REVIEW ARTICLE

Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis

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ABSTRACT

Recent studies have suggested that mycophenolate mofetil (MMF) may offer advantages over intravenous cyclophosphamide (IVC) for the treatment of lupus nephritis, but these therapies have not been compared in an international randomized, controlled trial. Here, the comparison of MMF and IVC as induction treatment for active lupus nephritis in a multinational, two-phase (induction and maintenance) study was shown in the different study. Lupus nephritis (LN) occurs in up to 60% of adults with systemic lupus erythematosus (SLE) and predicts poor survival. The prevalence of SLE and LN and treatment response vary by age, gender, location, and race/ethnicity; LN is especially common in black and Hispanic patients in the United States. MMF was at least as effective as IVC in induction treatment in previous trials in Hong Kong, Malaysia, China, and the United States. Meta-analyses of these and smaller trials suggested that MMF may offer advantages over IVC, but they have not yet been compared in an international randomized, controlled trial. Many comparative studies were undertaken in patients with LN, a two-part trial to assess the efficacy and safety of MMF as induction therapy and subsequently as maintenance therapy for LN. This article will describe the comparison of MMF with IVC, both with corticosteroids.

Introduction

Recent studies have suggested that mycophenolate mofetil (MMF) may offer advantages over intravenous cyclophosphamide (IVC) for the treatment of lupus nephritis, but these therapies have not been compared in an international randomized, controlled trial.

Lupus nephritis (LN) occurs in up to 60% of adults with systemic lupus erythematosus (SLE) and predicts poor survival.[1,2] The prevalence of SLE and LN and treatment response vary by age, gender, location, and race/ethnicity; LN is especially common in black and Hispanic patients in the United States.[3,4]

Use of intravenous cyclophosphamide (IVC) is based on studies in the 1970s and 1980s at the National Institutes of Health (NIH).[5,6] The subsequent induction regimen, widely considered the standard of care, requires monthly intravenous drug infusions.[7] Response is often slow, and treatment fails to control LN fully and is associated with increased risks for adverse effects, including gonadal toxicity.[8,9] Among other immunosuppressants, recent studies have focused on mycophenolate mofetil (MMF).[10] Unlike IVC, MMF has not been associated with an increased risk of bladder or ovarian toxicity in LN or during long-term use after transplantation.[10,11]

MMF was at least as effective as IVC in induction treatment in previous trials in Hong Kong,[12,13] Malaysia,[14] China, and the United States.[12-16] Meta-

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analyses of these and smaller trials suggested that MMF may offer advantages over IVC, but they have not yet been compared in an international randomized, controlled trial.[17-19] GB Appel *et al,* therefore, undertook one of the largest studies to date in patients with LN, a two-part trial to assess the efficacy and safety of MMF as induction therapy and subsequently as maintenance therapy for LN. This report describes the comparison of MMF with IVC, both with corticosteroids, for the induction treatment of active classes III, IV, and V LN. The hypothesis was that more patients with LN would respond to MMF than to IVC during 24 wks.

Discussion

GB Appel et al 2009, report the comparison of MMF and IVC as induction treatment for active lupus nephritis in a multinational, two-phase (induction and maintenance) study. They randomly assigned 370 patients with classes III through V lupus nephritis to open-label MMF (target dosage 3 g/d) or IVC (0.5 to 1.0 g/m^2 in monthly pulses) in a 24-wk induction study. Both groups received prednisone, tapered from a maximum starting dosage of 60 mg/d. The primary end point was a pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. Secondary end points included complete renal remission, systemic disease activity and damage, and safety. Overall, they did not detect a significantly different response rate between the two groups: 104 (56.2%) of 185 patients responded to MMF compared with 98 (53.0%) of 185 to IVC. Secondary end points were also similar between treatment groups. There were nine deaths in the MMF group and five in the IVC group. They did not detect significant differences between the MMF and IVC groups with regard to rates of adverse events, serious adverse events, or infections. Although most patients in both treatment groups experienced clinical improvement, the study did not meet its primary objective of showing that MMF was superior to IVC as induction treatment for lupus nephritis. To determine whether mycophenolate mofetil induces remission of active lupus nephritis as effectively as cyclophosphamide, and to compare adverse effects of these agents[20].

In another study of C Burchardi and D Schlondarff ,Starting in December 1999, patients with systemic lupus erythematosus, biopsy-proven lupus nephritis (class III-V) and evidence of active disease (e.g. elevated serum creatinine concentration, proteinuria or microscopic hematuria), were prospectively recruited in this open-label, multicenter US study. Exclusion criteria included creatinine clearance $<$30 ml/min, serum creatinine $>$3.0 mg/dl ($>$265.2 μmol/l), and previous exposure to mycophenolate mofetil. In addition to prednisone 1 mg/kg/day, patients were randomized to receive oral mycophenolate mofetil (starting at 1,000 mg/day and increasing to 3,000 mg/day, provided the white blood cell count remained $\geq$3,000/mm3) or monthly intravenous cyclophosphamide. Prednisone dosage was reduced by 10-20% every week or fortnight, depending on disease response. Patients who showed no response after 12 weeks were permitted to cross over to the other therapy. Outcomes at 24 weeks were analyzed by intention to treat.

Complete remission of disease (denoted by $\leq$10% variation from normal levels of serum creatinine, urine protein and urine sediment) was the primary endpoint and partial remission (50% improvement in abnormal serum creatinine, proteinuria and urine sediment values) was a secondary endpoint.

Of the 140 patients enrolled, 71 were randomized to mycophenolate (14% male; mean age 32.5 years) and 69 to cyclophosphamide (6% male; mean age 31.0 years). After 12 weeks' treatment, responses were noted in 56 and 42 patients, respectively. At 24 weeks, 22.5% (16) of mycophenolate patients showed complete remission, compared with 5.8% (4) of cyclophosphamide patients. The absolute difference in complete remission rates between treatments was 16.7% (95% CI 5.6-27.9%; P = 0.005), with the positive value of the lower limit of the 95% CI indicating that mycophenolate was superior to cyclophosphamide. Rates of partial remission were similar between patients given mycophenolate and those who received cyclophosphamide (29.6% vs 24.6%; P = 0.51). The overall (complete plus partial) remission rate was higher in the mycophenolate group than in the cyclophosphamide group (52.1% vs 30.4%; P = 0.009). Treatment failure occurred less frequently in

the mycophenolate group than in the cyclophosphamide group (47.9% vs 69.6%; P = 0.01). The mycophenolate group had fewer deaths and severe infections than the cyclophosphamide group (0 vs 2 and 1 vs 6, respectively), but more cases of diarrhea (15 vs 2)[21].

In order to reduce the toxicity of the therapeutic agents used in patients with proliferative lupus nephritis, dose regimens are divided into a 6-month induction phase followed by a maintenance phase, analogous to the approach employed in oncology. Previously, optimal long-term results were obtained using monthly intravenous cyclophosphamide and oral steroids for induction, and intravenous cyclophosphamide (every 3 months) or oral azathioprine for maintenance. In the search for less toxic but equally effective regimens, various drug dosages and combinations have been evaluated. In the Euro-Lupus Nephritis Trial, induction with a reduced dose of cyclophosphamide (six fortnightly doses of 500 mg) was as effective as a regimen comprising six monthly and two quarterly pulses of high-dose cyclophosphamide with respect to treatment failure, renal remission and renal flare at a median follow-up of 73 months.[22] Azathioprine was used as maintenance. Subsequently, Contreras et al. found that daily mycophenolate mofetil was less toxic and more effective in maintaining remission over 72 months than quarterly cyclophosphamide, and at least as effective as azathioprine, though the number of patients with long-term data who were analyzed was very small.[23]

Ginzler *et al*. now question intravenous cyclophosphamide as the gold standard for induction therapy of severe lupus nephritis. In Chinese patients, Chan *et al*. have previously reported comparable efficacy (partial and complete renal remission) for mycophenolate and daily oral cyclophosphamide induction, with less toxicity for mycophenolate.[24] In US patients with proliferative lupus nephritis, Ginzler and colleagues now show comparable, if not superior, results for oral mycophenolate compared with intravenous cyclophosphamide for induction. The question therefore arises: why not use mycophenolate, combined with steroids, for both induction and maintenance treatment of severe lupus nephritis?

The Chan et al. and Ginzler *et al*. reports are in favor of this approach. Not only were initial and final renal outcomes comparable in both studies (after median follow-up periods of 63 months and 36 months respectively), but there were also significantly fewer serious adverse effects in the mycophenolate groups. Because of this, and because of the lack of ovarian dysfunction observed with mycophenolate, the predominantly female lupus nephritis population might be more willing to adopt mycophenolate than cyclophosphamide.

There are, however, some reservations about using mycophenolate as an alternative to cyclophosphamide for induction treatment of severe lupus nephritis, based on the results of the Ginzler et al. study. These include the considerable drop-out rate (50%), and the dosage of mycophenolate (3 g/day), which is higher than would be used for a non-African-American population. The lack of long-term (i.e. 10-year) efficacy data for many patients on mycophenolate is of concern, as late renal flares can occur, and the influence of induction therapy on long-term renal outcomes might require follow-up for more than 5 years.[25] It could take even longer to detect any influence on cardiovascular events. Furthermore, the dosage of mycophenolate is difficult to adjust in patients with renal insufficiency and requires monitoring.[26]

In view of the above caveats, and because patients with renal insufficiency (creatinine clearance <30 ml/min and serum creatinine >3 mg/dl [>265.2 μmol/l] in the Ginzler study) or other severe coexisting conditions were largely excluded from clinical studies, most nephrologists would probably use intravenous bolus dosing of cyclophosphamide and steroids in this subgroup of patients. Mycophenolate mofetil offers an alternative to cyclophosphamide for induction and maintenance therapy of patients with proliferative lupus nephritis

Conclusion

Mycophenolate mofetil is superior to intravenous cyclophosphamide for inducing renal remission, and has a significant advantage over cyclophosphamide for reducing ESRD or death. Furthermore, mycophenolate mofetil has lower risks of

leukopenia, amenorrhoea and alopecia, but a higher risk of diarrhoea than cyclophosphamide. However, our conclusions need to be proved further in larger well designed trials.

Conflict of Interest: We have no conflict of interest.

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