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Therapeutic drug monitoring of mycophenolic acid and clinical outcomes of lupus nephritis: a systematic review and meta-analysis

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ABSTRACT

Introduction Mycophenolic acid (MPA) is a primary immunosuppressive agent used in the treatment of lupus nephritis (LN). While therapeutic drug monitoring (TDM) of MPA is well established in organ transplantation, its role in LN treatment remains uncertain. Our objective was to review and summarise current knowledge on TDM of MPA in the LN treatment.

Methods A systematic search was conducted in the online databases, specifically targeted patients diagnosed with LN receiving MPA treatment. The included studies had to report both MPA pharmacokinetic parameters and renal outcomes. A random-effects model meta-analysis was conducted to assess the relationship between clinical responses and MPA pharmacokinetics.

Results A total of 1507 studies were initially screened, resulting in the inclusion of 16 studies for meta-analysis, encompassing 433 patients. The response group exhibited significantly higher MPA area under the concentration-time curve (AUC) compared with the non-response group (51.44±21.73 mg·h/L vs 30.30±16.24 mg·h/L). The weighted mean difference (WMD) of MPA-AUC between responders and non-responders was 16.83 mg·h/L (95% CI 10.59 to 23.06; p<0.001). Similarly, trough concentration (C_0) of MPA showed a strong association with renal response, evidenced by C_0 values of 2.50±1.73 mg/L in the response group vs 1.51±1.33 mg/L in the non-response group (WMD 1.37 mg/L; 95% CI 0.77 to 1.97; p<0.001). There was no significant relationship identified between MPA-AUC and adverse events.

Conclusion This meta-analysis emphasised the meaningful correlation between MPA AUC and C_0 with renal response in LN treatment. Randomised controlled trials are necessary to validate this approach and determine its superiority over fixed dosing in the context of LN treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mycophenolic acid (MPA) is one of the most important immunosuppressive medications used in the treatment of lupus nephritis (LN) and kidney transplantation.

⇒ Although therapeutic drug monitoring (TDM) of MPA has been proven to benefit kidney transplant outcomes, its role in LN remains unestablished.

WHAT THIS STUDY ADDS

⇒ A systematic review and meta-analysis examined the evidence for performing TDM for MPA in patients with LN and demonstrated the correlation between renal response and the pharmacokinetic parameters of MPA, including the area under the concentration-time curve (AUC) and predose concentration (C_0).

⇒ The meta-regression provided an estimated response rate based on the AUC of MPA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This meta-analysis offers valuable insights for future clinical trials that aim to compare concentration-controlled and fixed-dose MPA regimens in the treatment of LN.

INTRODUCTION

Mycophenolic acid (MPA) stands as one of the most widely employed immunosuppressive medications for the management of autoimmune diseases and solid-organ transplantation.[1] It functions as a non-competitive, selective and reversible inhibitor of inosine-5′-monophosphate dehydrogenase.[2] The utilisation of MPA as an immunosuppressant to prevent allograft rejection after transplantation gained official approval from the US Food and Drug Administration in 1995.[3] Due to its ability to inhibit lymphocyte proliferation, MPA has also been applied within the domain of autoimmune and rheumatologic disorders. In this specific context, it plays a crucial role in addressing renal involvement in SLE. Numerous studies have substantiated the efficacy of MPA and its potential inclusion in both the induction and the maintenance phases of immunosuppressive regimens for

managing lupus nephritis (LN).[4–6] In the context of induction therapy, the findings from the Aspreva Lupus Management Study (ALMS) induction trial revealed that mycophenolate mofetil (MMF) was not inferior to monthly intravenous cyclophosphamide in achieving a reduction in urine protein/creatinine ratio (UPCR) and stabilising serum creatinine, encompassing LN class III through V.[3] Regarding maintenance therapy, the insights from the ALMS maintenance trial indicated that a dosage of 2 g/day of MMF outperformed azathioprine administered at 2 mg/kg/day.[5]

A consideration that has become evident in organ transplantation is the substantial inter-patient variability in MPA concentrations.[2] Randomised controlled trials (RCTs) employing therapeutic drug monitoring (TDM) to adjust MPA doses have shown significantly reduced rates of biopsy-proven acute rejection and treatment failure in transplant recipients compared with the fixed-dose strategy.[7–9] These adjustments enabled them to achieve the target area under the concentration-time curve (AUC) of 30–60 mg·h/L.[7 8 10] However, the role of TDM for MPA in the treatment of LN remains to be established, and there is significant variability in the evidence. For instance, some studies have suggested target MPA-$AUC_{0\text{-}12}$ levels of 45–60 mg.h/L during the maintenance period,[11] while others proposed higher MPA-$AUC_{0\text{-}12}$ levels of 60–90 mg·h/L.[12] Importantly, previous literature does not adequately address information about MPA concentrations that lead to adverse effects.

As of now, TDM of MPA in patients with LN has garnered attention due to the variability in drug metabolism between individuals, ethnicity and the necessity for personalised treatment strategies. This systematic review and meta-analysis aims to elucidate the advantages and pinpoint the optimal target MPA-AUC concentration that maintains therapeutic effectiveness while minimising potential toxicity.

MATERIALS AND METHODS

Literature search

The search protocol was registered in PROSPERO (CRD42023422371) and was executed following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] The literature search was conducted in PubMed, Scopus and Cochrane Library database published up to 22 September 2023. The Medical Subject Headings (MeSH) used for PubMed search were ((‘Lupus Erythematosus, Systemic’ (MeSH)) AND ‘Mycophenolic Acid’ (MeSH). For Scopus (TITLE-ABS-KEY (mycophenolate AND acid) AND TITLE-ABS-KEY (systemic AND lupus AND erythematosus)) AND (TITLE-ABS-KEY (concentration)) AND (LIMIT-TO (LANGUAGE, ‘English’)) were used as searching terms. The MeSH descriptor: (Mycophenolic Acid) AND [Lupus Erythematosus, Systemic], exploding all trees were applied to Cochrane Central Register of Controlled Trials. Only studies published in the English language were considered for inclusion in the final analyses. Additionally, the reference lists of the included articles were also examined to identify potentially eligible studies.

Study selection

Our primary objective was to investigate the concentration-effect relationship for MPA in patients diagnosed with LN. The articles were included if patients with LN were receiving MPA treatment, and the studies had to report at least one of the pharmacokinetic parameters of MPA, such as AUC and/or trough or predose concentration (C_0). Renal outcomes including clinical remission, serum creatinine, proteinuria or activity score of SLE must be present as part of the study outcomes. There were no restrictions regarding the age of participants, types of MPA used (mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS)), co-administered drugs, LN classification or the phase of LN treatment (induction therapy, maintenance therapy or treatment for relapse LN). Since the objective of this meta-analysis was to determine the correlation between clinical outcomes of LN and MPA pharmacokinetics, pharmacokinetic studies that did not report the results of patients with clinical remission versus non-remission were not included in this analysis. Studies were also included if they presented MPA pharmacokinetics in both patients with and without toxicity, and if the pharmacokinetic parameters were clearly reported for the respective groups. Only original articles studying in human were included. Article selection was performed independently by two investigators (TW and NN). Disagreements were solved through consensus and arbitration by a third author (SU).

Data extraction and quality assessment

The retrieved data included author names, year of publication, country of origin, study designs and objectives, patient characteristics and baseline demographic (including sex, age, race and LN classification), type and dosage of MPA used, other immunosuppression, follow-up period, pharmacokinetic parameters of MPA, outcomes of LN and the recommended therapeutic target of MPA (if available). Clinical responses were defined according to the definition presented in each study. The quality assessment of non-randomised studies was evaluated in accordance with the Newcastle-Ottawa Scales (NOS) quality assessment.[14] It evaluates the methodological quality of studies based on three areas: selection of study groups, comparability of groups, and ascertainment of the outcome of interest with a maximal score of nine. Studies were categorised as good, fair and poor quality according to the Agency for Health Research and Quality standards (online supplemental table 1).[15]

Data synthesis and analysis

From each study, the random-effects model was used to calculate pooled weighted mean difference (WMD) and standardised mean difference (SMD) of continuous

variables, and pooled odd ratio (OR) for binary variables, along with their 95% CI, in the responders and the non-responders based on the definition in each study. Statistical heterogeneity was calculated using Cochran Q test and the I^2 index. An I^2 >50% represents substantial heterogeneity, while I^2 30%–50% represents moderate heterogeneity and I^2 0%–30% is considered low-to-no heterogeneity.[16] If the studies provided solely medians, the approach described by Wan *et al* was used to estimate the means and SD.[17] Summary statistic of the continuous data was presented as mean±SD. Egger test was performed to assess the small-study effect and funnel plots were illustrated to determine the potential publication bias in each analysis. Meta-regression was analysed to demonstrate the association between mean MPA AUC of each study and renal response rates to determine the target MPA AUC for the treatment of LN. Statistical significance was defined as p value <0.05. The analyses were performed using Stata Statistical Software Release 17 (StataCorp LLC, College Station, Texas, USA).

RESULTS

Search results

A total of 1507 relevant citations were retrieved from PubMed, Scopus and the Cochrane Library database. After eliminating duplicate articles, 1076 titles and abstracts were further evaluated. Among these, 232 eligible studies underwent a full-text review. However, a significant number of studies were excluded either due to the absence of pharmacokinetic parameters for MPA or the lack of reported renal outcomes. Finally, 16 studies were incorporated into the meta-analysis. The flow diagram of study selection is visually presented in figure 1.

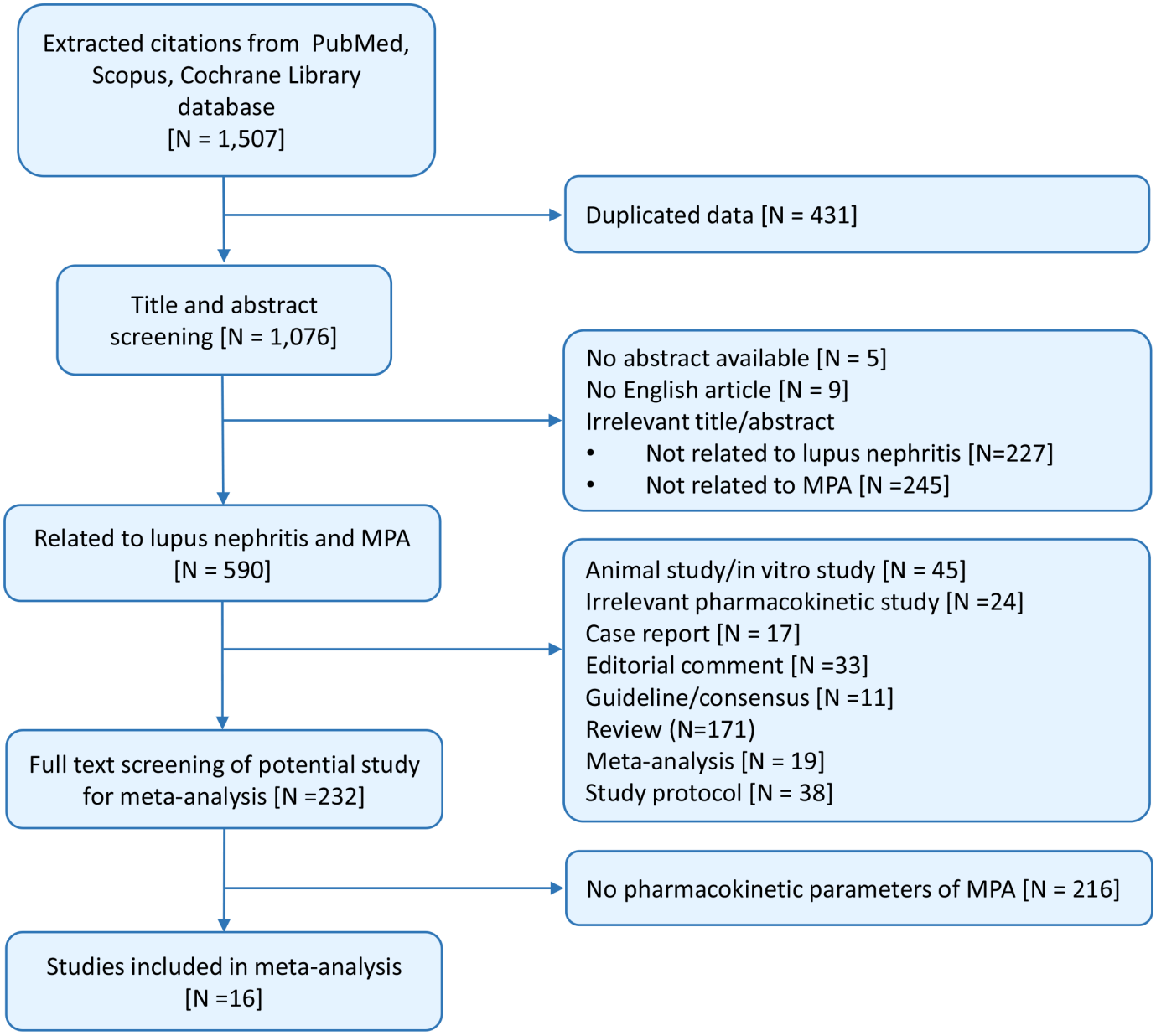

Figure 1 Flow diagram of study selection. MPA, mycophenolic acid.

Characteristics of the studies and patients

The main characteristics of the studies are summarised in online supplemental table 2. Five studies were from Europe,[11 12 18–20] nine studies from Asia[21–29] and two studies from USA.[30 31] Fourteen studies were cohort studies, while other two studies[11 20] were cross-sectional study. There were 433 patients in total which mean±SD of age was 32.5±15.1 years and 86.3% were female. Three studies focused on childhood SLE.[19 28 31] Almost all patients had proliferative LN (WHO pathological classification class III or IV). MPA was administered to patients during both the induction and maintenance phases. The majority of the studies examined the PK parameter of MMF, while Chariyavilaskul *et al*[29] used EC-MPS and Lertdumrongluk *et al*[21] investigated both MMF and EC-MPS. Concurrent immunosuppressive drugs were calcineurin inhibitors (ciclosporin and tacrolimus),[24 25] belimumab,[30] mizoribine[25] and cyclophosphamide.[25] While some studies were initially designed as cohort studies to investigate the treatment of LN and its outcomes, it is noteworthy that the measurement of MPA pharmacokinetics was consistently executed in a cross-sectional manner when correlated with the corresponding renal responses in each study. The quality assessment of the studies was performed according to NOS, and the results revealed that 13 studies were classified as good quality and 3 studies were classified as poor quality (online supplemental table 3).

MPA-AUC and renal response

Seven studies[19–21 24–26 28] examined the effects of MPA-AUC on clinical response. Among these studies, a total of 117 patients who responded to MPA exhibited significantly higher MPA-AUC values compared with 67 non-responding patients. The MPA-AUC for responders was 51.4±21.7 mg.h/L, whereas for non-responders, it was 30.3±16.2 mg.h/L. The WMD was calculated as 16.8 mg·h/L (95% CI 10.6 to 23.1), resulting in a p value <0.001. The heterogeneity statistic I^2 was 62.19%, and the p value of the Q test was 0.012. The Egger test displayed a p value of 0.024. The WMD and SMD of MPA-AUC between response and non-response patients are depicted in figure 2A,B, respectively. Online supplemental figure 1 demonstrates the funnel plot of studies investigating the association between MPA-AUC and renal response.

Three studies[19 21 26] conducted a comparison of renal response based on the therapeutic range of MPA concentrations. The results of the meta-analysis indicated that participants with MPA-AUC ≥30 mg·h/L had a significantly higher odds of achieving renal response in comparison to those with MPA-AUC <30 mg·h/L (OR 21.2; 95% CI 1.6 to 275.9, p value 0.020; I^2 53.70%; Q test p value 0.116; Egger test p value 0.048). Online supplemental figures 2,3 visually represent the forest plots and the funnel plots for these analyses.

Similar findings were found in the comparison between MPA-AUC 30–60 mg·h/L and MPA-AUC <30 mg·h/L. Patients with MPA-AUC 30–60 mg·h/L exhibited a higher renal response rate compared with patients with MPA-AUC <30 mg·h/L. The OR was 3.2 (95% CI 1.2 to 8.4), with a corresponding p value of 0.020 (I^2 0%; Q-test p value 0.771, Egger test p-value 0.501) (online supplemental figures 2,3).

MPA-C_0 and renal response

Four studies[21 24 26 27] collectively explored the relationship between C_0 and renal response, involving a total of 141 patients, with 115 categorised as responders and 26 as non-responders. Notably, the responder group exhibited higher C_0 levels compared with the non-responder group (2.50±1.73 mg/L vs 1.51±1.33 mg/L, respectively). The calculated WMD was 1.37 mg/L (95% CI 0.77 to 1.97; p value <0.001; I^2 = 0%; Q test p value 0.6117; Egger test p value 0.389). Figure 3 illustrates the forest plots of these findings and online supplemental figure 4 demonstrates the funnel plots.

MPA-AUC and adverse events

The association between MPA-AUC and adverse events was investigated in three studies,[19 24 25] encompassing a cohort of 32 patients who had side effects and 28 patients without any reported adverse events. The observed side effects included infections, haematological adverse events and gastrointestinal issues. On conducting a meta-analysis, no significant correlation emerged between MPA-AUC levels and the incidence of adverse events (40.3±41.8 mg·h/L vs 32.1±39.0 mg·h/L for patients with adverse effects and without adverse effects, respectively). The calculated WMD was 5.1 (95% CI −5.2 to 15.4; p value 0.335; I^2 =

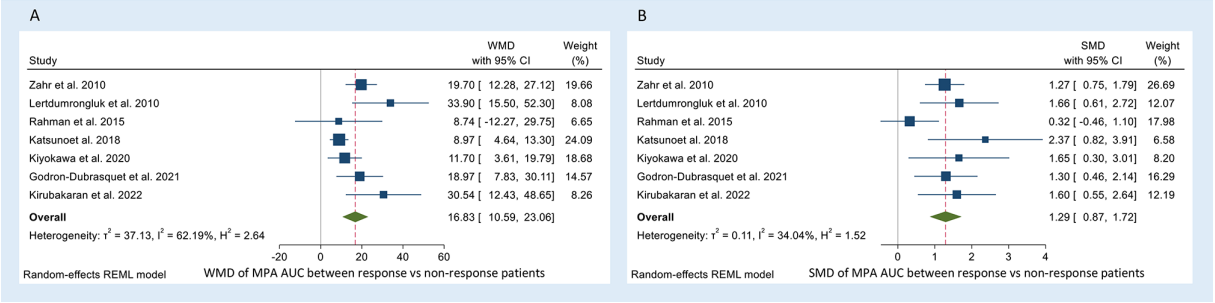

Figure 2 (A) Forest plot demonstrating weighted mean difference (WMD) of MPA-AUC between response and non-response patients. (B) Forest plot demonstrating standardised mean difference (SMD) of MPA-AUC between response and non-response patients. AUC, area under the concentration-time curve; MPA, mycophenolic acid.

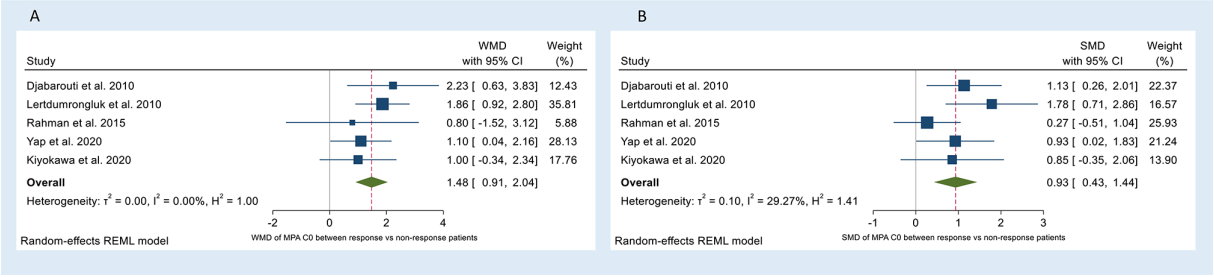

Figure 3 (A) Forest plot demonstrating WMD of C_0 MPA between response and non-response patients. (B) Forest plot demonstrating SMD of C_0 MPA between response and non-response patients. MPA, mycophenolic acid; SMD, standardised mean difference; WMD, weighted mean difference.

0%; Q test p value 0.653; Egger test p value 0.370; figure 4 and online supplemental figure 5). One study reported a significant association between anaemia and higher total and unbound MPA-AUC levels.[24]

Meta-regression for the association between MPA-AUC and renal response

Meta-regression analysis was conducted to investigate the relationship between MPA-AUC and the clinical response of LN, using the mean of MPA-AUC from 12 included studies.[12 19–26 28 30 31] As depicted in figure 5, the meta-regression plot demonstrates that MPA-AUC within the range of 40–60 mg·h/L was correlated with a clinical remission rate of 70%–80% (regression coefficient 0.005; 95% CI 0.003 to 0.007; p value <0.001; constant value 0.482).

DISCUSSION

This study marks the first meta-analysis to assess the potential benefits of MPA TDM in the treatment of LN. Our results underscore the association between the pharmacokinetic parameters of MPA, specifically AUC and C_0, and the response of LN treatment. Patients who maintained MPA-AUC within the range of 30–60 mg.h/L exhibited a 3.17-fold higher likelihood of being responders compared with those with lower MPA-AUC levels. Moreover, individuals with renal responses showed a higher MPA C_0, with a mean concentration of 2.5 mg/L. However, the meta-analysis did not establish an association between adverse events and MPA-AUC.

Prior studies focusing on kidney transplant patients have illuminated the substantial interpatient variability in MPA pharmacokinetics, revealing up to a 10-fold discrepancy among individuals receiving the same dosage.[32] Various factors, including genetic variations, drug interactions, gastrointestinal absorption, renal function and patient compliance, exert influence on the pharmacokinetics of mycophenolate.[10 32 33] While this understanding is robust in transplantation, its application in LN treatment remains less clear.[34]

Current guidelines from the Joint European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) and the Kidney Disease Improving Global Outcomes (KDIGO) recommend a combination of MPA and glucocorticoids as an initial therapeutic approach for LN class III or IV.[35 36] The KDIGO guideline expresses a preference for MPA-based regimens as the primary strategy for the treatment of proliferative LN. This preference is particularly emphasised for patients with a greater risk of infertility, individuals previously subjected to moderate to high doses of cyclophosphamide, and those of Asian, Hispanic or African descent.[36] Although standard dosages predominantly range between 2 and 3 g/day for induction and between 1 and 2 g/day for maintenance, specific target concentrations are not mentioned in these guidelines.[35 36] However, the measurement of MPA concentration is advised if suspected non-compliance or unsatisfactory response to treatment.[34]

In kidney transplantation, studies have previously investigated the potential benefits of MPA TDM. However, a recurrent challenge in these studies lies in the study design and interpretation of the results. The KDIGO guideline for the care of kidney transplant recipients in 2009 assigned a 2D recommendation for MPA monitoring, primarily based on data from RCTs during that period. However, a pivotal development occurred with

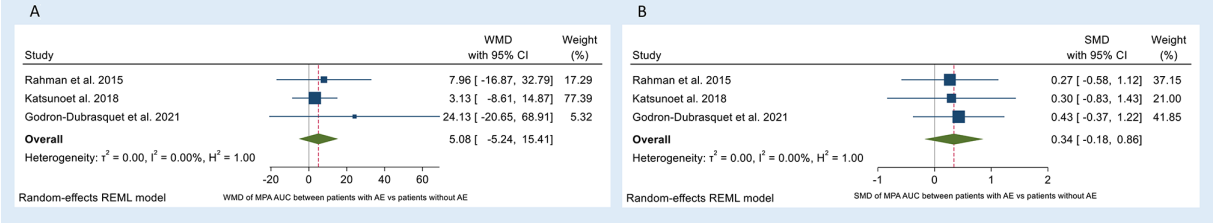

Figure 4 (A) Forest plot demonstrating WMD of MPA-AUC between patients with adverse events and patients without adverse events. (B) Forest plot demonstrating SMD of MPA-AUC between patients with adverse events and patients without adverse events. AUC, area under the concentration-time curve; SMD, standardised mean difference; WMD, weighted mean difference.

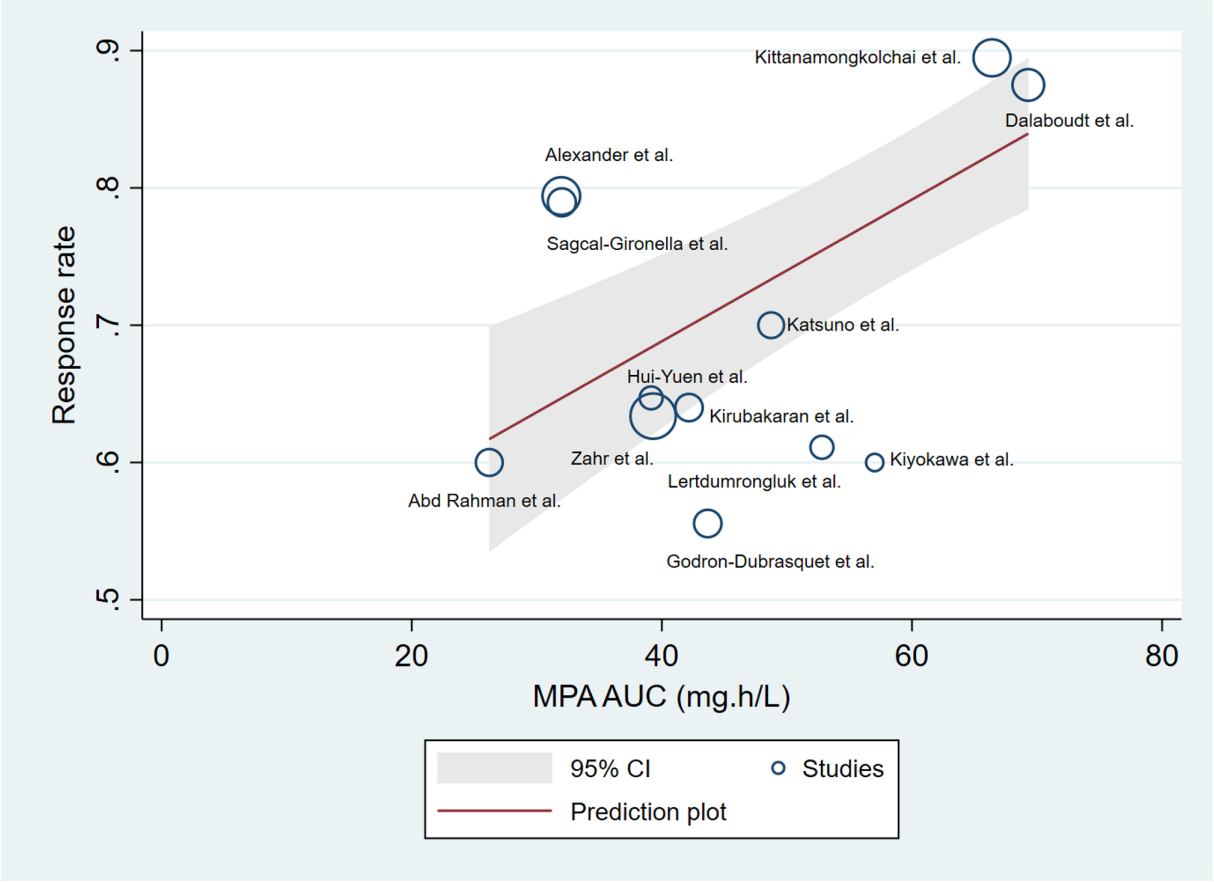

Figure 5 Meta-regression demonstrating the association between MPA-AUC and response rate in lupus nephritis studies. AUC, area under the concentration-time curve; MPA, mycophenolic acid.

the publication of the first meta-analysis on TDM of MPA in 2013.[37] Despite the results of this meta-analysis not demonstrating a significant difference in kidney transplant outcomes between concentration-controlled and fixed-dose MPA regimens, it sparked interest within the transplant community to explore the reasons behind these findings. A more recent systematic review in 2019 provided a comprehensive summary of the then-current evidence regarding MPA TDM.[32] Notably, the concentration efficacy of MPA was demonstrated in many RCTs.[7–9] These studies revealed that concentration-controlled MPA exhibited superior benefits, such as a lower incidence of rejection and treatment failure, compared with fixed-dose strategies. Importantly, the lack of proper MPA dose adjustment in the concentration-controlled arm emerged as a primary reason why some other studies failed to demonstrate these benefits, resulting in nonsignificant outcomes compared with fixed-dose MPA regimens.[32 38–40]

Unsurprisingly, the most recent international consensus on MPA TDM recommends a target MPA-AUC of 30–60 mg·h/L when used in conjunction with calcineurin inhibitors (CNIs) in kidney transplant recipients, with a strength of evidence rated as B and a quality of evidence classified as II.[1] The evolution of MPA TDM in kidney transplantation serves as an illustrative example of the development process—commencing with observational studies, followed by RCTs and/or meta-analyses—before definitive conclusions are drawn. Nevertheless, in the context of treating LN, a notable gap in knowledge exists as there have been no RCTs investigating the potential benefits of concentration-controlled versus fixed-dose regimens. This current meta-analysis represents a crucial initiative to address this gap and serves as a catalyst for promoting the undertaking of the mentioned RCTs.

The majority of studies analysed in our meta-analysis endorsed a target MPA-AUC of above 30 or 45 mg·h/L for patients with proliferative LN undergoing both induction and maintenance phases of MPA treatment. Nonetheless, data availability was limited for membranous LN and refractory LN cases. This meta-analysis revealed a correlation between a targeted MPA-AUC and the renal response rate through a meta-regression analysis. Employing the equation derived from this analysis (response rate=0.482+[AUC×0.005]), it is evident that an MPA-AUC of 64 mg·h/L corresponds to an 80% renal response rate.

For practical purposes, the target C_0 should also be taken into consideration. Due to the limited evidence regarding the association between MPA C_0 and clinical response in the existing studies (total five studies reported mean C_0 and response rate), a meta-regression analysis for MPA C_0 was not performed. Nevertheless, various studies have reported divergent target MPA concentrations, with

C_0 of 2.0–2.4 mg/L,[27] $C_{0.5}$ ≥2.03 mg/L[29] and C_1 ≥13 mg/L[22] being associated with a more favourable treatment response. In the context of our meta-analysis, patients demonstrating a renal response displayed an average C_0 of 2.5±1.7 mg/L, contrasting with 1.5±1.3 mg/L among non-responders. Considering these data, it could be proposed that targeting C_0 within the range of 2.5–4.2 mg/L might be suitable (ie, keeping C_0 between the mean and upper SD of the responder group). However, this estimation pertains primarily to studies involving MMF only. An interesting consideration arises when assessing EC-MPS, which exhibits greater C_0 variability despite the same MPA exposure as MMF.[41] As a result, a distinct target concentration for C_0 might be required for EC-MPS. However, because of its enteric coating, EC-MPS is absorbed more slowly than MMF, and the time to the maximal concentration is more variable.[42] The correlation between the MPA C_0 and MPA-AUC is very poor for EC-MPS. Therefore, estimating MPA-AUC based on C_0 in EC-MPS-treated patients is considered risky.[42] Conversely, if MPA-AUC serves as the basis for TDM, the same therapeutic target can be uniformly applied. This is supported by the equivalence between 720 mg of EC-MPS and 1000 mg of MMF in terms of resulting MPA-AUC.[43]

Regarding safety, our meta-analysis did not show a statistically significant association between MPA levels and adverse effects. However, this conclusion is grounded in a limited pool of studies, with only three investigations specifically addressing this relationship.[19 24 25] This limitation constrains the ability to draw definitive conclusions regarding the association between MPA pharmacokinetics and its adverse effects. Additionally, the absence of significant findings could be attributed to a dose-independent link between MPA levels and certain adverse events, such as hepatotoxicity, as indicated by previous studies.[44 45] It is worth considering that unbound MPA concentration, a pharmacologically active component of MPA, may offer greater accuracy as a surrogate for toxicity than total MPA concentration.[46] The majority of the studies included in our analysis did not provide explicit details regarding organ-specific side effects. As a result, a meta-analysis of organ-specific adverse effects of MPA such as diarrhoea or leucopenia (rather than overall adverse effect that could be influenced by other immunosuppressants) could not be conducted.

An important factor to consider is that certain existing studies conducted MPA TDM as a single measurement during the study period. To provide more insightful data, it would be valuable to establish a correlation between clinical outcomes and the long-term exposure to MPA. This can be best achieved through repeated measurements of the MPA C_0 or AUC. In future clinical trials seeking to elucidate the advantages of MPA TDM compared with the traditional fixed-dose MPA regimen, it is advisable to incorporate a protocol that includes multiple measurements of MPA at various timepoints such as trough or peak concentration. Such a design would more accurately reflect MPA exposure and drug compliance, which likely yield stronger correlations with clinical outcomes. Of particular interest, the limited sampling strategy for MPA can serve as a practical method for estimating total MPA exposure, providing a more feasible alternative to the complete AUC measurement.[1]

Our study possesses significant strengths, particularly as the first meta-analysis that incorporates studies examining the impact of MPA levels on renal outcomes in LN treatment. However, certain limitations warrant acknowledgement. First, the relatively small number of studies and enrolled patients in our meta-analysis is reflective of the limited published evidence pertaining to TDM of MPA in LN. Second, all the studies incorporated into our analysis were observational in nature, lacking the presence of RCTs for direct comparison. This absence of RCTs curtails our ability to derive definitive conclusions about the relative efficacy and safety of therapeutic drug monitoring versus fixed MPA dosing in the context of LN treatment. It should be emphasised that all available studies cross-sectionally evaluated the association between LN outcomes and MPA pharmacokinetics, involving a mixed population in the induction and maintenance phases of LN treatment in each individual study, as presented in online supplemental table 2. Consequently, we were unable to separate the treatment phases due to the mixed nature in each study and their reported results. However, evidence has demonstrated an existing correlation between MPA pharmacokinetics and clinical response. It is essential to recognise this as an association rather than causation, given the limitations of the included studies. Third, the heterogeneity of patient demographics and ethnicities, variations in the definition of clinical response, diverse LN treatment phases, differing treatment durations and the concurrent use of immunosuppressive agents, collectively contribute to patient heterogeneity. This diversity leads to an I^2 value exceeding 50% in some analyses. MPA concentration can be influenced by corticosteroids (via an increase in uridine 5′-diphospho-glucuronosyltransferase activity) and cyclosporine (through inhibition of multidrug resistance-associated protein 2).[47 48] The concurrent administration of both immunosuppressive medications may result in decreased MPA exposure, potentially altering or masking the concentration-effect relationship of MPA. The treatment regimen, which includes multiple drugs such as CNIs and corticosteroids along with MPA, may also attenuate the concentration-efficacy relationship of MPA alone to clinical outcomes due to potential confounding by other immunosuppressive medications. Additionally, the majority of analyses displayed asymmetrical funnel plots, implying the potential for publication bias. This necessitates cautious interpretation. However, it is crucial to note that relying solely on the presence of an asymmetrical funnel plot may potentially lead to the unwarranted exclusion of valid evidence.[49] A more comprehensive consideration should be given to factors such as the methodology of literature searching and overall transparency in study reporting. Lastly, the

inclusion of studies reporting only MPA C_0 in our meta-analysis was due to a lack of data on other timepoints. There remains a possibility that MPA concentrations at different timepoints, such as peak concentration (C_{max}) or C_1, might provide a more accurate representation of a single timepoint in predicting renal response.

In summary, this comprehensive meta-analysis has demonstrated a significant correlation between MPA-AUC and trough levels with renal response in LN treatment. These findings underscore the critical role of tailoring MPA doses through TDM to enhance treatment outcomes in LN. However, it is crucial to approach these results with awareness of the study's limitations and the inherent study-to-study variations. Our aim is not to bring about an immediate shift in clinical practice, but rather to stimulate the scientific community's contemplation of protocols evaluating the efficacy of MPA TDM in LN. Further advancement in our understanding necessitates RCTs that can investigate the effectiveness of concentration-controlled dosing in comparison to fixed dosing of MPA within the framework of LN treatment.

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Contributors TW and NN involved with study search and selection, data extraction, writing the first draft of manuscript. SU involved with study design, study search and selection, data analysis, writing the first draft of manuscript, manuscript review and edit and being a guarantor of the study. WK, AL, PC and NT involved with manuscript review and edit. YA involved with study design, manuscript review and edit.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Data in this systematic review and meta-analysis were derived from published literature without the possibility to identify the individual subject. There were no data that directly obtained from human or animal subjects. Consequently, this study is exempted from the requirement of ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to this study have been included in the manuscript. The data code supporting the findings of this study is available from the corresponding author on reasonable request.

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