**Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression**

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**Objective.** Since mycophenolate mofetil (MMF) has emerged as an immunosuppressant for treating proliferative lupus nephritis, the role of cyclophosphamide (CYC)-containing regimens is being challenged. Efficacy data from randomized controlled trials (RCTs) and previous meta-analyses comparing these two agents for treating lupus nephritis have been inconsistent as they were heterogeneous in design and of small sample size. An updated meta-analysis is therefore required.

**Methods.** Publications in the English literature were searched with the keywords ‘mycophenolate’, ‘mycophenolic’, ‘lupus nephritis’, ‘nephritis’ and ‘glomerulonephritis’ for RCTs in electronic databases. Primary outcome was relative risk (RR) of renal remission at 6 months. Secondary outcome included RRs of mortality, development of end-stage renal failure (ESRF) and side effects. Meta-regression was performed to identify factors explaining the heterogeneity of the effect sizes.

**Results.** Ten eligible RCTs involving 847 patients were included. MMF offers similar efficacy in inducing renal remission as CYC (RR 1.052; 95% CI 0.950, 1.166) and the risks of death (RR 0.709; 95% CI 0.373, 1.347) and ESRF (RR 0.453; 95% CI 0.183, 1.121) were comparable. Significantly fewer patients receiving MMF developed amenorrhoea (RR 0.212; 95% CI 0.094, 0.479) and leucopenia (RR 0.473; 95% CI 0.269, 0.832) while the risks of herpes infection and pneumonia tended to be lower and that of diarrhoea appeared higher in the MMF groups. Meta-regression revealed that the non-white and non-Asian ethnicities contributed significantly to the heterogeneity of the effect sizes of renal remission.

**Conclusion.** MMF offers similar efficacy in renal remission and survival as CYC. MMF appears safer than CYC in the treatment of proliferative lupus nephritis.

**Key words:** Mycophenolate, Cyclophosphamide, Lupus, Nephritis, Meta-analysis, Meta-regression.

**Introduction**

SLE is a multisystemic autoimmune disease with protean clinical manifestations and organ involvement. Proliferative glomerulonephritis (GN) is one of the most important organ manifestations of lupus affecting between one-half and two-thirds of patients during their disease course, leading to significant morbidity and mortality [1–3]. Although cyclophosphamide (CYC)-containing regimens have long been considered a gold standard in inducing renal remission and preventing renal flares for patients with proliferative lupus GN [3, 4], its significant toxicities raise a number of concerns [5]. Further, while CYC induces renal remission in a significant proportion of patients with proliferative lupus GN, the rate of disease relapse is considerable. Observational studies have demonstrated that the 5-year cumulative rate of renal relapse was as high as 44% [6, 7] and up to 15% of the patients with diffuse proliferative GN were refractory to CYC [8, 9].

Mycophenolate mofetil (MMF), a lymphocyte selective anti-proliferative agent which was first introduced into clinical use over a decade ago for preventing solid organ transplant rejection, has emerged as an efficacious and safe immunosuppressive agent for a number of lupus-related conditions [10–14]. The use of MMF in proliferative lupus GN has been repeatedly tested in a number of controlled trials [15–25]. While the majority of these trials showed that MMF was well tolerated and had a more favourable safety profile than CYC, whether MMF is more efficacious than CYC for inducing renal remission, preventing flares and prolonging survival is still uncertain because results from these trials which included relatively small numbers of patients with short duration of observation, have not been in complete agreement. Although three systemic reviews have been published in an attempt to answer these questions [26–28], the results of these meta-analyses are inconsistent, chiefly because of the small number of trials included, small sample sizes of the trials and the lack of uniformity of methodology used in these analyses. Additionally, heterogeneity of the trials and the potential factors which contribute to heterogeneity were not examined in the previous meta-analyses. We therefore carried out this meta-analysis with an aim to compare the efficacy and safety of MMF and CYC in the treatment of proliferative lupus GN by including the most recently published large randomized controlled trials (RCTs), conducting sensitivity analyses to test the robustness of the effect sizes and exploring trial- and patient-related factors which potentially contribute to heterogeneity of the trials by meta-regression.

**Materials and methods**

**Search strategy**

We performed an extensive literature search using the relevant keywords of ‘mycophenolate’, ‘mycophenolic’, ‘lupus nephritis’, ‘nephritis’ and ‘glomerulonephritis’ to identify RCTs published in the English language from different computerized databases: PubMed (1966 to April 2008), EMBASE (1980 to January 2008) and the Cochrane Central Register of Controlled Trials (2nd quarter of 2008). Abstracts presented in major international conferences (Annual European Congress of Rheumatology, International Congress on SLE and ACR meeting) over the past 10 years were manually searched. We also scanned the articles from the bibliographies of the retrieved trials and review articles.
The authors of correspondence were contacted for obtaining information essential for this meta-analysis which was lacking in the published articles.

Criteria for selecting articles included in this meta-analysis
All trials which randomly assigned patients to receive either MMF or CYC for the management of proliferative lupus GN were included. RCTs were included if they met the following criteria: (i) compare MMF and CYC as induction and/or maintenance therapy; (ii) concomitant therapy with corticosteroids equally to both treatment arms; and (iii) at least one of the following four outcomes were reported: mortality, end-stage renal failure (ESRF), achievement of complete and partial renal remission at 6 months and common adverse effects including herpes zoster infection, pneumonia, leucopenia, amenorrhoea and diarrhoea.

Four investigators (A.M., J.Y.S.T., R.C.M.H. and H.C.S.) independently assessed the papers generated for relevancy and papers with the following exclusion criteria were excluded: (i) not written in English for abstract; (ii) not comparing MMF and CYC in treating proliferative lupus GN; and (iii) investigating patients with pure membranous lupus GN. Data were independently extracted into a standard electronic data extraction form. Any discrepancies were resolved by consensus. If consensus could not be reached, the principal investigator (A.M.) would make the final decision for trial eligibility and data extraction. The senior author (C.S.L.) is the overall advisor of this meta-analysis.

Outcome measures of this meta-analysis
The primary outcome was the proportion of patients who achieved complete and partial renal remission at 6 months after induction therapy with MMF or CYC. The definition of complete and partial renal remission of this meta-analysis was based on individual studies’ remission criteria, which were essentially similar to one another. Secondary outcome measures included the proportion of patients who died, developed ESRF and the occurrence of events in the secondary outcomes would be higher with longer duration of treatment and/or observation.

Assessment of quality of trial
The quality of each trial was assessed according to a standard scoring system proposed by Jadad et al. [29]. The assessment was based on: (i) whether the randomization method was appropriate, (ii) whether double blindness is mentioned in the trial and whether it was appropriately performed; and (iii) whether the number of patients of and the reasons for withdrawal and drop-outs were clearly stated. The score ranges from 0 to 5 with higher scores denoting better quality of a trial.

In order to comply with the Cochrane Handbook for Systematic Reviews of Interventions in terms of quality assessment of the RCTs [30], we additionally assessed whether proper allocation concealment during randomization was performed in the RCTs eligible for this meta-analysis because allocation concealment is not assessed in the system suggested by Jadad et al. [29].

Statistical analysis
The proportion of patients who achieved renal remission at 6 months following induction therapy with either MMF or CYC was pooled for combined relative risk (RR). The RR of the pre-defined secondary outcomes at the end of the study period were pooled. Effect sizes of both the primary and secondary outcomes were expressed as RR and the corresponding 95% CI.

Heterogeneity was assessed by the Cochran Q-test. Since the number of trials of this meta-analysis is relatively limited, the Cochran Q-test for heterogeneity may yield a low statistical power [31]. A value of significance at 10% (P ≤ 0.1) was therefore considered statistically significant for heterogeneity [32]. Furthermore, we assessed heterogeneity with I², which describes the percentage of total variation across studies caused by heterogeneity rather than chance. High values of I² suggest increased heterogeneity. The fixed effects model was used for statistically significant homogeneous studies. If considerable heterogeneity (arbitrarily if I² > 40) was encountered, we applied the random effects model with the method suggested by DerSimonian and Laird [33].

For models with considerable heterogeneity, meta-regression was performed to identify patient- and trial-related factors which might contribute to the heterogeneity [34]. Trial-related factors included the sample size, duration of study, proportion of patients who were on CYC and quality of trials while patient-related factors were gender, age, duration of lupus or lupus nephritis, proportion of patients with Class IV nephritis and ethnicities (proportions of non-white and non-Asian patients). Chronicity and activity indices of renal biopsy were not included for meta-regression because they were not reported in a number of studies [19, 22–24]. Since the covariates chosen were not expected to explain all the heterogeneity of the trials, mixed-model regression was used in considering the presence of ‘residual heterogeneity’ [34]. The regression coefficients and the associated standard error (s.e.), the z-score and P-values were reported for the meta-regression analysis.

Sensitivity analyses were performed for testing the robustness of the effect sizes and the analyses were divided into two parts. In the first part, we evaluated the robustness of the pooled effect sizes based on elimination of publication which is the extension of an original cohort, route of administration of CYC (i.e. intravenous and oral administrations) and quality of trials. Because the observation time and duration of treatment differed between trials which assessed MMF and CYC as maintenance agents in the treatment of lupus nephritis, in the second sensitivity analysis, we tested the robustness of the RRs of the secondary outcome by comparing them with their corresponding incidence rate ratios (IRRs), which were derived by pooling the incidence per patient-years follow-up. This is important because theoretically the occurrence of events in the secondary outcomes would be higher with longer duration of treatment and/or observation. The patient-years follow-up was estimated from the product of the number of patients and mean duration of follow-up in respective studies.

Publication bias was not assessed because it has been proven to be unhelpful [35]. All statistical analyses in this meta-analysis were performed using the Comprehensive Meta-analysis Programme, Version 2 (Biostat, Englewood, NJ, USA). The QUORUM statement for improving the quality and result of meta-analyses of RCTs was adhered where appropriate [36].

Results
We initially identified 438 articles through database searches. All abstracts were scanned and 16 studies and 3 abstracts were retrieved for detailed scrutiny after we rejected 419 abstracts because they were non-human studies, observational studies, case reports and letters to the editors or editorials. We further excluded nine publications because they were reports of a meta-analysis (n = 3), an uncontrolled trial (n = 1), a non-randomized trial (n = 1) and RCTs which were not comparing MMF and CYC (n = 2), review of an RCT (n = 1) and an introduction of an RCT (n = 1). We identified one trial from the bibliographies of one of the retrieved articles, but it was subsequently excluded due to insufficient analysable information available in that report [25]. We realized that one of the RCTs [20] was partly an extension of observation of a previously reported cohort [15]. However, since there were some new patients in the latter trial and invaluable information on safety profile, ESRF development and mortality...
could be retrieved from this extended long-term study which spanned a median follow-up of 63 months [20], we decided to include it in the meta-analysis. The definitive analysis in this meta-analysis included 10 RCTs that were published between 2000 and 2008. The result of the literature search is shown in Fig. 1.

Among the 10 studies, 7 were published in full text while 3 were published in abstract form. Two of the 10 studies involved comparison of MMF and CYC in both the induction and maintenance phases [15, 20] and one compared MMF, CYC and AZA as maintenance therapies after successful induction with CYC for a duration between 4 and 7 months [17]. Apart from the two studies which involved the use of oral CYC [15, 20], all tested intravenous CYC against MMF. A total of 847 patients participated in the controlled trials. Amongst them, 411 were randomly assigned to receive MMF and 417 received CYC. Nineteen patients received AZA as maintenance therapy in one of the trials [17]. Seventy-four and 20 patients continued MMF and quarterly intravenous CYC as maintenance therapy, respectively, as noted in the three maintenance trials. The number of participants in individual trials ranged from 20 to 370. The mean (range) age of the patients was 33.3 (28.8–39.9) years and the majority of the patients were female (ranging from 82.6 to 94.0%). The calculated mean (range) patient-years follow-up was 38.9 (4.5–144.6) for MMF therapy and 38.0 (5.5–144.6) for CYC therapy. We used the median to estimate the patient-years follow-up for one of the trials because the mean duration of follow-up was not provided [17] (Table 1).

For the quality of the studies as assessed by the Jadad method [29], the mean Jadad score was 2 (range 1–3) and the majority of the trials (six studies) were of low quality (Jadad scale <2) (Table 1). Double blindness was impossible for most of the studies because patients received either CYC intravenously or MMF orally while the use of double dummy was not mentioned in any of the study protocols. Although two studies involved the use of oral CYC and MMF, implementation of

![Fig. 1. Results of literature search. *Reasons of rejection: (i) uncontrolled trial; (ii) review of an RCT; (iii) introduction of an RCT; and (iv) two RCTs not comparing MMF and CYC.](image)

**TABLE 1. Characteristics and quality of controlled trials comparing MMF and CYC in patients with proliferative lupus nephritis**

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Publication type</th>
<th>Study design</th>
<th>Comparison*</th>
<th>n (mean)</th>
<th>Age</th>
<th>Study duration (weeks)</th>
<th>Patient-years follow-up</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. [15]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF (n=21) vs oral CYC (n=21)</td>
<td>42</td>
<td>37.5</td>
<td>24</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Hu et al. [16]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF (n=23) vs IV CYC (n=23)</td>
<td>46</td>
<td>28.8</td>
<td>24</td>
<td>NA</td>
<td>11.5</td>
</tr>
<tr>
<td>Contreras et al. [17]</td>
<td>Full text</td>
<td>RCT</td>
<td>IV CYC (n=59) and then MMF (n=20) or Aza (n=19) or IV CYC (n=20)</td>
<td>59</td>
<td>32.7</td>
<td>28</td>
<td>–</td>
<td>48.3</td>
</tr>
<tr>
<td>Ong et al. [18]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF (n=19) vs IV CYC (n=25)</td>
<td>44</td>
<td>30.9</td>
<td>24</td>
<td>NA</td>
<td>9.5</td>
</tr>
<tr>
<td>Ginsler et al. [19]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF (n=71) vs IV CYC (n=66)</td>
<td>137</td>
<td>31.8</td>
<td>24</td>
<td>NA</td>
<td>36.2</td>
</tr>
<tr>
<td>Chan et al. [20]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF(n=33) vs oral CYC (n=31)</td>
<td>64</td>
<td>39.9</td>
<td>24</td>
<td>–</td>
<td>144.6</td>
</tr>
<tr>
<td>Wang et al. [21]</td>
<td>Full text</td>
<td>RCT</td>
<td>MMF (n=9) vs IV CYC (n=11)</td>
<td>20</td>
<td>31.5</td>
<td>24</td>
<td>NA</td>
<td>4.5</td>
</tr>
<tr>
<td>Flores-Suarez et al. [22]</td>
<td>Abstract</td>
<td>RCT</td>
<td>MMF (n=10) vs IV CYC (n=10)</td>
<td>20</td>
<td>NA</td>
<td>24</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Isenberg et al. [23]</td>
<td>Abstract</td>
<td>RCT</td>
<td>MMF (n=185) vs IV CYC (n=185)</td>
<td>370</td>
<td>NA</td>
<td>24</td>
<td>NA</td>
<td>92.5</td>
</tr>
<tr>
<td>Mulic-Bacic et al. [24]</td>
<td>Abstract</td>
<td>RCT</td>
<td>MMF (n=20) vs IV CYC (n=25)</td>
<td>45</td>
<td>NA</td>
<td>24</td>
<td>NA</td>
<td>10.5</td>
</tr>
</tbody>
</table>

*All patients received corticosteroids. **The median duration of treatment was 25 months and 29 months in the CYC group and MMF group, respectively. Maintenance therapies after CYC induction were MMF, AZA and quarter IV CYC. **The mean duration of treatment was 63.9 and 52.2 months in the CYC and MMF groups, respectively. Maintenance therapy in the MMF group could be MMF or AZA while that of the CYC group was AZA. #Appropriate allocation concealment was performed during randomization process (see text for details). IV: intravenous; NA: not available.
double dummy was also not described [15, 20]. In terms of allocation concealment during randomization, only four out of the 10 studies recruited may have performed it appropriately. Three studies randomized subjects with the use of sealed envelopes at central sites [17, 19, 21], whereas one used randomization codes that were generated separately for each participating centre by using the random permuted block method with random varying block size [18] (Table 1). Despite these, authors of these trials did not explicitly state whether any investigators involved in the recruitment and randomization processes had any role in generating those sealed envelopes or randomization codes.

**Agreement between investigators**

The inter-rater reliability agreement of the four investigators (A.M., J.Y.S.T, R.C.M.H and H.C.S) in terms of inclusion and exclusion of studies and quality of papers assessed by the Jadad’s method were 0.86 and 0.80, respectively, calculated based on the Fleiss’ $\kappa$-statistic [37]. Such level of agreement is considered to be substantially almost perfect [38].

**Primary outcome**

Data of eight studies were involved in pooling estimates for renal remission rate during induction therapy because one trial was a maintenance study which did not compare MMF and CYC as an induction therapy [17] and another one did not report data on renal remission [16]. MMF is comparable with CYC in the ability to induce complete and partial remission at 6 months after commencing the induction therapy (RR 1.052; 95% CI 0.950, 1.166; random effects model) (Fig. 2). Cochran’s $Q$ and $I^2$ statistics revealed a moderate degree of heterogeneity in these trials ($I^2 = 40.775$; $P = 0.1$). The random effects model was therefore used.

**Secondary outcome**

During the whole study period of all the trials, the RR of all-cause mortality was comparable between patients who received MMF and CYC (RR 0.709; 95% CI 0.373, 1.347; fixed effects model). Two studies reported no mortality and they were therefore not estimable for effect sizes [16, 21]. As far as the development of ESRF is concerned, the risk of ending up with ESRF at the end of the study period was comparable between patients who took MMF and CYC (RR 0.453; 95% CI 0.183, 1.212; fixed effects model). Although patients in the MMF tended to have lower risks of death and development of ESRF, it did not reach statistical significance. Only four studies were pooled for effect sizes of ESRF because no ESRF was reported in three trials [15, 16, 21] while no data were available in three studies [22–24]. Heterogeneity is minimal when effect sizes of mortality and ESRF were assessed (Fig. 3).

**Adverse events**

Significantly fewer patients who received MMF developed amenorrhea (RR 0.212; 95% CI 0.094, 0.479, fixed effects model) and leucopenia (RR 0.473; 95% CI 0.269, 0.832). Patients in the MMF group tended to have a lower risk of developing herpes infection (RR 0.7; 95% CI 0.391, 1.251, fixed effects model) and pneumonia (RR 0.565; 95% CI 0.235, 1.360, fixed effects model). However, patients receiving MMF appeared to have a higher risk to experience diarrhoea (RR 2.078; 95% CI 0.982, 4.397, fixed effects model), though it did not reach statistical significance. Apart from the assessment of the effect size of diarrhoea where mild heterogeneity was found ($I^2 = 23.158$), heterogeneity was undetectable when the effect sizes of other side effects were evaluated ($I^2 = 0$). The fixed effects model was thus used (Fig. 4).

**Sensitivity analyses**

The results of the primary outcome and the secondary outcomes including the RRs of mortality, ESRF and side effects such as herpes infection, pneumonia and amenorrhoea remained generally consistent upon sensitivity analyses based on exclusion of a study which is an extended observation of an original cohort, route of administration of CYC and quality of trials (Table 2). When only high-quality trials were pooled for analysis, the incidence of leucopenia became insignificant. Interestingly, the RR of diarrhoea was significantly worse in patients who received MMF when only high-quality trials were analysed. Additionally, the risk of death of patients who took MMF was much lower when only studies of high-quality and trials testing oral CYC were pooled for analyses, although the pooled effect size remained statistically insignificant. Nevertheless, these results must be interpreted with caution because the effect sizes were generated from a small number of high-quality studies ($n = 3$) and trials only involved oral CYC ($n = 2$), respectively [15, 20] (Table 2).

In the second part of the sensitivity analysis where effect sizes in terms of RRs and IRRs were compared, all the results remained robust except for the higher heterogeneity of the effect sizes of diarrhoea, herpes and pneumonia (Table 3). Different treatment

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**Fig. 2. Forest plot of the primary outcome: complete and partial remission.**
and observation time between these trials could partly explain the increased heterogeneity when IRRs were pooled. Due to the small number of trials which demonstrated moderate heterogeneity ($n = 5; \text{df} = 4$), meta-regression was therefore not performed.

**Meta-regression**

Meta-regression was performed for assessment of heterogeneity of the effect size of renal remission because a moderate degree of heterogeneity was evident ($I^2 = 40.775$) (Fig. 2). Meta-regression demonstrated that the proportion of non-white and non-Asian patients contributed significantly to the heterogeneity of the effect size of renal remission ($P = 0.050$). Other factors such as the mean age of patients, sample size, duration of study, route of CYC administration, trial quality, proportion of Class IV lupus nephritis and duration of SLE/nephritis did not significantly contribute to the heterogeneity of the renal remission effect size (Table 4). Although the effect sizes (IRRs) of diarrhoea and pneumonia were quite heterogeneous, meta-regression was not performed because of the small number of trials involved (Table 4).

**Discussion**

The current meta-analysis of 10 RCTs involving over 800 patients with proliferative lupus GN indicates that MMF has similar efficacy when compared with CYC in terms of induction of disease remission. In addition, MMF is not superior to CYC in conferring survival benefit in these patients. Our meta-analysis generally agrees with previously published RCT reports and systemic reviews, in that MMF does not provide additional benefits in reducing the incidence of ESRF when compared with CYC although MMF is a safer agent because of its more favourable safety profile. Additionally, meta-regression revealed that the non-white and non-Asian ethnicities contributed significantly to the heterogeneity of renal remission.

Uncontrolled experience in the use of MMF in patients with proliferative lupus GN was first reported in the late 1990s when clinicians recognized that CYC was neither an absolutely safe nor a completely efficacious agent [39, 40]. Despite the moderately high renal remission rate following treatment with CYC, up to 15% of the patients with proliferative lupus GN were refractory to treatment and as many as 50% of the patients developed ESRF [8, 9, 41, 42]. In addition, the safety profile of CYC raised significant concerns, in particular amenorrhoea, leucopenia and infection [43]. Thus, clinicians have long yearned for a more efficacious and safer agent in the treatment of this serious yet manageable condition of mostly women of reproductive age. Since the report of the first RCT comparing MMF with CYC in proliferative lupus GN was published in 2000 [15], MMF has been suggested to be safer than and at least as efficacious as...
FIG. 4. Forest plots of the secondary outcomes (adverse events).
leucopenia and infections between patients who received MMF and CYC for treating proliferative lupus GN were inconsistent. For example, Walsh et al. [26] and Moore et al. [28] respectively demonstrated striking 80 and 56% risk reductions in death or ESRF in patients who received MMF when compared with those who had CYC. This alarmingly encouraging benefit, however, cannot be reproduced by Zhu et al. [27]. As far as side effects are concerned, the significant reduction in leucopenia, infection and amenorrhoea demonstrated by Moore et al. [28] could not be repeated by Walsh et al. (besides infection) [26] and Zhu et al. [27]. These discrepancies largely reflect the small number of studies included in these meta-analyses and lack of uniformity in pooling data for analysis. In the current meta-analysis, apart from including the two recently published RCTs, one of which, the Aspreva Lupus Management Study (ALMS) is the latest and largest one to date, we also implemented a few steps of precautions with an aim to augment the robustness of the pooled estimates. First, we realized that treatment duration differed between studies when comparing MMF and CYC as maintenance agents [15; 17, 20]. If only the RRs of certain conditions were reported, a potential bias may arise because for studies of longer duration, a higher proportion of patients would experience certain events including death. To eliminate this bias, CYC in inducing disease remission and preventing renal relapses in a number of subsequently published controlled trials [15–25]. Probably due to the small sample size and short duration of observation of these trials, there is no total agreement as to whether MMF is superior to CYC in terms of its efficacy and effects on survival benefit. Three meta-analyses which attempted to address these questions have been published so far [26–28]. However, data regarding the risk of death, ESRF, amenorrhoea, and CYC for treating proliferative lupus GN were inconsistent. For example, Walsh et al. [26] and Moore et al. [28] respectively demonstrated striking 80 and 56% risk reductions in death or ESRF in patients who received MMF when compared with those who had CYC. This alarmingly encouraging benefit, however, cannot be reproduced by Zhu et al. [27]. As far as side effects are concerned, the significant reduction in leucopenia, infection and amenorrhoea demonstrated by Moore et al. [28] could not be repeated by Walsh et al. (besides infection) [26] and Zhu et al. [27]. These discrepancies largely reflect the small number of studies included in these meta-analyses and lack of uniformity in pooling data for analysis. 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Three meta-analyses which attempted to address these questions have been published so far [26–28]. However, data regarding the risk of death, ESRF, amenorrhoea,
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we converted all proportions into incidences (IRR) before pooling the data and compared them with the RR in the sensitivity analyses. Although the IRRs were roughly estimated from the mean duration of treatment and observation in respective trials, the results of the sensitivity analyses invariably confirmed the robustness of the pooled RRs. Secondly, response to either MMF or CYC could not be assumed uniform between patients and trials because patient- and trial-related factors may contribute to heterogeneity in treatment response. While being absent in the previous meta-analyses, we performed meta-regression to identify factors which explained the heterogeneity of the effect sizes. Our finding that the non-white and non-Asian race contributed to the heterogeneity of renal remission further underscores the existence of a differential response of nephritis towards immunosuppressive therapies between different ethnicities. Indeed, it has been well documented in a few observational studies that the white race is favourable, whereas the African–American ethnicity is an unfavourable predictor for renal response and remission [44, 45]. The ALMS, the only RCT which attempted to compare the renal response with MMF amongst difference races and ethnicities, showed that significantly more non-Caucasian and non-Asian patients (composed mainly of black and Hispanic patients) responded to MMF [46]. This is an interesting observation since factors such as access to healthcare, poverty and non-compliance are less influential in controlled trials, which are essentially protocol-based, and in addition, there were no clinically notable differences in the baseline disease-related characteristics amongst the patients that might explain the response variation by race and ethnicity. Therefore, difference in genetic makeup and immunopathology might play a more impactful role on the inter-ethnic difference in treatment response of nephritis [47, 48]. While further clinical and cost-effectiveness studies are required to address the influence of race and ethnicity on renal response to MMF, based on the current data, MMF is encouraged in non-Caucasian and non-Asian patients with severe lupus nephritis, at least for induction therapy.

Despite our added precautions, there are limitations to this study which mainly stems from factors intrinsic to systematic reviews, missing data of some of the trials, poor trial quality and the limitations of the original RCTs. Though statistically significant results with regard to several side effects were obtained, these should be interpreted with caution because the current meta-analysis is still based only on a few controlled trials and is subjected to random error. Analysable data with respect to side effects were not available in the ALMS and one of the latest trials published in abstract form [23, 24]. These may over- or underestimate the incidence of certain adverse effects of both MMF and CYC. In addition, the poor quality of the trials mainly resulting from the lack of double-blindedness and double-dummy might further compromise the validity of the results. In spite of this, one point to note is that the quality of trials published in abstract form might be underestimated because details regarding the process of randomization and drop-outs are usually not mentioned due to a tight word limit. Finally, apart from the ALMS, all trials were of small sample size and none of the studies were double-blinded. Therefore, results of this albeit comprehensive meta-analysis might not truly reflect the relative efficacy and safety profile of MMF and CYC and we should therefore interpret the results with caution. Nevertheless, every effort has been implemented to eliminate potential bias and the sensitivity analysis helped prove the robustness of the pooled estimates. Lastly, although we used meta-regression and were able to identify that the non-white and non-Asian population significantly explained the heterogeneity of the RR of renal remission, it was based on a few studies and the results might be potentially biased. Furthermore, the result was subject to aggregation bias because the analysis was not based on subjects’ individual data [49]. Although MMF has a more favourable side effect profile than CYC as shown in this meta-analysis, one point to note is that the CYC dosing regimens used in these RCTs were either based on the protocol adopted by the US National Institutes of Health (the NIH protocol) or daily oral CYC (2.5 mg/kg/day) during the induction phase. These regimens incur a higher cumulative CYC dose than that used in the Euro-Lupus Nephritis Trial (ELNT), which comprises six intravenous fortnightly CYC pulses of 500 mg [50]. With a comparable efficacy in terms of renal response, the ELNT demonstrated that patients who were exposed to lower CYC dose experienced half of the incidence of severe infection than those who received higher CYC dose (6 monthly intravenous CYC pulses initiating at 0.5 gm/m², with subsequent increment to the highest dose of 1500 mg/pulse) [50]. This finding poses an interesting question as to whether a lower CYC dose or a shorter duration of CYC exposure can narrow the side effect gap between MMF and CYC. Confirmation by further controlled trials is necessary to provide the answer.

In conclusion, our meta-analysis, which is based on the largest number of trials and patients to date, suggests that MMF is comparable with CYC in terms of efficacy in inducing renal remissions, prevention of development of ESRF and survival benefit in the treatment of patients with proliferation lupus GN. Nevertheless, MMF is a safer medication for its lower incidence of adverse effects including leucopenia and amenorrhoea. From our results, we conclude that the treatment selection for proliferative lupus GN should be individualized based on patient-, physician- and disease-related factors. Factors such as patients’ gender, age and ethnicity, presence of comorbidity, financial capability, physicians’ experience and patients’ concerns, especially side effects and fertility issues are to be considered and discussed with patients in order to provide them with the most appropriate management strategy. Without scepticism, larger RCTs with longer duration of observation and cost-effective analyses can invariably shed more light on the ever existing question of whether MMF is truly better than CYC in the treatment of proliferative lupus GN.

Rheumatology key messages

- MMF offers similar efficacy as CYC regarding renal remission, patient and renal survival.
- While being similarly efficacious, MMF possesses a more favourable side effect profile than CYC.
- There exists a differential response of lupus nephritis towards immunosuppressive therapies between different ethnic groups.

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