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REVIEW

Current treatment of lupus nephritis

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This review on the management of lupus nephritis is based on the results of randomized clinical trials, and discusses the principles of treatment and the current options for induction and maintenance therapy. The respective place of mycophenolate mofetil and intravenous cyclophosphamide are balanced, taking into account efficacy, safety and patients' perspective. The authors anticipate that, in a few years, when long-term data on lupus nephritis patients induced with mycophenolate mofetil becomes available, it is probably that intravenous cyclophosphamide, which has been for so long the 'standard of care', will be prescribed only in specialized conditions such as documented necrotizing vasculitis. *Lupus* (2008) **17,** 426–430.

Introduction

While treatment of lupus nephritis (LN) has considerably improved patients' survival rates over the last decades, mainly due to the use of glucocorticoids (GC) and cytotoxics, therapy-related toxicity remains a major concern.[1] Moreover, not all LN patients experience a satisfactory response.

Thus, not all respond to first-line immunosuppression, 35% suffer at least one episode of renal relapse and 5–20% develop end-stage renal disease (ESRD) at 10 years, the lower figures being obtained in series of patients included in prospective trials and followed in centers with a large experience of LN, the higher figures rather reflecting the 'real world'. Many prognostic factors have been associated with a poor renal outcome: Afro-American race, poor socio-economic status, non-compliance, chronic lesions on initial kidney biopsy, renal relapses and, last but not least, a poor initial response to therapy.[2] Taken together, LN still impacts the survival of lupus patients.[3]

Treatment options – Principles

The current paradigm for the treatment of LN is (i) to induce remission with a stringent immunosuppressive treatment combining moderate- to high-dose GC and a cytotoxic drug, given for a short period of time (3–12 months; induction phase); (ii) to achieve a response and (iii) to maintain this response in the long term by prescribing a safer immunosuppressant given for a longer period (5–10 years; maintenance phase).

Central to this scheme is the definition of a response, varying from a fair clinical response (e.g. a 50% reduction of proteinuria and stabilization of renal function) to a complete remission (CR) defined as a normal renal function (based on the modification of the Diet in Renal Disease (MDRD) equation), an absence of proteinuria (urinary protein/creatinine ratio <0.5 mg/mg) and a normal urinalysis. Importantly, only 5–20% of LN patients experience such a strictly defined CR after 6 months of treatment in recent controlled trials.[4,5] Therefore, a CR might be a very appropriate primary outcome measure for remission–induction trials, aimed at demonstrating the superiority of an 'add on' therapy, prescribed on a background of classical immunosuppression. It should be stressed, however, that CR criteria should be applied with caution at the bedside because of the risk of overtreating patients with unacceptable toxicity.

This treatment design (induction, response, maintenance) includes many areas of uncertainties that will not be discussed in this short review, such as the initial dose of GC, the GC tapering regimen or the timing of each treatment phase. In this respect, recent data indicates that patients, who did not suffer from a renal relapse after having achieved remission and having

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stopped treatment, had been immunosuppressed for a longer period of time, namely 5 years, compared with those who relapsed after treatment withdrawal.[6]

Induction treatment

Besides moderate- to high-dose GC (prescribed in every case), the choice is mainly between (i) high-dose intravenous (i.v.) cyclophosphamide (CY) according to the National Institutes of Health (NIH) regimen; (ii) low-dose i.v. CY according to the Euro-Lupus regimen (iii) azathioprine (AZA) or (iv) mycophenolate mofetil (MMF).

High-dose i.v. CY for induction – NIH regimen

In this induction regimen, i.v. CY pulses are given monthly for 6 months and the dose (starting at 0.75–1 g/m^2) is increased to reach a white blood cell count (WBC) nadir between 1500 and 4000/μl on day 14. Hyperhydration is required and mesna often utilized as well to avoid bladder toxicity. Leuprolide acetate depot injection can be used to prevent premature ovarian failure.[7]

The efficacy and toxicity of this regimen was tested in three clinical trials,[8–10] in which this induction regimen (six monthly pulses) was followed by a maintenance phase of quarterly high-dose i.v. CY pulses given for two additional years and/or 1 year after renal remission had been achieved. Therefore, the comments here below apply to the global protocol (induction and maintenance) and not strictly to the induction phase.

The two major messages from the NIH trials are: (i) long-term high-dose i.v. CY is superior to GC used alone for preserving kidney function[11] and (ii) a very long-term follow-up of patients is needed before conclusions can be drawn regarding efficacy of any immunosuppressive regimen over another in avoiding ESRD. Before 5 years, all groups have a similar outcome, significant differences being observed only after a follow-up of 10 years. The NIH regimen became the 'standard of care', because the other immunosuppressants available in those days were not shown superior to GC, although they were tested only in the first NIH trial. Yet, this standard of care was never shown to improve patient survival, was shown to be less effective in Blacks[12] and is associated with many side-effects, such as severe infections, and a 38–52% rate of ovarian failure, an unacceptable toxicity for young women.

Low-dose i.v. CY for induction – Euro-Lupus regimen

In the early 1990s, clinicians from the St Thomas' Hospital in London started treating connective tissue disease patients, including LN, with low-dose i.v. CY pulses, given at a fixed dose of 500 mg/pulse on fortnightly intervals. This approach was aimed at reducing treatment-related toxicity, considering the different ethnic background between LN patients from the United States and Europe. On the basis of uncontrolled studies suggesting that this approach would reduce side-effects while not compromising efficacy,[13,14] a controlled randomized trial was designed comparing a low-dose i.v. CY regimen (6 × 500 mg every 2 weeks) with a high-dose NIH-like i.v. CY course.

Importantly, the two i.v. CY regimens were followed by maintenance therapy with AZA, prescribed from week 12 or 44 in the low-dose and high-dose arm respectively. Therefore, the outcome data from the Euro-Lupus Nephritis Trial (ELNT) are, again, the results of a global approach combining an induction and a maintenance regimen. In other words, the so-called 'Euro-Lupus regimen' is the combination of a short course low-dose i.v. CY regimen followed by a maintenance phase with AZA. In this respect, the ELNT can be considered as a 'proof of concept' to demonstrate the feasibility of the aforementioned approach consisting of prescribing a toxic immunosuppressant for a short period of time followed by a less toxic drug for a long maintenance phase. The results of the ELNT are well known: comparable efficacy of the low-dose i.v. CY regimen, including in the long-term,[2,15] and less toxicity (though not statistically significant) with low-dose i.v. CY. The Euro-Lupus regimen is a 'patient friendly' protocol because the i.v. CY pulses can be infused over 30 min, without the need for hyperhydration, hospital stay or measurement of nadir WBC, not to mention the lower costs.

Azathioprine for induction

The relative safety of AZA led several opinion-leaders in the field to propose the use of this cytotoxic drug, in combination with GC, as induction treatment, instead of CY, and as steroid-sparing agent.[16,17] In this respect, the results of the Dutch Lupus Nephritis Study must be emphasized. These investigators compared a standard NIH i.v. CY regimen (CY arm) with AZA prescribed from the start, together with a few pulses of methylprednisolone (AZA/MP arm).[18,19] Most interestingly, after a median follow-up period of 6.4 years, the risk of achieving the primary study endpoint (unsustained doubling of serum creatinine) was

statistically higher in the AZA/MP arm. Moreover, while the pathological activity index dropped in both groups on repeated renal biopsy, the chronicity index remained stable in the CY arm, but significantly increased in the AZA/MP group. Taken together, these results do not support the use of AZA as part of the induction regimen for patients with proliferative LN.

Mycophenolate mofetil for induction

In recent years, few drugs have raised as many hopes within the lupus community as MMF. Although, initial enthusiasm must be tempered by more recently available data – as usual with new drugs – MMF has become an important player in the field because the very first study by Chan, *et al.*[20,21] suggesting similar efficacy compared with oral CY (followed by AZA). In a pivotal 24-week remission-induction randomized open investigator-initiated trial, Ginzler, *et al.* compared MMF and NIH i.v. CY. The primary endpoint was renal CR at week 24, defined as the return to within 10% of normal values of serum creatinine, proteinuria and of urine sediment. The trial was powered for equivalence between MMF and i.v. CY. The patient population was made of 56% Blacks and 44% had nephrotic-range proteinuria. CR rates were low in both arms, but statistically higher in the MMF group (22.5%) compared with the i.v. CY group (5.8%). Severe infections and sustained lymphopenia were less common with MMF.[4] Long-term follow-up of patients enrolled in this trial is not available.

The results of the induction phase of the ASPREVA Lupus Management Study (ALMS) have been recently released.[5] This 24-week remission–induction randomized open trial compared MMF (185 patients; target dose 3 g/day) and NIH i.v. CY (185 patients; 0.5–1 g/m^2 every month for 6 months). The primary endpoint was a response at 24 weeks, defined as (i) a decrease in proteinuria (urinary protein/creatinine ratio <3 if nephrotic-range proteinuria at baseline or >50% urinary protein/creatinine ratio if subnephrotic-range proteinuria) and (ii) stabilization (±25% baseline)/improvement in serum creatinine. The trial was powered for superiority of MMF over i.v. CY. Only 12.4% of the patients randomized in the trial were Blacks. For the overall population, the response rates at week 24 were 56.2% and 53% in the MMF and i.v. CY group respectively. While the primary endpoint was not met, a subset analysis demonstrated different responses to MMF and i.v. CY according to self-reported ethnicity. Thus, while the response of Caucasians and Asians did not differ between the two arms, MMF was significantly superior to i.v. CY in non-Caucasian, non-Asian (i.e. Blacks and mixed race) patients (60.4% response rate in the MMF group compared with 38.5% in the i.v. CY group). Regarding adverse events, there were more deaths in the MMF group (9 vs. 5; mainly caused by infection), but this difference was not statistically significant. More than half of the deaths were in Asia, and two of the deaths occurred 1 day after initiation of study therapy, reflecting severe underlying disease. There were no MMF deaths in North America and Europe. A *post hoc* analysis of possible contributing factors to the deaths and adverse events concluded that there were no associations of race/ethnicity, geographic region, body surface area or weight with the adverse outcomes for MMF. However, not surprisingly, baseline renal dysfunction was predictive of death, independent of the treatment regimen.

Mycophenolate mofetil is prescribed at a dose varying from 1 to 3 g/day, according to gastrointestinal tolerance and haematological toxicity. In this respect, divided doses per day might reduce nausea and diarrhoea.

In patients with renal impairment caution must be applied to avoid cytopenias, in particular central anaemia. Liver tests must be checked on a regular basis. The patient must be strongly advised against pregnancy during MMF treatment due to its possible teratogenicity.

MMF vs. CY for induction – a position statement in December 2007

Before trying to balance the respective place of MMF and i.v. CY as induction immunosuppressive therapy in LN (both unlikely to be ever licensed in this indication), the pivotal role of GC must be emphasized because most of the efficacy achieved within the first 6 months of therapy is probably attributable to steroids, as is toxicity. With this 'caveat' in mind, evidence-based medicine indicates that MMF is at least as efficacious as CY in Caucasians/Asians and superior to CY in non-Caucasians/non-Asians. In none of the controlled trials was MMF shown inferior to i.v. CY.

Moreover, clinical practice suggests that MMF is safer than NIH i.v. CY (no ovarian toxicity). The remaining, but strong, argument against an undiscriminate use of MMF as induction therapy for LN in December 2007, is that long-term data (>5 years) on patients induced with MMF are still lacking. In between, at the bedside, the decision process will be,

as always, influenced by several patient's characteristics and demands, on a patient per patient basis. Thus, it seems wise to favour MMF in non-Caucasians/non-Asians patients (based on the well-known relative resistance of Black patients to i.v. CY confirmed in ALMS). The same holds true for young women with future pregnancy wishes, who decline receiving an alkylating agent that would compromise their fertility. By contrast, doubts about compliance might skew the decision in favour of an i.v. regimen, namely CY. The availability of the drug and its costs may also be taken into account. Although i.v. CY is available worldwide and the cost for the drug itself is low, expenses for infusion, mesna and luprolide may mirror the cost for MMF, for which the branded patent will expire before the end of 2008.

As early response to immunosuppressive therapy was shown to be the best prognostic factor for a good long-term renal outcome,[2] patients who do not experience a satisfactory response after 3–6 months of treatment should be switched to an alternative drug, e.g. MMF for those induced with i.v. CY or vice-versa. Although, this flexible approach is not supported by evidence-based data, it might allow rescue of patients within the early months of the disease, which can be considered as a 'window of opportunity'.

Maintenance treatment

The choice is mainly between AZA and MMF, not high-dose NIH i.v. CY. We already discussed 'supra' the pros and cons of the NIH regimen. While we believe that a short course of i.v. CY (3–6 months) is still a reasonable option for induction therapy in selected LN patients, we strongly discourage the use of long-term high-dose quarterly CY pulse therapy based on toxicity. Thus, Contreras, *et al.* compared NIH i.v. CY, AZA and MMF for maintenance therapy of LN. Patient survival was significantly lower in the i.v. CY group compared with the AZA arm (no death in the AZA group; one death in the MMF group; four deaths in the i.v. CY group, all by sepsis, three of them between months 12 and 48). Moreover, relapse free survival was significantly shorter in the i.v. CY arm compared with the MMF arm.[22] Although, these results have been obtained with small series of patients (±20/group), they do not support the use of long-term i.v. CY for maintenance therapy.

Whether MMF is superior to AZA for maintenance therapy is not known, although data indicates that AZA does not adequately prevent renal relapses. Thus, in a retrospective analysis, it was shown that 80% of relapsing LN patients were on AZA when they flared.[23] In the Euro-Lupus Nephritis Trial, relapses occurred despite patients being on AZA, from week 12 or 44 onwards, according to their randomization arm.[15] Two trials are comparing MMF and AZA for maintenance are ongoing: 'MAINTAIN' and the maintenance phase of ALMS. 'MAINTAIN' is a European-based investigator-initiated study comparing the two drugs after induction with CY mini-pulses. ALMS is a company-sponsored trial comparing the two drugs after a successful induction course with MMF or NIH i.v. CY (only patients having reached a response were re-randomized between AZA and MMF). Results of these two trials will, at best, not be available before 2009 for 'MAINTAIN' and 2010 for ALMS.

Drug monitoring is an understudied topic in the field of LN that deserves much more attention, in particular for chronic maintenance therapy. Thus retrospective data obtained in transplantation indicate that higher 'areas under the curve' titres of mycophenolic acid (the active metabolite of MMF) are associated with lower rejection rates, a finding that was recently confirmed in a prospective trial.[24]

Biologics

On the basis of the many molecular and cellular players in the pathophysiology of LN, many biologics are currently tested in lupus and in LN, including rituximab (RTX, anti-CD20), ocrelizumab (anti-CD20), epratuzumab (anti-CD22), abatacept (CTLA-4 Ig), belimumab (anti-Blys), atacicept (TACI-Ig), abetimus sodium (LJP-394 20-mer dsDNA) and TRU-015 (CD20 SMIP^{R}). The only controlled trial whose results have been released so far are the abetimus sodium trials[25] and the first belimumab trial;[26] both missed their primary outcome, namely a reduction in renal flares for the abetimus trials and a reduction in the SLEDAI for the belimumab trial, although interesting biological activities were observed in the treatment arms.

Rituximab is one of the most promising biologics based on small uncontrolled series of lupus patients including LN patients. Thus, Sfikakis, *et al.*[27] treated 10 refractory LN patients with RTX. Half of them reached CR and most remained so at long-term follow-up. The results of the Genentech-sponsored LN controlled trial comparing RTX and placebo on a background of MMF are awaited before conclusions can be drawn on the added value of RTX.

Optimal care

The following recommendations are of utmost importance for optimal management of LN patients. Patients should be offered an obsessional follow-up. They should be specifically educated to their disease to stimulate their compliance to therapy (non-observance being the most common reason for treatment failure). Blood pressure control should be optimal (with a target diastolic ≤80 mmHg).

Proteinuria should be minimized by the use of on an ACEI and/or an ARB, in combination with loop diuretics. Dyslipidaemia should be treated (with a target LDL cholesterol <115 mg/dl).

Anticoagulation should be considered for patients with nephrotic syndrome, irrespective of their anti-phospholipid status. GC-induced osteoporosis should be prevented by calcium salts and vitamin D3 supplements. Smoking should be strongly discouraged in this high cardiovascular risk group.

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