Membranous nephropathy in systemic lupus erythematosus: a therapeutic enigma

Chi Chiu Mok

Abstract | Renal disease is a major cause of mortality and morbidity in systemic lupus erythematosus. Among the histological classes of lupus nephritis, membranous nephropathy comprises only one-fifth of all cases. Reported survival and rates of end-stage renal disease in membranous lupus nephropathy (MLN) vary considerably, because of substantial heterogeneity among the published studies. The risk of progression from MLN to renal failure is generally reduced in the absence of proliferative lesions, but patients are, nevertheless, at risk of thromboembolic complications. The optimal therapy for MLN remains elusive because of a lack of controlled trials; however, cardiovascular protection and blockade of the renin–angiotensin system should be instituted early in all patients. Mixed membranous and proliferative lupus nephritis should be treated in the same way as pure proliferative lupus nephritis. If MLN is not accompanied by proliferative lesions but is associated with clinically relevant proteinuria, renal insufficiency or failure to respond to supportive therapies, immunosuppressive treatment is indicated. Treatment options include glucocorticoids combined with azathioprine, calcineurin inhibitors or alkylating agents. The efficacy of mycophenolate mofetil in MLN remains to be confirmed. Controlled trials to compare existing immunosuppressive agents and experimental modalities such as sirolimus, rituximab and infliximab should be undertaken in the future.

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Introduction

Systemic lupus erythematosus (SLE) is the prototypical systemic autoimmune disease, and can affect multiple organs and systems. Kidney involvement is one of the most frequent and serious organ manifestations of SLE and is a major cause of mortality and morbidity.[1,2] Considerable interethnic differences exist in the incidence of renal disease in SLE: lupus nephritis is fairly common among Asian, African and Hispanic individuals but less common in white patients.[3–5] A prospective study of 146 Chinese patients with new-onset SLE showed that the cumulative incidence of renal disease, as defined by the American College of Rheumatology, was 60% after 5 years of follow-up.[6] However, this value probably underestimates the true incidence of renal disease in SLE because subtle renal involvement, such as proteinuria of less than 500 mg per day or microscopic hematuria—or both—was not included in the definition. The existence of 'silent' lupus nephritis has long been recognized.[7] Although most cases of silent lupus nephritis involve mild histological lesions, some do have diffuse proliferative nephritis. A 2007 retrospective study of 21 patients with SLE and a low level of proteinuria (<1 g per day) who underwent renal biopsy showed that proliferative lupus nephritis was present in 57% of patients.[8] This finding emphasizes the high frequency of renal involvement in SLE and illustrates that the histological severity of lupus nephritis does not necessarily correlate with the degree of proteinuria.

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Membranous nephropathy is an uncommon form of glomerulonephritis in SLE. According to the WHO histological classification,[9,10,11] membranous glomerulopathy (that is, class V lupus nephritis) accounts for only 8–20% of patients with biopsy-confirmed lupus nephritis in large, international series.[12–16] As only a few reviews have covered this type of lupus nephritis, this article summarizes the current histological classification, clinical presentation, outcomes and therapy of membranous nephropathy in SLE.

Histological classification

The histological classification of lupus nephritis has undergone several modifications. The original 1974 WHO classification of membranous lupus nephropathy (MLN)[9] was divided into four subclasses in 1982:[10] pure membranous nephropathy with or without mesangial hypercellularity (types Vb and Va, respectively), membranous nephropathy with segmental endocapillary proliferation and/or necrosis (type Vc) and membranous nephropathy with diffuse endocapillary proliferation and/or necrosis (Vd). However, the long-term prognosis of patients with MLN was later recognized to depend on the degree of glomerular inflammation and the extent of proliferative changes on renal biopsy;[17–19] individuals with Vc or Vd disease had a clinical course and prognosis similar to those with proliferative class III or class IV lupus nephritis. The WHO classification was, therefore, revised in 1995,[11] and types Vc and Vd were reclassified into classes III or IV. Class V retained only

the subclasses Va and Vb, under the category 'diffuse membranous glomerulonephritis'. The histological classification system was modified once again in 2003 by the International Society of Nephrology and the Renal Pathology Society.[20] MLN (that is, class V lupus nephritis) was defined by the presence of global or segmental continuous granular subepithelial immune deposits, often in the presence of concomitant mesangial immune deposits and hypercellularity (Figure 1). The distinction between pure membranous nephropathy and membranous nephropathy superimposed on mesangial changes was eliminated. When a diffusely distributed membranous lesion is associated with an active lesion of class III or IV, both diagnoses are now reported ('V + III' or 'V + IV').

Key points

- Membranous nephropathy is an uncommon subtype of glomerulonephritis in systemic lupus erythematosus
- The optimal therapy for membranous lupus nephropathy (MLN) is unclear
- Blockade of the renin–angiotensin system and cardiovascular protection should be instituted early in all patients with MLN
- Pure MLN with renal insufficiency, substantial proteinuria or failure to respond to supportive therapies is an indication for immunosuppressive treatment
- Immunosuppressive options include glucocorticoids combined with azathioprine, mycophenolate mofetil, calcineurin inhibitors or alkylating agents
- Repeat renal biopsy should be considered in patients with refractory MLN to detect any change in histological class, especially when lupus serology is persistently active

Clinical presentation

Among 12 published studies that included 15 or more patients with MLN,[17–19,21–29] 31–100% of patients presented with nephrotic-range proteinuria, but only 10–31% had abnormal renal function at the time of renal biopsy (Table 1). The frequency of nephrotic syndrome at presentation of MLN is, however, likely to be lower than these values in practice because some studies included patients who presented with nephrotic syndrome only. Series that included cases of mixed membranous and proliferative lupus nephritis (Vc or Vd) tend to show an increased frequency of nephrotic syndrome and impaired renal function.

Complement levels and titers of anti-double-stranded DNA antibodies (anti-dsDNA) in MLN, in contrast to proliferative forms of lupus nephritis, are frequently normal at presentation of renal disease. Although many studies did not report the exact frequency of normal lupus serology in MLN, data from my group suggest that around 58% of patients with pure MLN present with either normal complement levels or normal anti-dsDNA levels.[26] Occasionally, patients are initially diagnosed as having idiopathic membranous nephropathy despite the presence of renal histological features that suggest an immune-mediated mechanism, such as immunoglobulin and complement deposits on immunofluorescence study. Full-blown SLE might develop as late as months or years after the initial presentation of renal disease.

Outcomes and prognostic indicators

Few published studies have specifically reported the long-term outcomes of MLN, although data on actuarial survival of patients, end-stage renal disease and renal survival (that is, survival without dialysis) are available for MLN subgroups in some studies (Table 2).[12–14,19,21,22,25,28,30–32] Values for 10-year survival of patients and renal survival in MLN range from 55% to 98% and from 72% to 100%, respectively. The wide range of these values is a result of differences between the studies in many factors. These variables include the study design (retrospective versus prospective), the patient-selection strategy, the type of institution (academic versus non-academic; specialized center versus nonspecialized center; rheumatology center versus nephrology center), the histological subclasses of MLN analyzed (that is, whether mixed membranous and proliferative lupus nephritis was included), the length of follow-up, the treatment regimen (that is, whether it was designated by the study protocol or chosen by the treating physician), as well as the use of supportive therapies such as blockers of the renin–angiotensin system. In general, long-term outcomes were worse in studies that included mixed membranous and proliferative lupus nephritis than in those that included pure MLN only. Subgroup analyses also showed that patients with mixed membranous and proliferative lupus nephritis had a prognosis similar to that of patients with proliferative lupus nephritis and no membranous lesions.[17–19]

Few clinical predictors of deterioration in renal function in patients with MLN have been identified. This failure can be attributed to small sample sizes, short periods of observation and the heterogeneity of renal histology and therapy in published reports. Several studies have shown that patients with MLN who have superimposed proliferative lesions (Vc and Vd disease) have worse 10-year renal survival than those without proliferative lesions (Va and Vb disease).[13,17,19] One study suggested that a high serum creatinine level at presentation was a significant predictor of poor renal outcome,[19] but this predictive value lost significance when the analysis was restricted to Va and Vb disease only. Nephrotic syndrome at presentation of MLN was not significantly associated with renal function deterioration in two studies.[19,26] However, a 2008 study of Chinese patients reported that persistent nephrotic-range proteinuria despite treatment predicted development of end-stage renal disease.[28] None of age, sex, hypertension, lupus serology and serum albumin level were found to predict outcome in MLN. Finally, the prognosis of individuals with mixed membranous and proliferative lupus nephritis is known to be worse in black patients than in white ones.[33] Whether black ethnicity is a prognostic predictor of poor outcome in pure MLN warrants further evaluation.

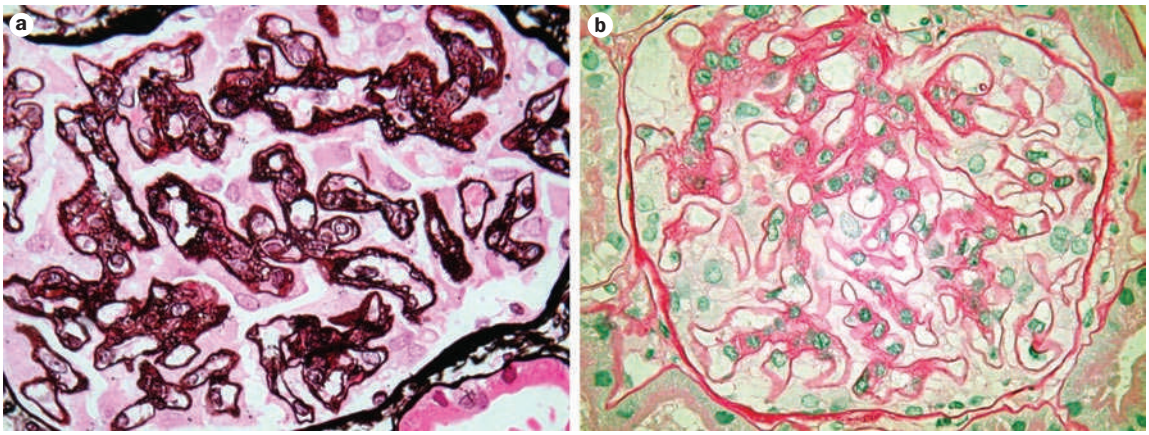

Figure 1 | Histological findings of pure membranous lupus nephropathy. Renal biopsy can reveal **a** | spike-like projections from the basement membrane, patent capillary loops and no evidence of endocapillary proliferation (periodic acid–silver methenamine stain; magnification ×400). Alternatively, biopsy might indicate **b** | mild mesangial proliferation with patent capillary loops, and slight thickening of the basement membrane (periodic acid–Schiff stain; magnification ×400). Permission obtained from W. H. Lo, Tuen Mun Hospital, Hong Kong.

Thrombotic complications

Patients with MLN are prone to both venous and arterial thrombosis. Venous thrombosis is related to persistently heavy proteinuria whereas arterial thrombosis is associated with a myriad of traditional and nontraditional vascular risk factors that have increased prevalence in patients with SLE and chronic renal disease. Only a few studies have specifically addressed the frequency of thrombotic complications in MLN (Table 3). Venous thrombosis is more likely than arterial thrombosis to complicate MLN, but the presence of antiphospholipid antibodies increases the risk of arterial thrombosis. In our experience with 162 patients with lupus nephritis, the cumulative risk of an arterial thrombotic event in MLN was 8.4% at 5 years and 16.7% at 10 years, which is marginally higher than the risk in nonmembranous types of lupus nephritis.[34]

Therapy

The optimal treatment of MLN remains enigmatic, as a result of a lack of controlled trials. Most data on the efficacy of treatment protocols have been obtained from anecdotal experience. As the natural history of MLN is unknown, evidence is usually extrapolated from studies of idiopathic membranous nephropathy. The variable risk of end-stage renal disease in idiopathic membranous nephropathy argues against the universal use of immunosuppressive therapies. Risk stratification is, therefore, essential when deciding whether to implement aggressive treatment.[35] Persistent proteinuria can be associated with clinical symptoms, thrombotic diathesis and dyslipidemia—all of which increase cardiovascular risk—and deterioration in renal function. Attempts should, therefore, be made to minimize proteinuria in membranous nephropathy. This goal is particularly important in patients with SLE, who are especially prone to accelerated atherosclerosis.[36] As SLE is an autoantibody-driven disease and a substantial proportion of patients with lupus nephritis have concomitant extrarenal manifestations, immunosuppressive treatment is more often indicated for patients with SLE than it is in those with idiopathic membranous nephropathy. A treatment algorithm for MLN is shown in Figure 2.

Nonimmunosuppressive treatment

A number of nonimmunosuppressive strategies can help to reduce proteinuria in MLN[37] and should, therefore, be instituted early in all cases. These strategies include the use of angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (or both), titrated up to the maximal tolerated dose, and tight control of cardiovascular risk factors such as hyperlipidemia and hypertension. The 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) are useful for their dual effects of assuaging hyperlipidemia and reducing urinary protein excretion.[38] Prophylactic low-dose aspirin or anticoagulation should be considered in patients who have multiple vascular risk factors and persistent, heavy proteinuria.

Immunosuppressive treatment

The indications for immunosuppressive therapy in MLN are serious renal disease, as shown by nephrotic-range proteinuria and/or impaired renal function; worsening of proteinuria and renal function despite nonimmunosuppressive or supportive treatment; mixed membranous and proliferative lupus nephritis; and the presence of concomitant extrarenal major organ manifestations of SLE. The optimal regimen and duration of immunosuppressive treatment for MLN is unclear because of the lack of controlled treatment trials; however, patients with mixed membranous and proliferative lupus nephritis should be treated in the same way as those with proliferative lupus nephritis. A repeat renal biopsy should

Table 1 | Clinical presentation of membranous lupus nephropathy[a]

Study	Number of patients	Histological subclasses included	Prevalence of nephrotic-range proteinuria at presentation (%)	Renal function at presentation
Kasitanon *et al.* (2008)[29]	29 (55% black)	V (34%); V+III/IV (66%)	31	CrCl <90 ml/min in 31%
Sun *et al.* (2008)[28]	100 (all Chinese)	Va or Vb (100%)	31	Mean serum creatinine 86±77 μmol/l
Cramer *et al.* (2007)[27]	26 (all children)	Va or Vb (72%); Vc or Vd (27%)	46	CrCl <90 ml/min in 31%
Mok *et al.* (2004)[26]	38 (all Chinese)	Va or Vb (100%)	58	Mean CrCl 79.6±28 ml/min
Mercadal *et al.* (2002)[25]	66 (47% black)	Va or Vb (100%)	64	Mean CrCl 97±32 ml/min
Chan *et al.* (1999)[24]	20 (all Chinese)	Va or Vb (100%)	100	Normal renal function in 90%
Moroni *et al.* (1998)[23]	19	Va or Vb (79%); Vc (21%)	100	Not reported
Sloan *et al.* (1996)[19]	79	Va or Vb (46%); Vc or Vd (54%)	Not reported	Mean serum creatinine 80±3 μmol/l (Va or Vb); 88±27 μmol/l (Vc); 186±106 μmol/l (Vd)
Pasquali *et al.* (1993)[22]	42	Va or Vb (62%); Vc or Vd (38%)	64	Normal renal function in 83%
Adler *et al.* (1990)[17]	18	Va or Vb (39%); Vc or Vd (61%)	Not reported	Normal renal function in all patients
Leaker *et al.* (1987)[21]	20	Not reported	70	Normal renal function in all patients
Schwartz *et al.* (1984)[18]	22	Va or Vb (41%); Vc or Vd (59%)	Not reported	Normal renal function in 77%

[a]In studies that included at least 15 patients. Abbreviation: CrCl, creatinine clearance.

be considered in patients with persistent proteinuria or deteriorating renal function to identify any change in histological class and determine residual disease activity, especially when titers of antibodies associated with active lupus remain elevated.

Glucocorticoids

No solid evidence exists to show that corticosteroids are effective in MLN. A retrospective analysis of 28 patients performed three decades ago revealed no difference in renal outcome among patients treated with low-dose, high-dose or no corticosteroids.[39] Another small retrospective study of 12 patients with MLN did not demonstrate a benefit of high-dose corticosteroids.[40] However, most patients with SLE and membranous nephropathy who have renal dysfunction or serious proteinuria should receive an empirical trial of corticosteroids, which are often administered in combination with another immunosuppressive agent, as described below.

Azathioprine

Azathioprine is often used for maintenance treatment of SLE and as a corticosteroid-sparing agent. In an open-label, prospective study, we demonstrated that a combination of prednisolone (0.8–1.0 mg/kg per day for 6–8 weeks, then tapered) and azathioprine (up to 2 mg/kg per day) was effective and well tolerated in 38 patients with MLN Va or Vb. Complete and partial responses occurred in 67% and 22% of patients, respectively, at 12 months.[26] At the end of the observation period (mean 8 years), only 13% of patients had a 20% decline in creatinine clearance, and no patient experienced doubling of serum creatinine. Relapse of nephritis was infrequent (19%) and remission could be reinduced in all cases with salvage therapies. Given the relatively low frequency of serious adverse effects (agranulocytosis 3%, hypersensitivity 3%, serious infection 0%), this regimen can be considered for first-line treatment of MLN.

Alkylating agents

Chlorambucil and cyclophosphamide have both been used with success in MLN. In a retrospective study of 19 patients who predominantly had Va or Vb lupus nephritis (79%), Moroni *et al.*[23] showed that chlorambucil combined with alternate-month cycles of intravenous pulse methylprednisolone was more effective than methylprednisolone alone in inducing remission of nephrotic syndrome (64% versus 38%) and preserving renal function over the observation period (mean 83 months). Another retrospective study reported successful induction of renal remission (55% complete and 35% partial) with oral prednisolone and oral cyclophosphamide (for 6 months, followed by azathioprine) in 20 patients

Table 2 | Cumulative 10-year survival, ESRD rate and renal survival in membranous lupus nephropathy[a]

Study	Number of patients	10-year survival of patients (%)	Incidence of ESRD (%)	Renal survival (%)[b]
Sun *et al.* (2008)[28]	100	98	Not reported	93
Mercadal *et al.* (2002)[25]	66	Not reported	12	Not reported
Huong *et al.* (1999)[13]	32	90	23%	Not reported
Bono *et al.* (1999)[31]	21	55	Not reported	Not reported
Mok *et al.* (1999)[12]	25	Not reported	Not reported	100
Sloan *et al.* (1996)[19]	36	Not reported	Not reported	72
Donadio *et al.* (1995)[14]	67	Not reported	37	Not reported
Pasquali *et al.* (1993)[22]	42	Not reported	Not reported	92
GISNEL (1992)[30]	91	Not reported	10	Not reported
Leaker *et al.* (1987)[21]	20	84	Not reported	Not reported

[a]In studies that included at least 20 patients. [b]Without dialysis. Abbreviations: ESRD, end-stage renal disease; GISNEL, Gruppo Italiano per lo Studio della Nefrite Lupica.

Table 3 | Incidence of and risk factors for thrombotic complications in membranous lupus nephropathy

Study	Number of patients	Mean duration of follow-up (years)	Incidence of thrombotic complications (%)	Risk factors for thrombosis
Sun *et al.* (2008)[28]	100	6.5	3.0 (2.0 venous; 1.0 arterial)	Not reported
Mok *et al.* (2004)[26]	38	7.5	13.1 (2.6 venous; 10.5 arterial)	Antiphospholipid antibodies
Mercadal *et al.* (2002)[25]	66	6.9	22.7 (all venous)	Persistent nephrotic syndrome
Pasquali *et al.* (1993)[22]	42	6	21.4 (11.9 venous; 9.5 arterial)	Antiphospholipid antibodies

with pure MLN (Va or Vb) and nephrotic syndrome.[24] However, the high incidence of ovarian failure associated with the use of oral cyclophosphamide is a concern.[41] On the other hand, life-threatening bone marrow failure with pancytopenia has been reported in six of six Chinese patients with MLN who received corticosteroids and chlorambucil.[42]

A randomized, controlled trial initiated by the NIH in 41 patients with MLN, published in abstract form, reported that alternate-day oral prednisone in combination with either alternate-month intravenous pulse cyclophosphamide or alternate-month ciclosporin was more effective than prednisone alone in terms of achieving remission and proteinuria reduction at 12 months (the complete remission rate was 46% for prednisone plus cyclophosphamide or ciclosporin versus 13% for prednisone alone).[43] A combination of a corticosteroid and another immunosuppressive agent seems, therefore, to be a better treatment strategy for MLN than a corticosteroid alone, as for proliferative lupus nephritis.

Calcineurin inhibitors

Case reports and small series have reported the successful use of ciclosporin in MLN.[44,45] Radhakrishnan *et al.*[44] treated 10 patients with MLN (7 with Va or Vb and 3 with Vc) with ciclosporin (4–6 mg/kg per day) alone (2 patients) or in combination with low-dose prednisone (8 patients) for 23–43 months and reported that proteinuria declined to less than 1 g per day in 6 patients. Another study by Hallegua *et al.*[45] also demonstrated the efficacy of combined prednisone and ciclosporin (2–6 mg/kg per day) in 10 patients with MLN. After the observation period (mean 2 years), proteinuria improved in all patients and its mean level dropped from 5.6 g per day to 1.4 g per day. Finally, in a 2003 study of 20 Chinese patients with MLN, Hu *et al.*[46] reported complete renal remission in 52% of patients after treatment with ciclosporin (up to 5 mg/kg per day) and variable doses of corticosteroids for a mean of 17 months. Relapse of proteinuria occurred in one-third of patients upon withdrawal of ciclosporin therapy. Although ciclosporin is effective in MLN, close monitoring of adverse effects, in particular nephrotoxicity, is mandatory.

Tacrolimus is a new calcineurin inhibitor that has demonstrated more potent and effective immunosuppression than that achieved by ciclosporin in transplantation studies. An open-label pilot study has shown that tacrolimus in combination with prednisolone is beneficial in the treatment of proliferative lupus nephritis[47] and a recent controlled trial has demonstrated the efficacy of tacrolimus compared with no treatment in idiopathic membranous nephropathy.[48] Anecdotal success of tacrolimus in the treatment of MLN has been reported.[49,50] The advantages of tacrolimus over ciclosporin in the treatment of lupus nephritis are lower incidences of blood pressure elevation, hyperlipidemia and adverse cosmetic effects. However, patients must be closely monitored for neurotoxicity and adverse metabolic effects. As with ciclosporin, relapse of proteinuria is common after discontinuation of tacrolimus.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is becoming the standard therapy for lupus nephritis in many centers. Randomized, controlled studies have shown that MMF is equivalent in efficacy to cyclophosphamide for the induction of remission in lupus nephritis and is superior to cyclophosphamide for maintenance treatment.[51,52] However, data on the efficacy of MMF in pure MLN are not available from these studies.

Several open-label or retrospective studies have reported outcomes of treatment of MLN with MMF, but their results are conflicting. Kapitsinou *et al.*[53] treated six patients with MLN with combined prednisone and MMF (2 g per day) and reported no response in four patients (three of whom had mixed proliferative lesions). Spetie *et al.*[54] studied 13 consecutive patients with MLN (including one with superimposed proliferative lesions) who were naive to immunosuppressive treatment and antagonists of the renin–angiotensin system. Treatment with a combination of moderate-dose to high-dose prednisone, MMF (up to 2 g per day) and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers for 6 months resulted in complete or partial remission in 10 patients. In a retrospective study of 10 patients with MLN (6 of whom had mixed proliferative lesions), Karim *et al.*[55] demonstrated a significant improvement in mean proteinuria after a combination of treatment with corticosteroids, MMF and antagonists of the renin–angiotensin system for 18 months. However, a reduction in proteinuria to less than 500 mg per day occurred in one patient only, and no clinically relevant improvements in proteinuria were seen in one patient with Va disease and two patients with Vc disease. Finally, a retrospective study of 29 patients with MLN (66% with mixed proliferative disease) reported in 2008 that complete remission was achieved in 38% of patients by use of a regimen that consisted of corticosteroids, MMF (up to 3 g per day) and renin–angiotensin system blockers.[29] No difference in the rate of complete remission was evident between patients with and without proliferative lesions, but a greater number of patients with pure MLN than those with mixed disease seemed to have a partial response to treatment.

MMF is generally well tolerated in lupus nephritis. In two reviews,[56,57] we summarized the adverse events observed in 241 patients with renal or nonrenal lupus who had been treated with MMF in various clinical trials. The most frequent adverse event was infection (32%; 2% of all patients had serious or life-threatening infection), followed by nausea or vomiting (24%), diarrhea (12%), leucopenia (7%) and skin rash. No cases of prolonged amenorrhea as a result of ovarian toxicity were reported and the incidence of major infections was lower than that reported with cyclophosphamide (20% permanent amenorrhea, 19% major infections that required hospitalization).[1]

Whether MMF is effective for membranous lesions of lupus nephritis remains controversial, although it seems to be a promising therapy. However, studies in idiopathic membranous nephropathy indicate that spontaneous remission of proteinuria can occur, which makes most forms of treatment seem effective to some extent.[35] In the absence of comparative trials, MMF should not, therefore, be regarded as the best option for MLN. Nevertheless, given that MMF has a milder toxicity profile than alkylating agents have, this agent can be considered as initial therapy. Further controlled studies are warranted to compare the efficacy of azathioprine, MMF, alkylating agents and calcineurin inhibitors in MLN.

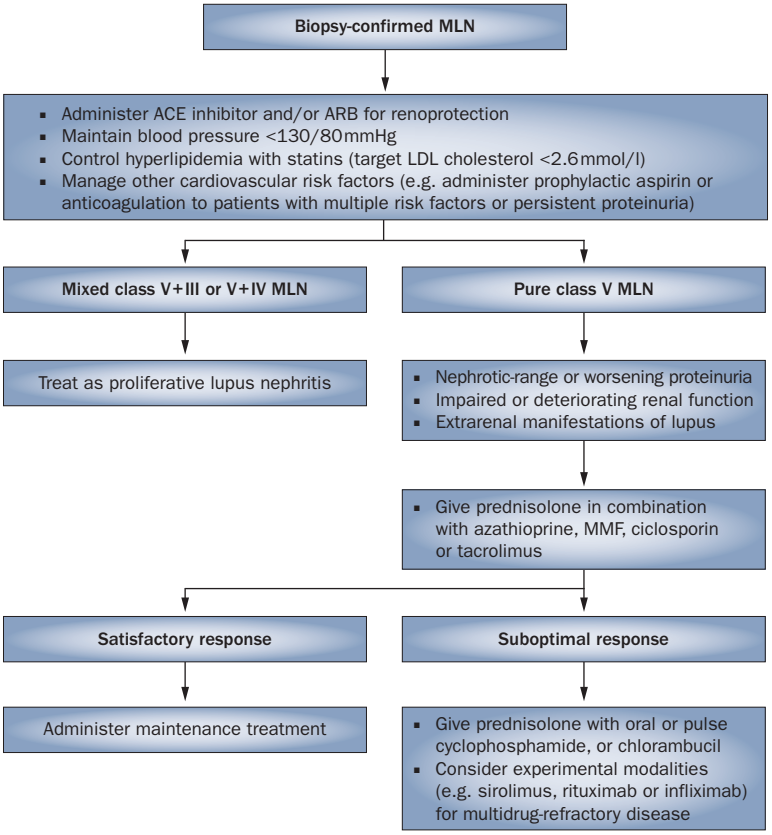

Figure 2 | A treatment algorithm for membranous lupus nephropathy. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MLN, membranous lupus nephropathy; MMF, mycophenolate mofetil.

Maintenance immunosuppressive therapy

Maintenance immunosuppressive therapy is increasingly recognized as necessary in patients with lupus nephritis in order to prevent renal relapses, and perhaps to retard progression of chronic kidney disease.[24,52,58,59] In our experience with 189 patients who had diffuse proliferative lupus nephritis and responded to initial treatment with either oral or intravenous pulse cyclophosphamide, maintenance therapy with azathioprine resulted in a significantly reduced incidence of renal flares at 60 months after cessation of cyclophosphamide (34% versus 66%; $P = 0.03$).[60] Another analysis of 212 patients with diffuse proliferative lupus nephritis revealed

that maintenance therapy (with azathioprine, MMF or ciclosporin) for less than 3 years after cyclophosphamide induction was independently associated with a greater likelihood of experiencing the composite outcome of doubling of serum creatinine, end-stage renal disease or death (hazard ratio 4.62 [95% CI 1.35–15.8]; $P = 0.02$), when compared with maintenance therapy for more than 3 years.[1] Whether MMF is more effective than azathioprine as long-term maintenance treatment for reducing renal and extrarenal flares in patients with lupus nephritis is the subject of two ongoing randomized, controlled studies.[58,59] Long-term use of calcineurin inhibitors is not encouraged because of the risks of nephrotoxic effects, hyperlipidemia and hypertension, which can further aggravate the increased thrombotic risk in MLN.

The optimal duration of maintenance therapy is unknown because of the lack of controlled studies. In a 2006 retrospective review of 32 patients with proliferative lupus nephritis in whom immunosuppressive therapy was stopped for a median of 203 months, clinical remission persisted in 47% of patients.[61] Patients who experienced sustained remission had received a longer total duration of immunosuppressive treatment since renal biopsy than those who did not experience remission (median of 57 months versus 30 months; $P<0.01$). This finding, coupled with the observation that maintenance treatment for less than 3 years after successful cyclophosphamide induction was a predictor of poor renal outcome in proliferative lupus nephritis,[1] suggests that maintenance immunosuppressive therapy should be continued for at least 3 years after a complete clinical response is achieved.

No consensus exists on the definition of renal flare in MLN; however, patients who develop a clinically relevant increase in proteinuria should be carefully evaluated. A repeat renal biopsy is usually necessary for those in whom serology results reveal active or deteriorating disease, declining renal function or active urinary sediments. On the basis of anecdotal evidence, relapsed, pure MLN can be treated by administering a repeat course of empirical high-dose corticosteroids, increasing the dose of an existing noncorticosteroid maintenance immunosuppressive agent or replacing this agent with another drug that has a different mechanism of action.

Experimental therapies

Sirolimus is a lipophilic macrolide with immunosuppressive actions similar to those of tacrolimus and ciclosporin. Unlike the calcineurin inhibitors, however, sirolimus is not associated with nephrotoxic effects. Animal studies have shown that sirolimus ameliorates proteinuria in lupus nephritis[62,63] and preliminary evidence suggests that sirolimus is useful in human lupus nephritis.[64] Further studies of this agent in MLN are eagerly awaited.

B-cell depletion therapy is becoming a popular treatment for SLE. A few clinical studies have shown that rituximab, a chimeric anti-CD20 monoclonal antibody, is beneficial in refractory lupus nephritis.[65,66] Another study showed that fludarabine is well tolerated in corticosteroid-refractory MLN.[67] The role of these B-cell-depleting agents, and others such as ocrelizumab, in MLN has to be defined by future trials. Finally, blockade of tumor necrosis factor, currently the standard therapy for early and refractory rheumatoid arthritis, has been tested in refractory lupus nephritis. Preliminary results are promising[68] and a study of the tumor-necrosis-factor-inhibiting antibody infliximab is underway in MLN.

Conclusions

Membranous nephropathy is an uncommon form of glomerulonephritis in SLE. As a result of the low frequency of this subtype of lupus nephritis, controlled trials with adequate sample sizes are lacking, and the optimal therapy remains unclear. However, blockade of the renin–angiotensin system and cardiovascular protection by vigorous control of blood pressure and lipid level should be instituted early in all patients. Mixed membranous and proliferative lupus nephritis should be treated in the same way as proliferative lupus nephritis. MLN without coexisting proliferative lesions but associated with renal insufficiency, substantial proteinuria, or failure to respond to supportive therapies is an indication for immunosuppressive therapy; treatment options include glucocorticoids combined with azathioprine, calcineurin inhibitors or alkylating agents. The efficacy of MMF in MLN remains to be confirmed but owing to its low toxicity, this agent can be considered as initial therapy. Maintenance immunosuppressive therapy seems to be necessary in MLN after a clinical response is achieved. Experimental modalities that warrant further study in MLN—particularly in refractory disease—include sirolimus, rituximab and infliximab.

Review criteria

Information for this Review was obtained by searching MEDLINE for articles published from 1974 to 2007, using the key words "membranous", "nephropathy", "nephritis", "glomerulonephritis" and "lupus". Only human and clinicopathological studies were considered; animal studies and laboratory studies were excluded.

1. Mok, C. C. *et al.* Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. *Am. J. Med.* **119**, 355 e25–e33 (2006).
2. Vu, T. V. & Escalante, A. A comparison of the quality of life of patients with systemic lupus erythematosus with and without endstage renal disease. *J. Rheumatol.* **26**, 2595–2601 (1999).
3. Mok, C. C., Tang, S. S., To, C. H. & Petri, M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. *Arthritis Rheum.* **52**, 2774–2782 (2005).
4. Bastian, H. M. *et al.* LUMINA Study Group. LUpus in MInority populations: NAture vs nurture. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus* **11**, 152–160 (2002).
5. Wadee, S., Tikly, M. & Hopley, M. Causes and predictors of death in South Africans with

systemic lupus erythematosus. *Rheumatology (Oxford)* **46**, 1487–1491 (2007).
6. Mok, C. C. & Tang, S. S. Incidence and predictors of renal disease in Chinese patients with systemic lupus erythematosus. *Am. J. Med.* **117**, 791–795 (2004).
7. Gonzalez-Crespo, M. R., Lopez-Fernandez, J. I., Usera, G., Poveda, M. J. & Gomez-Reino, J. J. Outcome of silent lupus nephritis. *Semin. Arthritis Rheum.* **26**, 468–476 (1996).
8. Christopher-Stine, L. *et al.* Renal biopsy in lupus patients with low levels of proteinuria. *J. Rheumatol.* **34**, 332–335 (2007).
9. Appel, G. B. *et al.* Renal involvement in systemic lupus erythematosus (SLE): a study of 56 patients emphasizing histologic classification. *Medicine (Baltimore)* **57**, 371–410 (1978).
10. Churg, J. & Sobin, L. H. *Renal Disease: Classification and Atlas of Glomerular Disease*. (Igaku-Shoin, Tokyo, 1982).
11. Churg, J., Bernstein, J. & Glassock, R. J. *Renal Disease: Classification and Atlas of Glomerular Diseases* 2nd edn (Igaku-Shoin, New York, 1995).
12. Mok, C. C., Wong, R. W. & Lau, C. S. Lupus nephritis in southern Chinese patients: clinicopathologic findings and long-term outcome. *Am. J. Kidney Dis.* **34**, 315–323 (1999).
13. Huong, D. L. *et al*. Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. *Medicine (Baltimore)* **78**, 148–166 (1999).
14. Donadio, J. V. Jr, Hart, G. M., Bergstralh, E. J. & Holley, K. E. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. *Lupus* **4**, 109–115 (1995).
15. Yang, L. Y., Chen, W. P. & Lin, C. Y. Lupus nephritis in children–a review of 167 patients. *Pediatrics* **94**, 335–340 (1994).
16. Neumann, K. *et al.* Lupus in the 1980s: III. Influence of clinical variables, biopsy, and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. *Semin. Arthritis Rheum.* **25**, 47–55 (1995).
17. Adler, S. G., Johnson, K., Louie, J. S., Liebling, M. R. & Cohen, A. H. Lupus membranous glomerulonephritis: different prognostic subgroups obscured by imprecise histologic classifications. *Mod. Pathol.* **3**, 186–191 (1990).
18. Schwartz, M. M., Kawala, K., Roberts, J. L., Humes, C. & Lewis, E. J. Clinical and pathological features of membranous glomerulonephritis of systemic lupus erythematosus. *Am. J. Nephrol.* **4**, 301–311 (1984).
19. Sloan, R. P., Schwartz, M. M., Korbet, S. M. & Borok, R. Z. Long-term outcome in systemic lupus erythematosus membranous glomerulonephritis. Lupus Nephritis Collaborative Study Group. *J. Am. Soc. Nephrol*. **7**, 299–305 (1996).
20. Weening, J. J. *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J. Am. Soc. Nephrol.* **15**, 241–250 (2004).
21. Leaker, B., Fairley, K. F., Dowling, J. & Kincaid-Smith, P. Lupus nephritis: clinical and pathological correlation. *Q. J. Med.* **62**, 163–179 (1987).
22. Pasquali, S. *et al.* Lupus membranous nephropathy: long-term outcome. *Clin. Nephrol.* **39**, 175–182 (1993).
23. Moroni, G., Maccario, M., Banfi, G., Quaglini, S. & Ponticelli, C. Treatment of membranous lupus nephritis. *Am. J. Kidney Dis.* **31**, 681–686 (1998).
24. Chan, T. M. *et al*. Treatment of membranous lupus nephritis with nephrotic syndrome by sequential immunosuppression. *Lupus* **8**, 545–551 (1999).
25. Mercadal, L. *et al*. Factors affecting outcome and prognosis in membranous lupus nephropathy. *Nephrol. Dial. Transplant.* **17**, 1771–1778 (2002).
26. Mok, C. C. *et al.* Treatment of pure membranous lupus nephropathy with prednisone and azathioprine: an open-label trial. *Am. J. Kidney Dis.* **43**, 269–276 (2004).
27. Cramer, C. H. Jr *et al.* Clinical presentation and outcome in a cohort of paediatric patients with membranous lupus nephritis. *Nephrol. Dial. Transplant.* **22**, 3495–3500 (2007).
28. Sun, H. O. *et al.* Long-term outcome of Chinese patients with membranous lupus nephropathy. *Lupus* **17**, 56–61 (2008).
29. Kasitanon, N., Petri, M., Haas, M., Magder, L. S. & Fine, D. M. Mycophenolate mofetil as the primary treatment of membranous lupus nephritis with and without concurrent proliferative disease: a retrospective study of 29 cases. *Lupus* **17**, 40–45 (2008).
30. Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). Lupus nephritis: prognostic factors and probability of maintaining life-supporting renal function 10 years after the diagnosis. *Am. J. Kidney Dis.* **19**, 473–479 (1992).
31. Bono, L., Cameron, J. S. & Hicks, J. A. The very long-term prognosis and complications of lupus nephritis and its treatment. *Q. J. Med.* **92**, 211–218 (1999).
32. Appel, G. B., Cohen, D. J., Pirani, C. L., Meltzer, J. I. & Estes, D. Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. *Am. J. Med.* **83**, 877–885 (1987).
33. Dooley, M. A., Hogan, S., Jennette, C. & Falk, R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. Glomerular Disease Collaborative Network. *Kidney Int.* **51**, 1188–1195 (1997).
34. Mok, C. C. *et al*. Risk and predictors of arterial thrombosis in lupus and non-lupus primary glomerulonephritis: a comparative study. *Medicine (Baltimore)* **86**, 203–209 (2007).
35. Lai, K. N. Membranous nephropathy: when and how to treat. *Kidney Int.* **71**, 841–843 (2007).
36. Asanuma, Y. *et al*. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N. Engl. J. Med.* **349**, 2407–2415 (2003).
37. Schieppati, A., Ruggenenti, P., Perna, A. & Remuzzi, G. Nonimmunosuppressive therapy of membranous nephropathy. *Semin. Nephrol.* **23**, 333–339 (2003).
38. Lee, T. M., Su, S. F. & Tsai, C. H. Effect of pravastatin on proteinuria in patients with well-controlled hypertension. *Hypertension* **40**, 67–73 (2002).
39. Donadio, J. V. Jr, Burgess, J. H. & Holley, K. E. Membranous lupus nephropathy: a clinicopathologic study. *Medicine (Baltimore)* **56**, 527–536 (1977).
40. Gonzalez-Dettoni, H. & Tron, F. Membranous glomerulopathy in systemic lupus erythematosus. *Adv. Nephrol.* **14**, 347–364 (1985).
41. Mok, C. C., Lau, C. S. & Wong, R. W. S. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. *Arthritis Rheum.* **41**, 831–837 (1998).
42. Wang, A. Y. *et al.* Severe bone marrow failure associated with the use of alternating steroid with chlorambucil in lupus membranous nephropathy in Chinese. *Lupus* **10**, 295–298 (2001).
43. Austin, H. A., Vaughan, E. M. & Balow, J. E. Lupus membranous nephropathy: randomized controlled trial of prednisone, cyclosporine and cyclophosphamide [Abstract]. *J. Am. Soc. Nephrol.* **11**, 81A (2000).
44. Radhakrishnan, J., Kunis, C. L., D'Agati, V. & Appel, G. B. Cyclosporine treatment of lupus membranous nephropathy. *Clin. Nephrol*. **42**, 147–154 (1994).
45. Hallegua, D., Wallace, D. J., Metzger, A. L., Rinaldi, R. Z. & Klinenberg, J. R. Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. *Lupus* **9**, 241–251 (2000).
46. Hu, W. *et al.* Cyclosporine A in treatment of membranous lupus nephropathy. *Chin. Med. J. (Engl.)* **116**, 1827–1830 (2003).
47. Mok, C. C., Tong, K. H., To, C. H., Siu, Y. P. & Au, T. C. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study. *Kidney Int.* **68**, 813–817 (2005).
48. Praga, M., Barrio, V., Juárez, G. F. & Luño, J. Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney Int.* **71**, 924–930 (2007).
49. Maruyama, M. *et al.* Good response of membranous lupus nephritis to tacrolimus. *Clin. Nephrol.* **65**, 276–279 (2006).
50. Tse, K. C., Lam, M. F., Tang, S. C., Tang, C. S. & Chan, T. M. A pilot study on tacrolimus treatment in membranous or quiescent lupus nephritis with proteinuria resistant to angiotensin inhibition or blockade. *Lupus* **16**, 46–51 (2007).
51. Ginzler, E. M. *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N. Engl. J. Med.* **353**, 2219–2228 (2005).
52. Contreras, G. *et al.* Sequential therapies for proliferative lupus nephritis. *N. Engl. J. Med.* **350**, 971–980 (2004).
53. Kapitsinou, P. P., Boletis, J. N., Skopouli, F. N., Boki, K. A. & Moutsopoulos, H. M. Lupus nephritis: treatment with mycophenolate mofetil. *Rheumatology (Oxford)* **43**, 377–380 (2004).
54. Spetie, D. N. *et al.* Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int.* **66**, 2411–2415 (2004).
55. Karim, M. Y. *et al.* Reduction of proteinuria with mycophenolate mofetil in predominantly membranous lupus nephropathy. *Rheumatology (Oxford)* **44**, 1317–1321 (2005).
56. Mok, C. C. & Lai, K. N. Mycophenolate mofetil in lupus glomerulonephritis. *Am. J. Kidney Dis.* **40**, 447–457 (2002).
57. Mok, C. C. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand. J. Rheumatol.* **36**, 329–337 (2007).
58. Sinclair, A. *et al*. Mycophenolate mofetil as induction and maintenance therapy for lupus nephritis: rationale and protocol for the randomized, controlled Aspreva Lupus Management Study (ALMS). *Lupus* **16**, 972–980 (2007).

59. Houssiau, F. A. & Ginzler, E. M. Current treatment of lupus nephritis. *Lupus* **17**, 426–430 (2008).
60. Mok, C. C. *et al.* Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum.* **50**, 2559–2568 (2004).
61. Moroni, G. *et al.* Withdrawal of therapy in patients with proliferative lupus nephritis: long-term follow-up. *Nephrol. Dial. Transplant.* **21**, 1541–1548 (2006).
62. Lui, S. L. *et al.* Rapamycin attenuates the severity of established nephritis in lupus-prone NZB/W F1 mice. *Nephrol. Dial. Transplant.* **23**, 2768–2776 (2008).
63. Ramos-Barrón, A. *et al.* Prevention of murine lupus disease in (NZB x NZW)F1 mice by sirolimus treatment. *Lupus* **16**, 775–781 (2007).
64. Medina, F., Fuentes, J., Carranza, I., Fraga, A. & Moreno, J. Sirolimus: a potential treatment for diffuse proliferative lupus nephritis [Abstract]. *Ann. Rheum. Dis.* **65** (**Suppl. 2**), S351 (2006).
65. Leandro, M. J., Cambridge, G., Edwards, J. C., Ehrenstein, M. R. & Isenberg, D. A. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. *Rheumatology (Oxford)* **44**, 1542–1545 (2005).
66. Gunnarsson, I. *et al*. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. *Arthritis Rheum.* **56**, 1263–1272 (2007).
67. Boumpas, D. T. *et al.* A pilot study of low-dose fludarabine in membranous nephropathy refractory to therapy. *Clin. Nephrol.* **52**, 67–75 (1999).
68. Aringer, M., Graninger, W. B., Steiner, G. & Smolen, J. S. Safety and efficacy of tumor necrosis factor α-blockade in systemic lupus erythematosus: an open-label study. *Arthritis Rheum.* **50**, 3161–3169 (2004).