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Treatment Options for Proliferative Lupus Nephritis

An Update of Clinical Trial Evidence

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Abstract

Systemic lupus erythematosus involves the kidney in up to 60% of patients, and if untreated, may result in complete loss of kidney function. In this article, we review meta-analyses and clinical trial data on the therapeutic options for proliferative lupus nephritis, and complete a meta-analysis of the use of mycophenolate mofetil (MMF) compared with cyclophosphamide-based regimens. Clinical trials have found that cyclophosphamide-based regimens result in a decreased risk of end-stage renal disease, but are associated with significant toxicity in lupus nephritis. Even though the survival advantage of the US National Institutes of Health and Euro-Lupus regimens based on intravenous and oral cyclophosphamide has not been established, these approaches are broadly adopted in proliferative lupus nephritis. Recent studies have confirmed the therapeutic equivalence and potential comparative superiority of MMF and cyclophosphamide in induction of remission in patients with lupus nephritis. Use of MMF resulted in a lower incidence of infection and loss of gonadal function compared with cyclophosphamide regimens. Cyclophosphamide plus corticosteroids could represent the induction agents of choice in patients with severe lupus nephritis, whereas MMF could be used as an induction agent in patients with mild disease, patients who wish to preserve fertility and those at high risk of infections. However, given the complexity of disease activity in patients with lupus nephritis, the initial treatment options

need to be individualized and altered based on the subsequent treatment response. Ongoing clinical trials will provide further evidence.

Renal involvement occurs in up to 60% of patients with systemic lupus erythematosus (SLE) as a result of the interactions of auto-antibodies, inflammatory cells, the complement system and cytokines in the kidney.[1] Lupus nephritis contributes substantially to the overall mortality in SLE patients even though cardiovascular disease remains the major cause of death in these patients. Twenty percent of these patients develop end-stage renal disease (ESRD) requiring dialysis or renal transplantation at 10-year follow-up.[2] The American College of Rheumatology proposed the following criteria to diagnose and classify renal involvement in patients with lupus: (i) presence of persistent proteinuria of >500 mg/day (or greater than 3+ urine dipstick reaction for albumin); and (ii) presence of cellular casts including red blood cells, haemoglobin, renal tubular cell or mixed.[3] The WHO, International Society of Nephrology and Renal Pathology Society classify lupus nephritis into six categories based on renal biopsy findings: class I – normal; class II – mesangial glomerulonephritis; class III – focal segmental proliferative glomerulonephritis; class IV – diffuse proliferative glomerulonephritis; class V – membranous glomerulonephritis; and class VI – advanced sclerosing lesions.[4] Class I and class II lesions do not warrant treatment given their better renal prognosis, but extra-renal manifestations may require therapy. Patients with severe class III or class IV disease progress to ESRD rapidly and need aggressive immunosuppressive therapy.[1,5] Patients with class V membranous lupus nephritis may not need aggressive therapy given their better renal survival rates, although disease severity may necessitate therapy.[6]

Current treatment options for lupus nephritis have significantly improved both renal prognosis and overall patient survival.[5-8] The 5-year survival rate for patients with lupus nephritis has improved from 60% in the 1960s to over 90% in recent years, secondary to the availability of several immunosuppressive agents.[1] Long-term data from a study that followed 93 patients with proliferative lupus nephritis reported a 97% 10-year survival rate and 82% 20-year survival rate.[9] Hypertension, elevated serum creatinine at the time of the kidney biopsy, African American race and high chronicity indices in the biopsy, including glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis, are associated with an increased risk of chronic kidney disease or death in patients with lupus nephritis.[10,11] High-dose pulse cyclophosphamide therapy (monthly for the first 6 months followed by quarterly infusion) combined with corticosteroids has been widely used in the treatment of proliferative lupus nephritis,[12-17] although this regimen is associated with the risk of premature ovarian failure, infections, and bone and metabolic adverse effects.[18-21] More recently, mycophenolate mofetil (MMF) has been added to the armamentarium of nephrologists for the treatment of lupus nephritis, in the interest of lower toxicity. A few trials have also analysed the efficacy of plasma exchange therapy, ciclosporin, tacrolimus and azathioprine in these patients.

We searched The Renal Health Library[1] for systematic reviews of randomized trials and individual randomized trials analysing the efficacy and safety of any immunosuppressive agents and other treatment options for patients with proliferative lupus nephritis. The systematic review approach to assessment of clinical evidence on the benefits and harms of interventions is of major importance in an era where a large amount of scientific information is available in the literature. Available clinical trial evidence is summarized in Cochrane systematic reviews of randomized controlled trials (RCTs), with specific sections on applicability, implications for practice and implications for research. Cochrane reviews are rigorously conducted and usually in-

1 See http://www.update-software.com/publications/Renal/default.html.

volve two phases: the protocol stage and the actual review. Both steps involve a peer-review process to ensure the higher quality of these reviews.

1. Systematic Reviews on Treatment Options for Lupus Nephritis

The search of the Renal Health Library identified six systematic reviews,[22-27] one of which was conducted by the Cochrane Renal Group (http://www.cochrane-renal.org).[22] The Cochrane systematic review, published in 2004, appeared to be the most comprehensive, and included 25 randomized trials (909 patients). It analysed the efficacy of cyclophosphamide, azathioprine, plasma exchange therapy and MMF in patients with diffuse proliferative nephritis.

In comparison with corticosteroids alone, cyclophosphamide plus corticosteroids was not found to reduce the risk of all-cause mortality significantly (five RCTs, 226 patients, relative risk [RR] 2.18; 95% CI 1.10, 4.34) with no significant heterogeneity between the included studies (test for heterogeneity $I^2 = 0\%$).[13-17] Even though regimens with cyclophosphamide plus corticosteroids significantly reduced the risk of doubling of serum creatinine (four RCTs, 228 patients, RR 0.59; 95% CI 0.40, 0.80), they were not found to significantly affect the long-term outcome of ESRD (five RCTs, 278 patients, RR 0.63; 95% CI 0.39, 1.03). There was significant heterogeneity between the included studies in these analyses ($I^2 = 49\%$). This could be attributed to the different treatment regimens used, different treatment duration and different study populations in the included studies. Combined treatment with cyclophosphamide plus corticosteroid resulted in a higher incidence of ovarian failure when compared with corticosteroids alone (three RCTs, 147 patients, RR 2.18; 95% CI 1.10, 4.34) with no significant heterogeneity between the included studies ($I^2 = 11.8\%$). The combination of cyclophosphamide plus corticosteroids was found to be associated with similar infection rates compared with corticosteroids alone (six RCTs, 291 patients, RR 0.87; 95% CI 0.50, 1.51) with no significant heterogeneity between the included studies ($I^2 = 0\%$). In summary, studies clearly favoured the use of the combination regimen in terms of renal outcomes, but not survival.

Azathioprine with corticosteroids conferred a survival advantage compared with corticosteroids alone (three RCTs, 78 patients, RR 0.60; 95% CI 0.36, 0.99), but no significant reduction in the risk of ESRD or doubling of serum creatinine levels was observed, but these data were derived from only two available trials (n = 54 patients). Azathioprine-based regimens did not result in a higher incidence of major infections (four RCTs, 94 patients, RR 0.74; 95% CI 0.08, 6.91). This review did not identify any 'head to head' trial of cyclophosphamide versus azathioprine. Because of the paucity of evidence, this regimen is not recommended for induction therapy.

Finally, plasma exchange with cytotoxic agents compared with cytotoxic agents alone did not reduce mortality (two RCTs, 125 patients, RR 1.62; 95% CI 0.64, 4.09) or progression to ESRD (three RCTs, 143 patients, RR 1.24; 95% CI 0.60, 2.57) with no significant differences in the toxicity profile. At the time of publication of this meta-analysis, there was also only one small RCT (n = 42) that analysed the efficacy of MMF plus corticosteroids versus cyclophosphamide plus corticosteroids for induction therapy of lupus nephritis.[28] Both agents had similar efficacy in inducing remission of lupus nephritis.

2. Recent Evidence on the Role of Mycophenolate Mofetil

The major focus of recent trials in proliferative lupus nephritis has been for use of MMF, a selective inhibitor of the inosine monophosphate dehydrogenase enzyme that causes a selective blockade of B-cell and T-cell proliferation. Use of MMF was found to be beneficial for both survival and renal function in animal models with lupus disease.[29] In the 1990s, numerous case series reported the benefits of MMF in patients whose disease had progressed while receiving conventional immunosuppressive agents or who did not tolerate these agents because of adverse events.[30] RCTs were warranted, and five have been published (in six publications) that ana-

lyse the efficacy of MMF in patients with lupus nephritis.[28,31-35] Four systematic reviews have evaluated the efficacy of MMF in lupus nephritis alone.[24-27]

Among the five available studies, three studies addressed the role of MMF as an induction agent compared with intravenous cyclophosphamide-based regimens.[32,33,35] One study, by Chan et al.,[28,34] analysed MMF as both induction and maintenance therapy, and a study by Contreras et al.[31] analysed the role of MMF as a maintenance therapy after induction therapy with intravenous cyclophosphamide in patients with lupus nephritis. Two studies included Asian patients alone,[34,35] the study by Contreras et al.[31] included predominantly Hispanic and Black patients and a study by Ginzler et al.[32] included predominantly African Americans. All these trials enrolled patients with WHO class III or IV lupus nephritis patients alone. The characteristics of the populations and interventions studied in these trials are reported in table I.

Induction doses for MMF ranged from 1.5–3.0 g/day and the maintenance doses ranged from 0.5–3.0 g/day. Most of the studies were of rather short duration (6–12 months), except for the studies of Contreras et al.,[31] which had a follow-up of 72 months, and Chan et al.,[28,34] which had a follow-up of 63 months. The outcomes analysed in these studies were complete or partial remission of disease activity, patient survival, and adverse events with particular focus on infections, gastrointestinal symptoms and malignancies. Complete remission was usually defined as a significant reduction of proteinuria, reversal or preservation of baseline renal function and improvement in urine sediments.

The primary outcomes in most of the trials were (i) complete remission, defined as proteinuria <0.3 g/day, normal urine sediment, normal serum albumin levels, stabilization or improvement or normalization of renal function as measured by serum creatinine; and (ii) patient and renal survival. The secondary outcomes were (i) partial remission, defined by stable or improved renal function with reduction of proteinuria by >50%, proteinuria within the range of 0.3–3 g/24 hours and serum albumin >30 g/L; (ii) renal relapse, as defined by a doubling of urinary protein : creatinine ratio or by an increase in serum creatinine level of 50% or more for more than 1 month; (iii) adverse effects such as amenorrhoea, hospitalization, infection, hair loss; and (iv) improvement in the SLEDAI (systemic lupus erythematosus disease activity index) score or complement concentration.

In our meta-analysis, in comparison with cyclophosphamide-based regimens, MMF used either as an induction agent or a maintenance agent resulted in an reduced all-cause mortality rate (five RCTs, 306 patients, RR 0.35; 95% CI 0.14, 0.86) [figure 1].[26] Progression to ESRD (five RCTs, 324 patients, RR 0.66; 95% CI 0.25, 1.70) and complete remission of nephritis (five RCTs, 325 patients, RR 1.36; 95% CI 0.82, 2.24) did not differ between the two regimens (figure 2 and figure 3). MMF had a better safety profile than cyclophosphamide-based regimens with lower rates of infections (four RCTs, 284 patients, RR 0.53; 95% CI 0.34, 0.83) [figure 4] and amenorrhoea (three RCTs, 259 patients, RR 0.22; 95% CI 0.06, 0.81). There was no significant heterogeneity between the included studies in this analysis.[26]

3. Recent Trials on Other Immunosuppressive Agents

3.1 Ciclosporin

Moroni et al.[36] compared the efficacy of ciclosporin and azathioprine as a maintenance agent in 75 patients who received cyclophosphamide induction therapy for diffuse proliferative lupus nephritis. At the end of 4-year follow-up, the reduction in proteinuria was similar in both groups, and the number of lupus flares was also similar.

3.2 Azathioprine

Grootscholten et al.[37] randomized 87 patients with proliferative lupus nephritis to pulse cyclophosphamide or azathioprine plus pulse methylprednisolone for 2 years, followed by azathioprine and prednisone in both groups for 3 years. At the end of a median follow-up of 5.7 years, there were

Table I. Characteristics of studies that analysed the efficacy of mycophenolate mofetil (MMF) compared with cyclophosphamide (CYC)-based regimens for diffuse proliferative lupus nephritis diagnosed by biopsy

Study (year)	WHO class of lupus nephritis; proteinuria; serum creatinine	Intervention	No. of pts	Duration of treatment (mo)	Follow-up (mo)	Outcomes
Chan et al.[28,34] (2000, 2005)	Class IV; >1 g in 24 h; <3.4 mg/dL	Oral MMF 1 g twice daily plus oral prednisolone vs CYC 2.5 mg/kg/d plus prednisolone for 6 mo followed by MMF 500 mg twice daily vs AZA 1 mg/kg/d for another 6 mo	62	12	63	Primary endpoint: complete remission (proteinuria <0.3 g/d, normal urine sediment, normal serum albumin) Secondary endpoint: partial remission, adverse effects, doubling of serum creatinine, relapse of lupus, death
Flores-Suarez and Villa[33] (2004)	Class IV or V NA NA	Oral MMF 2 g/d plus oral prednisone vs IV CYC once a mo plus oral prednisone	20	12	12	Primary endpoint: complete remission (proteinuria <0.3 g/d, normal urine sediment, normal serum albumin, no extra-renal symptoms) Secondary endpoint: partial remission, death
Contreras et al.[31] (2004)[a]	Class III and IV; >2 g/d; NA	Induction therapy with IV CYC plus oral CS for 7 mo followed by randomization to 0.5–1.0 g/m^2 of IV CYC every 3 mo or oral AZA 1–3 mg/kg/d or oral MMF 500–3000 mg/d	59	CYC 25 AZA 30 MMF 29	72	Primary endpoint: patient and renal survival Secondary endpoint: renal relapse, increase of serum creatinine >50%, hospitalization, infections
Ong et al.[35] (2005)	Class III or IV; NA; NA	Oral MMF 1.0 g twice daily plus CS vs IV CYC 0.75–1 g/m^2 every mo plus CS	44	6	36	Primary endpoint: remission of nephritis (improvement or stabilization of renal function, reduction of proteinuria) Secondary endpoint: SLEDAI score, complement concentration, commencement of RRT, death
Ginzler et al.[32] (2005)	Class III or IV or V; >2 g/d; 1.0–3.0 g/dL	Oral MMF 500–1000 mg two or three times daily plus oral prednisone vs IV CYC based on NIH protocol every mo plus oral prednisone	140	6	36	Primary endpoint: complete remission (normalization of renal function-serum creatinine, proteinuria and urine sediment) Secondary endpoint: partial remission, changes in auto-antibody and complement levels

a Excluded pts with creatinine clearance <20 mL/min.

AZA = azathioprine; **CS** = corticosteroids; **IV** = intravenous; **NA** = not available; **NIH** = National Institutes of Health (USA); **pts** = patients; **RRT** = renal replacement therapy; **SLEDAI** = systemic lupus erythematosus disease activity index.

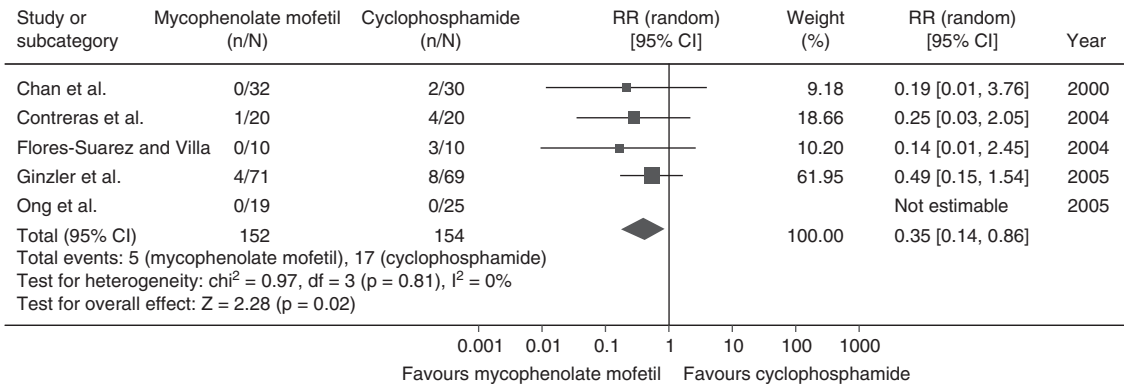

Fig. 1. Meta-analysis of all cause mortality rates in clinical trials comparing mycophenolate mofetil with intravenous cyclophosphamide-based regimens. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled relative risk (RR) plus 95% confidence interval.[28,31-35]

more relapses and an insignificant doubling of serum creatinine levels in the azathioprine group compared with placebo.

3.3 Abetimus

A 76-week, double-blind, placebo-controlled study[38] enrolling 230 patients with lupus nephritis compared abetimus (LJP 394), a novel drug, with placebo. Abetimus is an immunomodulatory agent that reduces the anti-double-stranded DNA levels and therefore the risk of renal flare in lupus nephritis. Patients were randomized to receive 16 weekly doses of abetimus 100 mg or placebo, followed by alternating 8-week drug holidays and 12 weekly doses of abetimus 50 mg or placebo. Treatment with abetimus in patients with high-affinity antibodies to its DNA epitope prolonged the time to renal flare, decreased the number of renal flares and decreased the requirement for high-dose corticosteroids and/or cyclophosphamide treatments compared with placebo.

3.4 Rituximab

Several case reports and case series have reported the beneficial effects of rituximab and intravenous

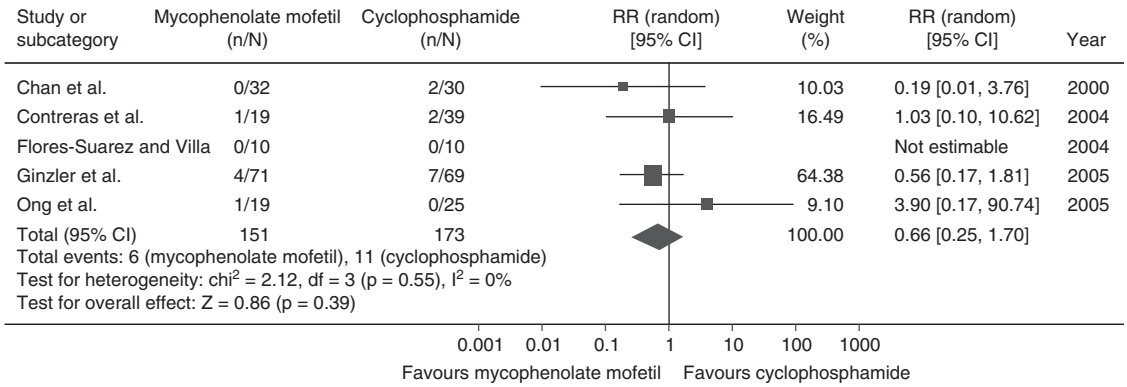

Fig. 2. Meta-analysis of development of end-stage renal disease in clinical trials comparing mycophenolate mofetil with intravenous cyclophosphamide. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled relative risk (RR) plus 95% confidence interval.[28,31-35]

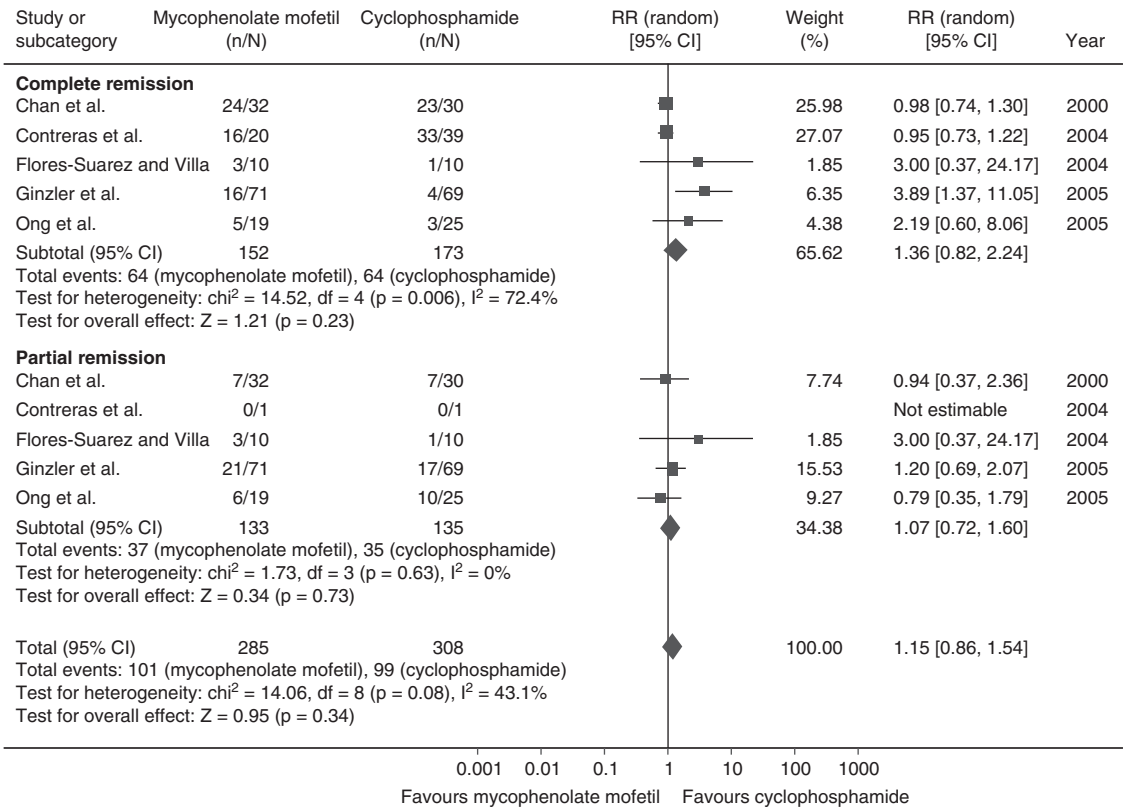

Fig. 3. Meta-analysis of complete and partial remission of lupus nephritis in clinical trials comparing mycophenolate mofetil with intravenous cyclophosphamide. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled relative risk (RR) plus 95% confidence interval.[28,31-34]

immunoglobulins, but clinical trial evidence on these agents is lacking.[39,40]

4. Implications for Practice

Current clinical trial evidence shows that induction therapy with high-dose pulse intravenous cyclophosphamide plus corticosteroids has been well studied and has been compared with various therapeutic options that are available today (azathioprine-based regimen, low-dose cyclophosphamide regimen, MMF-based regimen). This regimen has become the standard induction protocol in the US after the publication of the US National Institutes of Health [NIH] trials, published first in 1986 (original study) and later on in 1992, 1996 and 2001 (follow-up data from the original study).[13-16] Use of this induction regimen results in improved renal outcomes but does not provide a survival advantage. Also, this regimen carries the risk of a higher incidence of serious infections and amenorrhoea (40–50%) compared with other regimens.

The Euro-Lupus regimen (low-dose cyclophosphamide) is being used in European centres, based on the results of Euro-Lupus Nephritis trial.[17] The major differences between the NIH and Euro-Lupus Nephritis trials are the type of patient population enrolled and the degree of renal insufficiency. The NIH trials enrolled patients with severe kidney disease, in contrast to the Euro-Lupus Nephritis trial, which enrolled patients with mild disease (mean creatinine 1.0–1.3 mg/dL). This trial included mostly White patients, in contrast to the NIH trials, which

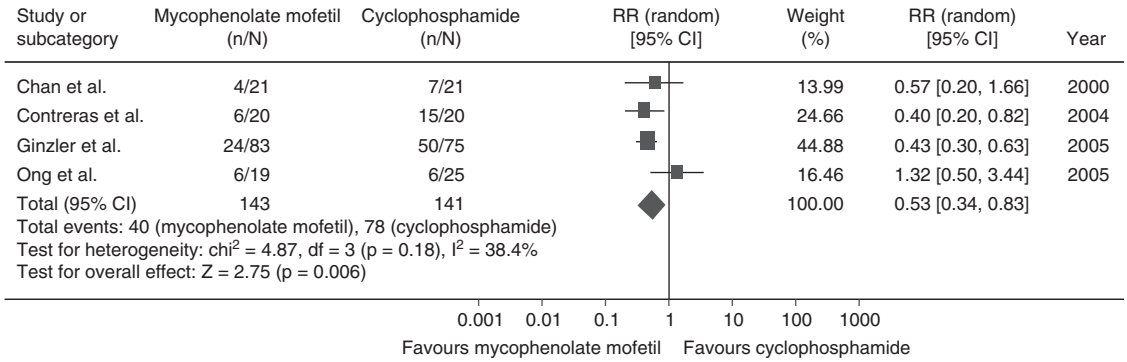

Fig. 4. Meta-analysis of the incidence of infections in patients treated with mycophenolate mofetil compared with intravenous cyclophosphamide. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled relative risk (RR) plus 95% confidence interval.[28,31,32,34,35]

enrolled predominantly African American patients, who have a poorer prognosis. The response rates to the induction regimen and remission rates at 5 years for African American patients have been low compared with White patients.[41] Thus, it seems appropriate to use low-dose regimens in patients with mild proliferative lupus nephritis and White patients, and high-dose pulse therapy in African American patients and patients with severe lupus nephritis.

Recent clinical trials analyzing the efficacy of MMF as an induction and maintenance agent have shown consistent and equivalent benefits in comparison with intravenous cyclophosphamide-based regimens. This has the added advantage of lower infection and infertility rates. Given the high incidence of lupus nephritis in women of childbearing age, this regimen with fewer infertility rates is an attractive option. Furthermore, patients with lupus nephritis need treatment for a long time and the fewer infection rates might reduce hospitalization and subsequent deaths. Two studies analyzing MMF have included predominantly Asian patients,[34,35] and in two studies (Ginzler et al.[32] and Contreras et al.[31]), >50% of participants were African American patients. However, MMF is at least ten times more expensive than other immunosuppressive regimens. Most of the RCTs analysing MMF included patients with mild renal disease, and long-term studies analysing its efficacy and safety are lacking. The studies that analysed MMF enrolled patients with varying disease severity and the duration of MMF therapy differed. Even though the published meta-analyses[24-27] on this topic did not find statistical heterogeneity for most major outcomes, biological heterogeneity is a possibility, especially in patients with lupus nephritis who have complex disease activity. Thus, the decision to use MMF should be based on various factors, such as the severity of disease, risk of developing infections and the patient's desire to preserve fertility.

Physicians should also consider the fact that infections are the most frequently reported adverse effects of pulse corticosteroids, occurring more often in patients with SLE than in other patients receiving corticosteroids.[42] Several other adverse effects, such as seizures, mania and psychoses, have been reported with pulse corticosteroids.[42] More importantly, long-term adverse effects, such as osteoporosis and skin changes, are well known, which reduces the compliance rates, resulting in higher relapse rates. These factors should also be considered when choosing the induction agent.

Results of a phase III trial that aimed to analyse the superiority of MMF over cyclophosphamide for induction therapy recently became available.[43] This study enrolled 369 patients and did not find any difference between MMF and cyclophosphamide for the primary outcome 'treatment response', which was defined as a decrease in protein-

uria and the stabilization or improvement of serum creatinine. The safety profile was similar in both arms.[43] Wang et al.[44] compared MMF and cyclophosphamide as induction therapy in patients with class IV lupus nephritis with non-inflammatory necrotizing vasculopathy (NNV). They found that MMF was superior to cyclophosphamide in inducing complete remission of lupus nephritis with NNV and had a better safety profile.[44]

In summary, intravenous cyclophosphamide plus corticosteroids would be the induction agent of choice in patients with severe proliferative lupus nephritis (patients with severe class III or class IV lupus nephritis), whereas MMF could be used in patients with mild renal insufficiency, patients who wish to preserve fertility and patients who are at high risk of infections. Azathioprine or MMF can be used as a maintenance agent. Ciclosporin is also evolving as an alternative agent for maintenance therapy. Physicians should recognize the differences among the regimens included in the clinical trials, and the treatment regimens need to be tailored in accordance with several factors, such as age, gender, baseline kidney function, patient preference and cost. The standard of care for chronic kidney disease, which includes ACE inhibitors and/or angiotensin II type 1 receptor antagonists and lipid lowering therapies, should be appropriately followed for all patients with proliferative lupus nephritis.

5. Implications for Research

With the rapid growth of science and technology, newer medications are introduced into the market, and the efficacy and the need for older agents gets reassessed. With the availability of MMF, the need for intravenous cyclophosphamide-based regimens might decrease (given the higher complication rates of this treatment). However, long-term data on MMF are lacking, and MMF has only been studied in patients with mild renal impairment and it needs to be studied in patients with severe renal dysfunction. Further cost-effectiveness analysis on the use of MMF compared with intravenous cyclophosphamide may also be conducted. There are several ongoing studies assessing the efficacy of MMF and other agents such as tacrolimus, abetimus, leflunomide and rituximab as both induction and maintenance agents.[45] Given the smaller number of patients available for inclusion in clinical studies, long-term follow-up of these studies should also be planned and large multicentre research efforts put in place.

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