To TDM or not to TDM in lupus nephritis patients treated with MMF?

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ABSTRACT

Mycophenolic acid (MPA) has become the cornerstone in the treatment of lupus nephritis. However, response rates are still far from ideal in clinical trials. Uncertainty exists regarding the correct dosing of MPA, and the recommended doses vary between recently published guidelines. Side effects are an additional problem resulting in frequent dose reduction and possible suboptimal exposure.

In this review, we discuss the large variability between patients in drug exposure to MPA and the evidence for a relationship between drug exposure and efficacy in lupus nephritis. Methods for drug monitoring of MPA are discussed, and based on the current literature, we suggest as potential target levels a pre-dose level of 3.0 mg/L and an area under the concentration-versus-time curve between 35 and 45 mg h/L.

Therapeutic drug monitoring may improve response rates in lupus nephritis by preventing low exposure and at the same time may reduce unnecessary side effects in patients who have high drug exposure with standard dose MPA. We specifically advise assessment of MPA drug exposure early after start of treatment and before concluding that treatment with MPA has failed.

Keywords: AUC, lupus nephritis, mycophenolate mofetil, mycophenolic acid, therapeutic drug monitoring

INTRODUCTION

Recently, the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) and the American College of Rheumatology have published recommendations for the management of adult and paediatric lupus nephritis [1, 2]. Based on the publication of the Aspreva Lupus Management Study (ALMS), together with the ease of administration and the more favourable gonadal toxicity profile of mycophenolic acid (MPA), MPA was recommended as initial treatment for most cases of class III–IV lupus nephritis [1–3]. The target mycophenolate mofetil (MMF) dose in the ALMS trial was 3 g/day. The EULAR/ERA–EDTA paper recommends gradual drug dosage titration to 2–3 g/day during induction to ensure the best possible efficacy/toxicity ratio, and doses of 1–2 g/day are considered as effective maintenance treatment [1, 2]. However, MMF dose often needs titration to reduce toxicity resulting in uncertainty of whether patients are still on an effective dose. A large variation in achieved doses is also observed in clinical trials on MMF in lupus nephritis, which additionally complicates the interpretation of these studies. Whether or not the measurement of MPA plasma concentrations can help to improve outcome is unclear, and no guidance is given regarding time of monitoring MPA, or regarding MPA target concentrations [1, 2]. In this paper, we offer information to physicians caring for patients with lupus nephritis on the principles of therapeutic drug monitoring (TDM), on clinically relevant pharmacokinetic characteristics of MPA, and we rationalize the basis for preliminary target exposure ranges for MPA. We will examine the current scientific evidence for adjusting the MMF dose based on TDM in patients treated for lupus nephritis.

THERAPEUTIC DRUG MONITORING

The aim of TDM is to optimize pharmacotherapy by maximizing therapeutic efficacy, while minimizing adverse events, in those instances where the blood concentration of the drug is a better predictor of the desired effect(s) than the dose [4]. If a drug fulfils the following criteria, TDM is likely to gain wide acceptance: (i) a high between-patient variability in the pharmacokinetics of the drug, (ii) a correlation between its concentration in the blood and clinical outcome (ideally for both efficacy and for toxicity), (iii) monitoring the clinical effect leads to impaired outcome if only the dose is changed...
after an event, rather than prior to the event based on drug concentrations, (iv) availability of reliable and relatively easy to use drug-monitoring assays and (v) above all, evidence that dosing based on TDM leads to a better clinical outcome than fixed dosing, ideally based on a randomized clinical trial comparing TDM with fixed dosing. In addition, TDM can also be useful in cases in which compliance is in question, where it is not clear whether the right drug is being taken, where dosage adjustment is required as a result of drug–drug or drug–food interactions, and where intoxication is suspected. In the remainder of this paper, we discuss the above-mentioned five criteria.

**HIGH BETWEEN-PATIENT VARIABILITY**

In the renal transplant literature, there are numerous papers that show a high between-patient variability in the pharmacokinetics of MPA. Shaw *et al.* demonstrated that in kidney, liver and heart transplant patients, the MPA area under the concentration-versus-time curve (AUC) varied 10-fold between patients treated with a daily dose of 2 g of MMF per day [5]. The high between-patient variability is caused by multiple factors, including renal function, albumin concentration, co-medication and pharmacogenetic factors [6]. A large between-patient variability in the pharmacokinetics of MMP has also been shown in 71 patients with systemic lupus erythematosus (SLE) (the majority of which suffered from lupus nephritis) with an MPA-AUC variation between 10 and 100 mg h/L [7]. Sherwin *et al.* reported high between-patient variability in MPA pharmacokinetics in MMF-treated children with SLE [8]. As albumin concentrations in patients with active lupus nephritis may be subnormal, this factor will add to the overall between-patient variability in drug exposure. Severe renal failure has been shown to result in reduced MPA exposure, possibly due to the higher non-protein bound fraction that facilitates a faster clearance, and this may also influence drug exposure in patients with active lupus nephritis [9].

**CONCENTRATION–EFFECT RELATIONSHIP**

Shortly after the introduction of MMF in the prevention of acute rejection after kidney transplantation, a concentration–effect relationship for MPA was demonstrated in many studies, including our own [10]. Subsequent studies have confirmed the significant correlations between MPA plasma concentrations and the likelihood of developing acute rejection after kidney transplantation, but the correlations with toxicity were largely negative [11]. In patients with lupus nephritis, several studies have shown correlations between MPA concentrations and efficacy. The main findings of several of these studies are mentioned in this paragraph. Due to the small numbers of patients in most studies, it is uncertain whether or not there is a linear or a sigmoidal concentration–response relationship.

In 2008, Neumann *et al.* reported that in subjects with SLE or ANCA-associated small-vessel vasculitis receiving MMF for remission maintenance therapy, higher MPA trough levels were associated with better protection from recurrence of active disease [12]. While at MPA concentrations of <3 mg/L, 29% of collected samples (43/147) were from patients with active disease, this was only the case in 2% of samples (3/147) with an MPA concentration of >3 mg/L. Remission persisted in all patients with MPA pre-dose concentrations of >3.5 mg/L. Upon combined analysis of efficacy and safety data, most favourable results were obtained with pre-dose MPA concentration between 3.5 and 4.5 mg/L. There was no discernable relationship between MMF dose and clinical endpoints. Based on the results, the authors decided to adjust the MMF dose, aiming for a targeted pre-dose MPA concentration of 3 mg/L. The mean MMF dose necessary to achieve MPA concentrations close to 3 mg/L was 1.8 ± 0.5 g of MMF per day, with a wide range. In some patients, 2.5 or 3 g of MMF per day was required to reach target; in other patients, 1 g was sufficient.

In a Thai patient population of 18 patients with biopsy-proven class III or IV lupus nephritis 1 month after initiating treatment with MMF or enteric-coated mycophenolate sodium (EC-MPS), a 12-h MPA-AUC was measured [13]. The mean MPA-AUC in responding patients was significantly higher (>45 mg h/L) than in those not responding. MPA-AUC was not associated with infectious episodes, gastrointestinal or haematological adverse events. Also in this study, the pre-dose MPA concentrations were associated with the response therapy in the patients on MMF, with responders having a significantly higher MPA concentration compared with non-responders (3.1 ± 1.1 mg/L versus 1.2 ± 0.9 mg/L; P < 0.001). There was no correlation between MPA-AUC and single time point concentrations in the patients on EC-MPS.

In a previously mentioned study by Zahr *et al.* [6] in patients using MMF, the mean MPA-AUC in the group with active SLE was significantly lower than that in the group with inactive SLE (26.8 ± 13.6 mg h/L versus 46.5 ± 16.3 mg h/L; P < 0.0001). In the multivariate analysis, MPA-AUC was the sole parameter associated with SLE activity, and an MPA-AUC threshold value of 35 mg h/L was associated with the lowest risk of active SLE.

Djabarouti *et al.* studied MPA exposure in MMF-treated SLE patients. MMF controlled disease activity in 17 patients (successes) and failed to do so for 8 others (failures) [14]. For failures and successes, respectively, median MPA-AUC were 37.7 versus 73.1 mg h/L (P = 0.003) and median MPA pre-dose concentrations were 1.5 versus 3.7 mg/L (P = 0.008). In a receiver operating characteristics curve analysis, MPA pre-dose concentrations were best able to discriminate a flare during follow-up. A 3 mg/L cut-off had 92% negative-predictive value for developing a flare during follow-up.

**DOSE ADJUSTMENT BASED ON THE CLINICAL EFFECT OR BASED ON DRUG EXPOSURE**

In daily practice, the typical approach in MPA-treated lupus patients is to either increase the dose in a step-wise fashion,
until clinical remission is achieved, or to start with a full dose treatment (3 g daily) and taper the dose based on side effects. A disadvantage of the former strategy is that it may take several dose increases before the effective concentration is reached and causes a delay in achieving disease remission. The EULAR/ERA–EDTA guideline therefore recommends a full daily starting dose of 3 g MMF. In patients improving after initial treatment, subsequent immunosuppression after 6 months is recommended with lower MMF doses (target 2 g/day). Considering the large between-patient variability in the pharmacokinetics of MPA, the fixed high dose treatment will result in a wide range of MPA exposure. Monitoring of MPA concentrations would allow for the identification of patients with MPA exposure (far) above the threshold values mentioned earlier and would allow for dose reductions in such patients and help in reducing toxicity. Daleboudt et al. reported their experience with TDM-guided treatment in 16 patients with lupus nephritis treated with MMF after induction with low-dose cyclophosphamide [15]. Within 1 month after starting MMF, MPA-AUC was assessed and the MMF dose was titrated to achieve an MPA-AUC of 60–90 mg h/L. Treatment based on TDM was feasible, and renal outcome was excellent with 87.5% partial or complete remission in this uncontrolled cohort. The data shown in Figure 1 come from the same study, now including more patients, and confirm the high between-patient variability in pharmacokinetics, for both pre-dose concentrations and AUC.

**AVAILABILITY OF DRUG-MONITORING ASSAYS**

In order to perform TDM in a routine clinical setting, the availability of reliable and relatively easy to use drug-monitoring assays is a prerequisite. Concentrations of MPA in plasma are in the milligrams per litre range and are substantially higher than concentrations of drugs such as tacrolimus, which are typically present in micrograms per litre. Analytical aspects are quite straightforward, and for the monitoring of MPA concentrations, there are several assays available. Commercial immunoassays, validated high-performance liquid chromatography (HPLC) methods as well as HPLC assays with mass spectrometric (MS) detection are available for the measurement of MPA plasma concentrations [16]. Typically, due to cross-reactivity with metabolites, immunoassays will report MPA concentrations, which are 10–20% higher compared with HPLC or MS. In the implementation of target concentrations, this bias between the assays should be taken into account.

In the management of transplanted patients, the MPA-AUC is considered the criterion standard for monitoring of MPA, which is a reflection of exposure to the drug over the entire dosing period. A lot of emphasis has been put on monitoring MPA with limited sampling strategies [17]. With this approach, it is possible to reliably predict the full AUC, based on measurement of a small number of samples. The data shown earlier suggest that in the studies performed so far, the association between pre-dose MPA concentrations and clinical outcome is not much worse than for MPA-AUC. In future studies, the predictive value of pre-dose concentrations versus MPA-AUC should be studied in more detail, but so far, it seems that clinical decisions can be based upon the more easily obtained pre-dose concentrations. Also, our own data (Figure 2) suggest that the correlation between pre-dose concentrations and MPA-AUC is sufficiently good to use pre-dose concentrations for patient management in patients treated with MMF. This makes treatment with MMF easier.

**RANDOMIZED CLINICAL TRIAL COMPARING TDM WITH FIXED DOSING**

For only few of the drugs, for which we routinely perform TDM, there is evidence that dosing based on TDM is better than fixed dosing. Randomized clinical trials designed with the goal of demonstrating the added value of TDM are exceptional. In the renal transplant field, there is a trial that shows that dosing MMF based on plasma concentrations results in a lower incidence of acute rejection compared with fixed dosing [18]. We do not expect such a trial will be performed in patients with MMF treatment for auto-immune disease.

**FIGURE 1:** (A) Dose-corrected MPA-AUC in 71 patients with lupus nephritis. Median 67.8 mg h/L (IQR 44.2–86.66). (B) Dose-corrected MPA pre-dose concentrations in 71 patients with lupus nephritis treated with MMF. Median 2.8 mg/L (IQR 1.8–5).

**FIGURE 2:** Correlation between MPA pre-dose concentrations and MPA AUC in 71 patients with lupus nephritis treated with MMF ($r = 0.83$, $P < 0.001$).
MMF VERSUS EC-MPS

MPA is the active immunosuppressive molecule of the prodrug MMF and of EC-MPS. Due to the enteric coating, the latter formulation releases its contents after a delay, and the time to maximum concentration varies between 0 and 6 h after oral intake, whereas for MMF, the maximum concentration is typically found after 0.5–2 h. Although the pharmacokinetic profiles differ, administration of equimolar dosages of EC-MPS and MMF (720 and 1000 mg, respectively) results in a similar MPA-AUC, if MPA exposure is assessed with a full 12 h pharmacokinetic curve. It has been demonstrated that the biologic effect of the two formulations, expressed as inosine monophosphate dehydrogenase inhibition, is the same [21]. It is therefore no surprise that the efficacy of the two compounds is the same, as shown in a large randomized trial in renal transplant patients [22]. In auto-immune disease, such a large study has not been performed, but the experience with EC-MPS is equally good as with MMF [23, 24]. It should be noted, however, that due to the more variable MPA pharmacokinetics, pre-dose concentration monitoring cannot be used as a guide to monitor MPA exposure in patients who are given EC-MPS [25, 26]. In MMF-treated patients, MPA-AUC is significantly correlated with pre-dose concentrations and associated with a therapeutic response [27].

CONCLUSIONS

Treatment of patients with lupus nephritis with MPA is characterized by a high between-patient variability in the pharmacokinetics. Several studies have shown a concentration–effect relationship, with an MPA-AUC threshold value of 35–45 mg h/L being associated with a higher chance of inducing disease remission, and a lower risk of disease recurrence. This range for the MPA-AUC corresponds with a pre-dose concentration of 3.0 mg/L in a twice-daily oral dosing regimen in patients on MMF. In some patients, these concentrations can be reached with dosages as low as 1 g of MMF per day, but in other patients, 3 g is required to reach adequate drug exposure. In patients on EC-MPS, full 12-h-AUCs remain necessary for the determination of drug exposure making TDM considerably more arduous with this drug.

The target range derived from the currently available literature may serve as an initial guidance for MPA monitoring in the context of further prospective controlled trials in patients with lupus nephritis or with other types of auto-immune disease. A first MPA concentration measurement can be performed after 1 week of treatment, and based on this value, the dose can be adjusted with subsequent measurements 1 week thereafter. We recommend that before concluding that MPA treatment has failed, at least one adequate drug exposure assessment is made. On the other hand, treating all patients with an MMF dose of 3 g/day will lead to very high exposure in some patients possibly leading to haematological and infectious side effects, which may be prevented with TDM initiated early in the course of treatment. As the literature does not clearly demonstrate levels above which toxicity occurs, it is not easy to define high or toxic MPA levels for the general population. However, this does not mean that the level of exposure is not associated with toxicity in the individual patient, and it does seem prudent to avoid exposure that is much higher than the levels that have been demonstrated to be effective. In patients who do not tolerate standard MPA doses, measurement of drug exposure may help to identify patients who cannot be treated with MPA adequately and thus should receive alternative treatment. Furthermore, TDM should be performed if disease activity increases to see whether or not adequate levels are achieved.

CONFLICT OF INTEREST STATEMENT

Dr van Gelder has previously acted as a lecturer for F. Hoffmann-La Roche and as a consultant to Novartis. Dr Berger has acted as a lecturer for F. Hoffmann-La Roche and as a member of an advisory board for Amgen. Dr Berden has received speakers-fees from Amgen.

REFERENCES

Interleukin-6 in renal disease and therapy

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ABSTRACT

Interleukin (IL)-6 has become a major target for clinical intervention in various autoimmune conditions. Here, drugs including the humanized anti-IL-6 receptor (IL-6R) antibody tocilizumab emphasize the clinical importance of IL-6 in driving disease and poor patient outcomes. During the course of this review, we will outline the biology surrounding IL-6 and discuss the impact of IL-6 in renal disease and the clinical complications associated with renal replacement therapies and transplantation. We will also consider the merit of IL-6 measurement as a prognostic indicator and provide a clinical perspective on IL-6-blocking therapies in renal disease.