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REVIEW

The treatment of systemic lupus proliferative nephritis

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Abstract Lupus nephritis is one of the most common and serious complications of systemic lupus erythematosus (SLE) in childhood affecting more than 80 % of patients. Treatment of this complication has undergone significant evolution in recent years. A series of randomized controlled trials has clarified the role of a variety of immunomodulating regimens including some novel biologic medications. This review touches on the major trials that have influenced practice and shaped current thinking about the treatment of proliferative lupus glomerulonephritis.

Keywords Lupus · Nephritis · Systemic lupus erythematosus · Pediatric lupus · Mycophenolate mofetil

Introduction

The treatment of lupus nephritis has undergone significant evolution in the past decade. A number of randomized controlled trials (RCTs) have helped to clarify the therapeutic role of a variety of immunosuppressive regimens in proliferative lupus nephritis. Novel medications, including biologics developed to specifically treat lupus have been tested in some of these trials. These latter trials have proved largely disappointing and have posed some provocative questions about our understanding of lupus pathogenesis. Although the optimal treatment for lupus remains elusive, the Federal Drug Administration (FDA) has approved the first new medication (belimumab) for the treatment of systemic lupus erythematosus (SLE) in over 50 years. This review will touch on the major trials that have influenced practice and shaped current thinking about the therapy of proliferative lupus nephritis.

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NIH trials

A series of randomized controlled trials (RCTs) spanning several decades from the National Institutes of Health (NIH) compared corticosteroids and cyclophosphamide for the treatment of proliferative lupus nephritis. These trials provided evidence for the efficacy of cyclophosphamide and helped to define treatment regimens.

In 1986, Austin et al. reported a comparison of four different immunosuppressive regimens (azathioprine, oral cyclophosphamide, the combination of oral cyclophosphamide and azathioprine, and intravenous cyclophosphamide every 3 months) plus low-dose prednisone, and high-dose (1 mg/kg) oral prednisone alone in 107 lupus nephritis patients [1]. Better preservation of renal function was statistically significant only for the intravenous cyclophosphamide plus low-dose prednisone group compared with the high-dose oral prednisone alone ($p=0.027$). This advantage of intravenous cyclophosphamide only became evident with long-term follow-up (median 7 years) and was most pronounced in those patients with chronic histologic changes in kidney biopsy at study entry. This trial was fundamental in establishing the preeminent role of cyclophosphamide in the treatment of lupus nephritis as well as demonstrating the importance of long-term follow-up in evaluating any lupus nephritis therapy.

Boumpas et al. subsequently reported 65 patients assigned to either monthly pulse methylprednisolone (1 g/m^2×3 for initial dose than once monthly) for 6 months, monthly cyclophosphamide (0.5–1 g/m^2) for 6 months, or monthly cyclophosphamide for 6 months followed by quarterly pulse cyclophosphamide for two additional years [2]. All patients received oral prednisolone. The probability of doubling serum creatinine was higher for the intravenous methylprednisolone (IVMP) group compared to either cyclophosphamide group. Furthermore, patients treated with short-course cyclophosphamide had a higher probability of renal or extra-renal flare than those treated with extended course cyclophosphamide. The

results of this trial served to reinforce the preeminent role of cyclophosphamide and were important in suggesting the need for longer treatment courses in the therapy of lupus nephritis.

In 1996, Gourley et al. reported 82 patients with active proliferative nephritis randomized to either bolus therapy with IVMP (1 g/m^2 given monthly for at least 1 year, cyclophosphamide (0.5–1 g/m^2) given monthly for 6 months, then quarterly, or a combination of these regimens with bolus therapy with both IVMP and cyclophosphamide [3]. At 5 years of follow-up, monthly bolus therapy with IVMP alone was less effective than monthly bolus with cyclophosphamide. There was a trend toward greater efficacy with the combination group but this did not reach statistical significance. A long-term follow-up of this same group of patients at a median of 11 years focused on rates of treatment failure as reflected by the need for further immunosuppressive therapy, doubling of serum creatinine or death, and adverse events [4]. In an intention-to-treat survival analysis, the likelihood of treatment failure was significantly lower in the cyclophosphamide (p=0.04) and the combination therapy group (p=0.002) than in the IVMP only group. For the 65 patients that completed the protocol, the number of patients who had doubling of serum creatinine was significantly lower in the combination group than the cyclophosphamide only group (relative risk 0.095 CI 0.1–0.84). Adverse events did not differ statistically between the cyclophosphamide-containing regimens, leading the authors to conclude that the combination of bolus cyclophosphamide and IVMP appears to provide additional benefit over bolus cyclophosphamide alone without adding additional risk for adverse events.

These early NIH trials were pioneering work and did much to establish and define the place of cyclophosphamide in the treatment of proliferative lupus nephritis. However, this treatment was far from universally efficacious and was soon noted to be less effective in African American patients [5, 6]. Toxicity was also considerable, especially increased risk of infections and premature ovarian failure. More recent trials have attempted to achieve clinical efficacy by inducing remission of nephritis while simultaneously minimizing the toxicity of treatment. These goals have also further driven the now widely accepted concept of two distinct phases of therapy: an intensive induction phase designed to achieve remission by the resolution of active inflammation, and a longer, less intense maintenance phase designed to sustain remission while minimizing side effects of the immunosuppressive therapy.

Euro-Lupus nephritis trial

An attempt to decrease the toxicity of cyclophosphamide was at the heart of the Euro-Lupus Nephritis Trial (ELNT) [8]. This randomized multicenter trial of 90 patients with proliferative lupus nephritis compared the efficacy and toxicity of a high-dose NIH-like cyclophosphamide regimen (six monthly pulses followed by two quarterly pulses titrated according to white blood cell count nadir to a maximum dose of 1,500 mg) versus low-dose intravenous cyclophosphamide at a fixed dose of 500 mg every 2 weeks for six doses. All patients received three daily 750 mg IVMP pulses followed by oral prednisolone therapy rapidly tapered from an initial dose of 0.5 mg/kg to low dose (5–7.5 mg/day), which was maintained at least until month 30 after inclusion. Both groups then received azathioprine as maintenance therapy starting 2 weeks after the last cyclophosphamide dose and continuing until at least 30 months after treatment inception. At a median of 41 months of follow-up, there was no significant difference in treatment failure, achievement of renal remission, occurrence of renal flares or adverse events. Ten-year follow-up of this cohort reaffirmed these conclusions [10]. There was no significant difference between treatment groups in terms of death, end-stage renal disease, mean serum creatinine, 24-h proteinuria or damage score at last follow-up. Most patients continued on corticosteroids and half on immunosuppressants at last follow-up as well as anti-hypertensive therapy with ACE/ARB (angiotensin converting enzyme/angiotensin receptor blockers). This long-term immunosuppression with optimal blood pressure control was felt by the authors to contribute to the overall good outcome of these patients.

There are several important differences between the NIH and ELNT trials. Notably, considerably fewer patients in the ELNT trial had clinically severe renal disease at study onset. In this European cohort, only 22 % had renal impairment and 28 % nephrosis compared to 62 and 64 %, respectively, in the trial by Boumpas [2]. Further, the ELNT cohort did not include many black patients (9 %) compared to the NIH cohorts (34–43 %). Since the outcome of nephritis in black lupus patients is worse compared to white patients, the underrepresentation of this ethnic group further calls into question the suitability of the ELNT regimen to non-white patients. This latter concern should be addressed when the NIH Abatacept and Euro-Lupus trial results become available. In this trial, which included 40 % each of African American and Hispanic patients, all received the Euro-Lupus protocol with half also receiving abatacept, a CTLA4 blocker.

Azathioprine

Azathioprine has also been studied as a potentially less toxic alternative to cyclophosphamide in the induction therapy of lupus nephritis. The Dutch Lupus Nephritis Study randomized 87 predominantly white European patients with proliferative lupus nephritis to either a combination of azathioprine (2 mg/kg/day) and IVMP (3×3 pulses of 1,000 mg) plus oral prednisone (initially 20 mg/day) or to intravenous cyclophosphamide

(750 mg/m^2) in 13 pulses plus oral prednisone (initially 1 mg/kg/day) [8]. After the first 2 years, both groups were treated with azathioprine plus oral prednisone. During the first 2 years, the frequency of remission was not different between the groups, but infections, especially herpes zoster, were more frequent in the azathioprine/IVMP group. At approximately median 6 years of follow-up, renal relapses were more frequent in the azathioprine group (RR: 8.8, CI1.5–31.8) and there was a trend toward increased doubling of serum creatinine in this same group, although it did not reach statistical significance. Protocolized renal biopsy in 39/87 patients at 2 years did not predict clinical outcome, but demonstrated that the chronicity index remained stable in the cyclophosphamide arm, but significantly increased in the azathioprine/IVMP arm [10]. Once again illustrating the importance of long-term follow–up, reassessment of this same cohort at a median of 9.6 years confirmed that induction therapy with intravenous cyclophosphamide was superior to azathioprine/IVMP in preventing renal relapse (AZA/IVMP 38 % vs. cyclophosphamide 10 %, p=0.002) [11]. These results offer little support for the use of azathioprine as induction therapy.

Plasmapheresis

Data from prospective controlled trials do not support the use of plasmapheresis as efficacious therapy for lupus nephritis. There has been no therapeutic advantage of additional plasmapheresis to a regimen of prednisone and daily oral cyclophosphamide or with synchronized plasmapheresis and pulse intravenous cyclophosphamide [12, 13]. The role of plasma exchange in lupus nephritis appears to be limited to the treatment of lupus patients with concurrent thrombotic thrombocytopenic purpura or catastrophic antiphospholipid syndrome.

Mycophenolate mofetil

In the past decade, mycophenolate mofetil (MMF) has emerged as a promising alternative to cyclophosphamide for both induction and maintenance therapy of lupus nephritis. In 2000, Chan et al. reported the results of a randomized trial of 42 Chinese lupus patients with proliferative nephritis to either 6 months of daily oral cyclophosphamide (2.5 mg/kg/day) or 6 months of MMF (2 g/day) [14]. The patients in the MMF group continued on the drug at a reduced dose (1 g/day) and those in the cyclophosphamide group switched to azathioprine (1.5 mg/kg/day) for a further 6 months. All patients received oral prednisolone tapered from a starting dose of 0.8 mg/kg/day to 10 mg at 6 months. At 1 year, there were no statistically different outcomes between the groups in complete remission, partial remission, or relapse. There were more adverse events in the cyclophosphamide group, but this difference did not reach statistical significance. Long-term follow-up of this cohort 5 years later continued to show equivalence between the groups with statistically similar rates of chronic renal failure and relapse [15]. The rate of amenorrhea was 36 % in the cyclophosphamide group compared to 4 % in the MMF group (p=0.004). Infections were fewer in the MMF group (13 vs. 40 %, p=0.013).

This was a ground-breaking study in that it appeared to offer a new option with equal efficacy and fewer side-effects than standard lupus nephritis treatment. However, the suitability of this therapy for non-Chinese populations was unclear. Further, the use of oral rather than a more standard intravenous bolus cyclophosphamide protocol did not allow a full comparison with standard practice and likely contributed to the number of adverse events attributed to the cyclophosphamide arm.

These issues were addressed in a 24-week randomized open label non-inferiority study by Ginzler of 140 patients with class III, IV, or V nephritis comparing MMF (initial dose 1,000 mg/day increased to 3,000 mg/day) with monthly intravenous cyclophosphamide (0.5 g/m^2 increased to 1.0 g/m^2) [16]. Adjunctive treatment and corticosteroid regimen was identical between groups. A cross-over to the alternative regimen was allowed at 12 weeks in those patients who did not have an early response. More than half of the patients enrolled were African American and over 40 % had nephrotic syndrome. In the intention-to-treat analysis, 16 of the 71 patients (22.5 %) receiving MMF and four of the 69 patients receiving cyclophosphamide (5.8 %) had complete remission (p=0.005), exceeding the standard needed to prove non-inferiority. With the exception of diarrhea, there were more side-effects in the cyclophosphamide group although the difference did not reach statistical significance.

This trial was criticized for its cross-over design, exclusively American cohort, and very short duration of follow-up.

The ASPREVA Lupus Management Study (ALMS) reported by Appel et al. utilized a similar design, but attempted to address these concerns [17]. In one of the largest trials to date in lupus nephritis, 370 patients worldwide (United States, China, South America, and Europe) were randomized to 6 months of induction therapy with either MMF or intravenous cyclophosphamide, but were not allowed to cross over. At the end of the 6-month induction phase, the study failed to demonstrate its primary endpoint of superiority of MMF for induction of severe lupus nephritis. There was no significantly different response between the MMF arm (56 %) compared to the cyclophosphamide arm (53 %). Individual renal and non-renal variables were also identical. There was no significant difference between groups in the rate of adverse events, although the side-effect profile differed. Sub-group analysis suggested that African American

and Hispanic patients had a better response rate to MMF than cyclophosphamide.

A recent meta-analysis of MMF for induction therapy of lupus nephritis included four trials and 668 patients. No difference in the clinical efficacy was found between MMF and cyclophosphamide, although MMF had significantly less amenorrhea and alopecia [18].

Maintenance therapy

The early NIH trials suggested that longer-term was superior to shorter-course cyclophosphamide in preventing renal/disease flare. Subsequently, sequential regimens of short-term cyclophosphamide induction therapy followed by either MMF or azathioprine maintenance therapy have been studied.

In a pivotal study, Contreras et al. randomized a predominantly African American and Hispanic cohort of 59 severe lupus nephritis patients to either standard quarterly intravenous cyclophosphamide, azathioprine (1–3 mg/kg/day), or MMF (0.5–3 g/day) maintenance therapy following 4–7 doses of intravenous cyclophosphamide induction therapy [19]. The 72-month event-free survival rate for the composite endpoint of chronic renal failure or death was higher in the MMF (p=0.05) and azathioprine (p=0.009) groups than in the cyclophosphamide group. The rate of relapse-free survival was also higher in the MMF group than the cyclophosphamide group (p=0.02). Adverse events, specifically hospitalization, infections, and amenorrhea, were significantly lower in the MMF and azathioprine groups than in the cyclophosphamide group, leading the authors to conclude that short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with either azathioprine of MMF appears to be both more efficacious and safer than longer-term therapy with intravenous cyclophosphamide.

This study was criticized for its higher-than-expected number of adverse events, which were considered likely due to the demographics of the patient population and the fact that the cyclophosphamide dose during the maintenance phase (slightly more than 500 mg/m^2) was lower than the doses recommended on the basis of NIH studies.

The issue of whether MMF was superior to azathioprine for maintenance therapy was addressed in an extension phase of the Euro-Lupus trial (MAINTAIN Nephritis Trial). Houssiau and colleagues reported 105 predominantly white European patients with proliferative lupus nephritis randomized after induction with low-dose intravenous cyclophosphamide to either azathioprine (target dose: 2 mg/kg/day) or MMF (target dose: 2 g/day) at week 12 [20]. At a mean follow-up of 48 months, the study failed to demonstrate the superiority of MMF compared to azathioprine for maintenance lupus nephritis therapy. There was no significant difference in the primary endpoint of time to renal flare between the groups, or any other parameters such as time to disease flare, time to renal remission, or a change in a variety of laboratory tests. Similarly, adverse events other than cytopenias, which were higher in the azathioprine group, did not differ statistically between the azathioprine and MMF groups. Beyond the fact that this was a trial in an ethnic group known to have less aggressive lupus, it is important to note that patients were not required to have a significant response to the induction phase in order to enter the maintenance trial.

In a larger, more ethnically diverse cohort of proliferative lupus nephritis patients, the investigators of the ASPREVA Lupus Management Study (ALMS) randomized 227 patients who had achieved renal response to induction therapy after 6 months [21]. In this 36-month, double-blind, double-dummy trial, the patients received either MMF (2 g/day) or azathioprine (2 mg/kg/day). MMF was superior to azathioprine with respect to the primary endpoint of treatment failure, which was defined as death, end-stage renal disease, doubling of serum creatinine level, renal flare, or rescue therapy for lupus nephritis. Observed rates of treatment failure were 16.4 % of the MMF group compared to 32.4 % in the azathioprine group. Serious adverse events occurred in 23.5 % of the MMF group and 33.3 % of the azathioprine group (p=0.11). The rate of withdrawal due to adverse events was also statistically higher in the azathioprine compared to the MMF group (39.6 vs. 25.2 %, p=0.02). Although minor side-effects were present in 95 % of the patients in both groups, serious infections were low in both groups. The authors concluded that in patients with lupus nephritis who had a response to induction therapy, MMF was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse. One criticism of this study was the lack of drug-monitoring data to ensure adequate dosing and patient adherence to the drug regimens.

Biologics and novel therapies

Rituximab

Rituximab is a chimeric monoclonal antibody that depletes CD20-positive B cells while sparing stem cells and plasma cells. The B cell has long been thought to play a critical role in the pathogenesis of lupus, including cytokine production, presentation of self-antigen, T cell activation, and autoantibody production, thus providing a rationale for the use of rituximab in the treatment of this condition. The results of uncontrolled trials in lupus suggested that rituximab might be efficacious and steroid-sparing. Unfortunately, two large controlled trials have failed to demonstrate efficacy. In the double-blind, multicenter Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial, Merrill et al. randomized 257 patients with moderate to severely active

extra-renal lupus in a ratio of 2:1 to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182 [22]. Background therapy was evenly distributed among azathioprine, mycophenolate mofetil, and methotrexate. Over half of the patients were steroid dependent at entry. There was no significant difference observed between rituximab and placebo in any primary or secondary end points, although Hispanic and African American patients appeared to do better on rituximab. Safety and tolerability were also similar between groups.

In the double-blind multicenter Lupus Nephritis Assessment with Rituximab (LUNAR) study, Rovin et al. randomized 144 patients with class III or IV lupus nephritis in a ratio of 1:1 to rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182 [23]. Both groups had the same background medications of mycophenolate mofetil (target dose 3 g/day) and corticosteroids. Although rituximab successfully depleted CD19-positive B cells in 71/72 patients and there were statistically significant improvements in serum complement C3, C4, and anti-dsDNA antibody levels with rituximab, the primary endpoint of superior renal response rate to rituximab was not met. Complete and partial renal responses were achieved in 45.8 % of placebo-treated and 56.9 % of the rituximab-treated patients, with the difference mostly accounted for by partial responses. Rates of serious adverse events including infections were similar between groups with more cytopenias and hypotension in the rituximab group.

Needless to say, these results were very disappointing. Multiple explanations for this have been advanced including insufficient length of follow-up, the use of proteinuria as an endpoint since this might have been a reflection of residual podocyte injury rather than ongoing active nephritis, and the fact that this trial was designed to include significant use of steroids rather than eliminate them [24]. However, at this point, rituximab does not have the evidence to support its use as a first-line agent in induction therapy, but may yet have a role in rescue therapy of refractory disease or in non-white patients.

It is also worth noting that clinical lupus nephritis trials of ocrelizumab, a fully humanized antibody that targets CD 20-positive B cells, were halted prematurely due to an imbalance in serious infections between blinded treatment groups.

Abetimus sodium

Abetimus sodium (LJP 394, Riquent) is an investigational drug composed of four double-stranded 20-mer oligodeoxynucleotides attached to an inert scaffold of triethylene glycol that was designed to bind antibodies to double-stranded DNA (dsDNA). The unique property of this drug to selectively reduce circulating dsDNA antibodies led investigators to focus on a renal flare protection trial design. The first efficacy study enrolled 213 of a planned enrollment of 300 lupus nephritis patients randomized in a 1:1 ratio to receive either 100 mg of abetimus sodium or placebo weekly for a 16-week induction phase, followed by an 8-week drug holiday after which the patients received drug or placebo weekly for 12 weeks [25]. The trial was to continue for 18 months with 8-week holidays alternating with each 12-week maintenance phase. An interim analysis performed at 26 months after study initiation showed no difference in the flare rate between the placebo and treatment groups so the study was prematurely terminated. A second efficacy trial eliminated drug holidays and maintained a dose of 100 mg throughout the study. Reductions in dsDNA antibodies occurred in the treatment group ($p<0.001$) and this correlated with increases in C3 ($p<0.001$) [26]. Although there were fewer flares in the abetimus group as well as longer median time to renal flare, the differences between groups were not statistically significant.

Belimumab

Belimumab is the first biologic drug approved for use in the treatment of lupus and the first new drug approved for lupus in >50 years. It is a fully humanized monoclonal antibody against soluble BLyS (also known as BAFF), a type II transmembrane protein that functions in a healthy immune response to prolong survival and promote differentiation of B cells. BLISS-52, a multicenter trial conducted in Latin America, Eastern Europe, and Asia-Pacific, randomized 867 seropositive (positive ANA and/or dsDNA ab) active lupus patients in a 1:1:1 ratio to belimumab 1 mg/kg or 10 mg/kg or placebo by intravenous infusion on days 0, 14, 28, and every 28 days until 48 weeks [27]. All patients were allowed "standard of care", which constituted a relatively stable (although extremely variable) dose of prednisone, antimalarial drugs, and an immunosuppressant (MMF, azathioprine, or methotrexate). Patients with severe renal disease were excluded from this trial. An improvement in the newly devised, and hence unvalidated, outcome measure termed the Systemic Lupus Erythematosus Responder Index (SRI) at week 52 was the primary efficacy endpoint and was achieved in the 1 mg/kg belimumab group (51 %, $p=0.0129$)), and the 10 mg/kg belimumab group (58 %, $p=0.0006$) compared to placebo (46 %). Serious adverse events were similar between groups.

Bliss-76 had a very similar design except the trial lasted for 72 weeks, and enrolled 819 patients in Western Europe, the United States, Mexico, and Canada [28]. This trial also met its primary efficacy endpoint, but only at a single time point, week 52, with belimumab 10 mg/kg generating a better SRI response than placebo (43.2 vs. 33.5 %, $p=0.017$).

Although these trials resulted in an approval for belimumab, enthusiasm among clinicians has been limited. Belimumab appears to offer modest efficacy and is currently

indicated only for mild lupus patients without significant organ involvement [29].

Adjunctive therapy: antimalarials

A recent systematic review of antimalarial drug use in lupus published in 2010 concluded that hydroxychloroquine should be given to most lupus patients during the whole course of the disease irrespective of disease severity [30]. High levels of evidence were found that antimalarials prevent lupus flares and increase long-term survival of patients with SLE. There was moderate evidence for protection against thrombosis, permanent organ damage and bone mass loss. Toxicity, especially with hydroxychloroquine, was generally infrequent, mild, and usually reversible. The authors recommend routine ophthalmologic screening according to the guidelines of the American College of Ophthalmology with dose adjustment and more frequent monitoring for adverse effects in those patients with impaired renal function. A study by Schmujak suggests that nephrologists may underappreciate the beneficial effects of hydroxychloroquine in the treatment of lupus [31]. In this longitudinal community-based study published in 2010, the probability of a patient with SLE receiving an antimalarial agent was substantially reduced (OR 0.51, 95 % CI 0.31–0.84) if the primary physician was a nephrologist rather than a rheumatologist.

Corticosteroids

Corticosteroids are a mainstay of lupus treatment and a component of virtually every therapeutic regimen for lupus nephritis. In a study of corticosteroid use in 539 members of the Hopkins Lupus Cohort, only 11 % of patients had never taken prednisone and 57 % of those with disease duration >10 years had always taken steroids [32]. An Italian cohort of 215 lupus patients had only one patient who had never received corticosteroids and 86 % of this group had been continuously treated [33]. Similarly, Watson et al. recently reported that 93 % of children in a pediatric lupus cohort from the UK were taking steroids [34]. Not surprisingly, steroids constitute a significant source of morbidity in lupus patients [32, 35]. In a cohort of 66 Canadian children with lupus, Brunner et al. reported that the children accumulated disease damage at almost twice the rate of adults and that long-term use of high-dose corticosteroids contributes to this disease damage [36].

Despite the ubiquity and toxicity of glucocorticoid use in lupus, treatment is essentially empiric. There is no evidence to support dosing, tapering, duration of therapy, or pattern of administration of either induction or maintenance steroid therapy in the treatment of lupus nephritis. Practice patterns vary widely and are determined more by physician preference than patient characteristics [37]. As part of an effort to develop consensus treatment plans (CTPs) for induction therapy of proliferative juvenile lupus nephritis, a consortium of North American pediatric rheumatologists were able to reach consensus on three corticosteroid regimens: one primarily by mouth, one primarily by frequent intravenous methylprednisolone pulses (IVMP), and one that is a combination [38].

Of note, there is some biologic rationale for the use of weekly IVMP during induction therapy [39, 40]. The predominant gene expression signature of active pediatric lupus is the up-regulation of type 1 interferons. These cytokines are thought to drive many of the downstream events in the pathogenesis of SLE, including the differentiation of B cells. The major source of type 1 interferons in the body is plasmacytoid dendritic cells (pDC). In lupus patients, the ligation of endosomal TLR 7 and TLR 9 by self-nucleic acids renders the pDC resistant to killing by lower-dose steroids. High-dose IVMP therapy, but not lower-dose oral steroids, overcomes this resistance and is able to kill pDCs, which are regenerated in about a week.

This study helps explain the relative resistance of SLE to steroid treatment and also suggests the importance of innate immunity in the pathogenesis of lupus. As detailed above, therapies directed at adaptive immune responses, such as antibodies or their production, i.e., plasmapheresis, rituximab, and abetimus sodium, have not been able to demonstrate therapeutic efficacy in controlled trials in lupus patients. The fact that autoantibody levels can be reduced without significantly improving the clinical picture suggests that these antibodies may have a limited role in pathogenesis. Even belimumab was only able to demonstrate very modest efficacy in an extremely large cohort. The reasons for the failure of these trials have been the subject of much debate, but it is possible that these results are indicative of interventions that are too far downstream to be most effective. It will be interesting to see if the results of current early stage trials in lupus that study agents, which specifically target the innate immune system, including anti-alpha interferon monoclonal antibodies, and a blockade of TLR7/9, are more encouraging.

Guidelines and consensus treatment trials

The past decade has seen an unprecedented number of large clinical lupus trials. More individualized therapy of nephritis accounting for factors such as race/ethnicity, type of lupus nephritis, extra-renal lupus features, and prior disease course has been proposed [41]. Clinical guidelines for the treatment of lupus nephritis have recently been published by the Dutch Working party on SLE, the American College of Rheumatology (ACR), and the joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/

ERA-EDTA) [42–44]. CTPs for newly diagnosed juvenile proliferative glomerulonephritis have also been developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a consortium of the majority of pediatric rheumatologists in North America [38]. The latter differ from guidelines in that they focus on the induction phase only of a prototypic pediatric lupus patient with newly diagnosed proliferative nephritis. However, it is clear that the available evidence for treatment as presented in this review has been carefully considered in the development of both the

Table 1 Summary of major recommendations from guidelines/CTPs for treatment of proliferative lupus nephritis

1. Treatment is best guided by renal biopsy classified by the current ISN/RPS classification
2. All patients should receive a background of hydroxychloroquine to reduce renal flare unless contraindicated
3. Induction therapy

A choice of MMF or CYC plus glucocorticoids for 6 months is recommended for initial treatment

1. MMF

a. CARRA – 600 mg/m^2/dose twice daily

b. EULAR/ERA-EDTA – 3 g/d

c. ACR – 2–3 g/d **"preferred to CYC for African Americans and Hispanics"*

OR

2. Low-dose CYC

a. EULAR/ERA-EDTA, ACR – 500 mg/IV every 2 weeks x 6 followed by maintenance with oral MMF or AZA **"regimen for whites with European background" (ACR)*

OR

3. High-dose CYC

a. CARRA – 500 mg/m^2 initial dose increased not to exceed 1,500 mg monthly x 6

b. ACR – 500–1,000 mg/m^2 IV every month x 6

c. EULAR/ERA-EDTA – 750–1,000 mg/m^2 IV monthly x 6 or 2–2.5 mg/kg/d orally x 3 months. *Only for "patients with adverse prognostic factors (acute deterioration of renal function, substantial cellular crescents and/or fibrinoid necrosis)"*

PLUS

4. Glucocorticoid regimens

a. CARRA (*specific tables provided in CTPs)

i. Primarily oral prednisone 2 mg/kg/d max 80 mg tapered to 20 mg/d for patient >30 kg by 6 months

OR

ii. Primarily IV – IVMP 30 mg/kg/dose to 1,000 mg max 1–3 x/week for 5–7 weeks, then monthly until 6 months with 10–20 mg prednisone daily by mouth tapered to 5–10 mg daily by 6 months

OR

iii. Mixed oral/IV – monthly IVMP (as above) plus oral prednisone 1.5 mg/kg/d up to 60 mg tapered to 15 mg or 0.5 mg/kg by 6 months

OR

b. EULAR/ERA-EDTA-IVMP – 500–750 mg daily x 3 followed by oral prednisone 0.5 mg/kg/d for 4 weeks reducing to≤10 mg/d by 4–6 months

OR

c. ACR-IVMP – 500–1,000 mg daily x 3, then oral prednisone 0.5–1 mg/kg/d tapered after a few weeks to lowest effective dose *(*with 1 mg/kg/d if crescents seen)*

4. Maintenance therapy after successful induction

a. EULAR-ERA/EDTA-MMF (2 g/d) or AZA (2 mg/kg/d) plus low-dose corticosteroids for at least 3 years **continuation of MMF in those patients with a successful induction by MMF*

b. ACR – 1–2 g/d MMF or AZA 2 mg/kg/d with or without low-dose corticosteroids

5. Refractory disease

a. EULAR-ERA/EDTA – For patients who fail either MMF or CYC due to lack of efficacy or adverse events, treatment should be changed from MMF to CYC or CYC to MMF or rituximab be given

b. ACR – For patients who fail either MMF or CYC, a switch to the other medication accompanied by IVMP pulses for 3 days. Rituximab may be used in some cases

c. ACR – Those patients failing both CYC and MMF may be treated with rituximab or calcineurin inhibitors plus glucocorticoids

ACR American College of Rheumatology [43], *AZA* Azathioprine, *CARRA* Childhood Arthritis and Rheumatology Research Alliance [38], *CTPs* Consensus Treatment Plans, *CYC* cyclophosphamide, *EULAR/ERA-EDTA* European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association [44], *ISN/RPS* International Society of Nephrology/Renal Pathology Society, *IVMP* Intravenous methylprednisolone, *MMF* Mycophenolate mofetil

guidelines and CTPs, since they share a striking number of commonalities. These include a strong recommendation for treatment to be guided by renal biopsy with ISN/RPS classification, the universal use of hydroxychloroquine as a background medication, and a choice of either a mycophenolate or cyclophosphamide regimen plus corticosteroids for 6 months of induction therapy, followed by maintenance therapy with either MMF or azathioprine. For a summary and comparison of the major recommendations published in the guidelines and CTPs, see Table 1.

As helpful as these recommendations will doubtless prove to be, the clinician is still left with a plethora of treatment dilemmas. The evidence to guide the treatment of truly refractory disease (not a rare scenario) or the treatment of patients with concomitant extra-renal manifestations of lupus, is scant. Despite the lack of data or even negative trial results for more routine patients, anecdotal information suggests that rituximab, plasmapheresis, calcineurin inhibitors, and immunoadsorption may all have roles to play in the patient who has failed or cannot tolerate standard therapy [45–48]. Certainly the patient with any component of thrombotic microangiopathy or in the circumstance of overlap between a lupus and ANCA-positive vasculitis phenotype may benefit from plasmapheresis [49, 50].

It should also be noted that the guidelines/CTPs are based largely on adult trial data as acknowledged in the EULAR/ERA-EDTA guidelines [44]. Despite the fact that children are known to have more renal disease with lupus, to require more aggressive medication regimens, and to have a higher risk than adults for permanent organ damage due to SLE or its treatments, optimal dosing, efficacy and safety of the commonly utilized therapeutic agents in pediatric lupus remain unknown, nor is it likely that funding will be produced for the RCTs to answer these questions [51]. In this regard, the CARRA CTPs offer an opportunity to assess standard lupus treatments in children. It is hoped that widespread use of these plans by both pediatric nephrologists and rheumatologists will reduce treatment variability to allow for future comparisons of outcome and standardization of therapy in children with lupus nephritis.

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