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Treatment of Lupus Nephritis

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Abstract

Renal involvement in systemic lupus erythematosus (SLE) is a serious complication of the disease. However, the prognosis of patients with lupus nephritis is continually improving with 10-year survival rates now greater than 75%. This improvement reflects earlier diagnosis due to more sensitive and specific diagnostic tests, better clinical appreciation of the natural history, and improved treatment of SLE and its manifestations. This review of the treatment of lupus nephritis

has graded the level of evidence of specific treatment using the guidelines of the US Preventive Service Task Force.

Although many new treatments have been advocated, the best evidence for treating proliferative lupus nephritis relies on a strategy combining specific treatment of the SLE as well as generalised treatment of the associated comorbidities. This strategy involves a combination of corticosteroids and cytotoxic agents plus or minus the adjunctive use of antimalarials, coordinated aggressive management of hypertension, proteinuria, infections, dyslipidaemia, thrombotic coagulopathy and potential renal replacement therapies.

Renal involvement is a common and serious complication in systemic lupus erythematosus (SLE). An abnormal renal biopsy is present in 90% of patients.[1,2] The presentation can range from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis leading to end stage renal disease (ESRD). The prognosis of patients with lupus nephritis has continually improved, with the most recent 10-year survival rate, in a retrospective series, being 75–85%, with more than 90% of patients surviving longer than 5 years.[3,4] The results from two prospective cohorts of 1000 European and 644 Canadian patients with lupus found 95 and 93% 5-year patient survival rates, respectively.[5,6] This continuous improvement in all cause mortality is a reflection of earlier diagnosis and specific treatment, coupled with a better understanding of the natural history of the disease and improved treatment of infections, dyslipidaemia, hypertension, coagulopathy, proteinuria and renal replacement therapies.[3,4]

1. Treatment Approaches

Despite decades of study, the optimal approach to patients with lupus nephritis remains controversial. Few, if any, studies have sufficient power or follow-up to detect a clear-cut end point in a group of patients balanced for significant prognostic risk factors such as age, sex, race, renal function and renal morphology. One of the best randomised, controlled prospective studies involved 82 patients in a three arm study with a 5- and an 11-year extended follow-up.[7,8] Another of the larger often-quoted studies has 86 patients with lupus nephritis, in which, after 136 months of follow-up, the authors conclude that the experimental therapy of plasma exchange implies no further benefit than the bolus cyclophosphamide therapy.[9] The number of patients enrolled in the study is not powered adequately to determine if there was an effect, let alone that there was no effect. A failure to demonstrate a difference does not indicate equality between the statements. This particular flawed methodological approach has become more popular in the last few years, in which small studies compare a new treatment versus conventional therapy and, showing no difference, conclude that the therapies are either of equal benefit or show no further benefit. Needless to say, these studies contribute to the element of uncertainty about optimal treatment approaches for patients with lupus nephritis. The variable nature of the natural history, which includes renal failure, accelerated atherosclerosis and sepsis, also contributes to the difficulty in assessing appropriate management.

Therapy includes both specific and adjunctive treatments of the disease, as well as management with generalised treatments of the associated comorbidities and renal replacement therapies. Renal biopsy is not only an important prognostic indicator in patients with lupus nephritis but the morphology is often used to decide on a specific type of therapy.[10-12] A summary of the current recommended treatments for patients with lupus nephritis is listed in table I. The strength of the evidence for specific therapeutic interventions is graded using the guidelines of the US Preventive Service Task Force (table II).[13] Where possible, the predominant mechanisms of action and adverse effects of each intervention are listed. A PubMed

Table I. Treatment of lupus nephritis

Specific agents	Adjunctive and experimental agents	General therapy for	Renal replacement therapies
Azathioprine	Ancrod	Anticoagulation	Dialysis
Cyclophosphamide	Anti-C5 monoclonal antibody	Dyslipidaemia	Renal transplantation
Cyclosporin	Antimalarials	Hypertension	
IV immunoglobulins	Bindarit	Proteinuria	
Mycophenolate mofetil	Bone marrow transplantation		
Plasmapheresis	Cladribine		
Corticosteroids	Dornase alfa (DNase)		
	Fish oil		
	Flaxseed		
	Fludarabine		
	Total lymph node irradiation		

IV = intravenous.

search of the National Library of Medicine for lupus nephritis, clinical trials, English language 1978–2001 was conducted to grade evidence for specific agents.

2. Specific Therapy

2.1 Azathioprine: Evidence Level 1

2.1.1 Mode of Action

Azathioprine is an antimetabolite that has an immune modulating effect by reducing intracellular purine synthesis that results in decreased numbers of circulating B and T lymphocytes, reduced immunoglobulin synthesis and diminished interleukin (IL)-2 synthesis.

Azathioprine combined with prednisone has been found to be superior to prednisone alone in patients with lupus nephritis.[14] There is a continuing controversy as to the role of azathioprine versus cyclophosphamide in the treatment of lupus nephritis. A meta-analysis combining the result of multiple controlled trials found that the addition of cyclophosphamide or azathioprine lowered the incidence of progression to ESRD by 40% when compared to therapy with corticosteroids alone[15] (table III). This meta-analysis demonstrated that the azathioprine and corticosteroid group had a significant reduction in ESRD compared with prednisone alone; however, unlike cyclophosphamide, it had no effect on total mortality. Some investigators believe that there is no definite superiority of cyclophosphamide over azathioprine.[16] A recent retrospective study showed that after 4.5 years of follow-up, patients treated with azathioprine and prednisone had similar outcomes to those reported for patients receiving pulse cyclophosphamide.[17] A different approach is to treat with a short course of intravenous cyclophosphamide for 6 months, sequentially following with azathioprine as a maintenance therapy. A recent retrospective study of sequential therapy (cyclophosphamide followed by azathioprine) showed no difference compared to prolonged cyclophosphamide therapy in preserving renal function with less incidence of ovarian failure.[18]

Table II. Grades of evidence for the purported quality of study design[a]

1. Evidence obtained from at least one properly randomised, controlled trial
2. I. Evidence obtained from well designed, controlled trials without randomisation
II. Evidence obtained from well designed, cohort or case-control analytic studies, preferably from more than one centre or research group
3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
4. Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

a The grades are those of the US Preventive Services Task Force (reproduced with permission from Concato et al.[13] © 2000 Massachusetts Medical Society).

Table III. Review of treatments and outcomes from randomised controlled trials (RCT) or meta-analysis of RCT in patients with lupus nephritis for 1978–2001

Reference	No. pts	Study design	Treatment	Outcome	Type of lupus
Ilei et al. 2001[8]	82	RCT, P	IV MP monthly × 1y vs IV cyc monthly ×6 mo then quarterly vs combination therapy with cyc and MP	Both cyc groups reduced the doubling in serum creatinine vs MP, and combination therapy significantly reduced doubling in serum creatinine vs cyc alone	FPGN, DPGN
Clark et al. 2001[19]	23	RCT, C	Flaxseed 30 g/d vs no flaxseed	Decrease in serum creatinine in treatment group	DPGN
Chan et al. 2000[20]	42	RCT, P	Pred + MMF × 12mo vs pred + cyc × 6mo then pred + AZA	No difference in remission rate, proteinuria, albumin and creatinine level	DPGN
Boletis et al. 1999 [21]	14	RCT, P	IV immunoglobulin vs IV cyc	No difference in remission rate	DPGN
Davis et al. 1999[22]	17	RCT, P	Dornase alfa (×2) vs placebo	No different in clinical or serological outcome	LN
Wallace et al. 1998[23]	18	RCT, P	IV cyc + pred vs IV cyc + pred + monthly 3 PE before IV cyc	Similar remission rate, ESRD, serum albumin, complement improved in both groups	DPGN
Bansal & Beto 1997[15]	440	MAY	Pred vs pred + AZA or cyc	Reduced mortality and ESRD pred + cyc or AZA vs pred alone	LN
Gourley et al. 1996[7]	82	RCT, P	IV MP monthly × 1y vs IV cyc monthly × 6mo then quarterly vs combination	Renal remission 85% in combination group vs 62% IV cyc group vs 29% IV MP group ($p < 0.001$)	FPGN, DPGN
Sesso et al. 1994[24]	29	RCT, P	IV cyc 4mo then bimonthly × 4mo then quarterly × 6mo vs IV MP	No significant difference in preserving renal function	DPGN
Clark et al. 1993[25]	26	RCT, C	Fish oil 15 g/day vs placebo (olive oil)	Decrease in proteinuria and lipids in fish oil group	LN
Boumpas et al. 1992[26]	65	RCT, P	IV MP monthly × 6mo vs IV cyc × 6mo vs IV cyc × 6mo followed by quarterly × 2y	Decreased risk of doubling serum creatinine in cyc group ($p < 0.04$), short course cyc had higher exacerbations than long course cyc ($p < 0.01$)	FPGN, DPGN, MG
Lewis et al. 1992[9]	86	RCT, P	Cyc + pred vs PE 3/w × 4w + cyc + pred	Improved serological outcome but no difference in clinical outcome	FPGN, DPGN, MG
Steinberg et al. 1992[27]	111	RCT, P	Pred alone vs pred + IV cyc or oral cyc or AZA + cyc	Renal function better preserved in cyc or AZA + cyc group vs with pred alone	DPGN
Austin et al. 1986[28]	107	RCT, P	Pred vs IV cyc + pred	Cyc reduced the incidence of ESRD	DPGN
Clark et al. 1984[29]	39	RCT, P	PE monthly	No significant reduction in serum creatinine with PE	DPGN
Felson & Anderson 1984[14]	250	MAY	Pred alone or pred + cyc or AZA	Renal function better preserved in pred + cyc or AZA ($p = 0.006$) vs pred alone	LN
Liebling et al. 1982[30]	9	RCT, P	Daily MP × 3/mo × 1y vs placebo	Significant improvement in serum creatinine	DPGN
Donadio et al. 1978[31]	50	RCT, P	Pred alone vs oral cyc + pred × 6mo	Renal relapse higher in pred alone ($p = 0.04$) but no difference in renal function	DPGN

AZA = azathioprine; **C** = crossover; **Cyc** = cyclophosphamide; **DPGN** = diffuse proliferative glomerulonephritis; **ESRD** = end-stage renal disease; **FPGN** = focal progressive glomerulonephritis; **IV** = intravenous; **LN** = lupus nephritis; **MG** = membranous glomerulonephritis; **MAY** = meta-analysis; **MMF** = mycophenolate mofetil; **MP** = methylprednisolone; **P** = parallel; **PE** = plasma exchange; **Pred** = prednisone.

2.1.2 Adverse Effects and Drug Interactions

Azathioprine is associated with a dose-related marrow suppression that results in leukopenia in up to 27% of patients and thrombocytopenia in up to 5%. Gastrointestinal intolerance, pancreatitis, malignancy and skin rashes also occur.[32]

Azathioprine interacts with allopurinol which slows the elimination of 6-mercaptopurine by inhibiting xanthine oxidase; thus, the dose of azathioprine should be reduced significantly (60–70%) in patients treated with allopurinol and this combination should be avoided if possible.[33]

2.2 Cyclophosphamide: Evidence Level 1

2.2.1 Mode of Action

Cyclophosphamide is an alkylating agent that results in impaired DNA replication and transcription. The degree of inhibition of immune function is dependent upon the dose and duration of therapy.

Cyclophosphamide has been used as a therapy for lupus nephritis since the 1960s. An early pooled analysis showed that patients receiving immunosuppressive drugs (cyclophosphamide or azathioprine) had less renal deterioration ($p = 0.006$), were less likely to have ESRD ($p = 0.023$), and were less likely to die from kidney disease ($p = 0.024$) than patients receiving corticosteroids alone[14] (table III).

The role of intermittent intravenous cyclophosphamide therapy was established by two prospective, controlled trials performed at the National Institutes of Health (NIH).[26,28] In 1986 Austin et al.[28] evaluated renal function in 107 patients with active lupus nephritis who were treated with either prednisone or intravenous cyclophosphamide plus prednisone. For patients receiving oral prednisone alone, the probability of renal failure began to increase substantially after 5 years of observation. Renal function was better preserved in patients who received intravenous cyclophosphamide plus low-dose prednisone compared with high-dose prednisone alone ($p = 0.027$) (table III). Boumpas et al.[26] performed another randomised, controlled trial (RCT) in which 65 patients with severe lupus nephritis were assigned randomly to monthly pulse methylprednisolone for 6 months, monthly pulse cyclophosphamide for 6 months, or monthly cyclophosphamide for 6 months followed by quarterly pulse cyclophosphamide for 2 additional years. Patients treated with pulse methylprednisolone had a higher probability of doubling serum creatinine levels than those treated with long-course cyclophosphamide ($p < 0.04$). Also, patients treated with short-course cyclophosphamide had a higher probability of exacerbations than those treated with long-course cyclophosphamide ($p < 0.01$)[26] (table III).

A RTC conducted in 1996 on 82 patients with proliferative lupus nephritis found that the combination of intravenous methylprednisolone and cyclophosphamide or cyclophosphamide alone was superior therapy to pulse methylprednisolone alone in inducing a renal response. Renal remission occurred in 17 of 20 patients in the combination therapy group (85%), 13 of 21 patients in the cyclophosphamide group (62%), and seven of 24 patients in the methylprednisolone group (29%), ($p < 0.001$). The combination of intravenous cyclophosphamide and pulse methylprednisolone produced a more rapid response and greater probability of renal remission at the cost of increased adverse effects secondary to immunosuppression[7] (table III). A recent extended follow-up of the same study showed that the likelihood of treatment failure was significantly lower in the cyclophosphamide ($p = 0.04$) and combination therapy ($p = 0.002$) groups than in the methylprednisolone group. The proportion of patients who had doubling of serum creatinine level was significantly lower in the combination group than in the cyclophosphamide group (relative risk, 0.095; 95% CI 0.01–0.842).[8]

Two meta-analyses combining the result of multiple RCTs found that the addition of cyclophosphamide or azathioprine lowered the incidence of progression to ESRD by 40% when compared to therapy with corticosteroid alone[14,15] (table III). Both meta-analyses indicate that the combination of cytotoxic agents and corticoste-

roids is superior to corticosteroids alone in both preventing total mortality and end-stage renal failure. However, the only specific cytotoxic and corticosteroid combination to reduce both ESRD and total mortality[15] is that of intravenous cyclophosphamide and oral prednisone.

2.2.2 Adverse Effects

Cyclophosphamide produces significant adverse effects including infertility, bone marrow depression and increased susceptibility to infections, haemorrhagic cystitis and bladder cancer. The increased rate of infections which increases mortality is thought to be due to bone marrow depression with neutropenia and interference with lymphocyte function. The sequential use of immunosuppressive agents such as azathioprine, mycophenolate mofetil (MMF) or cyclosporin will reduce the total dose exposure to cyclophosphamide.

Women receiving cyclophosphamide before the age of 25 years have a decreased incidence of sustained amenorrhoea (12%) compared with those treated over the age of 30 years (62%).[34] Birth control pills may be used to minimise cyclophosphamide-induced gonadal toxicity; however, the evidence of a benefit is limited to a small study which showed that women taking oral contraceptives during chemotherapy had normal menstrual cycles and more follicles on ovarian biopsy than historical controls.[35] Oncogenicity and teratogenicity are also complications but are less frequently reported when cyclophosphamide is given by the intravenous route.

Toxicity is dose-related and patients who receive intravenous cyclophosphamide receive a reduced cumulative dose compared with the oral dose administration regimen. Intravenous cyclophosphamide has become more common in treating severe lupus nephritis because of reduced toxicity and similar efficacy.

2.3 Cyclosporin: Evidence Level 4

2.3.1 Mode of Action

Cyclosporin is a calcineurin inhibitor that inhibits transcription of IL-2 and the generation of T-helper lymphocytes.[36]

There are only limited reports on its use in patients with lupus nephritis. Favre et al. studied 26 patients whose SLE was unresponsive to corticosteroids and antimetabolites and were treated with cyclosporin. Global disease activity and proteinuria were significantly reduced by the cyclosporin therapy,[37] unfortunately this was not a controlled, prospective study. Two studies have shown that cyclosporin can be used as a steroid-sparing agent.[38,39] There is an ongoing controlled trial at the NIH comparing the efficacy of cyclosporin alone, prednisone alone, or intravenous cyclophosphamide in 41 patients with lupus membranous nephropathy without proliferation. Compared with prednisone alone, cyclophosphamide and cyclosporin both had a higher remission rate (46 vs 13%) but there was a trend toward more relapses in the cyclosporin group compared with the cyclophosphamide group.[40] Needless to say, the follow-up is insufficient to demonstrate any statistical benefit for the cyclosporin.

2.3.2 Adverse Effects and Drug Interactions

Nephrotoxicity is the most significant adverse effect of cyclosporin. Other adverse effects include hypertension, hepatotoxicity, tremor, seizures, gingival hyperplasia, hirsutism and electrolyte abnormalities (hyperkalaemia, hyperuricaemia, hypophosphataemia and hypomagnesaemia).

A variety of important drugs will increase cyclosporin concentrations, for example, ketoconazole, itraconazole, diltiazem, verapamil, amiodarone, erythromycin and clarithromycin, and careful monitoring and dose alteration are required if they are to be used concomitantly.

2.4 Intravenous Immunoglobulins: Evidence Level 4

2.4.1 Mode of Action

Immunoglobulins are proteins synthesised by B lymphocytes and plasma cells. Although the mechanism of action is not known, it is thought that immunoglobulins act by interacting with Fc receptors on effector cells or by the presence of anti-idiotypic antibodies directed against idiotypes on the patient's own autoantibodies.[20] The discovery

of the FcRn receptor, which is a protective receptor that regulates plasma IgG levels, should improve understanding of the mechanism of action of intravenous immunoglobulin in the management of autoimmune disease.[41]

Immunoglobulin preparations have been used for the treatment of SLE associated thrombocytopenia with limited efficacy.[42-44] Lin reported improvement of histological and immunological parameters in nine patients with resistant lupus, who had failed to respond to pulse methylprednisolone and cyclophosphamide, when treated with intravenous IgG.[45] In a pilot trial, 14 patients with diffuse proliferative lupus nephritis treated with monthly intravenous cyclophosphamide for 6 months were randomised to monthly intravenous immunoglobulin for 18 months (n = 5) or standard intravenous cyclophosphamide (n = 9). Both groups maintained similar creatinine levels, creatinine clearance and degree of proteinuria; however, the study had inadequate power to indicate statistically significant similar efficacy[21] (table III).

2.4.2 Adverse Effects

Adverse effects associated with intravenous immunoglobulin therapy are uncommon and include fever, chills, headache and acute renal failure.[43,46,47]

2.5 Mycophenolate Mofetil: Evidence Level 4

2.5.1 Mode of Action

MMF is an inhibitor of purine synthesis that blocks the proliferation of T and B cells, and inhibits antibody formation and the generation of cytotoxic T cells. It differs from azathioprine by its selective effect on lymphocytes. Prospective RCTs in patients after renal transplantation have shown that MMF is superior to azathioprine or placebo in preventing renal allograft rejection.[48,49] In a murine model of lupus nephritis, MMF delayed renal function deterioration.[50] Glicklich and Acharya reported two cases of diffuse proliferative glomerulonephritis resistant to intravenous cyclophosphamide who responded to MMF therapy.[51] Clinical observations of 13 patients treated with MMF (twelve relapsing or resistant to cyclophosphamide, one refused cyclophosphamide) over a mean of 12.9 months showed significant improvement in proteinuria and serum creatinine.[52]

Two recent studies have shown the anecdotal benefits of MMF therapy in severe paediatric SLE and a pilot study looking at safety and efficacy in lupus nephropathy.[53,54] A recent multicentre RCT of 42 patients randomised to either prednisone and MMF for 12 months, or prednisone and oral cyclophosphamide for 6 months followed by azathioprine for 6 months has been reported. The study concluded that prednisone and MMF were as effective as oral cyclophosphamide and prednisone followed by azathioprine and prednisone. However, the follow-up was short, patients with severe disease were excluded and MMF was not compared with the standard intravenous cyclophosphamide[20] (table III). The major criticism of the study is that it did not have the statistical power to prove equal efficacy of MMF and cyclophosphamide because of the small sample size. A controlled, clinical trial with an appropriate power (number of participants) comparing the standard intravenous cyclophosphamide to MMF is needed to define its role in the management of lupus nephritis.

2.5.2 Adverse Effects

Gastrointestinal upset is the most common adverse effect seen with MMF, but acne, rash, anaemia, leukopenia and thrombocytopenia are other adverse effects seen with its use.

2.6 Plasmapheresis: Evidence Level 4

2.6.1 Mode of Action

The purpose of plasmapheresis in SLE is to remove autoantibodies and toxic immune complexes, which play a role in the pathogenesis of SLE.

Jones and coworkers noted that plasmapheresis may be of value as an adjuvant to the treatment of acute SLE.[55] A randomised, prospective trial by Wei et al. demonstrated that six plasma exchanges in patients with mild lupus did not produce any

significant alteration in disease activity, although there was a significant reduction in immune complex titre.[56]

The first controlled study in patients with diffuse proliferative lupus was reported in 1984. This showed a reduction in serum creatinine levels in the plasma exchange group, however, this reduction was not statistically significant[29] (table III). The Lupus Nephritis Collaborative study group published an RCT in 1992 of 86 patients with severe lupus nephritis.[9] Patients treated with plasmapheresis for two weeks, prednisone and cyclophosphamide had a significantly more rapid reduction of anti-double stranded DNA but no improvement in clinical outcome at 136 months follow-up when compared to treatment with prednisone and cyclophosphamide without plasma exchange[9] (table III).

A similar negative response was recorded by Wallace in 18 patients who were randomised to receive synchronised therapy with plasmapheresis or intravenous cyclophosphamide.[23]

The conclusion of these three studies is that they were unable to demonstrate a significant effect, however, they do not have level one evidence that there is no effect since all studies have insufficient power to determine a negative result.

2.6.2 Adverse Effects

There are few complications related to plasmapheresis, however, patients do receive blood products. The risk of transmission of infectious agents such as hepatitis and HIV are low but are present if plasma is used as the exchange product. However, the majority of plasma exchanges for treatments other than thrombotic thrombocytopenic purpura use 5% human serum albumin with an extremely low risk of an allergic-like reaction and no evidence of transmissibility of lipid soluble viruses. Infection of the venous access site and bleeding are also complications of plasma exchange.

2.7 Corticosteroids: Evidence Level 3

2.7.1 Mode of Action

Prednisone was first used in the 1950s to treat lupus nephritis. It has a beneficial effect on rash, arthritis, fever and other extrarenal manifestations of SLE. Prednisone exerts an immunosuppressive effect by blocking T-cell activation, and inhibits the expression of IL-1, IL-2, IL-3, IL-6, tumour necrosis factor (TNF)-α and interferon (IFN)-γ.

Despite the lack of controlled trials, corticosteroids became the standard of therapy as a result of dramatic responses to extrarenal manifestations in uncontrolled experiments. The best evidence for the use of corticosteroids in treatment of patients with lupus nephritis came from the retrospective pooled analysis published in 1979 by Albert et al. that observed the effect of corticosteroid therapy on 142 patients with SLE followed at the Massachusetts General Hospital between 1922 and 1966. This study reported improved survival in patients with renal involvement who were described as very ill;[57] however, it is difficult to interpret this retrospective study because of the lack of definition of high risk patients and other factors such as early diagnosis and better treatment of infections which may have contributed to improved survival over time.[57]

A number of uncontrolled studies demonstrated improved autoimmune parameters and renal function with pulse methylprednisolone therapy.[58-63] Three randomised controlled clinical trials of patients with proliferative lupus compared pulse methylprednisolone with pulse cyclophosphamide therapy (table III).[7,8,26] All three studies showed that the intravenous cyclophosphamide group had better remission rate and preservation of renal function, therefore, prednisone alone is not indicated for treatment of diffuse proliferative lupus nephritis.

2.7.2 Adverse Effects

Corticosteroids carry significant risk. Several authors have shown that the risk of infection is directly proportional to the corticosteroid dose.[64,65] Ginzler et al. found that the risk of infection rose from 1.5-fold, at an average prednisone dose below 10 mg/day, to over 8-fold in patients receiving doses above 40 mg/day.[64] Dosage of corticosteroids also correlates with dyslipidaemia in patients with lupus nephritis.[66] Osteoporosis is a major ad-

verse effect of corticosteroids, with bone loss occurring in up to 50% of patients receiving long-term corticosteroid therapy.[67-69] Most studies have reported more bone loss and fracture in patients receiving high doses of corticosteroids. Alternate day prednisone does not appear to protect against osteoporosis. Corticosteroids have also been implicated as a cause of avascular necrosis.[68] At high dose, corticosteroids can induce cosmetic deformity, hypertension, cataracts, myopathy, diabetes mellitus and hypothalamic pituitary adrenal insufficiency. Patients requiring prolonged corticosteroid therapy (3–6 months) should be considered for preventive treatment, for example, weight bearing exercise, calcium, vitamin D, antiresorptive agents and hormone replacement.[70-72]

3. Adjunctive and Experimental Therapies

3.1 Ancrod

Ancrod is a proteolytic enzyme derived from the venom of the Malayan pit viper, and causes hypofibrinogenaemia, hypoplasminogenaemia and an elevation in fibrin degradation products.[73] An observational study in patients with lupus nephritis suggests that ancrod may prevent endothelial injury that would lead to sclerosis.[74]

3.1.1 Adverse Effects

Bleeding and clotting complications due to activation of clotting and fibrinolytic systems are the obvious adverse effects of ancrod therapy.

3.2 Anti-C5 Monoclonal Antibody

The complement system plays an important role in the pathogenesis of lupus nephritis. Experimental studies in murine lupus have shown that monoclonal antibody to C5b delayed the onset of proteinuria and ameliorated the severity of nephritis.[75] Clinical studies are in progress.[76]

3.3 Antimalarials

There are no known trials of hydroxychloroquine therapy as a specific treatment for patients with lupus nephritis. However, it is the most commonly used antimalarial in the treatment of patients with SLE in general. It is mainly used as an adjunctive treatment for arthritic and cutaneous manifestations. An RCT in 47 patients with stable lupus (not nephritis) showed that hydroxychloroquine withdrawal is associated with a statistically significant increase in the incidence of flares that required corticosteroid treatment.[77] Hydroxychloroquine has a cholesterol lowering effect.[78] In view of the late vascular risk with lupus nephritis, the cholesterol lowering effect of hydroxychloroquine may have an added potential benefit.

3.3.1 Adverse Effects

Corneal deposition and retinopathy are potential risks for patients receiving hydroxychloroquine.[79] The risk is dose-dependent and low if the dose is less than 6.5 mg/kg. Chloroquine has a higher risk of ocular damage,[80] and it is recommended that if antimalarials are prescribed patients should be assessed annually by an ophthalmologist.

3.4 Bindarit

Bindarit is an indazolic derivative without immunosuppressive effects, which reduces the secondary phase of adjuvant arthritis in rats. It decreases acute phase protein production and glycosylation and inhibits protein denaturation. It has been shown to inhibit monocyte chemoattractant protein (MCP)-1 expression response to lipopolysaccharide stimulation and to inhibit human mesangial expression of MCP-1 after exposure to IL-1β or IL-6. It has also been shown to retard the onset and progression of proteinuria and prolong survival in the NZW lupus mouse.[81] In humans, seven patients with proliferative lupus nephritis receiving bindarit had a reduction in mean proteinuria and urinary IL-6 after 8 weeks of treatment.[82] The experience with bindarit is quite preliminary

and to date no significant adverse effects have been reported, although it is too early to comment.

3.5 Bone Marrow Transplantation

It was noticed that after bone marrow transplantation for leukaemia or aplastic anaemia, patients with coincidental autoimmune disease went into complete remission.[83] Burt treated ten patients with severe autoimmune disease (two with SLE) by intense immunosuppressive conditioning and autologous haematopoietic stem cell transplantation. All patients demonstrated stabilisation or improvement, although the durability of response is unknown.[84] The risk : benefit of stem cell transplant in humans with a variety of autoimmune diseases has not yet been well defined.[76]

3.5.1 Adverse Effects

Significant risk of infections, bleeding and graft versus host disease, as well as death are adverse effects associated with bone marrow transplantation.

3.6 Cladribine

Cladribine (2-chlorodeoxyadenosine; 2Cda) is a nucleoside analogue that interferes with purine metabolism that is used for treatment of chronic lymphoid malignancies. In a recent phase 1 study, 12 patients with proliferative lupus nephritis were treated with either weekly escalating intravenous cladribine or in a continuous 7-day infusion. After 12 months of follow-up, continuous infusion induced a better clinical response and reduction in proteinuria than a weekly infusion.[85]

3.6.1 Adverse Effects

Adverse effects associated most with the use of cladribine are an increased risk of infections secondary to bone marrow suppression, gastrointestinal upset and pneumonitis.

3.7 Dornase Alfa (DNase)

Antibodies to double-stranded DNA have a major role in the pathogenesis of lupus nephritis. Deoxyribonuclease (DNase) is a cleaving enzyme which has been reported to be low in both human[86] and murine[87] SLE. Treatment of murine lupus with dornase alfa (recombinant human DNase-1) has been reported to reduce proteinuria and serum creatinine and improve renal histology.[88] Preliminary results with dornase alfa in a clinical study in 17 patients with lupus nephritis showed no change in serum dsDNA antibody or complement level[22] (table III).

3.8 Fish Oil

The main constituent of fish oil is omega-3 fatty acids, which exert anti-inflammatory and anti-atherosclerotic effects. The omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acid) substitute for arachidonic acid resulting in inactive prostaglandins, and have a direct effect on reducing triglycerides and very low density lipoproteins.[89] Fish oil has been shown in experimental murine models of lupus to reduce proteinuria and renal morphological injury.[90-93]

A double-blind, two-year crossover study of 26 patients with lupus nephritis compared fish oil 15 g/day to placebo (olive oil).[25] The fish oil group had a greater reduction in proteinuria as well as hypertriglyceridaemia, but the interpretation of this significant effect is reduced by the fact that the olive oil did have some activity, that is, a lipid-lowering effect. In other words, in a crossover study when the placebo is active it threatens the validity of the interpretation of a positive crossover since it could be presumed the olive oil made the renal function worse and contributed to the positive effect of the fish oil during crossover time. There is no evidence to support this role for olive oil, but it does mar the interpretation of the positive crossover study and all other crossover studies in which fish oil was compared with olive oil[25] (table III).

3.8.1 Adverse Effects

Gastrointestinal upset with increased eructation is a common adverse effect of fish oil.

3.9 Flaxseed

Flaxseed is a rich source of α-linolenic acid, an omega-3 fatty acid precursor, which has both anti-

atherosclerotic and anti-inflammatory effects.[94,95] Furthermore, flaxseed contains lignans, which are platelet activating factor receptor antagonists. We have studied the effect of flaxseed in the MRL/lpr mouse and found that flaxseed significantly preserved glomerular filtration rate (GFR), and reduced proteinuria and mortality.[96] These findings led to a dose administration study in nine patients with SLE nephritis where it was found that 30 g/day of flaxseed is well tolerated and exerts a significant effect on renal function, plasma lipids and complement C3 level.[97] We have now completed a crossover study of the effect of flaxseed 30 g/day in 23 patients with lupus nephritis[19] (table III). This study was marred by a high dropout rate and a low level of compliance, with only approximately 40% of patients maintaining adherence throughout the 2-year crossover study. However, the patients who did adhere to the flaxseed regimen did demonstrate significant improvement in renal function with a reduction in serum creatinine level, as well as a trend towards reduced protein excretion when compared with the participants who dropped out of the study. Although the study is positive, its interpretation is marred by significant underpowering as well as potential Hawthorne effects (patients who participate in a study do better than patients who do not participate) when comparing patients who entered the study versus those who did not enter the study. This RCT led to recent experimental studies with the lignan precursor derived from flaxseed in the MRL/lpr mouse.[98] Flaxseed appears to be a relatively harmless potential adjunct to therapy for patients with lupus nephritis, but the evidence for its benefit is certainly weakened by underpowering and potential Hawthorne effects due to poor adherence to this diet over an extended time period.

3.9.1 Adverse Effects

Gastrointestinal upset and increased laxation are seen with larger doses of flaxseed.

3.10 Fludarabine

Fludarabine is a purine nucleoside analogue with selective activity against both dividing and resting lymphocytes. Boumpas et al. have evaluated its tolerance, toxicity, pharmacokinetics, and immunological and clinical effects in patients with membranous nephropathy in a single-arm pilot study; one of these eight patients had SLE with membranous nephropathy.[99] All patients showed an improvement in their filtration fraction and the majority showed a 50% reduction in protein excretion following monthly cycles of fludarabine (cycles one and two: 20 mg/m^2/day x 2 days, and cycles three to six: 20 mg/m^2/day x 3 days). This very preliminary pilot study concludes that low dose fludarabine treatment in patients with membranous nephropathy with and without lupus is well tolerated, and results in significant lymphopenia involving B more than T cells and a reduction in proteinuria and improvement in filtration fraction.

3.10.1 Adverse Effects

One of the patients in the study discussed in section 3.10 above developed an infectious complication and therefore there is an increased risk of infection secondary to leukopenia.[99]

3.11 Total Lymph Node Irradiation

Total lymph node irradiation has been studied by Strober et al. in an uncontrolled trial of ten patients with lupus nephritis and marked proteinuria that did not respond to prednisone or prednisone in combination with azathioprine.[100] These patients were treated with total lymphoid irradiation and showed increased serum albumin, complement level and decrease in serum levels of anti-DNA antibodies that persisted during 1 year of follow-up. Further follow-up for 3–10 years showed progression of renal disease.[101,102]

3.11.1 Adverse Effects

Total lymph node irradiation has a significant risk of sepsis, bone marrow depression, infertility and mortality.

4. General Therapy

The majority of patients with lupus nephritis who progress to ESRD have clinically inactive disease.[103,104] Secondary factors, including systemic

hypertension, intraglomerular hypertension, proteinuria, hyperlipidaemia and hypercoagulability play an important role in the progression of chronic renal failure.[105] The final stages of renal function loss are often mediated by non-immune mechanism. Effective treatment of the non-immune factors in lupus nephritis may delay progression of the renal disease. Hypertension, proteinuria and dyslipidaemia are closely interrelated. Proteinuria is related to the degree of hypertension in many renal diseases and an increase in proteinuria can result in significant dyslipidaemia.[106]

4.1 Anticoagulation

Lupus anticoagulant and anticardiolipin antibodies are acquired antiphospholipid antibodies that are frequently found in patients with SLE or related autoimmune disease. Antiphospholipid antibodies have been reported to be present in as many as 44% of patients with SLE.[107,108] Although the detection of antiphospholipid antibodies is frequent, the actual risk of the antiphospholipid antibody syndrome (thrombotic episodes or complications of pregnancy) occurs at a much lower frequency.[109] In SLE patients with renal insufficiency, a thrombotic microangiopathy may be the sole complication making renal biopsy mandatory for correct diagnosis.[110] Prophylactic therapy for asymptomatic individuals with either primary or secondary antiphospholipid antibodies is not currently recommended.[111] Patients with a history of or renal histology showing thrombosis are at risk of recurrence and therefore prevention is important.

There is a significant amount of retrospective evidence to suggest the use of long-term anticoagulation therapy with warfarin (coumadin) should be used in patients who have the antiphospholipid antibody syndrome. The best retrospective evidence would suggest that the target INR (international normalised ratio) should be 3–4, however, this has not been demonstrated in a RCT and early smaller studies have failed to demonstrate the need for achieving this INR.[111] On balance, this issue is somewhat controversial but many authors do target for an INR of 3–4 in light of the two large retrospective studies and the rather high number of endpoints in terms of thrombotic episodes considered.[112,113]

4.1.1 Adverse Effects

The most important adverse effect is bleeding as a result of anticoagulation, but the largest retrospective analysis shows a greater benefit : risk for patients with a history of thrombosis when anticoagulated to an INR of 3–4.[112]

4.2 Dyslipidaemia

Hyperlipidaemia is common in patients with SLE treated with corticosteroids or with progressive renal injury or nephrotic syndrome.[114] Patients with SLE have a 10-fold greater age- and sex-matched risk of vascular events than the general population.[115] Currently there is not enough evidence to support dyslipidaemia as an independent risk factor for progressive renal injury in lupus nephritis; however, proteinuria is an independent risk factor for progressive renal injury in lupus nephritis and there is a strong relationship between total cholesterol levels and proteinuria. In addition to accelerating the development of atherosclerosis, experimental studies suggest that high lipid levels may promote progression of renal disease.[114] Although there is not enough evidence to treat hyperlipidaemia in patients with SLE for prevention of progression of lupus nephritis, there is substantial evidence to suggest that hyperlipidaemia should be treated to reduce the overall risk of vascular disease.

A meta-analysis completed by Massey et al. on treatment of the different form of dyslipidaemia associated with renal dysfunction concluded that, in patients who fail to respond to dietary measures, HMG-CoA reductase inhibitors would be suitable for lowering low density lipoprotein cholesterol, and fish oil and fibric acid derivatives might be considered to reduce hypertriglyceridaemia and raise the high density lipoprotein cholesterol levels.[116,117] Although, as indicated, there is insufficient evidence to support dyslipidaemia as an independent risk factor for progressive renal injury

in lupus nephritis, there is a recent meta-analysis of the effect of lipid reduction by lipid-lowering agents on the progression of renal disease.[118] This meta-analysis clearly indicates that lipid reduction preserves GFR and decreases proteinuria in patients with renal disease. Thus, evidence is starting to accumulate that specific treatment of dyslipidaemia in patients with progressive renal injury, such as lupus nephritis, should be considered.

4.2.1 Adverse Effects

Hepatotoxicity, myopathy, rhabdomyolysis and neurotoxicity are major adverse reactions to HMG-CoA inhibitors and fibric acid derivatives.

4.3 Hypertension

It is well known that essential hypertension in the general population is associated with progressive renal injury.[119-121] The Multiple Risk Factor Intervention Trial (MrFit), which evaluated 323 544 men with 16 years of follow-up, demonstrated a step-grade relationship between systolic and diastolic blood pressure and progressive renal injury that was independent of age, race, use of medication for diabetes, history of myocardial infarction, serum cholesterol level and cigarette smoking.[119] The Modification of Diet in Renal Disease (MDRD) study showed that patients with non-diabetic renal dysfunction and proteinuria >1g had a slower progressive loss of their renal function when the mean arterial pressure (MAP) was <92mm Hg than those with a higher MAP.

The Stanford University group, Stanford, CA, USA, using serial studies of progressive renal injury in lupus nephritis, demonstrated that higher MAP was associated with an increased rate of progression.[122] Similar studies from the NIH and from Yale University, New Haven, CT, USA have shown that hypertension is associated with progressive renal injury in this population.[123,124]

There are no specific reports in patients with lupus nephritis that treatment of blood pressure results in renal benefit but there is substantial evidence in the general progressive renal disease population to aim for a blood pressure of <130/70mm Hg.[125,126]

ACE inhibitors have a renoprotective effect independent of reduction in blood pressure. ACE inhibitors reduce intraglomerular pressure by reversal of the angiotensin II-induced increase in resistance at the efferent arteriole, and also may directly reduce permselectivity and change the ultrastructure of the renal glomerulus.[127-129]

4.3.1 Adverse Effects

ACE inhibitors can induce hypotension, acute renal failure, cough, hyperkalaemia and angioneurotic oedema.

4.4 Proteinuria

Proteinuria is a common feature of patients with lupus proliferative nephritis and progressive renal impairment. Proteinuria itself may contribute to disease progression. Serial studies by the Stanford University group demonstrate that heavy proteinuria is a predictor of progressive renal impairment in patients with lupus nephritis.[101] The mechanism of increased macromolecular protein traffic due to loss of permselectivity is a feature of progressive models of renal injury and also of patients with lupus nephritis.[108] Previous studies have shown that an increase in macromolecular protein traffic results in mesangial proliferation with an increase in mesangial matrix, epithelial cell structural and functional changes, and dislocation from the basement membrane with resultant increase in protein traffic to the proximal tubule and distal collecting duct that is associated with inflammation and scarring and progressive loss of renal function.[111] There is evidence that reduction of proteinuria independent of a reduction in blood pressure is associated with beneficial effects on the progression of renal disease in general.[130-133] In these studies, ACE inhibitors were used and it was found that they reduced proteinuria and progression of renal injury independent of reduction in blood pressure. Addition of a no-added-salt diet to potentiate the ACE inhibitor protein-sparing effect is important and, if this fails, use of a diuretic is appropriate.[134-136]

Although we do not have evidence from the lupus population about the specific treatment of pro-

teinuria, a recent meta-analysis of protein level data from the non-diabetic progressive renal disease population indicates that ACE inhibition slows the progression of renal disease.[119]

5. Renal Replacement Therapy

5.1 Dialysis and Renal Transplantation in Lupus Nephritis

Despite aggressive treatment of lupus nephritis, 10–30% of patients develop ESRD and require renal replacement therapy. Non-immune mediated injury is thought to be the major factor. In most patients, partial or complete resolution of disease activity occurs with renal replacement therapy.[137,138] Patient survival appears to be similar to the general population with either haemodialysis or continuous ambulatory peritoneal dialysis.[104] Several reports have recommended that patients be on dialysis an average of 3–6 months or longer before transplantation is considered because of the high rate of renal recovery in SLE patients and to ensure that the disease is immunologically inactive.[104,138,139] Renal graft survival is similar to graft survival for other causes of renal failure.[138,140] Recurrence of SLE in the graft is approximately 10–40% but graft loss because of recurrence of SLE is extremely low (<2–4%).[141] There is evidence that patients with a history of antiphospholipid antibody syndrome with thrombotic events can experience thrombotic microangiopathy and further thrombotic events after transplantation.[142] It is recommended that patients with a history of recurrent thrombosis and antiphospholipid antibodies who undergo transplantation should be anticoagulated perioperatively and post-transplantation.[143,144]

6. Conclusion

In order to provide optimal therapy for patients with lupus nephritis, the group at risk should have pathology confirmed with a renal biopsy. Not all patients with SLE have significant clinical renal disease and most clinicians use assessments of renal function at the time of seeing the patient to determine whether a biopsy is appropriate. Usually patients are considered for biopsy if they experience heavy proteinuria or a decrement in GFR. In approximately 50% of patients who are biopsied, a proliferative lesion will be seen (WHO Type 3 or 4) and these patients will be considered for treatment with a combination of corticosteroids and immunosuppressive therapy. Patients with lupus nephritis type 1, 2 and 5 lesions usually receive corticosteroids and/or adjunctive therapy only. Occasionally patients with type 5 lesions (membranous nephropathy) because of progressive decline in GFR or severe nephrotic syndrome, qualify for more aggressive corticosteroid and immunosuppressive treatment.

The corticosteroid and immunosuppressive regimen with the most evidence for benefit to date is the use of oral prednisone coupled with bolus intravenous cyclophosphamide and methylprednisolone.[8,15] The duration of bolus therapy will depend on the age, fertility and the potential for malignancies of the patients. The oral prednisone therapy is usually rapidly tapered and is used to treat extrarenal manifestations. The combination of increasing age and fertility concerns spawned the use of sequential therapy with oral azathioprine, MMF or cyclosporin after the initial 6 months of intravenous cyclophosphamide therapy, rather than completing the 3 monthly cyclophosphamide protocol for 2 years that is recommended by the NIH. This approach has not been validated by controlled studies, but a growing concern for long-term complications of cyclophosphamide therapy and need for its reuse has prompted consideration in individual patients.

The best evidence for reduction in total mortality and preservation of renal function at this point lies with the use of intravenous cyclophosphamide and corticosteroids in patients with proliferative lupus nephritis.[8,15] Hydroxychloroquine is often used as a steroid-sparing agent and appears to be effective for both skin and joint manifestations of the disease.[77] Fish oil or flaxseed (crushed) are not popular but, if tolerated, may be a useful adjunct to specific therapy with low toxicity.

General therapy has a major role to play in preventing progression of renal disease with targeting of blood pressure ≤130/70mm Hg with the use of ACE inhibitors and the addition of a no-added-salt diet. If the patient has a history of thrombotic events with the antiphospholipid antibody syndrome, then long-term anticoagulation with warfarin with a target INR of 3–4 is recommended. The identification of dyslipidaemia and its treatment with diet, exercise and, if necessary, HMG-CoA reductase inhibitors is also an important part of the overall general therapy of patients with lupus nephritis.

In terms of specific therapy, the renal biopsy is used to identify those who require early aggressive cytotoxic therapy (WHO classes 3 and 4). If renal failure is advanced or chronic, then strategies that avoid heroic aggressive immunosuppressive regimens will result in better survival with transplant or haemodialysis treatment.

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