Evidence-based Rheumatology

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Sequential therapies with intravenous cyclophosphamide and oral mycophenolate mofetil or azathioprine are efficacious and safe in proliferative lupus nephritis

Title: Sequential therapies for proliferative lupus nephritis
Authors: G. Contreras *et al*.
Source: *N Engl J Med.* 2004; 350: 971-80.

Aims

Long-term therapy with cyclophosphamide improves renal survival in patients with proliferative lupus nephritis. However, the beneficial effect of long-term cyclophosphamide must be weighed against its considerable toxic effects. Duringthe past decade, there have been reports on the use of mycophenolatemofetil or sequential mycophenolate mofetil and azathioprine for induction and maintenance treatment of lupus nephritis. This is a prospective controlled trial comparing threemaintenance regimens: quarterly intravenous injections of cyclophosphamide(pulse cyclophosphamide), oral mycophenolate mofetil, and oralazathioprine

Methods

Fifty-nine patients with lupus nephritis (12 in World Health Organization class III, 46 in class IV, and 1 in class Vb) received induction therapy consisting of a maximum of seven monthly boluses of intravenous cyclophosphamide (0.5 to 1.0 g per square meter of body surface area) plus corticosteroid (prednisone up to 0.5 mg/kg/day or an equivalent corticosteroid). Subsequently, the patients were randomly assigned to one of three maintenance therapies: quarterly i.v. injections of cyclophosphamide, oral azathioprine (1 to 3 mg per kilogram of body weight per day), or oral mycophenolate mofetil (500 to 3000 mg/day) for one to three years. The baseline characteristics of the three groups were similar, with the exception that the chronicity index was 1.9 points lower in the cyclophosphamide group than in the mycophenolate mofetil group ($p = 0.009$). The primary endpoints of the study were patient and renal survival. The secondary endpoints were renal relapse, amenorrhea for 12 months or more, hospitalisation, infection and other adverse events. Remission was defined as some degree of reduction in proteinuriaand stable or improved serum creatinine levels.

Results

Of the 59 patients with proliferative or mixed membranous and proliferative lupus nephritis who were enrolled in the study, 46% were black, 49% were Hispanic, and 5% were white. On the basis of improvements in renal function, the degree of proteinuria,serum albumin levels, and lupus antibodies and complement values,cyclophosphamide induction therapy led to substantial improvements in all groups between study entry and random assignment to thevarious maintenance therapies. Remission of nephritis occurredin 83% of patients during the pulse-cyclophosphamideinduction phase. The proportions of patients who met thecriteria for remission were evenlydistributed among the three maintenance therapy groups. During maintenance therapy, 5 patients died (4 in the cyclophosphamide group and one in the mycophenolate mofetil group), and chronic renal failure developed in 5 (3 in the cyclophosphamide group and one each in the azathioprine and mycophenolate mofetil groups). There were no significant differences in actuarial renal survival, but the 72-month event-free survival (based on a composite endpoint of deathand renal failure), was significantly better in both the azathioprine and mycophenolate mofetil groups than in the cyclophosphamidegroup ($p = 0.05$ and $p = 0.009$, respectively). The rate of relapse-free survival was higher in the mycophenolate mofetil group than in the cyclophosphamide group ($p = 0.02$). Finally, the rate of unscheduledhospital admissions, total hospital days, and the number of infectious episodes were significantly higher in the cyclophosphamidegroup than in either the azathioprine or the mycophenolate mofetil group.

Conclusions

Following induction therapy with cyclophosphamide, both azathioprine and mycophenolate mofetil offer better benefit–risk profiles for maintenance therapy than does cyclophosphamide.

Recommended readings

1. HOCHBERGMC: Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
2. POLLAK VE, PIRANI CL, SCHWARTZ FD: The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 1964; 63: 537-50
3. AUSTIN HA III, MUENZ LR, JOYCE KM, ANTONOVYCH TT, BALOW JE: Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int* 1984; 25: 689-95.

Comment

Controlled randomized studies have shown that intermittent pulse cyclophosphamide therapy (IV-CY) is the treatment of choice for moderate to severe proliferative lupus nephritis. Following induction with pulse IV-CY therapy, a mainte - nance regimen is essential to decrease the risk of flares (1). However, extended courses of IV-CY increase the rates of sustained amenorrhea and are associated with significant expense and inconvenience. Because of these concerns, recent random controlled (RCT) studies have explored the use of mycophenolate mofetil(MMF) for both the induction and maintenance of remission of proliferative lupus nephri - tis. A study from Hong Kong (2) and a more recent one from New York (presented at the annual ACR meeting in 2003) have concluded that MMF is comparable – if not superior to – CY in inducing remission. In this study, Contreras and col - leagues conclude that after induction therapy with IV-CY, both azathioprine (AZA) and mycophenolate mofetil (MMF) are superior as a maintenance therapy to IV-CY. Do these studies suggest that IV-CY therapy may soon become obsolete ?

Lupus nephritis is a notoriously heterogeneous disease with histology, race, duration and delay in immunosuppressive therapy all impacting on renal outcomes. Outcomes from short-term follow-up studies may differ from those after longer follow-up, a finding that dictates caution in over-interpreting the results from studies of short duration such as the studies on MMF. Thus, with a longer follow-up, the Hong Kong study demonstrated rates of relapse with MMF that were twice as high.

Taken together, the available evidence indicates that for patients with severe nephritis (rapidly progressive glomerulonephritis, crescent nephritis or nephritis with a combination of high activity with moderate to high chronicity features) combination pulse therapy with CY and methylprednisolone (MP) is the treatment of choice (3, 4). For selected patients with moderately severe nephritis, MMF (or azathioprine) may be used initially to induce remission. In such cases, the initial use of less intensive regiments with clear-cut short-term endpoints (achievement of complete remission within the first 3 to 6 months) may be a reasonable approach. But is MMF or azathioprine better in terms of efficacy and toxicity than IV-CY to maintain remission, as the study by Contreras suggests ? A close look at this study raises questions about the validity of the claim of superiority.

First and foremost, it is not clear whether this was designed as a superiority trial. In general, superiority trials require a larger patient population, a longer follow-up or both, especially if potent therapies are being compared. Second, there were no differences in renal survival among the treatment groups, a factthat challenges the authors' claim that azathioprineand MMF are superior to IV-CY. The observed differences in survival were detected only when a composite outcome was used. Third, the risks of death, renal failure, serious side effects and relapse of nephritis were higher than expected during maintenance therapy with cyclophosphamide. Fourth, duringthe maintenance phase, the doses of cyclophosphamide (mean: slightly more than 500 mg per square meter of body surface area)were lower than the doses recommended on the basis of the NIHstudies. Although lower doses of IV-CY were used, the rate of unscheduledhospital admissions, total hospital days, and the number ofinfectious episodes were significantly higher in the cyclophosphamide group than in either the azathioprine or the MMF group. Concomitant corticosteroids were used in higher doses than in the NIH trials. Thus, the high rate of infections in the cyclophosphamide group may havebeen falsely attributed to CY alone.

There are additional issues casting doubts on the applicability of these data to other patient populations. There were very few white patients in this cohort. Moreover, there was a high rate of remission (up to 83% of all patients treated for 3-6 months with IV-CY), raising the question as to whether this population may have nephritis, which may be more responsive to treatment compared to the NIH cohort. Finally, rates of relapse during maintenance therapy with azathioprine and MMFwere lower than those reported by the Hong Kong group.

The recent Cochrane review of all RCT in lupus nephritis published until January 31, 2003 concludes that "until future RCTs of newer agents are completed, the current use of cyclophosphamide combined with steroids remains the best option to preserve renal function in proliferative lupus nephritis. The smaller effective dose and duration of cyclophosphamide therapy should be used to minimize gonadal toxicity without compromising efficacy". To this end, the current RCT study by Contreras demonstrates that both azathioprine and MMF can be used as maintenance therapy in patients with proliferative lupus nephritis. While waiting for the longer follow-up of this interesting study, physicians caring for patients with proliferative nephritis may use these drugs as maintenance therapy under close observation. Additional, RCT with a longer follow up involving more representative patient populations are needed to further substantiate these findings.

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References

1. BOUMPAS DT, AUSTIN HA III, VAUGHAN EM *et al.*: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741-5.
2. CHAN TM, LI FK, TANG CSO *et al.*: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; 343: 1156-62.
3. ILLEI GG, AUSTIN HA, CRANE M, COLLINS L: 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.
4. FLANC RS, ROBERTS MA, STRIPPOLI GFM, CHADBAN SJ, KERR PG, ATKINS RC: Treatment for lupus nephritis (Cochrane Review). *The Cochrane Library*, issue 1, 2004. Chichestere, UK, John Wiley and Sons, Ltd.

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