis. The presence of lipocalin-2 in the urine of patients with lupus nephritis correlated significantly with the renal SLEDAI score \( r = 0.452, P = 0.009 \), but not with extrarenal disease activity. Mosley, et al. used surface enhanced laser desorption/ionisation time-of-flight spectrometry to study urine proteomics in patients with lupus nephritis. Discriminant function analysis was used to define minimum number of proteins whose levels best distinguished between the two groups. Proteins with masses of 3340 and 3980 distinguished active from inactive lupus nephritis with 92% sensitivity and 92% specificity.

**Control of proteinuria**

Proteinuria has been identified as both an important risk factor and a mechanism for the progression of renal disease. Studies in this area with respect to lupus nephritis are limited, and the approach has been largely to extrapolate from the data on chronic renal impairment and from diabetic nephropathy.

The renoprotective effects of ACE-inhibitors (ACE-I) and angiotensin receptor blockers (ARB) have been reviewed elsewhere. Briefly, ACE-I and ARB can be used as antiproteinuric agents without necessarily inducing a change in blood pressure. Both agents have been shown to decrease progression to ESRD in patients with non-diabetic and diabetic chronic renal impairment. It may be that combination therapy with ACE-I and ARB is more effective in reduction of proteinuria than the use of either agent alone.

Tse, et al. reported a retrospective study of effects of ACE-I/ARB in lupus nephritis with persistent proteinuria >1 g despite resolution of active nephritis with immunosuppressive treatment. Fourteen out of 92 patients were included. Patients with systolic blood pressure >150 or diastolic >100 mmHg were excluded. Patients were started on ACE or ARB and follow-up was 52 ± 35.7 months. Proteinuria and serum albumin were significantly improved at 6 and 24 months of treatment. Systolic blood pressure was significantly reduced from 6 months onwards, but this did not correlate with proteinuria reduction.

Kanda, et al. retrospectively studied the use of ARB for 6 months in lupus nephritis patients, who remained proteinuric despite treatment with steroids and/or immunosuppression. Median proteinuria reduced from 2530 mg/g creatinine to 459 mg/g creatinine \((P = 0.030)\), reducing in 83% of patients. As with Tse, et al., the antiproteinuric efficacy did not correlate with reduction of blood pressure.

These small studies together with the large studies in chronic renal impairment and diabetic nephropathy suggest that treatment with ACE-I/ARB could reduce proteinuria in patients with lupus nephritis. However, long-term prospective studies are needed to investigate the effect of these drugs on renal preservation in lupus nephritis.

In an interesting recent publication from the multi-ethnic LUMINA lupus cohort in North America, it was reported that ACE-I use delayed the occurrence of nephritis. Eighty of 378 patients (21%) were ACE-I users. The probability of renal involvement free-survival at 10 years was 88.1% for ACE-I users and 75.4% for non-users \((P = 0.0099, \text{log-rank test})\). Users of ACE-I developed persistent proteinuria and/or biopsy-proven lupus nephritis (7.1%) less frequently than non-users (22.9%, \(P = 0.016\)). ACE-I use was associated with a longer time-to-renal involvement occurrence, whereas African-American ethnicity was with a shorter time. ACE inhibitor use (54/288 case and 254/1148 control intervals) was also associated with a decreased risk of SLE disease activity (HR 0.56; 95% CI 0.34, 0.94).

**Blood pressure control**

It is important to control blood pressure both for reducing the progression of renal disease, but also...
for the reduction in vascular risk in these patients. The agent of choice ideally would be an ACE-inhibitor or an ARB drug as this would have the combined effect of reduction in proteinuria, renal protection, and blood pressure reduction.

Combinations of more than one drug may be required to achieve satisfactory blood pressure reduction. Diuretics and calcium-channel antagonists are among the other possible agents.5

In terms of target blood pressure in lupus nephritis, a stricter figure of <130/80 mmHg is desirable. We have extrapolated this figure from guidelines for management of hypertension in diabetes given its increased vascular risk, and from guidelines for chronic renal impairment.44,51 A target figure of 125/75 mmHg has been proposed in general for patients with renal impairment with proteinuria >1 g/day.

A recent meta-analysis has shown that blockade of the renin-angiotensin system in patients with chronic renal impairment of all causes decreased the risk for cardiovascular outcomes and heart failure compared with control therapy in patients with proteinuria.52

One caveat, regarding use of ACE-I which may be important in lupus with associated APS, is that the risk of renal artery stenosis is increased in this group.53 It may be useful to consider magnetic resonance angiography of the renal arteries in SLE patients with resistant hypertension and APS.

**Vascular risk and hyperlipidaemia**

It is well known that patients with SLE have an increased vascular risk.54 This would most likely be further increased in lupus nephritis, as these patients may be hypertensive, and have hyperlipidaemia related to steroids, nephrotic syndrome and chronic renal impairment. Abnormal lipid profile has been reported in SLE, and lipoprotein (a) has been reported to elevated in lupus nephritis.55,56 It is, therefore, critical to address classical risk factors to include smoking, blood pressure, glycaemic control and lipid levels.

To draw a parallel with diabetes, the impact of tight control of risk factors was shown by Gaede, et al.,57 who showed tight glucose regulation and use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents reduced the risk of nonfatal cardiovascular disease in patients with type 2 diabetes mellitus and microalbuminuria. Although, not all risk factors have been identified as yet for the increased vascular disease in lupus, it is clear that some of the traditional Framingham risk factors are important, and hence merit close control. Bruce55 suggested that the increased vascular risk in SLE was not accounted for by classical risk factors alone. It may also be that close control of lupus itself could contribute by decreasing systemic inflammation which may increase vascular risk.

For SLE, as with most other causes of hyperlipidaemia, the drug of choice would be a statin.58 The patient should be advised of the risk of statin-associated myositis. Care with fibrates is necessary in chronic kidney disease, because of increased risk of a myositis-like syndrome, and risk of increase in SCr. The combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis).

It has been clearly shown that statins have significant effects on reduction in morbidity in cardiovascular disease, and there may be some additional effect on renal disease. A meta-analysis from 2006 suggested that statin therapy reduced proteinuria modestly, with a small reduction in the rate of kidney function loss, especially in populations with cardiovascular disease.59 However, a more recent meta-analysis from 2008 suggested reno-protective effects of statins were uncertain due to lack of data and possible outcomes reporting bias.60 Currently, the LORD trial61 is a randomised double-blind placebo controlled trial assessing the effect of atorvastatin on the progression of kidney disease.60

**Infection risk and vaccination**

Understandably, much of the attention in SLE recently has focused on the increased vascular risk in these patients. However, though this is responsible for a high proportion of late mortality, early mortality often relates to either overwhelming lupus activity or severe infections.62 It is, therefore, important to take an infection history to assess the nature of previous infections, the patient has experienced. Infections may relate to immunosuppressive therapy or to a number of immune defects associated with SLE. Such defects include congenital or acquired immunoglobulin deficiency, complement deficiency, mannose-binding lectin deficiency, impaired splenic function and an increased risk of salmonella infections.63,64 It is likely that further predisposing factors for infection in lupus will be identified in the future.

The issue of vaccination is important as this may help to reduce the risk of infection. However, it is also recognised that vaccinations in some instances can trigger lupus flares. It may be that the risk might vary with the nature of the vaccine, being highest with live vaccines. We adopt an approach based on
the individual patient, assessing both the infection risk and whether the disease has previously flared with vaccinations. Our general advice is that pneumovax and influenza vaccination would be reasonable, as these are subunit and inactivated vaccines respectively. Live vaccines would be contraindicated in any patients on immunosuppressive medication, or high doses of corticosteroids. We would refer readers to a review on the subject by O’Neill and Isenberg.65

**Antiphospholipid antibodies**

It is increasingly recognised that aPL can affect the kidney. There is evidence that aPL can affect both the micro- and macro-vascular circulations of the kidney. Associations have been reported with renal artery stenosis and renal artery thrombosis.53,66 Microvascular disease, particularly renal thrombotic microangiopathy (TMA), and glomerulopathy may be seen. The term APS nephropathy has been coined to describe renal TMA, and other suggestive renal histological appearances, listed in Table 5.67 APS nephropathy can occur in primary and in secondary APS, such as in patients with lupus nephritis. However, APS nephropathy is not yet considered a clinical criterion for APS.67

The presence of aPL may adversely affect outcome, although this has not been found in all studies. Moroni et al.68 reported an association between aPL and development of chronic renal impairment. Tektonidou, et al.69 reported that patients with APS nephropathy had a higher frequency of hypertension and raised SCr levels at renal biopsy, but no higher rates of renal impairment, ESRD or death during follow-up. These effects on renal function may relate to an effect on the renal microcirculation. It is, therefore, important to test patients with lupus nephritis for the presence of aPL, and to examine the renal biopsy closely for any evidence of APS nephropathy. There is a lack of any controlled data for treatment of APS nephropathy, and evidence is mainly based from case reports where patients have been treated with anticoagulation, or with aspirin and ACE-inhibition (reviewed in Karim, et al.70). Post-transplant renal thrombosis has been reported with aPL,71 which is, therefore, important to check prior to transplantation in lupus nephritis.

**Bone protection**

Patients with lupus nephritis will undoubtedly be receiving or have received corticosteroids with consequent impact on calcium absorption in the bowel, and on bone metabolism. It is essential, therefore, that all such patients, who have no contraindication, receive calcium supplementation usually in the form of calcium together with vitamin D. This is also important as deficiency of vitamin D is common in SLE.72

It is important to recognise that compliance of calcium/vitamin D supplementation is poor as patients do not like the chalky taste. In this event, effervescent calcium/vitamin D can be tried and if this also is not tolerated, then the next step could be vitamin D injections. It is advisable to ensure calcium and vitamin D intake and compliance is adequate when considering any further levels of osteoporosis prophylaxis. The use of a bisphosphonate for corticosteroid osteoporosis prophylaxis would be encouraged in high risk patients, or in patients who have completed their family. Studies of bisphosphonates in osteoporosis have used concomitant calcium/vitamin D supplementation, and the impact of suboptimal vitamin D levels on efficacy of bisphosphonates is not clear.73 Regular assessment of the bone mineral density on a 2–3 yearly basis is recommended.

In patients with significant reduction in GFR, there may be also contribution from secondary hyperparathyroidism and consequent renal osteodystrophy. Management would include the use of phosphate binders, and calcitriol to suppress PTH secretion, in a chronic kidney disease clinic.

**Compliance and polypharmacy**

**Polypharmacy**

With the increasing sophistication of management, this invariably results in a longer list of medications for patients. This increases the risk of drug interaction, especially in patients with APS who are receiving oral anticoagulation. We do know that patient adherence to prescribed medication is not perfect.74 It is likely
that as the list of medications increases that the degree of compliance may reduce. It may be that patient will not end up taking the most important medications from their list. There are particular drugs where there is known to be poor compliance, e.g. calcium supplementation.

Therefore, it is important to assess compliance and to reiterate the importance of the medication and to stress the reasons for the different medications. In important situations, the use of intravenous medication may ensure delivery of the drug to the patient where compliance otherwise might be poor, e.g. use of IVC for remission induction.

Patient choice

Patient choice is likely to impact on the choice of drug prescribed with the introduction of MMF and low dose cyclophosphamide. A major demographic population in SLE consists of women of child bearing age. Low dose cyclophosphamide has low incidence of ovarian toxicity.\(^1\) MMF has no ovarian toxicity, although must be discontinued before pregnancy.\(^65,66\)

Adjunctive therapies – antimalarials

Further medications may be identified which contribute to the patient’s prognosis, although this may add further to the patient’s prescription. Most recently, the use of antimalarials has been reviewed. It has been shown that such therapy may influence mortality rate in SLE. Sisó, et al.\(^77\) studied the effect of exposure to antimalarial drugs at diagnosis of lupus nephritis on the outcome of disease in a cohort of 206 consecutive patients with lupus nephritis. They showed that exposure to antimalarials before the diagnosis of lupus nephritis was negatively associated with the development of renal failure, hypertension, thrombosis and infection, and with a better survival rate at the end of the follow-up. Withdrawal of antimalarials increases the risk of flare in lupus nephritis.

There has been a revival in the use of antimalarials in SLE, and we would recommend continuing rather than stopping these drugs in patients who develop nephritis. It is important to focus on overall mortality, as well as renal survival. The data with antimalarials is interesting when one considers that cyclophosphamide has been reported not to influence overall mortality. Flanc, et al.\(^78\) reported in a meta-analysis that cyclophosphamide plus steroids reduced the risk for doubling of SCr level (four RCTs, 228 patients; RR 0.59; 95% CI 0.40–0.88) compared with steroids alone, but had no impact on overall mortality (five RCTs, 226 patients; RR 0.98; 95% CI 0.53–1.82).

Kasitanon, et al.\(^79\) reported that patients with membranous lupus nephritis treated with hydroxychloroquine did better: 7/11 (64%) were in remission within 12 months compared with 4/18 (22%) of those not on hydroxychloroquine (\(P = 0.036\) based on a log-rank test).

Summary

Management of lupus nephritis in the clinic in the modern era goes beyond selection of immunosuppressive therapies for induction and maintenance of remission. It is important to consider the patient as a whole, focusing on strategies to reduce progression of renal disease, development of vascular disease, minimisation of side effects of therapy. We must remember that patients may not share our enthusiasm for starting medication for the various aspects of their disease. Taking time to explain the rationale for the pills we prescribe may be an essential part of management.

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