Special Feature

What Have We Learned about Optimal Induction Therapy for Lupus Nephritis (III through V) from Randomized, Controlled Trials?

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From 2001 to 2007, five randomized, controlled trials (RCT) of induction protocols for the treatment of lupus nephritis (stages III through V) seem to have captured the interest of the nephrology community (1–5). It is not difficult to critique analytically the shortcomings in study design of these previously published RCT; however, it is a more daunting task to try to assess dispassionately the strengths and weaknesses of these RCT to synthesize a simple, accurate, and useful therapeutic strategy for a practicing nephrologist.

Table 1 lists five RCT and some of the salient features about these studies. The first study was reported in 2001 by Illei et al. (1) from the National Institutes of Health (NIH) and represents an extension of a previously reported RCT with extended follow-up design (6). This was a three-armed study (intravenous cyclophosphamide 1 g/m² monthly for 6 mo and then every 3 mo versus intravenous methylprednisolone 1 g/m² monthly for 12 mo versus both therapies, combined) of 82 patients, 65 of whom completed the study protocol. The major strengths of this study were that it is an RCT of 82 patients who had lupus with biopsy-proven type III or type IV proliferative lesions with an extended follow-up period (median 132 mo). Two major weaknesses of the study were that it was three armed (reducing its power) and had a very high rate of secondary crossover (63%) to cyclophosphamide treatment among patients who initially were assigned to the methylprednisolone group. The authors indicated that this explains the apparent equity in long-term renal outcomes in the intention-to-treat analysis for the cyclophosphamide and methylprednisolone groups (doubling of serum creatinine, progression to ESRD, and death); however, a composite outcome for treatment failure (death, doubling in serum creatinine, and need for additional immunosuppressive therapy not specified in the original protocol) was significantly less likely to occur among the patients who received cyclophosphamide or combination therapy as compared with those who received methylprednisolone. The potential for variation in investigator interpretation of “need for additional therapy” and the presumed post hoc development of this measure tends to reduce the strength of this conclusion. A further analysis of the subgroup of 65 patients who completed the study revealed that no patient in the combination group progressed to ESRD or had a doubling of the serum creatinine concentration. In contrast, three patients in the cyclophosphamide group experienced ESRD, and five had doubled serum creatinine concentrations. The rate of premature amenorrhea in the cyclophosphamide group was reported at 52% for the combination group, 60% for the cyclophosphamide group, and 33% for the methylprednisolone group (five of seven received cyclophosphamide after completion of the methylprednisolone therapy). The rate of serious infection during the protocol was higher in the cyclophosphamide groups than in the methylprednisolone group, and this was predominantly due to herpes zoster infection.

The next study to evaluate cyclophosphamide was the EURO Lupus Nephritis Trial (2). This RCT compared low-dosage versus high-dosage intravenous cyclophosphamide therapy for 90 patients with systemic lupus erythematosus (stage III or IV). In each arm, cyclophosphamide therapy was followed by azathioprine therapy. This was an intention-to-treat analysis, and follow-up was continued for a median of 41.3 mo. The primary end point was treatment failure, which was defined as one of the following: (1) Absence of primary response after 6 mo of therapy, (2) a glucocorticoid-resistant flare, or (3) doubling of the serum creatinine level. The definition of primary response was defined according to serum creatinine and severity of renal disease at baseline.

Treatment failure occurred in 16% of patients on low-dosage and 20% of patients on high-dosage treatment. In terms of secondary outcomes, remission was achieved in 71% of the low-dosage and 54% of the high-dosage group, which was not statistically significantly different. Renal flares were noted in 27% of the low-dosage group and 29% of the high-dosage group during the 41-mo follow-up. The serious infection rate was twice as high in the high- versus low-dosage group, and only two patients in the low-dosage group at age 44 had premature menopause. These results suggest that treatment with low- versus high-dosage cyclophosphamide produces a more favorable outcome with fewer adverse events; however, the lack of statistically significant differences makes these results difficult to interpret.
The next three studies were driven by an expressed desire to achieve comparable or better treatment outcomes with a reduction in serious infections and premature menopause with mycophenolate mofetil (MMF) relative to cyclophosphamide (3–5). Chan et al. (3) reported on the extended follow-up of a prospectively randomized trial of 64 patients who had lupus with type IV proliferative lesions. The first arm received oral cyclophosphamide plus oral prednisone for 6 mo followed by 6 mo of azathioprine; the second arm received 6 mo of oral MMF plus prednisone followed by 6 mo of MMF. The primary outcome was the serial measurement of serum creatinine. At the median follow-up of 63 mo, both groups had maintained their serum creatinine levels. Infection rates were 1 (0.4%) in 234 patient-months for MMF versus 1 (1.0%) in 103 patient-months for oral cyclophosphamide. Amenorrhea occurred less frequently in patients who were treated with MMF than with oral cyclophosphamide (3.6 versus 36%). The average cyclophosphamide dosage was approximately 25 to 35 g. The major strengths of this RCT were its lengthy follow-up time (median 63 mo) and use of a prognostically significant outcome. This study’s conclusions about toxicity were not surprising considering that most patients will receive two to three times the National Institutes of Health protocol and 12 times the EURO protocol for cyclophosphamide, the toxicity of which is known to be entirely dosage dependent. As well, the racial homogeneity of the study group (100% Chinese) threatens the study’s generalizability.

The RCT by Ginzler et al. (4) was a 24-wk randomized, prospective, open-label, noninferiority trial comparing oral MMF (initial dosage 1 g/d, increased to 3 g/d) with intravenous monthly cyclophosphamide (0.5 to 1 g/m²) involving 140 patients who had lupus nephritis with types III, IV, and V renal lesions. The primary end point was complete remission: Return to 10% of normal for serum creatinine + urine protein and sediment 6 mo/MMF > intravenous cyclophosphamide + < toxic. The primary end point was complete remission at 6 mo, defined as a return to within 10% of normal values of serum creatinine, proteinuria, and urine sediment. In the intention-to-treat analysis, 16 of the 71 patients who were treated with MMF and four of the 69 patients who were treated with cyclophosphamide met the prespecified criteria for noninferiority, and this result demonstrated the superiority of MMF to cyclophos-
phamide. Major strengths of this trial were that (1) it represents one of the largest published at that date and (2) it fulfilled most of the Consolidated Standards of Reporting Trials (CONSORT) dictates for an RCT (7). Fewer severe infections and zero versus two cases of amenorrhea were noted in the respective arms. Unfortunately, there were some weaknesses that may undermine this study’s conclusions (5). The composite end point included serum creatinine, 24-h urine protein, and urinalysis. At 6 mo, the two parameters that are known to correlate highly with a better renal outcome (serum creatinine and 24-h urine protein) favored the cyclophosphamide group. It was the re-
duction in urine red blood cells and white blood cells that favored the MMF group and drove the positive MMF result (4). It is even more interesting that the cellular casts were less frequent in the cyclophosphamide group. This finding suggests that the mild chemical cystitis of cyclophosphamide at 6 mo could have been responsible for the positive MMF outcomes. The second weakness relates to the short 6-mo follow-up in terms of providing a clinically meaningful result that will correlate with long-term outcome.

The last RCT was recently reported at the American Society of Nephrology (San Francisco, CA) as the Aspreva Lupus Man-
agement Study (ALMS) results and is in abstract form (5). This was the first large, multinational, multicenter, phase 3 RCT to examine the efficacy and safety of oral MMF versus intravenous cyclophosphamide induction therapy for 6 mo. This study in-
volved 370 patients who had lupus nephritis with types III, IV, and V renal lesions and used a composite end point of a decrease in proteinuria (urine protein/creatinine ratio) and improvement or stabilization in serum creatinine level. In this largest study to date for MMF versus cyclophosphamide, 56.2% of the MMF group and 53% of the cyclophosphamide group achieved the primary end point. MMF was shown to be not statistically superior when a more prognostically meaningful primary outcome that would be unaffected by a chemical cystitis was used. This study was well constructed but has yet to be peer reviewed and was a very early report with only a 6-mo outcome for comparison; however, it is somewhat disquieting that the serious adverse event rates accounted for 24 withdrawals in the MMF group (12 as a result of infection) compared with 13 in the cyclophosphamide group (four as a result of infection). More important, there were nine deaths in the MMF versus five in the intravenous cyclophosphamide group.

In surveying Table 1, it is easy to see that any comparison of these studies requires cautious interpretation because of the variability of primary outcome measurements, post hoc outcome measures, follow-up times, crossovers, serum creatinine levels at baseline, classification types, and racial heterogeneity, to mention a few of the most salient differences. In fact, the degree of variability underlines the current frailty of determining meaningful information by the use of a meta-analysis (8,9); however, these studies deserve praise for providing valuable insight into better treatment strategies and future study designs and are testament to the difficulty of constructing and carrying out an RCT in this subject area. The NIH study, although designed before the CONSORT document, placed intravenous cyclophosphamide plus methylprednisolone as the standard for induction therapy in lupus nephritis (types II and IV) (1,7). The EURO Study did adhere to the CONSORT document and clearly demonstrated noninferiority for low- versus high-dosage intravenous cyclophosphamide induction with half the infection rate and a low rate of premature menopause (two at age 44) in the low-dosage group (2). Unfortunately, using the advantage of hindsight, the three subsequent RCT that were planned to compare MMF with cyclophosphamide to demonstrate noninferiority with a reduced toxicity may not have used the best comparator (low-dosage intravenous cyclophosphamide) (3–5). The study by Chan et al. (3) did demonstrate noninferiority for MMF versus oral cyclophosphamide and a significantly lower rate of infection and amenorrhea, but these adverse effects would be expected because of the high dosage of the cumulatively toxic oral cyclophosphamide used (approximately 25 to 30 g). The study by Ginzler et al. (4) and the more recent ASPREVA study (5) by many of the same investigators compared MMF with high-dosage (NIH) cyclophosphamide. Both studies reported a 6-mo outcome with somewhat differing results. In the smaller study by Ginzler et al., the treatment advantage observed for MMF over high-dosage cyclophosph-
amide was driven by the urine red blood cells and white blood cells, whereas the larger Aspreva study with a prognostically more meaningful composite renal outcome indicated noninferiority with MMF versus high-dosage intravenous cyclophosphamide with surprisingly more infections and deaths in the MMF group.

One might justifiably argue that variation in the proportion of black participants in these studies threatens generalizability and comparability as well as differences in serum creatinine at baseline. Both factors have been shown to have strong correlation with a negative renal outcome (10). Unfortunately, we do not have direct RCT evidence that one form of therapy is superior to the other in groups with differing racial composition or baseline creatinine measurement.

At the present time, it seems (opinion based) that most pa-
tients who have types III, IV, and V lupus nephritis without preexisting chronic renal failure should initially be offered the course of therapy that provides a known long-term renal ben-
EFIT with a low rate of death, serious infections, and premature menopause. That therapy is the EURO low-dosage intravenous cyclophosphamide protocol followed by azathioprine therapy (2). If this fails, then the use of high-dosage intravenous cyco-
phosphamide versus MMF should rest on the patient’s fertility concerns and the experience of the treating physician; however, in the future, the long-term results of the Aspreva Study may alter this opinion (5). Until then, we encourage future RCT in preparation to consider using the EURO protocol as the gold standard comparator for initial induction therapy in proliferative forms of lupus nephritis.

The future looks much improved as a result of the efforts of these investigators and their five RCT. Also, the widespread adoption of clinical trial registries supported by the research community and reputable medical journals with an emphasis on CONSORT documentation will provide a valuable reference framework (11). It will reduce the propensity for post hoc analysis and provide the opportunity for standardization of clini-
cally meaningful outcome measurements with appropriate follow-up time and prognostically robust composite outcome measures that will facilitate systematic reviews and meaningful meta-analyses. Its success will obviate the need for this type of commentary.

**Disclosures**
None.

**References**