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REVIEW

Mycophenolate revisited

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Summary

The patent of mycophenolate mofetil (MMF) has expired, and for enteric-coated mycophenolate sodium (EC-MPS), this will happen in 2017. In the twenty years these drugs have been used, they have become extremely popular. In this review, the reasons for the popularity of mycophenolate are discussed, including the benefits compared to azathioprine. MMF and EC-MPS are therapeutically equivalent. Although neither is considered to be a narrow therapeutic index drug, this should not lead to careless switching between the innovator drug and generic formulations, or between one generic formulation and another. The pipeline of new immunosuppressive drugs is dry, and it is very likely that we will be using mycophenolate for many more years to come as a first-line immunosuppressive drug in our transplant population. Whether or not the development of donor-specific anti-HLA antibodies is related to drug exposure (mycophenolic acid concentrations) remains to be investigated.

Introduction

The phase III studies that led to the registration of mycophenolate mofetil (MMF) for the prevention of acute rejection in kidney transplantation by the U.S. Food and Drug Administration and European regulatory agencies were published 20 years ago. MMF has become a first-line drug in the field of solid organ transplantation, and the vast majority of renal transplant patients in the United States and in Europe are treated with MMF at discharge from the hospital, and also as maintenance treatment years later [1]. MMF has become a consistent member of many different immunosuppressive regimens. In calcineurin inhibitor (CNI) weaning or withdrawal protocols, in steroid avoidance and in belatacept-based regimens, MMF is part of the regimen. In fact, there are hardly any mycophenolate weaning or mycophenolate avoidance protocols. Early CNI withdrawal, or CNI avoidance from the start, and relying on mycophenolate plus glucocorticoids only, leads to an unacceptable high risk of rejection [2–4]. In a systematic review, several other strategies were compared in which mycophenolate was the sole adjunct immunosuppressant [5]. This included *de novo* CNI minimization (rather than complete avoidance); elective CNI

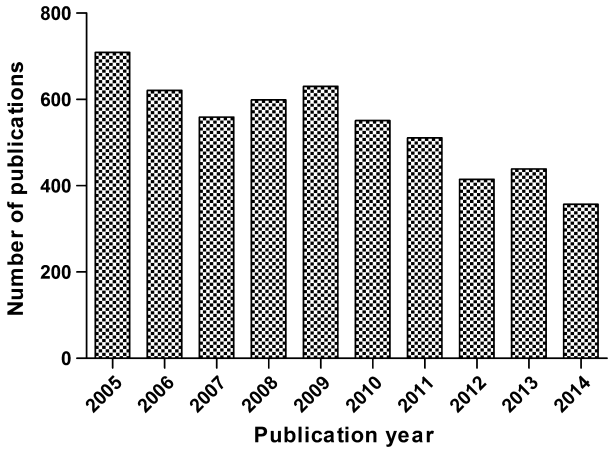

Figure 1 Number of publications per year in PubMed, searching for 'mycophenol*' and 'transplantation'.

sparing (minimization or elimination) in established transplant recipients; and CNI sparing (minimization or elimination) in patients with deteriorating renal transplant function [5].

The popularity of mycophenolate is partly based on its reputation as a drug associated with little or at least manageable, toxicity. Gastrointestinal and haematologic side effects typically respond well to dose reductions and are fully reversible. A literature search in PubMed, searching for 'mycophenol*' and 'transplantation', showed a steady decline in the number of hits (Fig. 1, search performed on 30 December 2014). In this manuscript, we look back on the history of MMF, ask ourselves whether MMF is really better than azathioprine (AZA) or worse than the enteric-coated formulation, touch upon the optimal dose of MMF, the sense or nonsense of therapeutic drug monitoring (TDM), and the risks and benefits of substitution for generic mycophenolate. The focus of this review is on the use of MMF in the prevention of rejection after kidney transplantation. For nonrenal organ transplantation, the interested reader is referred to the literature.

MMF versus azathioprine

The addition of mycophenolate mofetil (MMF) to a cyclosporin (CsA; Sandimmune® formulation)-based immunosuppressive regimen, compared to regimens containing placebo or AZA, reduced the incidence of acute rejection after renal transplantation from 40–45% to 20–25% [6–8]. These three studies, the so-called pivotal trials, formed the basis for the registration of MMF for the prevention of acute rejection after renal transplantation.

Later studies showed that MMF added to a combination of tacrolimus (Tac) and prednisolone significantly reduced the incidence of acute rejection from 44% in the double-therapy group, to 27% in the triple therapy group ($P = 0.014$) [9]. In a second trial comparing three treatment regimens (Tac/AZA vs. Tac/MMF vs. CsA/MMF), it was shown that acute rejection rates in the Tac-/MMF-treated patients were similar to those in the Tac/AZA group but that Tac-/MMF-treated patients had a significantly lower risk of steroid-resistant acute rejection requiring the use of antithymocyte globulin (ATG) [10]. That these studies did not show a benefit with respect to kidney allograft survival or patient survival did not keep prescribers from adding MMF to their standard immunosuppressive protocols, often at the expense of AZA.

Initially it was expected that with longer follow-up, the benefits of MMF on graft outcome would become evident. However, also the 3-year follow-up data of the three registration trials did not show convincing data regarding the benefits of MMF over AZA in this respect [11–13]. Sample size and attrition of patients from study treatment to other treatment regimens were potential explanations for the lack of evidence of such a benefit [14].

Ojo *et al.* [15] then published their registry study. With data of 66,774 renal transplant recipients from the U.S. Renal Transplant Scientific Registry, they showed that MMF reduced the relative risk of graft loss by 27% ($P < 0.001$) [15]. Death-censored graft survival at 4 years was significantly better among MMF-treated versus AZA-treated patients (86% vs. 82%, respectively). Importantly, the improved long-term graft survival was not only caused by a reduced acute rejection risk but was also caused by an effect independent of acute rejection [15]. In addition, both patient and death-censored graft survival were also better in MMF- over AZA-treated patients of African American ethnicity [16].

These data definitely strengthened the position of MMF as a first-line immunosuppressive drug. Not even the results of the Mycophenolate Steroids Sparing (MYSS) study, published by Remuzzi *et al.* in 2004, could affect the popularity of MMF [17]. The MYSS study concluded that in combination with the newer CsA microemulsion formulation (Neoral®), MMF offers no advantages over AZA in terms of preventing acute rejection while being about 15 times more expensive [17,18].

A systematic review published a few years later, however, concluded that MMF does offer a clinical benefit over AZA and that this effect is independent of whether MMF is used in combination with CsA-Sandimmune®, CsA-Neoral® or Tac [19]. This systematic review found that MMF significantly reduces the risk of acute rejection when used in combination with any CNI (relative risk 0.62; 95%-CI: 0.55–0.87; $P < 0.00001$) and that the hazard for graft loss, including death with a functioning graft, was also significantly reduced in patients treated with MMF (hazard ratio 0.76; 95%-CI: 0.59–0.98; $P = 0.037$) [19].

When MMF and azathioprine are compared with respect to toxicity, there does not seem to be penalty for the lower incidence of acute rejections in terms of more serious adverse events in patients treated with MMF compared to azathioprine [20]. The lower use of anti-T cell antibody treatment for steroid-resistent acute rejections is considered an important safety advantage of MMF therapy. The efficacy of azathioprine is based on the formation of 6-thioguanine nucleotides (6TGN). High 6TGN levels can lead to haematologic toxicity, and other azathioprine metabolites have been associated with development of hepatotoxicity. In contrast to the treatment of inflammatory bowel disease, therapeutic drug monitoring for azathioprine has never reached the transplant field to a significant extent, although there may be an additional benefit in terms of both efficacy and toxicity [21]. Likewise, the introduction of pharmacogenetic testing for the thiopurine S-methyltransferase (TPMT) gene polymorphism may improve safety [22]. In genetically TPMT-deficient patients, cellular accumulation of 6TGN results in acute dose-limiting toxicity. The Clinical Pharmacogenetics Implementation Consortium recommends testing for TPMT status prior to initiating thiopurine therapy, so that starting dosages can be adjusted accordingly [23].

MMF versus enteric-coated mycophenolate sodium

Enteric-coated mycophenolate sodium (EC-MPS; Myfortic®) was developed to reduce the high incidence of gastrointestinal adverse events associated with the use of MMF. In two clinical trials, EC-MPS in a dose of 720 mg twice daily and MMF 1000 mg twice daily showed similar efficacy and safety profiles [24,25]. A double-blind study in 423 *de novo* kidney transplant recipients showed that not only efficacy (a composite endpoint consisting of biopsy-proven acute rejection [BPAR], graft loss, death or loss to follow-up) between MMF and EC-MPS was similar (EC-MPS 25.8% vs. MMF 26.2%), but also that the safety profile and incidence of gastrointestinal adverse events were similar for both groups [24]. Within 12 months, 15.0% of EC-MPS patients and 19.5% of MMF patients required dose changes for gastrointestinal adverse events (P = ns) [24]. Also in a double-blind, double-dummy, conversion study in which stable kidney transplant recipients on MMF were randomized to switch to EC-MPS (n = 159) or to continue receiving MMF (n = 163), the incidence of gastrointestinal adverse events was similar at 3 months (EC-MPS 26.4% vs. MMF 20.9%; P = ns) and at 12 months (EC-MPS 29.6% vs. MMF 24.5%; P = ns) [25]. Furthermore, equimolar doses of EC-MPS and MMF were shown to produce equivalent mycophenolic acid (MPA) exposure and to result in inhibition of the activity of the target enzyme inosine 5′-monophosphate dehydrogenase (IMPDH) to a similar degree [26]. Following these well-designed double-blind controlled trials, several open-label studies did report an improvement in GI complaints following a switch from MMF to EC-MPS [27–29].

The main difference between the two formulations is in their pharmacokinetic profile. Due to the enteric-coating, EC-MPS is absorbed more slowly than MMF and the time to the maximal concentration is more variable [30,31]. In addition, the correlation between the predose MPA concentration and the MPA area under the concentration versus time curve (AUC) is poorer for EC-MPS [32]. Therefore, assessing the MPA-AUC in patients on EC-MPS will require more samples, or samples taken more hours after drug intake, compared to patients on MMF [33]. In a study from Naples, it was nicely demonstrated that including one sample drawn in the terminal phase of the EC-MPS pharmacokinetic profile, particularly at 8 h postdose, improved the performance of the limited sampling strategy [34].

To TDM or not to TDM

Whether or not the higher variability in the pharmacokinetic profile of EC-MPS is an issue will depend on the wish to assess MPA exposure. A lot has been written about the need for TDM of MMF and EC-MPS [35]. At fixed-dose treatment, there is considerable between-patient variability in MPA-AUC [36]. Low MPA plasma concentrations have been found to correlate with a higher incidence of BPAR after kidney transplantation, especially in patients at higher risk of rejection [37]. In a time-to-event model, Daher Abdi showed that exposure to calcineurin inhibitor (CNI) was a less powerful predictor of acute rejection incidence compared to MPA exposure [38]. The logical next step would be to perform TDM and adjust the dose in order to reach the therapeutic window. This strategy was found to reduce the incidence of BPAR in a French randomized controlled trial in patients treated with MMF [39]. In whom and when to measure MPA concentrations, and whether predose concentrations or AUC measurements are to be preferred for TDM purposes, has been reported in papers offering guidance for clinical practice [40]. The interested reader is referred to a pro/con debate and to a consensus paper on this topic for more information [35,41,42]. A special population for which TDM for MPA might be highly relevant is the group of patients in whom CNI treatment is discontinued. Hazzan *et al.* showed that in patients in whom 3 months post-transplantation CsA was stopped the MPA-AUC at 3 months was a predictor for acute rejection after CsA discontinuation [43].

The detection of circulating, donor-specific, anti-HLA antibodies (DSA) has received much attention in recent years. There is much debate on the best assay to detect such

DSA and on the interpretation of DSA measurement results [44]. Nevertheless, it is clear that there is a population of patients with poor graft survival due to chronic humoral rejection. Nonadherence has been postulated as a factor that increases the likelihood of developing DSA, and also CNI withdrawal has been suggested to play a causal role [45]. Whether or not low MPA concentrations also play a role in this process is unclear, and this needs to be the subject of future studies. The better long-term outcome observed for patients on mycophenolate compared to AZA be at least in part be the result of an effect of MPA on B-cell function and thus on production of DSA.

Genetic variants within the genes involved in MPA uptake and metabolism (*UGT1A9*, *UGT2B7*, *SLCO1B1*, *SLCO1B3*) and in its targets (*IMPDH*) have been reported to affect MPA pharmacokinetics and response in transplant patients [46,47]. However, for none of these genetic polymorphisms is there a direct clinical application [48].

The optimal dose of MMF

In the pooled analysis of the 3 registration trials (n = 1493 patients), it was shown that MMF significantly reduced the incidence of rejection from 40.8% in placebo-/AZA-treated patients to 19.8% and 16.5% for the MMF 2 gram and MMF 3 gram groups, respectively. At 1 year, the graft survival rates were 90.4% and 89.2% in the MMF 2 gram and 3 gram groups, respectively, compared with 87.6% in the placebo/AZA group (P = ns). In view of the lack of additional benefit of the 3 g daily dose, the 2 g dose became the standard of care [20]. For African American patients, the 3 gram dose was assumed to be the preferred dose, not because in African American patients MMF pharmacokinetics are different, but because they have a higher risk of rejection due to other factors [49]. For Asian patients, a lower dose is required, as they do have a higher MPA exposure with the same dose as compared to Caucasian or African American patients [50].

As a result of CsA-induced inhibition of enterohepatic recirculation, the MPA-AUC is significantly lower in case of CsA as compared with Tac cotreatment [51,52]. In a recent study, Colom *et al.* showed that with increasing CsA predose concentrations, there is an incremental inhibition of the enterohepatic recirculation, leading to a progressively lower MPA-AUC with increasing CsA exposure [53].

In patients cotreated with CsA and 1000 mg MMF twice daily, the median MPA-AUC in the first two weeks after transplantation is about 30 mg*h/l [54,55]. This value is considered the lower limit of the optimal therapeutic range [56]. Consequently, about half of the patients are potentially underexposed in the early post-transplant period, which puts them at an increased risk of rejection. A higher MPA exposure may thus be required when co-administered with CsA and an MMF dose of 1.5 gram twice daily may be more appropriate, at least in the first few weeks post-transplantation. Sommerer *et al.* studied the benefits of an intensified dosing regimen for EC-MPS in a CsA-based regimen [57]. In this study, 128 *de novo* kidney transplant recipients were randomized to receive a standard, fixed-dose of EC-MPS (1440 mg/day) or an intensified dose (days 0–14: 2880 mg/day; days 15–42: 2160 mg/day; followed by 1440 mg/day, thereafter). Although the study was not powered for evaluating efficacy, there were less acute rejections in the intensified dose group (2 patients or 3.2%) compared to the standard-dose group (11 patients or 16.9%; $P < 0.001$) [57]. The higher dose during the first 6 weeks did not result in more gastrointestinal side effects. With this regimen, the percentage of patients reaching an MPA-AUC >30 mg*h/l by day 3 after transplantation was more than 80% in the intensified dosing group (intensified dose versus standard dose on day 3: 81.8% vs. 40.7%; $P < 0.001$)[58]. A larger study will be needed to evaluate the benefits and risks of applying intensified dosing in a CsA-based immunosuppressive regimen.

A starting MMF dose of 2 g in patients on Tac will lead to adequate MPA exposure during the course of the first weeks, and subsequently the dose can be reduced in order to prevent toxicity. When MMF therapy is not guided by MPA plasma concentrations or by the occurrence of side effects, some centres use a protocolized MMF tapering strategy, aiming for a 750 mg or 500 mg twice daily dose for maintenance treatment. This 25–50% dose reduction corresponds with the difference in AUC between patients treated with either CsA or tacrolimus [59]. An alternative approach is to continue the starting dose and taper in case of side effects [60].

As, however, also in Tac-based regimens, 25% of the patients on 1000 gram MMF bid is below the therapeutic range, a similar approach of using a loading dose has also been tested. In the CLEAR-study, it was demonstrated that a 5-day MMF loading dose of 1.5 grams twice daily resulted in more patients reaching an MPA-AUC above 30 mg*h/l and that this did not lead to more adverse events [61].

Kiberd *et al.* even went so far as to test a 5-day MMF loading dose of 2 g twice daily. The rationale was the observation that with 3 grams of MMF still about 15% of patients remained below the lower therapeutic threshold of 30 mg*h/l early post-transplant and that a target MPA-AUC above 40 mg*h/l was considered to be most effective [62]. Remarkably, however, in this study, the 4 g daily dose did not result in a greater proportion of patients adequately exposed to MPA compared to a 3 g daily MMF dose. The nonlinear pharmacokinetics of MPA, that becomes manifest when MPA exposure does not increase proportionally with (increasing) MMF doses, may be an explanation of these findings [63].

For maintenance treatment, there are fewer data on the best dose of MPA. In a retrospective cohort study, including 213 renal transplant recipients, it was found that MMF dose reductions were an independent predictor of acute rejection [64]. In the CTS registry, Opelz *et al.* found that reduction of MMF dose to less than or equal to 1.0 g/day in patients during the second year post-transplant was associated with a statistically significant reduction in graft survival. Also withdrawal of MMF during year 2 was associated with an increase in the risk of graft loss compared with continuing treatment [65]. Whether or not there is a minimum dose, or a minimum MPA concentration above which efficacy in maintenance treatment is preserved is unclear. The expression of the target enzyme of MPA, inosine monophosphate dehydrogenase (IMPDH), may change over time. There are indications that patients on MMF therapy have an upregulation of IMPDH expression after transplantation and that this may be attributed to an induction by MPA [66]. This observation may also be of relevance for the optimal dose of MMF in maintenance treatment.

Substitution for generic variants

For MMF, the patent has expired already, and for EC-MPS, this will happen in 2017. Because mycophenolate is not considered a narrow therapeutic index drug, the wider bio-equivalence criteria are applied for registration of generic MMF formulations [67]. Potentially this is also interpreted as an indication that interchangeability of all mycophenolate formulations is not a problem. However, a major issue regarding generic substitution is the fact that following a first substitution from innovator drug to a generic formulation, there will be multiple subsequent substitutions, from one generic to the other. These substitutions are the result of a competitive bidding process, in which payers offer contracts to the supplier that offers the lowest price. After 6 or 12 months the contracts expire, and for an additional few cents lower pricing, the contract can move from one company to another. Over and over, at the pharmacy, patients will be confronted with boxes that look different, with pills that have a different size, shape and colour. Repetitive generic substitutions provide minimal cost savings, cause annoyance, confusion and medication errors. Following a first switch from innovator to generic, no further substitutions from one generic to another should be performed. Therefore, it is best to prescribe a branded generic, that is a generic drug that has a brand name, in order to specify which formulation should be dispensed to the patient. Furthermore, pharmacists should not be forced to deliver generic formulations to patients by payers. The initiative to substitute to generic should be taken by the prescriber [68].

Conclusions

Mycophenolate-containing drugs have been used in transplantation medicine for almost 20 years now, and they are very popular. The vast majority of transplant recipients is using these drugs, not only in the first post-transplant year but also for long-term maintenance treatment. There is evidence that mycophenolate offers a better graft survival compared to azathioprine treatment, but the difference may be smaller than initially assumed. MMF and EC-MPS are therapeutically equivalent, and the main difference lies in their pharmacokinetic profiles. TDM for mycophenolate is a heavily debated topic. Some centres do it on a regular basis, others have never ever measured an MPA concentration. When TDM is the preferred strategy to guide mycophenolate therapy, preferential use of MMF over EC-MPS seems rational. Whether or not MPA exposure is one of the determinants of the development of DSA and chronic antibody-mediated rejection remains to be demonstrated. If the mycophenolate dose is not guided by drug concentrations, then the dose may be adjusted based on side effects, or based on a (standard) tapering protocol. For CsA- and Tac-based regimens, the optimal mycophenolate dose is likely to be different. Also, in the first few weeks after transplantation, a higher than standard dose may contribute to efficacy, seemingly without paying a penalty in terms of increased toxicity. Although mycophenolate is not a narrow therapeutic index drug, repetitive generic substitutions must be avoided. There are no upcoming competitors for mycophenolate within eyesight, and it is likely we will be using this drug for many more years as a first-line immunosuppressive drug in our transplant population.

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