The evidence base for the treatment of lupus nephritis in the new millennium

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Introduction

At the start of the new millennium, it is important to reassess progress in the treatment of lupus nephritis. The aims of treating lupus nephritis are to induce and maintain remission thereby reducing the risks of progression to renal failure and of dying. At the same time, patients with lupus nephritis may have extra-renal disease, the most severe of which is central nervous system disease and this requires treatment. A further and important aim is to minimize treatment-related toxicity. Prednisolone and cyclophosphamide are accepted as the optimal treatment for proliferative lupus nephritis [1] but have substantial toxicities. What then is the evidence base for the treatment of lupus nephritis and why does the treatment of lupus nephritis still generate such strong differences of opinion?

Steroids plus alkylating agents or azathioprine

Patients with mesangial proliferation (WHO class II) typically present with proteinuria and haematuria. Such patients are usually treated with steroids in the hope of preventing progression to more severe disease although there have been no controlled trials of treatment. Similarly, there have been no controlled trials of treatment of lupus membranous nephropathy, which is found in between 12 and 26% of patients with lupus nephritis. Using the old WHO classification the 10-year survival free of end-stage renal failure or death was 72–90% for class Va and Vb (membranous nephropathy with mild mesangial hypercellularity and scattered deposits) [2,3] and 48–81% for WHO class Vc and Vd (membranous nephropathy with focal or diffuse proliferative glomerulonephritis) [2,3]. These patients had been treated with prednisolone and cyclophosphamide or azathioprine. In the revised WHO classification patients with WHO class Vc and Vd (membranous nephropathy with focal or diffuse proliferative glomerulonephritis, respectively) were reclassified as WHO classes III and IV [4]. Our practice is to treat patients with WHO class Va and Vb with prednisolone and to use azathioprine as a steroid sparing agent and to treat patients with WHO class Vc and Vd as for a proliferative lupus nephritis.

In the 1960s the 3-year patient survival in patients with a proliferative lupus nephritis who were treated with steroids was 50–60% [5,6] and patients with these lesions became the focus of the controlled trials of treatment comparing prednisolone alone versus prednisolone and azathioprine or cyclophosphamide. In a narrative review, Donadio and Glassock argued that the addition of immunosuppressants to steroids could not convincingly be shown to confer benefit in terms of preventing end-stage renal failure or deaths as compared with steroids alone [7]. In a pooled analysis, Felson and Anderson [8] came to the opposite view and reported that patients receiving immunosuppressive drugs were less likely to develop end-stage renal failure or to die from this than patients receiving steroids alone. The meta-analysis carried out by Bansal and Beto [9] concluded that the addition of immunosuppressants (cyclophosphamide or azathioprine) to steroids reduced the risk of dying or of developing end-stage renal failure as compared with prednisolone alone.

In view of the importance of this question of the additive efficacy of immunosuppressants to steroids, we have carried out a meta-analysis of randomized controlled studies that compared steroids alone (given either orally or intravenously) with steroids and immunosuppressants (again given orally or intravenously) [1,10–18]. The addition of immunosuppressants to steroids significantly reduced the risk of renal failure or death by about 40%, but the confidence intervals on this estimate were wide ranging from no benefit to a reduction of about 60%. Most of this benefit related to the prevention of renal failure (60% reduction 95% CI 30–80%) whilst there was no significant benefit on mortality. There was a non-significant increased risk of infections with cyclophosphamide and an almost sevenfold increased risk of sustained amenorrhea. There were too few data to examine possible differences between the cyclophosphamide and azathioprine. In conclusion,

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the addition of immunosuppressants to prednisolone may reduce the risk of renal failure but not of death in patients with lupus nephritis, but since only 443 patients in total have been studied in randomised trials to date, the size of any overall benefit remains uncertain.

Nevertheless, these preliminary findings do lend some support for the widely held view that the optimum treatment of proliferative lupus nephritis is with aggressive immunosuppression together with steroids. The reduction in the risk of developing end-stage renal failure must, however, be traded off against the very significant risk of sustained amenorrhoea with cyclophosphamide in a disease that predominantly affects young women.

Plasma exchange

Two published randomized controlled studies have examined the effect of plasma exchange in the treatment of patients with lupus nephritis. In both studies, the patients received concurrent treatment with prednisolone and immunosuppressants. In the study of Lewis et al. plasma exchange conferred no benefit in terms of death, renal failure, death or renal failure or remission of renal disease [19]. The study of Clark et al. suggested that the rate at which renal function deteriorated was less in the plasma exchange treated group but this did not achieve statistical significance [20]. In conclusion, plasma exchange confers no benefit when added to prednisolone and cyclophosphamide in patients with lupus nephritis.

New treatment

The age- and dose-related toxicity of cyclophosphamide with oligospermia in men and premature ovarian failure in women [21,22] together with its oncogenicity has prompted a search for equally effective but less toxic treatment for lupus nephritis. One such drug might be mycophenolate mofetil (MMF), which inhibits the de novo pathway of purine synthesis and therefore lymphocyte proliferation [23]. MMF is an immunosuppressive drug that is of established efficacy in renal transplantation [24].

MMF and lupus nephritis

We have recently reviewed the role of MMF in the treatment of lupus nephritis [25]. There have been several case reports and case series of the use of MMF together with steroids in treating patients with lupus nephritis whose disease was relapsing or was resistant to cyclophosphamide and steroids. In addition, open pilot studies suggested that MMF might have a beneficial role in lupus nephritis. This was confirmed by preliminary analysis of the ongoing pilot study of MMF in the treatment of lupus nephritis organized by the UK Renal Association Clinical Trials Committee [DRW Jayne, personal communication].

Randomized controlled trials of MMF

Chan et al. reported a randomized controlled trial of 42 patients with WHO Class IV lupus nephritis that compared the effect of MMF (1 g twice daily for 6 months, then 0.5 g twice daily for 6 months), and prednisolone with oral cyclophosphamide (2.5 mg/kg daily for 6 months followed by azathioprine (1.5 mg kg daily) and prednisolone [26]. Both drugs led to comparable rates of complete remission (MMF 81%; cyclophosphamide 76%), partial remission (MMF 14%; cyclophosphamide 14%), deaths (MMF 0%; cyclophosphamide 10%) and relapse (MMF 15%; cyclophosphamide 11%). Infections were more common in the patients treated with cyclophosphamide (33 vs 19%) and amenorrhoea (23%), hair loss (19%) and leukopenia (10%) only occurred in the patients treated with cyclophosphamide. The numbers of patients studied was small and the patients had mild renal impairment. There is, therefore, a requirement for a larger appropriately powered study in patients with proliferative lupus nephritis to study the efficacy and toxicity of prednisolone with MMF as compared with prednisolone and cyclophosphamide.

Conclusion

There has been a substantial improvement in the prognosis in patients with lupus nephritis with an increase in survival from around 60% at 3 years to 80% or higher at 10 years. Nevertheless, the evidence base as reviewed here for the treatments used in the treatment of lupus nephritis is alarmingly slight. The case for designing and carrying out careful controlled trials comparing any new treatments with established therapy is overwhelming.

References


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