Editorial Comment

Therapeutic drug monitoring for mycophenolic acid in patients with autoimmune diseases

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Introduction

Mycophenolate mofetil (MMF, CellCept®) has become the most frequently used immunosuppressive drug in kidney transplant recipients [1]. Since its approval for the prevention of acute rejection after kidney transplantation in 1995 in the USA and in 1996 in Europe, the use of azathioprine has been rapidly diminishing, giving way to the use of MMF. A second formulation of mycophenolic acid (MPA), the active metabolite of MMF, has become available as enteric-coated mycophenolate sodium (EC-MPS, Myfortic®). Randomized clinical trials have shown that EC-MPS 720 mg b.i.d. is therapeutically equivalent to MMF 1000 mg b.i.d. with a comparable safety profile [2,3]. These equimolar doses of EC-MPS and MMF produce equivalent MPA exposure. The delayed release formulation, EC-MPS, exhibits more variable pre-dose MPA concentrations and more variable peak concentrations [4].

Because of the favourable experience with MMF in transplant recipients, combining good efficacy with relatively few side effects, its use has also been tried in patients with autoimmune diseases [5]. Following case reports and case series of the successful use of MMF, controlled trials have been started [6]. Increasing evidence suggests that MMF can be used not only for the prevention of rejection in solid organ transplant recipients, but also for the treatment of several immunologically mediated (renal) diseases [7].

Lupus nephritis

Of the diseases for which MMF may be a first-line drug, systemic lupus erythematosus or lupus nephritis is the most promising [8]. A recent meta-analysis of randomized controlled trials, published in this journal, showed that MMF not only had higher efficacy in inducing remission in severe lupus nephritis, but also caused fewer side effects compared to pulsed cyclophosphamide [9]. Also for maintenance therapy in lupus nephritis MMF seems to be a good alternative to azathioprine [9]. The upcoming publication of the results of a large phase III clinical trial (Aspreva Lupus Management Study, ALMS) should provide us with more comparative data on the efficacy and safety of MMF as induction and maintenance therapy in lupus nephritis [10].

ANCA-associated vasculitis

In 2007, Stassen et al. reported on the use of MMF for induction of remission in 32 patients with active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [11]. The patients in this study could not be treated with cyclophosphamide, for varying reasons. Complete remission was obtained in 25 (78%) patients and partial remission in 6 (19%) patients. Only one patient did not respond. Also, other groups found high percentages of responders on MMF therapy in ANCA-associated vasculitis [12,13].

Optimal dosing

Initially, in patients with lupus nephritis MMF doses of up to 2 g daily were used. Subsequent dosing regimens started with 1 g MMF/day and titrated on a weekly basis up to a maximum of 3 g/day [14]. A similar dose escalation is used in the ALMS trial. It is questionable whether standard dose therapy is the best way to treat a patient, given the large inter-individual variability in pharmacokinetics [15]. In renal transplant patients, monitoring of MPA exposure to optimize MMF treatment is a heavily debated topic [16–19]. Several studies have shown a correlation between MPA exposure and efficacy [20]. This is remarkable, as most renal transplant patients are being treated with three or sometimes four immunosuppressive drugs in the first months after transplantation. Apparently exposure to only one (MPA) of these three or four drugs is so important that it affects the incidence of acute rejection in these patients. Recently, a French study showed a reduced incidence of acute rejection in concentration-controlled MMF-treated renal transplant...
Correlating MPA exposure to clinical outcome

In this issue of the journal, Neumann et al. report on the value of measuring MPA plasma concentrations in patients with autoimmune diseases [26]. The study consisted of two parts. In the first part of the study the correlation between 12-h trough MPA concentrations and full area under the concentration–time curve (AUC) of MPA was investigated. Despite a rather weak correlation between trough and AUC the authors decided to longitudinally monitor a cohort of patients in the second part of the study, collecting serial trough values, which were linked to the occurrence of adverse events and to disease recurrence. Optimal efficacy, i.e. prevention of recurrence to active disease, was associated with higher MPA trough concentrations (> 3.0 mg/L). A remarkable finding is the observation that in this study adverse events were clustered in patients with a high MPA exposure. This is in contrast with studies in renal transplant patients, in whom tolerability was poorly correlated with MPA concentrations. The authors define the upper threshold of the therapeutic window based on toxicity. In renal transplant patients, the upper threshold of the therapeutic window is not based on increased toxicity, but merely on a lack of further improvement of efficacy above a certain exposure.

What can we do now?

The data presented should not be considered strong evidence in favour of MPA monitoring. Nor should their predictions of a therapeutic window be looked upon as an established guidance for routine clinical practice. We need more pharmacokinetic/pharmacodynamic analyses to decide on the value of therapeutic drug monitoring for MPA in this patient population.

For current patient care, however, even at this moment measurement of MPA plasma concentrations can be of some help. In patients with lupus nephritis in whom MMF is used as induction therapy, one would expect to see a clinical response within a period of 1 month in most patients. If, after 1 month of therapy, in non-responders MPA (trough) plasma concentrations are found to be low (say <2 mg/L), then a dose increase may have favourable effects on the likelihood of reaching remission. However, if in the same patient MPA trough is >4.0 mg/L already, then a further dose increase does not seem to be a good idea, as it may cause toxicity without additional benefit in efficacy. In such patients switching to another agent may be the preferred way to go.

Conclusion

MMF is an effective immunosuppressive drug, which is increasingly used in the remission induction and maintenance therapy of lupus nephritis. Therapeutic drug monitoring may be beneficial considering the between-patient variability in MPA exposure and the first indications of a correlation between exposure and efficacy/safety in patients with autoimmune diseases. Prospective pharmacokinetic/pharmacodynamic studies are needed to elucidate the true value of dose individualization for this indication and...
Table 1. Factors influencing MPA pharmacokinetics.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Creatinine clearance &lt;25 mL/min</td>
<td>Increased MPA clearance (through higher free fraction)</td>
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<tr>
<td>Plasma albumin concentration (&lt;32 g/L)</td>
<td>Increased MPA clearance (through higher free fraction)</td>
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<tr>
<td>Sex (male gender)</td>
<td>Increased MPA clearance (more glucuronidation activity)</td>
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<tr>
<td>Aluminium/magnesium containing antacids</td>
<td>Lower MPA bioavailability</td>
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<tr>
<td>Sevelamer co-therapy</td>
<td>Mechanism unknown, possibly lower MPA bioavailability</td>
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<tr>
<td>Glucocorticoid co-therapy</td>
<td>Lower MPA exposure due to interruption of enterohepatic recirculation</td>
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<tr>
<td>Cyclosporine co-therapy</td>
<td>Lower MPA exposure due to interruption of enterohepatic recirculation</td>
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<tr>
<td>Colestyramine co-therapy</td>
<td>Mechanism unknown, possibly due to faster glucuronidation of MPA</td>
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<tr>
<td>Rifampicin co-therapy</td>
<td>Increased MPA exposure due to drug interaction with rifampicin</td>
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<tr>
<td>Antibiotic co-therapy</td>
<td>Increased MPA clearance (more glucuronidation activity)</td>
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<td>Polymorphisms in metabolizing enzymes</td>
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to identify the subsets of patients that can benefit from monitoring.

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References


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