Lupus Nephritis—An Enriching Opus

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There has been a continuing quest for better treatments for lupus nephritis over the past few decades. Against the backdrop of a veritable clinical exigency, our group has sought to refine existing treatments and to establish new therapies that can improve patient outcomes. Our original research on mycophenolate mofetil, which demonstrated its efficacy and tolerability, has led to a change in the treatment paradigm for proliferative lupus nephritis. This article reviews our clinical research studies in the different types of lupus nephritis. [Hong Kong J Nephrol 2009;11(1):5–8]

Key words: cyclophosphamide, lupus nephritis, mycophenolate mofetil

INTRODUCTION

Lupus nephritis is an important disease for nephrologists in Asia for three reasons. First, it is common. Indeed, data from mainland China has shown that it is the most common underlying systemic disease leading to renal biopsy [1]. Second, owing to the multifarious manifestations of the disease and its complications, the management of lupus nephritis is both challenging and educational. The clinician must be competent in handling immunosuppression, infections, and other complications related to different medical subspecialties. Also, the degree of clinical complexity often demands both clinical acumen and experience in order for appropriate decisions to be made. Third, and a point that cannot be overemphasized, is that while the disease can be very severe and result in rapidly progressive renal failure, it is also very amenable to available treatments. The long-term prognosis can be favorable provided that diagnosis and treatment are not delayed.

Focal or diffuse proliferative lupus nephritis and membranous lupus nephritis are the varieties that most commonly call for the attention of the clinician. Our group has an established interest in the clinical studies on the therapeutics of lupus nephritis and the basic research into its immunopathogenesis. This article gives an overview of our clinical studies over the past 15 years on severe lupus nephritis.

SEVERE PROLIFERATIVE LUPUS NEPHRITIS

Severe proliferative lupus nephritis typically presents with an acute nephritic syndrome, often accompanied by active serological markers, and results in rapid destruction of nephrons if untreated. Combination therapy with corticosteroid and cyclophosphamide has been the mainstay of immunosuppressive treatment for severe proliferative lupus nephritis since the 1970s, the basis of which is the observation that the addition of cyclophosphamide resulted in more sustained remissions and better renal outcome compared with corticosteroid treatment alone [2,3]. The use of combined corticosteroid and intravenous pulse cyclophosphamide as first-line treatment became popular after reports in the 1980s which demonstrated its efficacy in inducing remission and preventing relapses, and the lower incidence of adverse effects associated with intermittent intravenous

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pulse cyclophosphamide compared with prolonged oral cyclophosphamide treatment. However, despite it being regarded as standard-of-care therapy for severe lupus nephritis, the long-term follow-up data on patients who were treated with this regimen have shown suboptimal renal survival and an alarming association between excessive mortality and cyclophosphamide exposure [4]. There was thus a pressing clinical need for an alternative to cyclophosphamide.

Mycophenolate mofetil—a new paradigm of treatment
The selective inhibitory action of mycophenolate mofetil on lymphocyte proliferation makes it an attractive candidate for the treatment of lupus, and the extensive experience in kidney transplant recipients demonstrating its high efficacy and favorable tolerability provided an encouraging impetus.

It has been more than 8 years since we published our initial results on mycophenolate mofetil in the treatment of lupus nephritis, with that being the first prospective randomized clinical trial to compare mycophenolate mofetil against cyclophosphamide, given together with corticosteroid, in the treatment of diffuse proliferative lupus nephritis [5]. The objective of this proof-of-concept 12-month study was to examine the efficacy and tolerability of combined prednisolone and mycophenolate mofetil treatment, in comparison with our then “standard therapy” of sequential immunosuppression. The latter started with prednisolone and oral cyclophosphamide as induction therapy, given for 6 months, following which cyclophosphamide was substituted with azathioprine. Our results showed comparable efficacy between mycophenolate mofetil-based treatment and sequential immunosuppression, with both regimens inducing complete remission in around 80% and partial remission in 14% of patients. Unresponsiveness to immunosuppressive treatment was not observed. A distinct difference between the two treatments was the incidence and severity of treatment-related adverse effects. Mycophenolate mofetil treatment, at a starting dose of 1 g twice daily, then tapered after 6 months, was generally well tolerated. Leukopenia, alopecia, and amenorrhea were only observed in cyclophosphamide-treated patients. The trend towards fewer infections in the mycophenolate mofetil group that was observed in the 12-month study achieved statistical significance when follow-up was extended to 3 years. The incidence of severe infections that required hospitalization was also lower in the mycophenolate group. The reduced incidence of adverse events during mycophenolate mofetil treatment was associated with a better quality of life and reduced time loss from work compared to cyclophosphamide induction [6]. Our results were subsequently confirmed by other investigators. All the studies have been consistent in demonstrating the efficacy, which is at least comparable to that of cyclophosphamide, and tolerability of mycophenolate mofetil, which is much improved compared with cyclophosphamide. Furthermore, data from our extended observation after approximately 5 years of follow-up showed that the favorable short-term results were associated with a low rate of chronic renal failure [7].

Renal impairment in lupus nephritis can result from variable combinations of acute inflammatory lesions and chronic irreversible damage, and this presents a challenge in the selection and definition of study endpoints [8]. The rates of complete or partial remission are major endpoints in short-term therapeutic studies. Other investigators have previously shown that a follow-up duration of not shorter than 5 years would be necessary to discern the efficacy of a treatment regimen in terms of renal preservation, since deterioration of renal function following nephron loss is a relatively slow and progressive process. Even longer follow-up durations would thus be required to reveal potential differences in renal survival rates when comparing different efficacious treatment regimens that result in a relatively small difference in nephron loss. Our data showed that serum creatinine in both treatment groups, continuous mycophenolate or sequential cyclophosphamide-azathioprine, remained stable over a median follow-up of 63 months [7]. While creatinine clearance increased significantly only in the mycophenolate group, the between-group difference was not statistically significant. A relatively low percentage of patients (6% in the mycophenolate group and 10% in the cyclophosphamide-azathioprine group, \( p=0.667 \)) showed doubling of baseline creatinine during follow-up. Our data also showed that prolonged treatment with mycophenolate mofetil for several years was well tolerated. However, the data to date from our group and others have not shown a significant difference in the rate of disease flares between patients receiving maintenance immunosuppression with mycophenolate mofetil or azathioprine [7,9].

Although the efficacy, high tolerability, and convenience of administration associated with mycophenolate mofetil treatment present distinct advantages, access to therapy could be prohibited by its cost. Although it has been speculated that the high medication cost of mycophenolate can be partly offset by the reduced complications and hospitalization, the financial implications of treatment have remained undefined. Data from our recent study showed that, while the cost of immunosuppressive drugs was approximately 14-fold higher in the mycophenolate mofetil treatment arm compared with cyclophosphamide-azathioprine sequential immunosuppression, the former was associated with an 80% reduction in the cost of treatment and hospitalization for infections. Consequently, the overall treatment expenditure on immunosuppressive drugs, hospitalization and

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treatment of infections was 1.57-fold higher in the mycophenolate group [10].

**MEMBRANOUS LUPUS NEPHRITIS**

In contrast to the proliferative varieties, pure membranous lupus nephritis is less commonly associated with serologic activity, but is characterized by proteinuria and a relatively slow progression of renal function impairment. It is not uncommon to encounter patients whose renal biopsies show both proliferative and membranous features. According to the ISN/RPS 2003 Classification for lupus nephritis, when subepithelial immune deposits or their light-microscopic morphologic sequelae involve ≥50% of the glomerular surface area in at least 50% of glomeruli, membranous lupus nephritis should be diagnosed [11]. In this regard, the clinical course is critically influenced by the concomitant presence of proliferative lesions such as endocapillary proliferation and/or necrosis, since these portend a more aggressive disease process and are more often associated with serologic activity. Accordingly, there is general agreement that in patients with both proliferative and membranous lupus nephritis, the proliferative element is to assume priority with regard to immunosuppressive therapy.

There is marked diversity in the treatment of patients with pure membranous lupus nephritis. Treatment with corticosteroid alone has been associated with a response rate of less than one third. Consequently, patients have been treated with variable combinations of immunosuppressive agents including corticosteroid, azathioprine, and cyclophosphamide, and with inhibition or blockade of the renin–angiotensin system [12]. We have also investigated the efficacy and tolerability of sequential immunosuppression, comprising prednisolone and cyclophosphamide for 6 months followed by low-dose prednisolone and azathioprine maintenance, in membranous lupus nephritis. In a cohort of 20 patients with pure membranous lupus nephritis and nephrotic syndrome, this sequential regimen induced complete remission in 55% and partial remission in 35% of patients within 12 months [13]. None of the patients developed hemorrhagic cystitis or permanent amenorrhea, but 40% had infectious complications, 15% had leukopenia, and 40% of those who achieved remission had subsequent flares. Considering the relatively slow progression of renal failure, it may not be appropriate to subject patients with relatively mild symptoms to treatment regimens that could lead to severe adverse effects.

While the optimal therapy remains to be established, there is accumulating evidence to support a role for calcineurin inhibitors in the management of patients with persistent proteinuria due to membranous lupus nephritis. Tacrolimus offers the advantage of reduced cosmetic adverse effects compared with cyclosporine, which could be important in ensuring patient compliance, although its adverse effects on blood pressure and glycemic control still warrant attention. In a pilot study on patients with membranous or inactive lupus nephritis who showed persistent proteinuria despite angiotensin inhibition and/or blockade, we showed that tacrolimus treatment effectively reduced proteinuria and increased serum albumin, so that >80% of patients had their proteinuria reduced by >50% [14]. In those with biopsy-proven membranous lupus nephritis, the proteinuria improved by >80%. However, in view of the potential nephrotoxicity of these drugs, it is imperative that circulating drug levels be regularly monitored and the lowest effective level be targeted.

In view of the potential adverse effects of the various treatment options, the choice of optimal treatment for membranous lupus nephritis should be informed by the severity of proteinuria. Persistent heavy proteinuria results in immediate complications such as peripheral edema, serous effusions, hypalbuminemia, hypercholesterolemia, and hypercoagulability. Important long-term complications, which may not be evident in the early stage, include accelerated progression of renal failure and cardiovascular disease. Risk versus benefit considerations in the choice of treatment would thus vary according to the degree of proteinuria, with the minimization of proteinuria being an important treatment objective.

**CONCLUSIONS**

It is encouraging that the management of lupus nephritis and the clinical outcome of patients have improved significantly over the past few decades. This is due to advancements in both immunosuppressive treatment and supportive care. Improved immunosuppressive strategies relate not only to their potency, but also to a more advantageous benefit-to-risk ratio. In this regard, the advent of mycophenolate mofetil-based therapy has resulted in a reduced reliance on corticosteroid and a reduced incidence of treatment-related adverse effects compared with previous treatment regimens [15]. It is not difficult to appreciate why mycophenolate mofetil is preferred by doctors and patients, but it is of interest to note that the drug is increasingly covered by health insurance or health care providers despite the absence of formal regulatory approval in most countries. The latter is due to the accumulating favorable frontline clinical experience which confirms the data from clinical trials, and to the efforts of clinicians, patient advocates, and health care administrators. There are, however, outstanding issues that need to be resolved. For example, patients are still exposed to the adverse effects of corticosteroid. The optimal maintenance immunosuppressive
treatment to prevent disease flares also remains to be defined. It is hoped that further research will be able to provide answers to these questions. The research endeavor in lupus is reminiscent of a work of music, with the disparate pace and flavors of the different movements culminating in an enriching experience.

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