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Pharmacotherapy of Lupus Nephritis in Children

A Recommended Treatment Approach

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Contents

Abstract

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease of unknown aetiology, which is characterised by recurrent disease flares that may affect any organ system. Renal involvement remains one of the chief causes of morbidity and mortality in children with lupus. Nephritis occurs in approximately two-thirds of patients, ranging from mild glomerulitis to life-threatening occurrences of diffuse proliferative glomerulonephritis. As lupus nephritis is a condition of no single aetiology, there is no single cure. Corticosteroids, although still the first line of treatment, are increasingly being superseded by cytotoxic drugs, in particular cyclophosphamide and corticosteroid-sparing agents. Newer agents such as mycophenolate mofetil, although effective in the treatment of lupus in adults, are less effective in children. Standard of care for highly active lupus nephritis in children remains intravenous cyclophosphamide, although preliminary experience suggests that the addition of rituximab may allow for remission induction with a reduction in cumulative cyclophosphamide dose. Combination therapies and newer agents appear promising for the future as our understanding of the immune system and its dysregulation in SLE improves. In this review, we discuss the current standards of care, newer therapies currently in use, and emerging treatments still undergoing development and investigation. We conclude by discussing our guidelines for treatment at the present time and suggestions for the comprehensive care of children with lupus nephritis.

The annual incidence of systemic lupus erythematosus (SLE) in adults is estimated at 2–7.6/100 000 per year.[1] In children, the incidence in the US is somewhat lower, estimated at 0.53–0.60/100 000 per year. In one study, the prevalence of lupus in the first decade of life in Los Angeles was investigated. Cases per 100 000 patients aged <10 years ranged from 1.27 for Caucasian females to 6.6 for Oriental females, with intermediate results for Black and Hispanic girls. For all races, the number of males aged <10 years affected was 1/100 000.[1-4] Approximately 15% of all cases have onset in childhood.[1] There are significantly more women affected by SLE, but the imbalance in sex incidence is less striking in young children, with earlier and more severe disease seen in male patients.[1,4]

The clinical manifestations of SLE are legion and have been well described. Lupus can cause inflammation in any organ system, and the disease course varies in chronicity, severity and organ involvement. The kidneys, skin, lungs, heart, liver and CNS are all commonly affected.

Renal involvement, which occurs in approximately two-thirds of patients, ranges from mild glomerulonephritis to severe diffuse proliferative glomerulonephritis (DPGN), and remains a major cause of morbidity and mortality in children with lupus.[5] In addition, children may develop nephrotic syndrome and/or cardiac, vascular or cognitive sequelae related to poorly controlled renovascular hypertension. Without aggressive intervention, the prognosis for children with significant renal involvement remains poor. McCurdy et al.[6] report 71 children with lupus nephritis, of whom 16 (22%) developed chronic renal failure. Ten of the children were maintained on dialysis, of whom five died of sepsis. Hagelberg et al.[7] report only 56% survival for non-Caucasian patients treated in a less aggressive setting.

Corticosteroid dependence is a major issue for children with lupus. As our ability to treat complications of SLE has improved, with longer survival we are confronted by unacceptable levels of corticosteroid-induced toxicity. These treatment-related morbidities have become a prominent aspect of the long-term morbidity and mortality of childhood lupus.[8-12] In this review, we highlight the use of cytotoxic medications and other steroid-sparing agents, which play a major role in reducing treatment-related morbidity and improving the quality of life for children with SLE. Early and aggressive treatment is critical if physicians wish to attain a satisfactory long-term outcome for children with lupus.

1. Systemic Lupus Erythematosus (SLE)

The clinical manifestations of lupus are the end result of a complex interplay of immunologically mediated events in a genetically predisposed individual. These events may be influenced by hormonal, infectious or environmental triggers in any combination. Immune dysregulation with polyclonal B-cell activation results in the formation of pathogenic immune complexes with tissue deposition, complement activation and consequent end-organ damage. Although the pathological event underlying tissue damage in SLE appears to be the formation of immune complexes, the driving force behind the production of self-reactive antibodies remains unclear. B cells, T cells and dendritic cells appear to have diverse effects on the immune dysregulation seen in SLE. All or only some of these factors may come into play in a particular individual, which may explain not only the diversity of clinical manifestations but also the variability in disease course between individuals. Emerging information regarding defective apoptosis and various genetic influences in SLE may pave the way for still further advances in therapeutics with new targets for therapy.

There is no single 'cause' of SLE and, in the absence of a single cause, it is uncertain whether there will ever be a single 'cure'. However, we have been able to improve the prognosis for affected children markedly with the advent of improved understanding, decreased use of corticosteroids and increased use of advanced medications.

1.1 WHO Classifications

When discussing lupus nephritis, it is important to have a standard frame of reference. Although some additional refinements and modifications have

Table I. WHO classification system for lupus nephritis[13]

Class	Clinical signs	Histological appearance[a]
Class I	Normal urinary sediment, renal function, blood pressure	No evidence of disease
Class II Mesangial nephritis	Mild protineunuria/haematuria Normal renal function	Hypercellularity, Immune deposits
Class III Focal proliferative glomerulonephritis	Haematuria Proteinuria (typically below nephrotic range)	<50% glomeruli involved segmental areas of hypercellularity invasion of glomerular space
Class IV Diffuse proliferative glomerulonephritis	Haematuria Nephrotic-range proteinuria Hypertension Declining renal function	≥50% glomeruli involved Generalised hypercellularity 'Full house' pattern of immune complex deposition (IgM, IgG, IgA, C3, C4) in subendothelium and subepithelium
Class V Membranous nephropathy	Proteinuria Haematuria less common	Thickening of basement membrane Immune complex deposition No glomerular hypercellularity
Class VI Glomerular sclerosis	End-stage renal disease Hypertension	Glomerular sclerosis, fibrous crescents

a Histological appearance of renal biopsy tissue by light and electron microscopy, and immunofluorescence.

Table II. Measures of chronicity and activity included in indices used to characterise lupus nephritis[13]

Activity	Chronicity
Cellular proliferation	Glomerular sclerosis
Neutrophilic infiltration	Thickening of capillary basement
Cellular crescents	membrane
Hyaline thrombi	Fibrous crescents
Necrosis	Tubulointerstitial scarring

been proposed, the WHO classification remains widely accepted. This system has classified lupus nephritis into six categories based on the histological appearance of renal biopsy tissue by light and electron microscopy and immunofluorescence (table I).

Lupus nephritis can be further characterised according to chronicity and activity indices (table II). The chronicity index measures irreversible renal damage, whereas the activity index represents ongoing inflammation and disease activity. When scoring activity, each of the indices are graded from 0 to 3, with 2 extra points given for the presence of fibrous crescents and necrosis, for a maximum possible activity score of 24. When scoring chronicity, each of the four indices is scored from 0 to 3 for a maximum possible chronicity score of 12. In patients with high activity and low chronicity scores, aggressive therapy is likely to preserve kidney function. However, if extensive chronicity is present (e.g. chronicity scores in excess of 6) without significant activity, cytotoxic therapy is unlikely to be of benefit.

2. Agents Used in the Treatment of SLE Nephritis

Monthly intravenous cyclophosphamide (with or without solumedrol pulses) followed by intermittent intravenous cyclophosphamide or other oral immunosuppressive agents has been widely considered to be the gold standard of therapy for aggressive lupus nephritis (in particular WHO class IV). The addition of agents such as rituximab that selectively target specific subsets of immunomodulatory cells may allow for more complete disease control, with a reduction in cumulative cyclophosphamide and corticosteroid-related toxicities.

In this review, we propose a treatment algorithm for the treatment of children with various forms of lupus nephritis (see section 3). Although mild renal involvement might require only low doses of corticosteroids and antimalarials, more severe forms with deteriorating renal function require prompt and aggressive treatment. Appropriate aggressive intervention includes not only high-dose oral or intravenous corticosteroids but also cytotoxic agents such as cyclophosphamide, rituximab and combinations thereof. Other immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine and ciclosporin (cyclosporine), are being used with increasing success to maintain remission in children with lupus nephritis. The appropriate role of all of these agents in inducing and maintaining long-term disease-free remission remains under investigation.

2.1 Corticosteroids

Corticosteroids remain the first line of treatment for SLE patients. The immunosuppressive and anti-inflammatory effects of corticosteroids are rapid and non-specific. However, the beneficial effects must be balanced against the many adverse effects of long-term corticosteroid use. These include increased risk of infection, poor wound healing, Cushing's syndrome, hypertension, diabetes mellitus, premature atherosclerosis, osteoporosis, avascular necrosis, cataracts, glaucoma, pseudotumour cerebri, psychosis, acne, hirsutism and striae. Of particular and immediate concern to many children and their families is the profound linear growth retardation seen with corticosteroid use.[8-12]

The increased risk of infection must be of particular concern to the treating physician. Corticosteroids not only increase the risk of infection but might also mask the initial manifestations of infec-

tion, making early recognition difficult. Over an increased period of survival, the increased risk of premature arteriosclerosis associated with excessive corticosteroid usage by children with lupus may be of even greater concern.[14,15] The excessive use of corticosteroids contributes to the morbidity and mortality of lupus in children.

High doses of corticosteroids may be required during the initial phase of remission induction in some children with lupus nephritis. However, it is imperative that the dose be reduced as quickly as possible. In most clinical situations, and in refractory or steroid-dependent cases, it is imperative that aggressive steroid-sparing therapies be implemented early. Adolescents and young adults often find the undesirable cosmetic effects of corticosteroids particularly disturbing, and even in the best therapeutic partnerships may refuse to continue on high doses despite increasing disease activity. The resultant non-compliance can have life-threatening consequences.

There remains debate as to the optimal route and dose of corticosteroids for lupus nephritis. In 15 paediatric patients with biopsy-proven DPGN treated with oral prednisone 2 mg/kg/day, compared with seven similar DPGN patients treated with six daily pulses of methylprednisolone (30 mg/kg/day to maximum of 1 g/day) followed by the same oral dose of prednisone, a more rapid clinical improvement was seen in the intravenous pulse group.[16] A later study compared the efficacy of intravenous methylprednisolone and low-dose daily prednisone with high-dose daily prednisone in patients with SLE nephritis. High dose was defined as 2 mg/kg/day, which was weaned to between 0.2 and 0.5 mg/kg/day after remission. With relapse, patients were treated with methylprednisolone pulses (20 mg/kg/day) on alternate days and continued the pre-pulse dose of prednisone. There were no significant differences between the patients in each phase of treatment.[17] However, the unusual study design in which patients served as their own controls and received different treatment regimens at different points in their clinical courses makes it difficult to draw specific conclusions. Our recommendations are outlined in section 3.

2.2 Cyclophosphamide

Cyclophosphamide has been shown to modify the disease course of lupus nephritis in children.[18,19] Cyclophosphamide is a cytotoxic agent that is an inactive phosphamide ester of mechlorethamine. It is transformed by the cytochrome P450 system to active metabolites (4-hydroxycyclophosphamide, aldophosphamide, acrolein and phophoramide mustard), which cross-link DNA strands, preventing cell division. Therefore, cyclophosphamide therapy targets all active, rapidly dividing cells. Cyclophosphamide is widely considered to be the gold standard for the treatment of active WHO class IV or DPGN.

In 1989 a multicentre study first examined the safety and efficacy of intravenous cyclophosphamide in children with lupus nephritis. Sixteen children (eight with steroid-refractory disease and eight with steroid-dependent disease) were treated monthly for 6 months and then every 3 months. At 1 year of follow-up, there was a significant improvement in haemoglobin and C4 levels, renal protein excretion and creatinine clearance, and a significant reduction in prednisone dosages.[18] A prospective study of the safety and efficacy of a 36-month course of cyclophosphamide was undertaken at our institution in 2000.[19] Sixteen additional children with biopsy-proven lupus nephritis were treated for 36 months, after which time renal biopsies were repeated and re-scored. No adverse events were noted during the 3 years of treatment. Significant improvements were seen in activity score, creatinine clearance, protein excretion, SLE Disease Activity Index (SLEDAI) scores and prednisone dosage. No progression was seen in the chronicity index, indi-

cating that cyclophosphamide may halt the renal scarring of untreated lupus nephritis.

The optimal duration and dose administration of cyclophosphamide therapy in children remains uncertain. Following the initial seven monthly doses, different centres use a variety of alternative regimens. The standard published regimen calls for continuation of dose administration every 3 months for a total of 36 months of treatment.

The use of cyclophosphamide is not without risk. Serious adverse events are minimised by administering the drug intravenously in an inpatient setting, which allows careful monitoring of laboratory indices, clinical status, infectious risk and hydration prior to and during the course of each infusion. Commonly encountered adverse effects include nausea and vomiting, alopecia and leukopenia. Unsuspected infection is a major concern, and cyclophosphamide infusion should be withheld in any febrile or otherwise suspect patient because of the risk of overwhelming sepsis.

Haemorrhagic cystitis has been reported with cyclophosphamide but is common only with daily oral administration. We circumvent this problem with 12 hours of inpatient pre-hydration and 24 hours of inpatient post-cyclophosphamide hydration, with close monitoring of the urinary sediment, fluid status and electrolytes. Post-cyclophosphamide hydration includes mesna, which protects the bladder by binding acrolein, one of the active metabolites of cyclophosphamide. To date, we have seen no haemorrhagic cystitis related to intravenous cyclophosphamide administered in this way. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is also a known complication of cyclophosphamide therapy, but it can be easily avoided with inpatient cyclophosphamide administration and careful monitoring.

Gonadal toxicity is a frequently stated concern of physicians caring for adolescents and young adults. However, only those patients who have received more than a lifetime cumulative dose of cyclophosphamide 17 g/m^2 have developed infertility with an unacceptable frequency. Lupron has been suggested for those female patients for whom the risk of infertility is a major concern. Male patients may be offered the option of using a sperm bank before cyclophosphamide therapy. Cyclophosphamide is a potential teratogen and so it is imperative that all post-pubertal women be screened for pregnancy before each cyclophosphamide administration.

The use of cyclophosphamide has allowed for significant reductions in corticosteroid dosages in the majority of patients. However, there is an ongoing search for alternative therapies or drug combinations, with the goal of minimising medication-associated morbidity and maximising outcome.

2.3 Combination Therapy with Cyclophosphamide and Methotrexate

In children with cyclophosphamide-refractory or relapsed class IV lupus nephritis in which the maximum dosage of cyclophosphamide has already been administered, there are no clear guidelines for treatment. There is a concern that cyclophosphamide beyond 36 months confers a significant risk of amenorrhoea and secondary malignancies.[20] In one report, five children with recurrent class IV lupus nephritis were treated with combination cyclophosphamide and methotrexate. Nine monthly doses of intravenous cyclophosphamide (750–1000 mg/m^2/dose) and intravenous methotrexate (50–300 mg/m^2/month) were given on the same day. In all patients, disease was controlled with improvement in SLEDAI, creatinine, C3, albumin and corticosteroid dosages, with persistence of the effect at 4-year follow-up.[20] Although this study represents only a small number of patients, all five experienced long-term remission.

As with any chemotherapeutic agent, there are significant risks associated with the use of methotre-

xate. These include nausea, vomiting, pulmonary fibrosis, mucositis, and liver and bone marrow toxicity. These toxicities may be somewhat alleviated with the use of folic acid. Combination therapy with cyclophosphamide and other cytotoxic agents may have a synergistic immunosuppressive effect, targeting both the humoral and cell-mediated arms of the immune system. Treating physicians must maintain a high index of suspicion for infection, particularly with the use of combination immunosuppressive therapy, given the risk of profound immunosuppression. In such patients, a low threshold for withholding therapy and initiating appropriate treatment for any potential infection is crucial. Given the potential risks, combination therapy should be reserved for those rare patients who are refractory to aggressive therapy with standard single-agent regimens.

2.4 Rituximab

It has recently become apparent that B cells play a significant role in the pathogenesis of autoimmune disease. Identifying the surface molecules on lymphocytes was a first step. CD20 was identified as being a specific marker for B cells. It is highly expressed on pre-B cells and on mature B cells in the activated and resting state. CD20 is no longer present after terminal differentiation to plasma cells, nor is it found on pro-B cells or in the normal tissues. CD20 is an integral membrane protein that is thought to be a calcium-channel subunit with a role in B-cell activation and differentiation. Its specific expression on the B cell has presented CD20 as a sustained and high-density target for immunotherapy, particularly since CD20 is neither significantly internalised nor is it shed.

Rituximab is a chimeric mouse/human monoclonal antibody against the B cell-specific antigen CD20. It comprises murine anti-human CD20-variable regions fused with human κ- and IgG-constant regions. Its therapeutic potential was discovered when it became clear that treatment with anti-CD20 causes B-cell death without the need to link a toxic agent to the antigen. Rituximab also induces the activation of B-cell death by apoptosis by inducing phospholipase C, which activates caspases. This process has the advantage of taking place without inciting an inflammatory response in neighbouring cells.[21]

Rituximab was initially licensed for use in the treatment of B-cell malignancies. It has been administered to more than half a million people, and has been shown to be effective and well tolerated. The fact that it does not affect plasma cells has been postulated as a reason for the lack of effect on immunoglobulins and a low incidence of infection. It has been shown to profoundly deplete B cells in these patients for many months. As it is well tolerated and selective, it has recently been used in autoimmune disease, with some marked initial success.

Dose administration in lupus nephritis initially emulated treatment in lymphoma where the recommended dose is 375mg/m^2 for four weekly doses. Initial work by Looney et al.[22] gave patients increasing doses of rituximab to a maximum of the standard lymphoma dosage. They showed a depletion to less than five CD19+ cells/μL (normal ~20 CD19+ cells/μL) in 10 of 16 patients. These patients showed a rapid improvement with Systemic Lupus Activity Measure (SLAM) scores decreased within 1 month. This improvement persisted for 1 year (flare was correlated with increase in CD19+ cell count). Non-response with failure to deplete CD19+ cells was greater in African-Americans.

Human antichimeric antibodies (HACAs) >100 ng/mL developed in 6 of 16 patients. These were associated with lower doses of rituximab and less B-cell depletion, and occurred more frequently in African-American patients with higher baseline disease activity.

Interestingly, rituximab did not have any effect on anti-dsDNA levels, which suggests a lack of

effect on the plasma cell where CD20 is not expressed.[22]

More recent work shows that almost complete B-cell depletion is achieved when the full rituximab regimen is given. For example, in work by Sfikakis et al.[23,24] using lymphoma-dose rituximab and tapering corticosteroids, B-cell depletion was achieved in all patients who had received full-dose rituximab. They also showed significant decreases in anti-dsDNA in all patients and increases in serum complement levels. A clinical improvement was achieved in 80% of patients, who showed partial remission of active proliferative lupus nephritis, with subsequent complete remission in 50% of patients. The authors remark that although complete B-cell depletion was achieved in all patients, there was no consistent pattern between B-cell depletion and clinical outcome or B-cell recovery time. They also note that the expression of T cell co-stimulatory molecule CD40L decreased 4-fold. CD40L has previously been shown to be overproduced in patients with SLE and it is suggested that CD40L/CD40 interactions may play a significant role in lupus nephritis. In this study, downregulation of CD40L on T cells was noted to precede improvement of lupus nephritis and to be sustained in patients in remission. This suggests that rituximab treatment with B-cell depletion has a direct effect on preventing the activation of lupus T cells. Thus, targeted CD40L therapy may have a significant role to play in the treatment of SLE.

Patients with SLE have been demonstrated to have various abnormalities in peripheral B-cell homeostasis. Rituximab has been shown to have caused resolution of a number of these. Anolik et al.[25] report that, although rituximab effectively depletes circulating B cells, it is possible to detect the presence of CD19+ cells. Thus, although absolute depletion of B cells is not necessary for clinical effectiveness, multiple doses may be necessary to maintain a lasting clinical response with 'restoration of tolerance'. They define this as "proper regulation of emerging auto-reactive B cells and establishment of a normal B cell repertoire". They suggest that the VH4.34 B cell provides a good marker for this 'restoration of tolerance', but further investigation of this is necessary.

Infusion reactions may be seen with the initial administration of rituximab. These are usually mild, with pruritus, mild facial erythema and transient hypotension most commonly seen. Fever and rigors have also been reported. In our clinical practice, we have found that symptoms usually resolve rapidly with a brief cessation of therapy, and the remainder of the infusion is well tolerated at a slower rate. These reactions have been minimised by pre-medicating children undergoing rituximab infusion with methylprednisolone 60 mg/m^2 and diphenhydramine 25–50mg.

It has been noted that the development of HACAs is increased in patients with autoimmune conditions in comparison with those treated with rituximab for lymphoma where rates of <1% are seen. In the work of Looney et al.,[22] HACAs were seen in 30% of patients. HACA development poses difficulties as they could potentiate severe allergic reactions and a decrease in efficacy when patients are retreated with rituximab. Re-treatment may be necessary, at least in the short term, to maintain B-cell inactivity until further treatments become available, which will potentially eliminate all disease-associated autoimmune cells.

2.5 Combination Therapy with Rituximab and Cyclophosphamide

Rituximab achieves effective depletion of CD20-carrying B cells in the majority of patients. However, the associated disease remissions are often only 6–12 months in duration. This may be because CD20 is not produced on all B cells. Therapy with rituximab leaves a pool of plasma cells, which may contain auto-reactive memory B cells. In

an effort to address this residual cell population, some investigators are utilising the combination of cyclophosphamide and rituximab with each treatment course.

In recent work, Marks et al.[26] demonstrate that children with refractory SLE respond well to the combination of rituximab and cyclophosphamide. Although this is a small study (seven children), significant improvements were seen in both systemic disease activity and renal parameters. These children had been treated previously with multiple immunosuppressive agents, including cyclophosphamide alone. The addition of rituximab resulted in an improvement in BILAG (British Isles Lupus Assessment Group) scores from 22 to 6, with two dialysis-dependent children having this therapy successfully withdrawn, and continued significant improvement in renal function and proteinuria.

The use of well tolerated, effective immunosuppressive agents such as rituximab, which appears to have an improved safety profile with fewer fertility concerns, is of particular interest in the paediatric population. Combination therapy may allow us to minimise the cumulative dose of cytotoxic immunosuppressive agents.

Marks et al.[26] used a regimen of rituximab 750 mg/m^2 (to a maximum dose of 1g) on days 1 and 15, with a pre-medication of methylprednisolone, chlorpheniramine and paracetamol (acetaminophen) each at 100mg, followed by cyclophosphamide 750mg or 500mg if the patient's dry weight was <50kg on days 2 and 16. Oral prednisolone in tapering doses was given on days 2, 3, 4, 16, 17 and 18. In our practice, we have adopted an aggressive approach to patients with persistent or newly diagnosed lupus nephritis, using a similar dose administration schedule to induce B cell depletion.

2.6 Mycophenolate Mofetil

MMF is a derivative of mycophenolic acid, which was isolated from the genus *Penicillium* in the late 1800s. Mycophenolic acid was originally recognised as having antifungal and anticancer properties, and has been used extensively for the treatment of psoriasis and renal transplant rejection. Of note, MMF has been found to be of particular benefit in renal transplant patients, with decreased creatinine clearance with decreased clearance of the drug. This suggests that MMF may have wider applicability in other renal diseases. Renal transplant trials in adults have examined 2 g/day versus 3 g/day oral administration and found an increase in efficacy but significant gastrointestinal toxicity in the 3 g/day regimens.[27] When compared with azathioprine-treated transplant patients, those treated with MMF had decreased antibody levels following immunisation, suggesting a role for MMF in autoimmune antibody-mediated diseases such as SLE.[28] Additional studies of MMF have demonstrated a variety of anti-inflammatory effects, including decreased expression of adhesion molecules and nitric oxide production, and reduced endothelial injury and arteriosclerosis.[29-31] These effects make MMF a therapeutic consideration for patients with lupus nephritis, but its long-term efficacy in comparison with other regimens and its efficacy in children remain uncertain.

In a randomised, non-blinded 2003 study, Ginzler et al.[32] showed superior effect in adult SLE patients with severe lupus nephritis receiving MMF 3 g/day compared with those receiving monthly intravenous cyclophosphamide over a 6-month period. Other studies in adults have indicated that MMF may be effective for maintaining remission for patients previously induced with cyclophosphamide. Hu et al.[33] compared daily MMF to monthly intravenous cyclophosphamide and showed, with serial renal biopsies, a greater fall in activity scores, as well as in clinical indices of disease activity in those lupus nephritis patients treated with MMF. In a 2004 study, 59 lupus nephritis patients who had received monthly intravenous cyclophosphamide induction

were randomised to three maintenance therapy groups, namely, quarterly intravenous cyclophosphamide, oral azathioprine (1–3 mg/kg/day) and MMF (500mg–3g daily). With 72 months of follow-up, those patients receiving maintenance therapy with MMF had a higher rate of relapse-free survival.[34]

However, in children with lupus nephritis the experience with MMF has not been as satisfactory. A 2001 case report describes two Chinese children with cyclophosphamide- and ciclosporin-resistant lupus nephritis who were successfully treated with MMF.[35] A study from the same year of 11 children with lupus nephritis treated with MMF at a mean dosage of 22 mg/kg/day (in addition to prednisone and hydroxychloroquine) saw a greater improvement in renal function in those patients with class V than class IV lupus nephritis. In addition, 73% of patients experienced adverse effects.[36] In our experience, MMF has been less effective and is complicated by more adverse effects than quarterly intravenous cyclophosphamide. To date, we have no lupus nephritis patients who have successfully maintained a cyclophosphamide-induced remission with MMF. This may be the result of poor compliance by children and adolescents. This is primarily related to adverse gastrointestinal effects. MMF may have a role in children who have completed 3 years of cyclophosphamide use, patients with class V lupus nephritis, or those whose families object to the use of cyclophosphamide. In patients with active class III or IV lupus nephritis, we continue to strongly recommend the use of cyclophosphamide (or a combination of cyclophosphamide and rituximab).

2.7 Ciclosporin and Azathioprine

A number of other immunosuppressive medications have been used as steroid-sparing agents in the treatment of lupus nephritis in children. Among these are ciclosporin and azathioprine.

Ciclosporin is a fungal peptide that is known to decrease T cell proliferation. In adults, ciclosporin has been shown to have a steroid-sparing effect in stable lupus patients with proteinuria.[37] There is no evidence to suggest a role for ciclosporin as induction therapy for lupus nephritis. The major concern with the use of ciclosporin lies in its potential for nephrotoxicity and hypertension in lupus patients with decreased renal function. Careful monitoring of creatinine and blood pressure (BP) in those patients receiving ciclosporin is essential. Ciclosporin seems most appropriate for the treatment of class V nephritis with nephrotic syndrome.

Azathioprine is a purine analogue that suppresses cell-mediated immunity by interfering with DNA synthesis. A retrospective study from 2000 indicates 5- and 10-year survival rates similar to those seen with cyclophosphamide therapy among those patients treated with a combination of prednisone and azathioprine for proliferative lupus nephritis. However, 15-year survival results remain poor.[38]

No controlled studies comparing these medications with cyclophosphamide and intravenous methylprednisolone exist for children. In a retrospective review, Hagelberg et al.[7] suggest a satisfactory response to long-term oral azathioprine. However, the non-Caucasian children in their study had only a 56% long-term survival, which most centres would find unsatisfactory. The beneficial effect they ascribe to azathioprine may only be applicable to Caucasian patients. The use of azathioprine for children with lupus nephritis has been largely abandoned in favour of newer, more effective therapies. As a result, few studies of its use are available in children.

2.8 Therapies Directed at T Cells

2.8.1 Anti-CD40 Ligand

CD40 is present on B cells and modulates the activity of CD4+ T helper cells via the CD40 ligand, which, in turn, promotes production and differentia-

tion of B cells. Increased levels of CD40L have been documented in patients with active SLE. In murine experiments, interrupting the CD40-CD40L bond leads to reduced lupus nephritis activity. Early clinical trials were less promising, demonstrating either no benefit or having an unacceptably high adverse effect profile.[39,40] Rituximab may have a significant role to play in the modulation of T-cell activity via depletion of B cells, which can interact with the CD40L.

2.8.2 CTLA4-Ig

Activation of the T cell requires not only recognition of the MCH molecule but also activation of the co-stimulatory pathway. Interruption of the co-stimulatory pathway may provide yet another target for immunosuppressive therapy. CTLA4-Ig (abatacept), a murine fusion protein, binds with higher affinity than CD28 to B7 antigen, thus blocking the B7/CD28 interaction and preventing activation of the T cell. In a murine lupus model, CTLA4-Ig led to decreased anti-dsDNA and improved renal parameters.[41] CTLA4-Ig has not yet been studied in human lupus, but trials in rheumatoid arthritis have shown clinical improvement using American College of Rheumatology (ACR) 20, 50 and 70 scores with significant slowing in structural damage progression.[42]

2.9 Other B Cell-Directed Therapies

2.9.1 Anti-CD22

Epratuzumab is a monoclonal antibody against B cell-specific antigen CD22. This agent has undergone early trials in non-Hodgkin's lymphoma and may prove useful in treating autoimmune diseases.

2.9.2 LJP-934

LJP-934 selectively leads to the elimination of B cells, making anti-dsDNA antibodies by binding to anti-dsDNA on the cell surface. The molecule has been shown to be extremely effective in depleting murine anti-dsDNA antibodies, with subsequent improvement in renal function in the mice. Clinical trials have unfortunately demonstrated only minimal clinical benefit. LJP-934 may prove a useful treatment for subgroups of lupus patients who have high-affinity antibodies directed against this protein.[43]

2.10 Anticomplement Therapies

2.10.1 Anti-C5b Monoclonal Antibody

Eculizumab is an anti-C5b monoclonal antibody that effectively blocks the progression of the complement cascade. In mouse models of lupus nephritis, it has been shown to reduce proteinuria and increase survival. Early clinical trials indicate that the drug is tolerable and safely used, but there are no data on efficacy currently available.[43]

2.11 Anti-Cytokine Therapies

The autoantibody-induced formation of immune complexes and the resultant activation of inflammatory pathways play a major role in initiating lupus disease activity. The possibility of blocking the pro-inflammatory cascade by selective inactivation of cytokines is an area of new and ongoing research. Early results by Smolens et al.[44] in a small number of patients suggest that the use of anti-tumour necrosis factor (TNF) agents such as infliximab may provoke a slight rise in antinuclear antibody levels but is associated with a meaningful decrease in symptoms.

2.12 Anti-BLyS Monoclonal Antibody

BLyS protein is a 285-amino acid member of the TNF ligand superfamily. It is also referred to as BAFF (B cell activator belonging to the TNF family), THANK (TNF homologue that activates apoptosis, natural killer [NK]-kB and JNK), TALL-1 (TNF and ApoL-related leukocyte ligand 1), TNFSF13B or zTNF4. BLyS binds strongly to B cells, poorly to T cells, does not bind to monocytes or NK cells and acts as a promoter of B-cell activity.

It has three receptors: BMCA (B-cell maturation antigen), BAFFR or BR3 (BAFF receptor or BLyS receptor 3) and TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor). In mice, administration of BLyS causes B lymphocytosis with hypergammaglobulinaemia. Treatment of murine lupus models with a BLyS antagonist has led to improved renal function and survival. However, preliminary clinical results were less satisfactory, perhaps because of the ability of other receptors such as TACI to be stimulated by APRIL (A PRoliferation-Inducing Ligand), which is not inhibited by BLyS. A phase I clinical trial using TACI-Ig is ongoing. The outcomes in humans are awaited.[43,45,46]

2.13 Anti-Interleukin-10 Monoclonal Antibody

IL-10 is one of the many interleukins that is being assessed as a target for monoclonal antibody therapy. Others include IL-6 and IL-1; however, utilising these monoclonal antibodies is at a very early stage. IL-10 levels have been noted to be increased in active SLE and, as such, provide a target for specific anti-interleukin therapy. In murine models, anti-IL-10 antibody has been demonstrated to delay onset of renal disease. In a small clinical trial, anti-IL-10 antibody was noted to modify disease activity and reduce the requirement for corticosteroids.[44] Further research and evaluation in adults will be necessary to determine whether any of these agents will prove a means of effectively treating lupus nephritis without unacceptable adverse effects.

2.14 Nucleoside Analogues

Fludarabine and cladribine are two nucleoside analogues that are both used extensively in leukaemia chemotherapy. They are directly incorporated into the DNA of lymphoid cells, leading to cell death. Early trials in lupus suggest an improvement in renal function. However, the use of these agents is associated with a dramatic increase in infection rates, as patients remain lymphopenic for extended periods.[43]

2.15 Autologous Stem Cell Transplantation and High-Dose Immunoablative Therapy

High-dose cyclophosphamide with and without stem cell transplantation is being evaluated for the treatment of lupus nephritis and a variety of other autoimmune diseases. For children, case reports suggest occasional efficacy, but with a significant procedure-related morbidity and mortality and significant risk of relapse. The adverse effects appear far greater than those of standard 3-year cyclophosphamide regimens or any of the newer agents on the horizon. Although there may be advantages to the use of high-dose cyclophosphamide without stem cell transplantation, this approach continues under study at present.[47]

2.16 Renal Transplantation in Lupus Nephritis Patients

Renal transplantation in children with lupus nephritis encompasses some particular concerns. These children have extra-renal organ involvement, which impacts on their suitability for surgery and recovery. Activity of the SLE in other organs, corticosteroid effects and marked immunosuppression must all be considered when evaluating the suitability of these children for transplantation. These patients have an increased incidence of diabetes, atherosclerosis and antiphospholipid syndrome, as well as an increased risk of infection. All of these factors pose increased risk at the time of renal transplantation and increased risk of ultimate complications or graft rejection.[48]

In the face of active SLE, transplantation should be delayed. In addition, transplant should not be performed within the first 3 months following the onset of renal failure, as it may be reversible.

The risk of renal recurrence after transplant is small, with studies citing rates from 2% to 30%.[49,50]

Recurrences tend to be mild, with histology showing mesangial or mild focal proliferative disease. Graft rejection is rare.

Immunosuppression post-transplantation is similar to that used following renal transplantation for other aetiologies. There is debate about the use of corticosteroids post-transplantation. Recent reports suggest that patients do better without corticosteroids. These reports describe similar rates of graft survival and renal function and improved cardiovascular outcomes in patients who do not receive corticosteroids, with fewer episodes of osteoarthritis. There is a small increased risk of acute rejection, which is usually reversible.[51]

3. Proposed Guidelines for the Treatment of Lupus Nephritis in Childhood

For patients with suspected lupus nephritis class III at the time of diagnosis, but with normal renal function, BP and proteinuria below the nephrotic range, oral prednisone should be started at 1 mg/kg/day in a single daily dose (which is less adrenosuppressive than twice-daily administration). If patients with a pre-existing SLE diagnosis manifest signs of new or worsening nephritis, the prednisone dosage should be increased to 1–2 mg/kg/day. In these patients, it may be helpful to obtain a renal biopsy and await further treatment pending the biopsy results (provided that this can be done quickly). Time is of the essence in such patients and biopsy should be undertaken quickly. WHO class III with high activity should be considered on a spectrum with class IV, with a significant risk of progression. Many authorities would consider cytotoxic therapy. In patients with WHO class II and mild class III nephritis, corticosteroids alone (up to a dosage of 0.5 mg/kg/day) may be sufficient to revert to normal urinary sediment and decrease proteinuria. In such patients, an antimalarial such as hydroxychloroquine (7 mg/kg/day up to 200 mg/day) may have some steroid-sparing effect. ACE inhibitors such as enalapril and angiotensin-II inhibitors such as losartan should be added as needed to control hypertension and decrease renal protein excretion.

A child with SLE who is nephrotic, hypertensive or experiencing declining renal function may require intravenous methylprednisolone pulses (30 mg/kg/day up to a maximum dosage of 1 g/day for 3 consecutive days) and consideration for immediate initiation of cytotoxic therapy. We recommend 3 consecutive days of methylprednisolone 30 mg/kg up to 1g pulses in the 3 days surrounding the start of cyclophosphamide. This allows for rapid immunosuppression while awaiting the initial effects of cyclophosphamide. Intravenous methylprednisolone pulsing may provide rapid control of lupus nephritis but should not be considered as an option for long-term therapy. The use of pulse methylprednisolone in nephrotic and hypertensive patients can be dangerous. Therefore, pulse corticosteroids should only be administered to patients in an inpatient setting in which frequent vitals signs, fluid status, BP and electrolytes can be closely monitored. A randomised, controlled trial of the treatment of proliferative lupus nephritis demonstrated increased benefit for patients treated with a combination of intravenous cyclophosphamide and pulse methylprednisolone compared with those treated with cyclophosphamide alone or pulse methylprednisolone alone.[52] At the same time, hypertension and fluid overload must be managed appropriately with antihypertensives, diuretics and a low sodium diet. If severe nephrotic syndrome is present, albumin infusions may allow for intravascular mobilisation of fluid followed by diuresis. However, class V lupus nephritis typically responds to a short course of high-dose oral corticosteroids, with few patients requiring more prolonged or aggressive immunosuppression.

Initial dose administration of cyclophosphamide is between 500 and 750 mg/m^2 depending on the

patient's white blood cell count (WBC) and extent of renal disease. The dose is escalated by 250 mg/m^2 with each subsequent infusion to a maximum dose of 1 g/m^2 if tolerated. Each patient should be followed with appropriate testing at the time of the WBC nadir, approximately 2 weeks post-treatment. For nadir WBC values <2500/mm^3, or persistent leukopenia, dose reduction should be considered. In severely affected patients with highly active disease, pulse methylprednisolone should be administered contemporaneously with cyclophosphamide, as described at the start of this section.

Rituximab in combination therapy with cyclophosphamide is part of an aggressive regimen for lupus nephritis patients, which may allow the induction of more durable disease remissions. However, rituximab is not currently considered standard therapy and may not be available in all centres. We use rituximab 600 mg/m^2 (to a maximum dose of 1g) with pre-medication with methylprednisolone 100mg and diphenhydramine 25–50mg on days 1 and 15, followed by cyclophosphamide at a dose of 750 mg/m^2 on days 2 and 16. This has led to prompt and dramatic decreases in symptomatology and improvement in laboratory parameters. All available data would suggest that flare of disease is not seen while CD20+ cells remain depleted. This regimen is associated with a marked decrease in the need for corticosteroids in many of the children (figure 1).

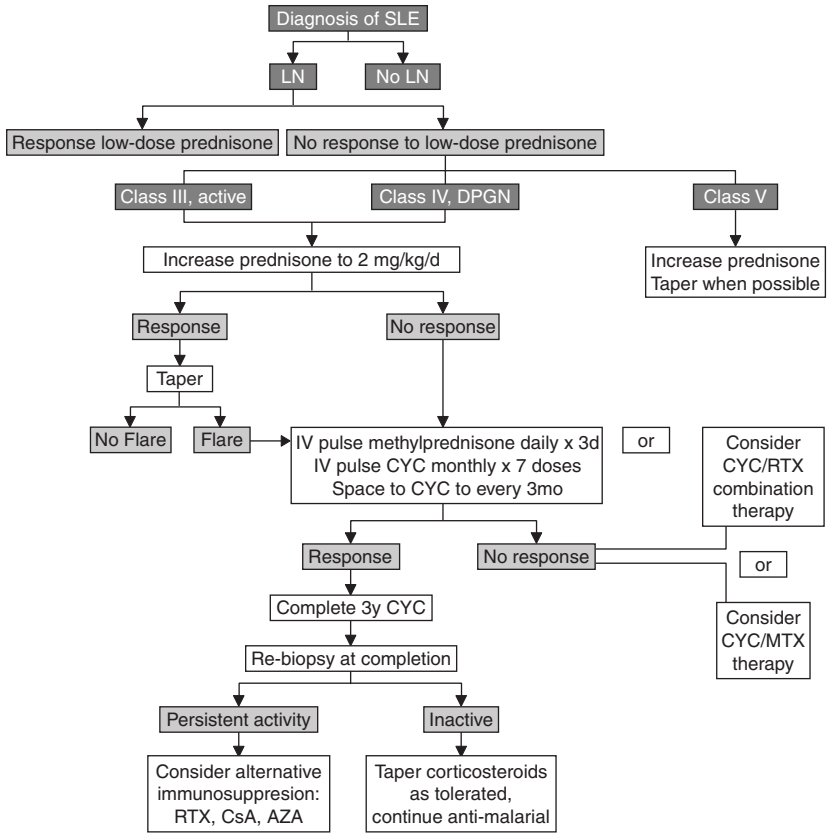

Fig. 1. Algorithm for the treatment of children with lupus nephritis (LN). See table I for classification. **AZA** = azathioprine; **CsA** = ciclosporin; **CYC** = cyclophosphamide; **DPGN** = diffuse proliferative glomerulonephritis; **IV** = intravenous; **MTX** = methotrexate; **RTX** = rituximab; **SLE** = systemic lupus erythematosus.

4. Comprehensive Care of the Child with Lupus Nephritis

In addition to the suppression of lupus nephritis, it is vital that treatment be implemented to minimise the progression of renal disease and to prevent and control co-morbidities. Children with lupus nephritis must have their BP tightly controlled, with the early addition of angiotensin-converting enzyme inhibitors with or without angiotensin-receptor blockade to minimise proteinuria and resultant renal damage. BP may be difficult to control in lupus nephritis. However, additional agents and diuretics should be used to bring BP under tight control. The importance of home BP monitoring (with or without home nursing services) should be stressed, as should adherence to a low sodium diet.

In addition, cardiac risk factors must be minimised. Excessive hyperlipidaemia should be looked for and promptly treated. The addition of an HMG-CoA reductase inhibitor (statin) may be especially beneficial because, in addition to their cholesterol-lowering properties, these drugs have a possible anti-inflammatory role. The Lupus APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) study is currently under way to address the effects of statin use in children with SLE. This multicentre, double-blind trial is designed to investigate the effects of atorvastatin versus placebo in children with SLE. Careful monitoring of liver enzymes and creatine phosphokinase (CPK) is crucial, however, as there are few data in children on the incidence of hepatotoxicity and muscle toxicity related to statin use. Patients must be encouraged not to smoke and to maintain a healthy body mass index. Although weight-loss programmes are not encouraged in children, healthy diet and exercise within their abilities should be facilitated, with multidisciplinary input from dieticians and physical and occupational therapists.

Every effort should be made to preserve bone density in children taking corticosteroids. Patients should be on calcium-containing multivitamins, and vitamin D levels should be monitored and corrected as necessary. The use of antiresorptive agents such as bisphosphonates in children is controversial. It is difficult to assess their effects on growing bone, which naturally increases in density with time. In addition, the issue of residual bisphosphonates leeching from bone over years and potentially causing fetal anomalies if these patients become pregnant remains unresolved.[53] At this time, it would be our recommendation to follow dual energy x-ray absorptiometry (DEXA) scans for monitoring of bone density, to supply supplemental calcium and vitamin D, and to encourage weight-bearing activities. We await further studies of the use of bisphosphonates in children and adolescents, particularly female patients with reproductive potential.

5. Conclusions

Current regimens for the treatment of lupus nephritis remain a stepping stone towards optimal treatment. Although the use of corticosteroids remains the first line of therapy, it is essential that every effort be extended to minimise their dosage because of their extensive adverse effect profile. The early use of chemotherapeutic/cytotoxic agents provides the opportunity to minimise corticosteroid usage and to address directly disease activity at the cellular level. However, these agents are not without significant adverse effects. Targeted therapies, acting on a single cell type or cytokine, are now in early clinical use, with many similar agents in earlier stages of evaluation.

The aim of therapy at all stages of lupus in childhood is to maximise therapeutic effect while minimising adverse effects. There are many promising drugs in early trials and/or the developmental stage, which may provide dramatic improvements in our therapy.

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