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Editorial Comments

Update on the management of lupus nephritis

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Abstract

The treatment of lupus nephritis still represents a therapeutic challenge for the clinician. Besides early recognition, appropriate guiding by the histologic classification at presentation as well as at relapsing disease, is essential. The most severe proliferative and mixed forms require aggressive induction therapy. Nevertheless, recent but established by RCTs advances, as low dose iv cyclophosphamide, lower doses of corticosteroids and mychophenolate acid (MPA) allow us to achieve remission induction with lower toxicity without any cost in terms of efficacy. For maintenance, azathioprine and mycophenolate acid with concomitant low dose steroids have shown both good results with a slight superiority of mycophenolate acid. Emerging therapies as B cell targeting-either by depleting agents as the anti-CD 20 mAb Rituximab, or by modulating agents as the anti-Bliss Belimumab, further contribute to the effort to minimize toxicity. This review mainly focuses on the recent efforts to treat the most aggressive form of lupus nephritis effectively with the minimal possible toxicity.

Key words: lupus nephritis, treatment, cyclophosphamide, corticosteroids, mychophenolate acid

Introduction

Systemic lupus erythematosus (SLE) is a complex disease with variable presentations, course and prognosis. Nephritis is a common manifestation of SLE; it occurs in up to 60% of patients at some time in the course of the disease [1]. Nephritis not only leads to ESRD in 10-20% of patients, but it is also a major contributor for morbidity and mortality. Despite signifycant improvement in early mortality, long-term prognosis still remains suboptimal [2]. Severe SLE manifesttations, including nephritis require more aggressive treatment. Therefore, those patients are exposed to higher doses of immunosuppression [3]. So, accurate treatment of SLE nephritis still remains a challenge.

At first, effective treatment of lupus nephritis depends on early recognition of the renal involvement, since the presenting features may be subtle. Secondly, renal injury varies widely from mild to very severe; the spectrum of renal injury can most accurately be assessed only by renal histology. Based on the newest ISN/RPS 2003 classification, SLE nephritis comprises six classes (I to VI) [4]. Lupus nephritis (LN) class I and II are the mildest and generally do not warrant specific immunosuppressive therapy. Based on the recently published EULAR-ERA/EDTA recommendations [5], LN class I in the presence of podocytopathy on electron microscopy and clinical evidence of nephrotic syndrome should be treated as minimal change disease. In the cases of class II nephritis with proteinuria>1g/24hrs despite adequate rennin-angiotensin-aldosterone-system (RAAS) blockade, low-to-moderate doses of corticosteroids (0.25-0.5mg/kg/d) alone or in combination with azathioprine should be used. Class VI describes a kidney with advanced sclerosis (more than 90% of glomeruli) and requires only supportive treatment.
Proliferative (class III and IV) as well as the mixed classes of proliferative with concomitant membranous lupus nephritis (class III+V, IV+V) with the even worst prognosis, represent the most severe forms of lupus nephritis. Those classes have to be treated promptly and aggressively.

Adjunctive treatment

Strict blood pressure control with a target BP of 130/80 mmHg is warranted in all patients with lupus nephritis. When proteinuria is more than 500 mg/24 hrs, renin-angiotensin-aldosterone-system (RAAS) blockade is the antihypertensive treatment of choice or needs to be given without hypertension. Since SLE is associated with accelerated atherosclerosis, cholesterol lowering with statins is indicated for persistent hyperlipidemia with a target low-density-lipoprotein (LDL) of ≤100 mg/dl. Hydroxychloroquine (HCQ) should be administerred to all patients with LN; it seems to reduce flares and to prevent thrombotic events [6].

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Treatment of proliferative lupus nephritis

Induction therapy

The initial induction period consists of combined intensive immunosuppressive therapy.

Corticosteroids

Corticosteroids as intravenous pulses of 500-1000 mg/d for three days and thereafter given orally as 0.5-1mg/kg/day of prednisone for one month tapered to 5 mg/day at six months, still remain the cornerstone of induction therapy for severe, proliferative lupus nephritis. The use of intravenous methylprednisolone (MP) pulses in current induction treatment protocols is based on circumstantial data that support the evidence for its use [7]. One study has evaluated the efficacy of conventional (1 mg/kg/d) versus low-dose (0.5 mg/kg/d) steroids in conjunction with a MPA (enteric-coated mycophenolate sodium, EC-MPS) as induction in severe, proliferative LN. It showed equal efficacy of both steroid regimens in inducing remission at 24 months [8].

Cyclophosphamide

The pioneering studies by investigators at the National Institute of Health (NIH) have demonstrated the importance of intravenous cyclophosphamide in the management of lupus nephritis [9,10].The so-called "NIH-regimen", consisting of monthly, intravenous pulses of 0.5-1 g/m^2 of cyclophosphamide (CYC) and steroids, became the standard of care for three decades, despite its high toxicity. The Eurolupus Nephritis Trial (ELNT) showed that equal efficacy could be achieved with lower doses (a total of 3 g) and shorter duration (3 months) of cyclophosphamide [11]. Nevertheless, responses are often slow [12] and treatment with cyclophosphamide is associated with significant toxicity. In order to completely avoid cyclophosphamide, other immunosuppressive agents have been tested for induction therapy.

Azathioprine

One effort to use azathioprine instead of cyclophosphamide as induction failed; not only cyclophosphamide was superior to azathioprine in means of efficacy and safety, but also repeat biopsies after two years showed progression of chronic lesions with the use of azathioprine [13].

Mycophenolate acid

Recent studies have focused on the use of mycophenolate acid (MPAs), for induction. The recommended dose in non-Asians is 3000 mg of mycophenolate mofetil or its equivalent 2160 mg of the enteric-coated mycophenolate sodium daily. Asian patients seem to respond as good to lower doses of 2000 mg of MMF daily [14].The largest randomized controlled trial in lupus nephritis was the Aspreva Lupus Management Study (ALMS) [15] comprising a mixed population of 370 patients with lupus nephritis class III, IV and V. Although in the induction phase the study did not meet its primary objective of showing that MMF was superior to CYC, it was at least equally effective. After subgroup analysis, MMF showed superiority in African-Americans and Hispanics.
One meta-analysis of trials comparing MMF and CYC as induction in a total of 306 patients, published in 2006 [16], showed that MMF was more effective than CYC, with a remission rate for MMF of 66-80% versus 54 for CYC and lower rates of serious adverse events.
A second meta-analysis [17], 6 months later, in 268 patients, showed again better efficacy of MMF over CYC but most importantly, lower risk of death and end-stage renal disease (ESRD).
In terms of safety concerns, MPA therapy may be also preferable to those young patients with proliferative LN, for whom fertility preservation is of essential importance; it is known that six or more iv courses of high-dose CYC causes sustained infertility in at least 10% [18].
So, both based on efficacy and safety data, there is substantial evidence to conclude that MPA may be considered a first line treatment for induction therapy of class III and IV lupus nephritis.
The only exception seems to be crescentic lupus nephritis i.e. the presence of cellular crescents and necrotic lesions in renal biopsy. In this case, despite the lack of evidence by RCTs, as also stated in the American College of Rheumatology Guidelines, experts still favor the use of high-dose iv pulses of CYC in combination with iv steroid pulses followed by high-dose (1 mg/kg/d) oral steroids as induction [19].

Maintenance therapy

Despite high remission rates, relapses are common; nephritic or nephrotic flares occur in about 30% of patients and severe relapses are a prognostic factor for adverse renal outcome [20]. The goal of maintenance therapy is to sustain remission and to prevent relapses with the minimal possible toxicity long-term. Currently, the most common choices for maintenance therapy are MPA and azathioprine (Aza) in conjunction with low-dose steroids. MPA and Aza act both as purine antimetabolites; they have similar but also distinct mechanisms of action. Currently, the two largest multicenter RCTs directly comparing the two agents as maintenance therapy are the European MAINTAIN Study and the multiethnic US ALMS Study.
In the MAINTAIN trial [21], 105 patients were randomized after 12 weeks of induction therapy with Euro-

lupus regimen, either to azathioprine or to mycophenolate mofetil (MMF). Over three years, there was no difference in terms of efficacy.These results differ from those of the ALMS study. In this study, from a total of 370 patients, those patients who achieved complete remission (n=227) after 6 months either on MMF or CYC, were re-randomised to MMF or Aza again in conjunction with low-dose steroids. There was superiority of MMF over Aza in terms of efficacy: there was a significantly higher percentage of patients reaching the primary end-point i.e. treatment failure at 3 years in the Aza than in the MMF group (32% versus 16%) [22]. If this difference reflects the larger number of patients in the ALMS study or the differences in ethnicity (since MMF is known to be more effective in blacks and Hispanics), or the fact that the ALMS included patients only after remission, remains to be elucidated. The last EULAR/ERA-EDTA recommendations suggest as a reasonable approach, continuation of MPA without switching to Aza, if MPA therapy has proven successful as induction therapy.
Today, based upon current evidence, we can assume that maintenance therapy with either MPA or Aza with low-dose steroids is both safe and effective with possible advantages of MPAs. Those refer to the lower risk of malignancy long-term, its better cardiovascular profile, a trend towards less flares and their superiority in certain ethnic groups and may-at least in part-be counteracted by its higher cost and its contraindication in pregnancy.
The optimum duration of maintenance therapy is still a matter of debate; current evidence suggests that once patients enter remission, maintenance should be continued for at least 3 years [23].

Emerging therapies in lupus nephritis: B-cell depletion

In the past years there has been important success in the development of B-cell targeted therapies in the treatment of lupus nephritis.

Rituximab

The anti-CD20 mAb Rituximab was the first biological widely used agent in the treatment of autoimmune diseases including SLE.
The rationale for its use, especially in lupus nephritis, is that B-cells play a central role in the autoimmune response of this disease. Besides autoantibody production and immune deposit formation, B-cells also interact with autoreactive T-cells. In a study by our group [24], we investigated the therapeutic effect of Rituximab in 10 patients with proliferative lupus nephritis; moreover, we examined the changes in peripheral T-cell subsets after B-cell depletion. One month after B-cell depletion, a 4-fold decrease in the expression of the costimulatory molecule CD40 ligand on CD4+ cells and a significant decrease of the T-cell activation markers CD69 and HLA-DR was observed, in parallel with partial and complete clinical remission which was achieved in 8/10 and 5/10 patients, respectively. Cumulative evidence, mostly from small, open-label trials suggests that Rituximab is effective in SLE and lupus nephritis with minimal toxicity [25,26]. As induction, it is most often used concomitantly with low-dose "conventional" therapy, or in refractory cases [25]. However, a multicenter phase II-III trial in 144 patients with SLE nephritis (LUNAR) [27] that was designed to detect a beneficial effect of Rituximab, given additionally to MMF and high-dose steroids on the induction of renal response, did not attain its primary end-point at 52 weeks.
This study disappointed many investigators worldwide about the true efficacy of Rituximab in lupus nephritis but one of the possible explanations in favor of Rituximab seems reasonable: the trial was intended to detect a large clinical effect in patients with very active disease and this was not possible for a biological therapy given additionally to high-dose conventional therapy.
Additional studies in targeted populations are needed. For the use of Rituximab as maintenance, again data from small, uncontrolled studies show that B-cell depletion with Rituximab is effective and safe. In these trials Rituximab is used with different dosing-regimens, alone or in combination with maintenance therapy, as a single or as repeated doses, either after B-cell reappearance or after clinical indication of relapse. In another study by our group [28], we used Rituximab in 10 young women with a relapse of proliferative lupus nephritis. A single course of four weekly doses of 375 mg/m^2 of Rituximab was given additionally to 2 g/d of mycophenolate mofetil and 0.5 mg/kg/day of prednisolone for one month, with rapid tapering thereafter. Complete remission was achieved in 7/10 and partial remission in the remaining 3 patients, with excellent tolerability. Remission was sustained for 38 months in 6/10 patients [22]. Overall, with all the limitations of the small, uncontrolled trials, Rituximab shows promising efficacy with good tolerability and can be used in order to either minimize therapy-related toxicity for a considerable period or to control resistant disease.

Newest B-cell targeting agents: Belimumab, Atacicept

Besides B-cell depletion, B-cell modulation is another option and a growing field of research. New biological agents that inhibit B-cell activating factor (BAFF/BLyS) are currently under investigation. The most promising agent is Belimumab, a fully human monoclonal antibody against soluble BAFF. In humans, BAFF levels are elevated in SLE and correlate with disease activity. Preliminary results of two phase III trials of Belimumab in patients with moderate to severe lupus (BLISS-52 and BLISS-76) showed promising efficacy.

The primary end-point that was SRI (systemic lupus erythematosus response index) at 52 weeks, showed a significant effect of Belimumab compared to placebo and given additionally to conventional therapy, with very good tolerance [29].
Atacicept, a chimeric molecule formed by a receptor for BAFF and a proliferation-inducing ligand (APRIL) with IgG, which binds both BAFF and APRIL, has induced profound depletion of plasma cells, resulting also in a reduction of immunoglobulin levels. Unfortunately, a phase II study of Atacicept with mycophenolate in patients with lupus nephritis was stopped because of the high rate of infections [29].
Combining BAFF-blockade with B-cell depletion is the next step in B-cell targeted therapies.

Treatment of membranous lupus nephritis

Pure membranous (class V) nephritis is a relatively rare entity, comprising 8-20% of patients with lupus nephritis and its optimal treatment is still not fully answerred. Most of the therapeutic evidence comes from small, open-label trials. There are only a few small RCTs. Non-immunosuppressive strategies including angiotensin-converting-enzyme inhibition, should be instituted early in all cases. Immunosuppressive treatment should be initiated when proteinuria exceeds 3 g/24 hrs.

Alkylating agents

The first RCT in membranous lupus nephritis comes from the NIH [30]. In this study, 42 patients received either alternate-day oral prednisone (control group) or alkylating agents i.e. alternate-month intravenous pulse cyclophosphamide for 6 months or cyclosporine for 11 months. Both iv CYC and cyclosporine were more effective in inducing remission (60% and 83% remission rates, respectively) than prednisone alone (27% remission rate). However, a significantly higher relapse rate upon withdrawal of cyclosporine was noted.

Mycophenolate acid (MPA)

Given its milder toxicity profile than alkyating agents and CNIs, MPA therapy has emerged in this class of LN, too. A pooled analysis of two RCTs demonstrated comparable antiproteinuric effects between MMF and iv cyclophosphamide [31]. The American College of Rheumatology recommends MPA in conjunction with 0.5 mg/kg/d of prednisone as first-line treatment in patients with pure membranous lupus nephritis and nephrotic-range proteinuria [19].

Treatment of lupus nephritis in pregnancy

Almost all immunosuppressive agents, except Aza, as well as high-dose and pulse steroids are contraindicated in pregnancy. Immunosuppression with MPA or CY should ideally be stopped 3 months before gestation, whereas biological agents should not be used for at least 4 months preceding pregnancy. RAAS-blockade is also prohibited during pregnancy.
Hydroxychloroquine (HCQ) should not be stopped as it prevents renal flares in pregnant women with mild systemic lupus activity. Low dose acetyl-salicylic acid is recommended in order to decrease the risk of pre-eclampsia. In cases of severe lupus nephritis flares, Aza ($\leq$ 2 mg/kg/d) and moderate-dose steroids are the only treatment options. In very severe cases, early delivery after the 28th gestation week may be indicated [5,32].

Treatment of relapses

In general, initial management of moderate-to-severe renal flares requires re-initiation of induction therapy for at least 3-6 months. Various agents, including biologicals as Rituximab, have been used for the treatment of relapses in order to minimize toxicity for longer period, but the small number of patients and the limited duration of most studies require caution in the interpretation of the often promising results.

Treatment of refractory disease

Since for most cases of LN the treatment of choice consists either of MPA or CyC, for patients failing to respond partially in 6-12 months or completely in 24 months [5], treatment may be switched from the first drug to the other, or Rituximab may be added [19]. For cases of resistance or toxicity to conventional therapy additional alternatives may include calcineurin inhibitors, iv immunoglobulin or plasma treatment. The evidence for the use of calcineurin inhibitors (cyclosporine and tacrolimus) mostly comes from open-label and some recent prospective trials [33-35]. They can both be used as maintenance therapy in cases of persistent or relapsing proteinuria with good preserved renal function, in conjunction with low-to-moderate-dose steroids with or without MPA according to the clinicians' judgment (level C evidence). Additionally, IVIG has been used as a rescue therapy in several uncontrolled trials. Although results were satisfactory, they could be attributed to the pharmacologic action of the concomitant immunosuppressants the patients were receiving [36]. Plasma exchange techniques are applied in cases of rapidly progressive glomerulonephritis or treatment failure [37,38].
However, repeat kidney biopsy is mandatory for the management of the cases of nephritic or nephrotic flares, since transformation from one class of LN to another or to mixed classes are common.

Conclusions

Recent evolutions in the treatment of lupus nephritis

include the proven efficacy of either low dose CYC or MPA for induction as well as the use of MPA or AZA for maintenance treatment. They all contribute to long term lower toxicity of therapy that is essentially important for this young patient population. Emerging therapies, mainly those targeting B-cells seem also promising.

Conflict of interest statement. None declared.

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