Concise report

Maintenance therapy of lupus nephritis with mycophenolate or azathioprine: systematic review and meta-analysis

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Abstract

Objective. The objective of this study was to summarize the comparative efficacy and safety of MMF and AZA as maintenance therapy for LN.

Methods. Systematic review and meta-analysis of randomized clinical trials of MMF and AZA as maintenance therapy for LN were performed based on a sensitive search. Meta-regression was used to explore causes of heterogeneity. Safety was explored using crude and combined incidence rate ratios (IRRs) of the more frequent adverse events (AEs).

Results. The search produced 7341 hits. Four randomized clinical trials and one long-term study were selected for detailed analysis. No significant differences between MMF and AZA were found in sustained remission, relapse, renal failure, creatinine increase or death. However, there was high heterogeneity in the design of studies, drug doses and treatment in the previous induction phase. Significant lower rates of discontinuation due to AEs occurred in the MMF group, with a relative risk (RR) of 0.60 (95% CI 0.41, 0.88) but significant risk of publication bias (Egger test, \( P = 0.012 \)). Gastrointestinal manifestations were more common [combined IRR 1.68 (95% CI 1.06, 2.68)] and leucopenia less frequent in the MMF group [combined IRR 0.14 (95% CI 0.05, 0.42)].

Conclusion. The available data does not support the superiority of MMF or AZA as maintenance therapy for LN. Nevertheless, the high heterogeneity of studies included in the analysis makes this contention questionable.

Key words: lupus nephritis, azathioprine, mycophenolate mofetil.

Introduction

SLE is a complex autoimmune disease with multiorgan involvement. The course is usually characterized by remissions and relapses [1, 2]. LN is one of the most severe complications of this disease. It is estimated to affect up to 60% of adult patients with SLE [3]. Different types of LN ranging from mild mesangial proliferation to severe epithelial/endothelial proliferation progressing to glomerular sclerosis may ensue. Severe renal involvement in the absence of proper treatment leads to progressive deterioration of renal function and increased morbidity and mortality [4]. Therefore a main objective of the treatment of LES is the sustained control of LN to normalize renal function or to prevent the progressive loss of renal function.

Treatment of severe LN consists of an induction phase and a maintenance phase. Generally, high doses of corticosteroids and CYC are used as induction treatment of patients with International Society of Nephrology/Renal Pathology Society class III or IV disease. The new recommendations of the European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) also consider the possibility of induction with MMF [5]. No significant difference in efficacy between CYC and MMF as induction
therapy in LN was reported in meta-analyses [6, 7]. Because CYC therapy may cause a significant number of adverse events (AEs), including malignancy, the maintenance phase of the treatment consists of a combination of low doses of corticosteroids and MMF or AZA. However, the superiority of MMF vs AZA is disputed. One previous meta-analysis of MMF and AZA as maintenance therapy did not include all outcomes and the safety analysis was incomplete [8]. In the present review we summarize the efficacy and safety of MMF and AZA as maintenance therapy for LN, expanding the outcomes and the safety profile.

Materials and methods

A systematic literature review was performed to identify all publications that compared the efficacy and safety of MMF and AZA as maintenance treatment in LN. The protocol of the review is available by email upon request. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus was followed for the review and meta-analysis [9].

Systematic literature research

Medline, Embase and the Cochrane Library were searched for articles published between 1960 and March 2013. The search strategy focused on synonyms for LN, MMF and AZA (see details in Search in PubMed section, supplementary data, available at Rheumatology Online) and was limited to articles published in English, Spanish, French, Italian or Portuguese.

Selection of articles

The selection criteria for articles were (i) inclusion of patients with LN, (ii) MMF and AZA were compared as maintenance treatment, (iii) efficacy and/or safety were available and (iv) the studies were intervention studies. Two reviewers (J.R.M. and N.L.C.) screened articles and abstracts for selection criteria independently, using a third reviewer (E.S.) for consensus. Once unrelated articles were excluded, the full report of all the selected studies was reviewed. Subsequently articles not fulfilling all selection criteria were excluded. In addition, a hand search of articles found in the reference lists of the included articles was made.

Data extraction

Data collected included publication details, study design, characteristics of patients, treatment results, definition of response and safety results. The definition of variables of response is in supplementary Table S1, available at Rheumatology Online.

Risk of bias

The quality of studies was analysed using the Jadad scale [10]. The level of evidence was analysed according to Levels of Evidence of the Oxford Centre for Evidence Based Medicine.

Statistical analysis

Meta-analyses were performed using the random-effects approach with the DerSimonian and Laird method for computing summary relative risks (RRs) [11]. Meta-analysis was only planned if at least three studies or sub-analyses with similar designs were available. For each available analysis, the effect was plotted by the inverse of its standard error to identify the risk of publication bias, assessing visually the symmetry of funnel plots, and its statistical significance using the Egger test [12]. Heterogeneity was tested as proposed by Higgins and Thompson using $I^2$ [13, 14]. An $I^2$ value $>$40% was arbitrarily chosen as a high level of heterogeneity. If high statistical heterogeneity was present, possible explanations were investigated using sensitivity analysis and meta-regression. In the safety analysis, AEs were expressed using the incidence rate (IR). Differences in the more frequent AEs between MMF and AZA were calculated using crude and combined IR ratios (IRR) by the Mantel-Haenszel method. A $P$-value <0.10 was considered significant in the meta-regression and $P < 0.05$ was considered significant in other analyses. Stata software (Stata/IC 11.1 for Windows, StataCorp, College Station, TX, USA) was used in all statistical analysis.

Results

The search captured 7341 references. After title and abstract screening, 41 articles were retrieved for full-text review. A total of 36 articles were excluded after detailed review (supplementary Fig. S1 and Table S2, available at Rheumatology Online). Five articles fulfilled the inclusion criteria [15–19]. A total of 433 patients were included in four randomized clinical trials and one long-term study. Details of selected the articles, populations and treatments are presented in Table 1. The results of individual studies are shown in supplementary Table S3, available at Rheumatology Online. Three studies analysed sustained remission as outcome and no significant differences were observed between MMF and AZA [16, 18, 19]. The meta-analysis showed an RR of 1.01 (95% CI 0.89, 1.14) and an $I^2$ of 0% (Fig. 1). The Egger test was not significant ($P = 0.757$). Four studies analysed relapse as outcome [16–19]. Only one study showed significantly lower rates of relapse in the MMF group [18]. The meta-analysis showed an RR of 0.69 (95% CI 0.48, 1.00) with an $I^2$ of 0%. The Egger test was not significant ($P = 0.943$). Four articles analysed renal failure as an outcome and no significant differences were observed [16–19]. The meta-analysis showed an RR of 0.36 (95% CI 0.10, 1.33) with an $I^2$ of 0%. The Egger test was significant ($P = 0.043$). Four articles analysed a doubling of serum creatinine from baseline as an outcome and no significant differences were observed between MMF and AZA [16–19]. The meta-analysis showed an RR of 0.52 (95% CI 0.21, 1.26) with an $I^2$ of 0%. The Egger test was significant ($P = 0.043$).

Four studies reported no differences in the rate of death in the MMF and AZA groups [16–19]. This meta-analysis
showed an RR of 0.96 (95% CI 0.28, 3.25) with an $I^2$ of 5.8%. The Egger test was not significant ($P=0.939$). Three studies reported data on discontinuation of treatment for AEs [16, 18, 19]. One showed a significantly lower rate of suspension in the MMF group [18]. The meta-analysis showed an RR of 0.60 (95% CI 0.41, 0.88) with an $I^2$ of 0% (Fig. 1). The Egger test was significant ($P=0.012$).

The results of the crude and combined IRR of AEs are shown in supplementary Table S4 available at Rheumatology Online. Gastrointestinal manifestations (including nausea, vomiting and diarrhoea) were more frequent in the MMF than AZA group, with a combined IRR of 1.68 (95% CI 1.06, 2.06). Leucopenia was less frequent in the MMF group, with a combined IRR of 0.14 (95% CI 0.05, 0.42). No differences were found for other AEs such as infections, serious infections, herpes zoster or pneumonia. Three tumours were reported in the five studies included in the review. Two were cervical carcinoma [19] and the other an in situ uterine carcinoma [18]. All tumours occurred in the AZA group. This IRR could not be calculated for AEs due to the absence of events in the MMF group.

**Discussion**

In the present study we summarize the comparative data about the efficacy and safety of MMF and AZA as maintenance therapy for LN. These data are limited, but suggest no significant differences in the efficacy and safety of these drugs.

Our study has several limitations. First, the meta-analysis aggregated results from clinical trials with high heterogeneity in design, drug doses and treatment of the induction phase. Also, the quality of studies was low. Only one randomized, double-blind trial compared the efficacy and safety of MMF and AZA [18]. Another important limitation was the heterogeneity in variable definitions. Our study has several strengths, including consistency and the absence of significant heterogeneity in the results and no significant risks of publication bias in the included articles.

A meta-analysis of safety was not done because of the low frequency of some events and the expression of events as IR per 100 patients-years. However, to analyse differences in safety the IRRs of the most frequent AEs were calculated for MMF compared with AZA.

MMF is used as an immunosuppressant in transplant medicine. It seems superior to AZA at preventing graft rejection. However, in our analysis, no significant differences were found in efficacy. Nevertheless, a meta-analysis of relapse as a surrogate for lack of efficacy suggests a lower risk for MMF. The one randomized, double-blind trial showed relapse with MMF was less frequent than with AZA [18].

Meta-analysis of mortality showed no differences between the MMF and AZA groups. Interestingly, discontinuation due to AEs was significantly lower with MMF than with AZA. The majority of patients treated with MMF as maintenance therapy were treated with MMF as induction therapy. Patients at risk of discontinuing because of AEs or inefficacy were probably excluded in the induction
phase, hence their number in the maintenance phase was lower.

Results of subanalyses suggest a difference in response to the different regimens of induction and different populations. In patients with low estimated GFR, MMF may be faster in recovering kidney function compared with CYC [20]. Also, MMF may present advantages in response in Black and Hispanic patients [21]. However, these data could not be proved in the meta-analysis due to the small number of observations.

Although the safety profile of MMF and AZA was not significantly different, there were some variations. As expected, gastrointestinal AEs were more common with MMF and leucopenia was more common with AZA. This is not surprising because these are common AEs of these drugs [22-25]. Three malignancies were reported: two cervical carcinomas and one uterine carcinoma in situ in the AZA group. A relationship to previous use of CYC cannot be excluded [26].

In conclusion, no significant differences in efficacy and safety were seen between MMF and AZA as maintenance treatment of LN. Nevertheless, the high heterogeneity of the studies included in the analysis make this contention questionable.

### Rheumatology key messages

- Data of comparative efficacy and safety of MMF and AZA in maintenance treatment of LN is limited.
- No significant differences in efficacy and safety appear between MMF and AZA in LN.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References