decreased renal function: (i) increase in the serum creatinine concentration to 50% or more, or (ii) 100% or doubling above the lowest concentration during protocol treatment. End-stage renal disease was defined as the requirement of dialysis or renal transplantation. Treatment failure was defined as the need for supplemental immunosuppressive therapy or a doubling of the serum creatinine concentration, or death.

Adverse events due to the different therapeutical options were also recorded.

Results

Follow-up data were available for 65 pts who completed the protocol; 17 pts did not due to pregnancy, non-adherence, protocol violation, allergy to methylprednisolone or death, but data on renal outcome and death were available for 15 of these. Thirty-four pts required additional immunesuppressive therapy after the protocol: 18 of them were assigned to the methylprednisolone group, 10 to Cyc, and 6 to the combination therapy group, respectively.

Among the 82 enrolled pts, 20 (8 in the Cyc, 4 in the combination therapy, and 8 in the methylprednisolone groups, respectively) showed a doubling of serum creatinine. Fifteen of them (5 Cyc, 4 combination therapy and 6 methylprednisolone) progressed to end-stage renal disease. 11 pts died during the course of the study. Among the protocol completers, 54/65 (83%) had preserved renal function at the end of follow-up, while 11 (17%) had doubled serum creatinine, including 6 pts (9%) who reached end-stage disease.

In an intention-to-treat survival analysis, the likelihood of treatment failure was significantly lower in the Cyc and combination therapy groups than in the methylprednisolone group ($P = 0.04$ and 0.002, respectively). Combination therapy and Cyc therapy alone did not differ statistically in terms of effectiveness or adverse events (premature amenorrhea, bacterial infections necessitating hospitalization, avascular necrosis, osteoporosis, and ischemic heart disease) ($P > 0.05$).

Four non-completer ($n = 17$) pts died and 8 reached end-stage renal disease. Overall, renal outcome was significantly worse among non-completers than completers. Only 6 pts in the completer group reached end-stage renal disease. Among completers ($n = 65$), the proportion of pts who experienced a doubling of their serum creatinine concentration was significantly lower in the combination group than in the Cyc group (relative risk, 0.095 [95% CI, 0.01 to 0.842]).

Conclusion

After the extended follow-up, pulse Cyc showed superior and persistent efficacy over pulse methylprednisolone alone for the treatment of lupus nephritis. The combination of pulse Cyc and methylprednisolone seems to provide additional benefit over pulse Cyc alone, without conferring an additional risk of adverse events.

References

1. GOURLEY MF *et al.*: Methylprednisolone and Cyc, alone or in combination, in patients with lupus nephritis. *Ann Intern Med* 1996; 125: 549-57.

In patients with severe lupus nephritis treated with pulse immunosuppressive therapy, renal flares are common but do not necessarily lead to loss of renal function

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Title: Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: Long-term followup of a cohort of 145 patients participating in randomized controlled studies

Source: *Arthritis Rheum* 2002; 46: 995-1002

Aim

In systemic lupus erythematosus (SLE) patients with proliferative nephritis, immunosuppressive agents have become the standard therapy because they are effective in controlling disease activity and preventing end-stage renal disease (ESRD). Nevertheless, despite such therapies some patients may experience relapses. In order to investigate the prevalence, outcome, and predictive factors of renal flares in lupus nephritis, the cases of flares during post-study follow-up in a cohort of 145 patients who had participated in 2 randomized controlled clinical trials at the National Institutes of Health (1, 2) were reviewed.

Methods

Data were obtained on 145 patients with proliferative lupus nephritis who had participated in either one of two long-term, prospective, randomized controlled trials conducted at the National Institutes of Health between 1981 and 1990, in which they had been treated with pulse cyclophosphamide, pulse methylprednisolone, or a combination of the two.

When the data was collected the patients had not received immunosuppressive therapy for at least 6 months, and had showed a complete or partial response to the protocol therapies according to the following criteria. Complete response was defined as the presence of the following 3 criteria for at least 6 months: serum creatinine < 130% of the lowest level seen during treatment, proteinuria < 1 gm/day and the absence of cellular casts,and < 10 red blood cells (RBCs)/high-power field (hpf) in the urinary sediment in at least one 20 ml sample. Patients had to be off immunosuppressive therapy, with the exception of hydroxychloroquine (< 400 mg/day) and prednisone (< 10 mg/day) or their equivalents. Stabilization was defined as the presence of stable levels of serum creatinine (< 150% of the lowest level during treatment) for at least 6 months without immunosuppressive therapy, regardless of the levels of urinary protein or sediment. Such patients could have either fixed proteinuria or hematuria, or an incomplete response to therapy. The term "flare" was used to describe an episode of increased lupus nephritis activity. Based on changes in urinary protein and sediment, flares were classified as proteinuric or nephritic, and nephritic flares were further classified as mild, moderate, or severe. Most patients who experienced a flare received additional immunosuppressive therapy.

The following data were collected and evaluated for their association with flares: age at SLE onset and at nephritis

diagnosis, ethnicity, sex, histologic indices of activity and chronicity in the renal biopsy at therapy start, and the time lapse between initiation of immunosuppressive therapy and the nephritis diagnosis.

The following data (collected when a complete response or stabilisation was reached) were evaluated for their predictive value for subsequent flares: anemia, elevated serum creatinine level, low C4 or C3 levels, positive anti-double-stranded DNA (anti-dsDNA) antibody titer, and proteinuria (> 0.5 gm/24 hours).

Results

92/145 patients who had entered either of the 2 studies showed a complete or partial response to immunosuppressive therapy. Seventy-three patients had a complete response, and 19 had a partial response/stabilisation, while 53 did not achieve a complete or a partial response at any time during the follow-up. After a mean follow-up of 117 months, 29/73 complete responders (40%) and 12/19 partial responders (63%) experienced renal flares, which mostly occurred within 4 years after meeting the response criteria.

The total number of patients experiencing a renal flare (nephritic in 33, proteinuric in 8) in the 2 groups was 41 (45%). Thirty-one of the patients experiencing a flare received additional immunosuppressive therapy. The median time to renal flare was 36 months in the complete responders and 18 months in the partial responders. Eleven of the 41 patients (27%) progressed to ESRD; 9 had nephritic flares (severe in all except for 1) and 2 had proteinuric flares (1 in each responder group). In both the complete response and partial response groups, low C4 at the time of response and African American ethnicity were significant independent risk factors for renal flare, while the serum creatinine level > 2.0 mg/dl, severe nephritic flare, not achieving a complete response, and higher activity and/or chronicity indices at baseline renal biopsy were most strongly associated with ESRD. Compared with complete responders, partial responders were more likely to experience a flare, to have a severe nephritic flare, or to progress to ESRD.

Conclusion

Nephritic flares are common in patients with proliferative SLE nephritis, even in those with a complete response to immunosuppressive therapy. However, they do not necessarily lead to loss of renal function if adequately treated with additional immunosuppressive agents. Renal flares should be also considered as important features of the natural history of SLE nephritis, requiring additional preventive strategies in the patient, and providing a parameter of efficacy for future therapeutic trials.

References

1. BOUMPAS DT *et al*.: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741-5.
2. GOURLEYMF *et al*.:Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. *Ann Intern Med* 1996; 125: 549-57.

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Comment

There are few topics in the world of lupus that generate such fierce controversy as the treatment of lupus nephritis. Indeed, the contrast between a large amount of 'Eminence-based medicine' based on clinical experience, intuitive observations and retrospective case series and 'Evidence-based medicine' based on a relatively small number of prospective randomised clinical trials could not be sharper. Some have even observed that the tenacity of opinion held by an author appears to be inversely proportional to the strength of the supporting evidence. It is certainly true that, compared to the cardiology world where evidence of therapeutic effect for a particular approach is based on studies of thousands of patients, controlled trials in lupus nephritis are pitifully small. Thus any prospective study especially with a significant follow-up period is to be welcomed.

Two studies from the renowned NIH lupus nephritis study group are considered (1,2). The first paper is the extended follow-up of an initial 82 patients with proliferative lupus nephritis who had received monthly treatments of bolus methylprednisolone, cyclophosphamide or both. Follow-up data was available in 65 patients with 17 not completing the original treatment protocol for a variety of reasons. The original protocol did not include any long term maintenance immunosuppressive therapy. At follow-up 34 patients, 18 of whom were in the methylprednisolone group, required additional therapy, mostly with further bolus cyclophosphamide, for on-going disease activity after the initial protocol. At the end of the whole study period there was no significant difference between the three treatment groups in the risk for death or end-stage renal disease in an intention-to-treat analysis. Only when a composite end-point was used did a significant benefit over methylprednisolone alone emerge. Importantly, the numbers remaining at risk of failure of therapy at the end of ten years were relatively small (25 of the original 82). As in previous studies, the rate of herpes zoster was high (26 - 32%) as was the premature amenorrhoea rate (52 - 60%) in patients receiving cyclophosphamide. There were 21 patients who developed avascular necrosis of bone, representing a high percentage (26%) of the original entry although there was no difference between the three treatment groups.

So what does this study add to the existing literature? Certainly it supports the widely held (but not conclusive) view that corticosteroids alone should not be the mainstay of therapy for proliferative lupus nephritis. Should we all adopt the addition of bolus methylprednisolone to bolus cyclophosphamide in extended treatment regimens? Probably not: the numbers treated in this study are really too small and the rate of protocol non-completers, who generally fared badly, was too high to advocate the widespread use of additional bolus methylprednisolone for all patients with proliferative lupus nephritis. Most physicians reserve the use of bolus methylprednisolone for the short term control of severe disease. Most would be cautious about its extended widespread use especially as there are several reports in the world literature of death, usually from arrthymias associated with electrolyte disturbances.

The other study considered here examined the renal flare rates in patients who had previously entered two randomized controlled trials of cyclophosphmide and/or methylprednisolone (2). Briefly, there was a significant renal flare rate in the group as a whole (45% of 91 responders) with a higher flare rate in the 19 patients who only had a partial response or stabilization of their condition. Low complement C4 and African American ethnicity were predictors for renal flares.

What is interesting about these studies is that once remission had been achieved, no further immunosuppression was considered in these patients and so it is not surprising that there was a significant flare rate. Other aspects of these studies include the lack of any global lupus disease activity or damage indices, which makes it harder to get a feel for the extent of non-renal disease which can contribute significantly to morbidity.

Since these studies, other approaches have been considered using both old and new treatments. One approach in a European wide study was to use a three-month low dose bolus cyclophosphamide regimen followed by azathioprine. This approach appeared to be similar to the conventional high dose cyclophosphamide regimen in terms of renal outcome but the study was not powered to demonstrate direct equivalence. Both groups received three bolus methylprednisolone pulses as part of the induction regimen. What is clear from all these studies is that lupus is a not a curable disease as yet and that there is a clear need for long term maintenance therapy. Our current therapies, including azathioprine, are useful following cyclophosphamide containing induction regimens and may obviate the need for long term bolus methylprednisolone pulses implied by the studies reviewed above. However, these therapies could certainly be better and new agents such as mycophenolate mofetil do offer the prospect of long term disease control that so far appears to be safe and well tolerated. Mycophenolate remains expensive but it is still cheaper than long term renal replacement therapy and numerous studies are currently in progress.

References

1. 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.
2. ILLEI GG, TAKADA K, PARKIN D *et al.*: Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term follow-up of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum* 2002; 46: 995-1002.
3. HOUSSIAU FA, VASCONCELOS C, D'CRUZ D *et al.*: Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121-31.

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