Evidence-Based Rheumatology

edited by M. Matucci-Cerinic

Systemic lupus erythematosus (SLE) affects youngsters, severely impairing their quality of life and prognosis. This issue's Evidence-based Medicine section is dedicated to a difficult problem – the management of SLE nephritis, a complication that requires rapid therapeutic intervention.

Here, we present two important studies conducted by a single group that was aimed at evaluating the efficacy and safety of pulse immunosuppressive therapy, the present gold standard therapy for SLE nephritis. The first paper provides evidence of the long-term efficacy of combination pulse therapy with cyclophosphamide and methylprednisolone in SLE nephritis.

The second demonstrates that pulse immunosuppressive therapy (cyclophosphamide, pulse methylprednisolone, or a combination of the two) is very – even if not completely – effective in controlling disease activity and preventing end-stage renal disease in patients who have shown a complete or partial response to immunosuppressive therapy.

These studies on the one hand underline the efficacy and importance of the immunosuppressive drugs now used for the treatment of SLE nephritis, and on the other hand shed light on the limitations of these drugs. They point to the need for new therapeutic strategies and new agents for the treatment of SLE nephritis, which can rapidly and fatally compromise renal function.

Combination therapy with pulses of Cyc and methylprednisolone improves long-term renal outcome without increasing toxicity in patients with lupus nephritis

Authors: G.G. Illei *et al*.
Title: Combination therapy with pulse Cyc plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis
Source: *Ann Intern Med* 2001 :135: 248-257

Aim

Controlled trials in systemic lupus erythematos (SLE) nephritis have demonstrated that the combination of cyclophosphamide (Cyc) and corticosteroids is superior to corticosteroid therapy alone in preserving renal function. The long-term effectiveness and side effects of Cyc pulses need further study, however. In order to define the long-term risks and benefits of monthly treatment with pulses of methylprednisolone, Cyc, or both, an extended follow-up (median 11 years) of a randomised, controlled trial in lupus nephritis was conducted (1).

Methods

Eighty-two patients (pts) with proliferative lupus nephritis were enrolled between 1986 and 1990 and randomised to receive: 1) monthly I.V. boluses of methylprednisolone (1 g/m^2 of body surface area) for at least 12 months and up to 36 months; 2) monthly I.V. boluses of Cyc (1 g/m^2 of body surface area) for 6 months and then once every 3 months for at least 24 additional months; 3) a combination of the 2 regimens (1).

After the first year, pts in any one of the treatment groups who were no longer receiving I.V. therapy but who showed active glomerular disease were recycled to their original regimens, but no more than twice. If therapy failed 3 times, pts were classified as non-responders.

All pts initially received oral prednisone 0.5 mg/kg/day, tapered by 5 mg every other week, to the minimal dose required to control extra-renal disease or to 0.25 mg/day. For severe extra-renal SLE flares, pts received prednisone 1 mg/kg/day for 2 weeks (1).

Up through August 1999, all pts were contacted and surviving pts were asked to return for evaluation. Pts unable or unwilling to return were asked to complete a questionnaire on renal function, current therapy (comprising immunosuppressive drugs from the end of protocol) and co-morbid conditions. For deceased pts, the family and physicians were asked about the causes of death. Pts who were re-evaluated had a detailed history taken (in order to assess renal anamnesis, ovarian failure and serious infections) and underwent a physical examination, laboratory studies to assess renal function and hyperlipidemia, a cardiac work-up to assess ischemic and valvular heart disease and hypertension, bone densitometry to assess osteoporosis, and magnetic resonance of the hips to assess avascular necrosis. A persistent increase in serum creatinine concentration (by at least 50%), persistent doubling of the serum creatinine concentration, or end-stage renal disease were recorded as renal outcomes.

Pts were divided in "protocol completers" and "protocol non-completers"; the latter included pts whose response to therapy could not be analysed because they died before reaching an end point, did not return for follow-up or were excluded because of protocol violation.

"Renal response" was defined as a erythrocyte count < 10 cells/field in a centrifuged 50 ml urine sample, the absence of cellular casts, and proteinuria < 1 g/day. These criteria were applied to protocol completers at the 5-year study visit. Pts were classified as non-responders if they did not fulfill the above criteria at their 5-year visit or if they received additional immunesuppressors beyond those allowed in the protocol before the end of 5-year follow-up.

Renal insufficiency was measured based on 2 grades of

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

Authors: G.G. Illei *et al.*

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