Evidence-based Rheumatology

edited by M. Matucci Cerinic

Mycophenolate mofetil and prednisolone are as effective as cyclophosphamide and prednisolone in treating diffuse proliferative lupus nephritis

Authors: T.M. Chan *et al.*
Title: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis
Source: *N Engl J Med* 2000; 343: 1156-62

Aim

The combination of cyclophosphamide (Cyc) and prednisolone is effective in treating in severe diffuse proliferative glomerulonephritis (DPGN) in systemic lupus erythematosus (SLE). However, Cyc can have severe, immediate and cumulative, adverse effects. Mycophenolate mofetil (MMF) is a purine antimetabolite that selectively suppresses lymphocytes, which usually depend on purine nucleotide synthesis. MMF has been suggested as a potential substitute for Cyc, and this randomized trial was conducted in order to verify the efficacy of oral MMP combined with oral prednisone in treating lupus DPGN.

Methods

42 patients (pts) with SLE and DPGN (based on kidney biopsy), WHO class IV (according to classification), urinary protein excretion ≥ 1g/24 hrs, and serum albumin ≤ 3.5 g/dl were enrolled and, within 48 from the kidney biopsy, randomly assigned to one of two treatments: prednisolone plus MMF for 12 months, or prednisolone plus Cyc for 6 months, followed by prednisolone plus azathioprine for 6 months.

MMF was initiated at 1 g twice a day for 6 months and then reduced to 500 mg twice a day for the second 6 months, then replaced with azathioprine 1 mg/kg/day at 12 months. Cyc was administered orally at a dose of 2.5 mg/kg/day for 6 months and then replaced by azathioprine 1.5 mg/kg/day at 6 months, then lowered to 1 mg/kg/day at 12 months. The starting dose of prednisolone was 0.8 mg/kg/day, tapered by 5 mg/day after 2 weeks, with reductions of 2.5 mg/day every 2 weeks and then every 4 weeks until the maintenance dose of 10 mg per day was reached.

Pts were seen weekly for 4 weeks, then every other week for 8 weeks, then monthly. At each follow-up visit the pts were evaluated for manifestations of lupus nephritis and for adverse effects of the therapy. Urinanalysis, renal and liver function, serum anti-double-stranded DNA antibodies, serum C3, urinary protein excretion/24 hours, and creatinine clearance were evaluated. Blood pressure was measured and hypertension was treated with calcium-channel blockers.

Primary outcomes were complete or partial remission. Complete remission was defined as a value for urinary protein excretion < 0.3 g/24 hours, with normal urinary sediment, a normal serum albumin concentration, and values for serum creatinine and creatinine clearance no more than 15% above the baseline values. Partial remission was defined as a value for urinary protein excretion between 0.3 and 2.9 g/24 hours, with a serum albumin concentration of at least 30 g/liter.

Results

The mean C3 serum concentration increased significantly in both groups after 2 weeks of treatment ($p < 0.05$ in both groups), while the proportion of pts with high serum anti-double-stranded DNA antibodies significantly decreased in both groups ($p = 0.001$ in group 1 and $p = 0.03$ in group 2). The mean creatinine serum concentration significantly decreased with respect to baseline values in group 2 after 2 weeks of therapy ($p = 0.04$) and in group 1 ($p = 0.04$) after 12 weeks of therapy. Compared to baseline values, urinary protein excretion significantly decreased and serum albumin significantly increased in group 2 after 2 weeks of therapy and in group 1 after 4 weeks of therapy, remaining lower and higher, respectively, with respect to baseline values for each subsequent evaluation ($p < 0.05$ in all comparisons). At 12 months creatinine clearance did not differ significantly from baseline values in either group and also serum creatinine and C3 were stable in respect to baseline values ($p > 0.05$ in all comparisons).

81% of the 21 pts in group 1 had a complete remission, and 14% had a partial remission, as compared with 76% and 14% respectively of the 21 pts in group 2. The improvements in the degree of proteinuria and the serum albumin and creatinine concentrations were similar in the two groups. One patient in each group discontinued treatment because of side effects. Infections were noted in 19% of the pts in group 1 and in 33% of pts in group 2 (P = 0.29). Only the latter experienced amenorrhea (23%), alopecia (19%), leukopenia (10%), and death (10%). The relapse rates were 15% and 11% in group 1 and in group 2, respectively ($p > 0.05$).

Conclusions

In the management of lupus DPGN, the combination of MMF and prednisolone is as effective as a Cyc and prednisolone followed by azathioprine and prednisolone but is less toxic. This very important result indicates that MMF may be a safe alternative to Cyc. It could be used to avoid the toxicity and mutagenic effects of Cyc, or as an an alternative treatment in pts who fail to respond to Cyc.

Recommended readings

1. WALLACE DJ: Management of lupus erythematosus: Recent insights. *Curr Opin Rheumatol* 2002;14: 212-9.
2. CONTRERAS G, ROTH D, PARDO V, STRIKER LG, SCHULTZ DR: Lupus nephritis: A clinical review for practicing nephrologists. *Clin Nephrol* 2002; 57: 95-107.
3. KINGDON EJ, MCLEAN AG, PSIMENOU E *et al.*: The safety and efficacy of MMF in lupus nephritis: A pilot study. *Lupus* 2001; 10: 606-11.
4. BURATTI S, SZER IS, SPENCER CH, BARTOSH S, REIFF A: Mycophenolate mofetil treatment of severe renal disease in pediatric onset systemic lupus erythematosus. *J Rheumatol* 2001; 28: 2103-8.
5. ADU D, CROSS J, JAYNE DR: Treatment of systemic lupus erythematosus with mycophenolate mofetil. *Lupus* 2001; 10: 203-8.
6. KARASSA FB, ISENBERG DA: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2001; 344: 382-3.
7. AHSAN N, JOHNSON C,GONWA T *et al.*: Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: Results at 2 years. *Transplantation* 2001; 72: 245-50.
8. BUSQUE S, SHOKER A, LANDSBERG D *et al.*: Canadian multicentre trial

of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus neoral/mycophenolate mofetil/steroids in renal transplantation. *Transplant Proc* 2001; 33: 1266-7.
9. GAUBITZ M, SCHORAT A, SCHOTTE H, KERN P, DOMSCHKE W: Mycophenolate mofetil for the treatment of systemic lupus erythematosus: An open pilot trial. *Lupus* 1999; 8: 731-6.
10. DOOLEY MA, COSIO FG, NACHMAN PH *et al.*: Mycophenolate mofetil therapy in lupus nephritis: clinical observations. *J Am Soc Nephrol* 1999; 10: 833-9.
11. GLICKLICH D, ACHARYA A: Mycophenolate mofetil therapy for lupus nephritis refractory to intravenous cyclophosphamide. *Am J Kidney Dis* 1998; 32: 318-22.
12. JONSSON CA,SVENSSON L, CARLSTEN H: Beneficial effect of the inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil on survival and severity of glomerulonephritis in systemic lupus erythematosus (SLE)-prone MRLlpr/lpr mice. *Clin Exp Immunol* 1999; 116: 534-41.
13. HALLORAN P, MATHEW T, TOMLANOVICH S, GROTH C,HOOFTMAN L, BARKER C: Mycophenolate mofetil in renal allograft recipients: A pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 1997; 63: 39-47.

Comment

The data in the literature available so far strongly support the combination of cyclophosphamide (Cyc) and prednisolone as the "gold standard" in the treatment of severe lupus nephritis, particularly diffuse proliferative glomerulonephritis (DPGN). Indeed, Cyc is generally used both to induce the remission of lupus nephritis as well as a maintenance therapy.

The use of Cyc is largely supported by the NIH studies, which are the only randomized controlled studies with a long-term follow-up so far published. These same studies, however, have raised many concerns regarding the long-term safety of Cyc, with particular reference to its gonadal toxicity and carcinogenicity. In the studies by Gourley et al. *and Illei* et al. *premature menopause was observed in 56% and cervical dysplasia in 9% of the patients treated with Cyc versus 10% and 0% respectively in patients treated with steroids. Furthermore, one recent meta-analysis on the treatment of LN has shown that clear data on the superiority of Cyc over other immunosuppressive drugs is lacking, since the NIH studies have demonstrated the superiority of Cyc regimens over predisone alone.*

Therefore, alternative ways of treating LN are now under evaluation and protocols based on shorter courses of Cyc or on the administration of drugs such as azathioprine, cyclosporine, mycophenolate are under evaluation both for the induction of remission as well as in the maintenance of remission of LN.

MMF appears to be a very promising drug for the treatment of autoimmune diseases since data on transplanted patients show a good efficacy in the prevention of acute rejection, associated with a good tolerability and a lower incidence of side effects compared with azathioprine. Many case reports have suggested the efficacy of MMF in the treatment of active SLE, which is ususally resistant to "conventional" therapies including Cyc. However, most of the data available has been derived from the analysis of case reports with the inevitable limitations of such studies.

The article by Chan et al. represents a important report on the efficacy and safety of MMF and evaluates its role as a remission-inducing drug in DPGN. Some caution, however, is needed in the interpretation of these data, particularly in relation to the efficacy of the drug.

The first problem is posed by the limited number of enrolled patients. This is of course a common limitation in controlled randomized studies of rare diseases such as SLE, and can be overcome only by multicenter studies such as the Eurolupus nephritis trial. The number of patients may in fact have been too small to detect significant differences between the two treatment groups and indeed the authors do not provide any information on the power of the study to detect clinically meaningful treatment effects.

The hypothesis of a low power of the study appears to be supported by the observation that no statistically significant differences in adverse events were observed between the two treatment groups, although patients in the Cyc group had a 33% incidence of infections versus 19% of the MMF patients, and 3 cases of amenorrhea were observed in 13 premenopausal patients in the Cyc group while no cases were observed in the MMF group.

A second limitation lies in the shortness of the follow up period. Although the aim of the study was to evaluate the efficacy of MMF in controlling "acute" disease activity, recent observations underline the importance of renal flares in the prognosis of LN. Thus the efficacy of a protocol in controlling not only acute disease activity but also in the prevention of early and late renal flares must be considered. A longer follow up would therefore be required to prove the efficacy of this protocol,since the remission induced by MF followed by AZA may be less "stable" than a remission induced by Cyc followed by AZA.

The data on the safety of the drug is certainly very interesting and demonstrates the good tolerability of MMF in SLE patients. In fact, although limited by the low power of the study, the incidence of side effects appears to have been lower in the MMF group than in the Cyc group. Unfortunately, the data on cancer development cannot be evaluated for two reasons: first; the inadequate follow-up period, and secondly the additive effects of the maintenance drug (i.e. azathioprine). Future studies may help to shed light on this all important point.

Despite these limitations, Chan's study provides important indications on the effects and safety of MMF in SLE and supports the need for randomized controlled trials. In view of the evident difficulties in the recruitment of patients, multicenter studies would appear advisable.

M. MOSCA, *MD*
Rheumatology Unit, Dept. of Internal Medicine
University of Pisa, Pisa, Italy.

References

1. AUSTIN HA, KLIPPEL JH, BALOW JE *et al.*: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986:314:614-9
2. BOUMPAS DT, AUSTIN HA, VAUGHN EM, KLIPPEL JH, STEINBERG AD: Controlled trial of pulse mephtylprednisolone versus 2 regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741-5.
3. D'CRUZ D, CUADRADO MJ, MUJIC F *et al.*Immunosuppressive therapy in lupus nephritis. *Clin Exp Rheumatol* 1997; 15: 275-82.
4. ILLEI GG, AUSTIN HA, CRANE M *et al.*Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001; 135: 248-57.
5. GOURLEY MF, AUSTIN HA, SCOTT D *et al.*: Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. *Ann Intern Med* 1996; 125: 549-57
6. BANSAL VK,BETO JA: Treatment of lupus nephritis: A meta-analysis of clinical trials. *Am J Kid Dis* 1997; 29: 193-9.

(This report was prepared with the assistance of Dr. Angela Del Rosso)