Use of mycophenolic acid in non-transplant renal diseases

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Keywords: enteric-coated mycophenolate sodium; mycophenolate mofetil; mycophenolic acid; renal disease; review; treatment

Introduction

Mycophenolic acid (MPA) is a relatively new immunosuppressive drug, used since the nineties for the prevention of rejection in kidney transplantation. MPA has not only proved effective in preventing rejection, being even superior to azathioprine, but also seems to cause less adverse effects than other immunosuppressive drugs [1]. Because of these favourable experiences with MPA in renal transplantation, the drug is currently used in patients with liver, lung and bone marrow transplantation as well. Given its favourable profile, MPA has also been used in autoimmune diseases. Following many cases and open series on the successful use of MPA, mostly in the form of mycophenolate mofetil (MMF), in renal, rheumatological, gastrointestinal, ophthalmological, dermatological and neurological autoimmune diseases, the first controlled studies have been published or are underway.

MPA is the active metabolite of the two currently available formulations: mycophenolate mofetil (MMF, Cellcept®) and the slow release formulation enteric-coated mycophenolate sodium (EC-MPS, Myfortic®). The mode of action and the pharmacokinetics of MPA are elegantly described by Allison [2]. In short, MPA is a non-alkylating drug that suppresses the immune response by inhibiting the proliferation of activated lymphocytes. MPA blocks the enzyme inosine monophosphate dehydrogenase (IMPDH), which is essential for the de novo synthesis of the purine guanine, and thereby inhibits lymphocytes from proliferating. While lymphocytes depend completely on IMPDH for synthesis of guanine, most other human cells use other pathways for this synthesis, and are therefore not or less affected by the anti-proliferative effect of MPA. In addition, MPA has anti-fibrotic effects, as reviewed by Eugui [3].

Following oral ingestion, both MMF and EC-MPS are resorbed and hydrolysed to MPA, which is conjugated in the liver into inactive mycophenolic acid glucuronide before being almost completely cleared by the kidney. Altered pharmacokinetics in patients with renal insufficiency might explain the increased rate of adverse effects, which can be managed by decreasing the dose of MMF [4]. MPA is not substantially cleared by peritoneal or haemodialysis [4].

We hereby review the clinical experience with MPA in the treatment of renal diseases.

MPA in proliferative lupus nephritis

Proliferative lupus nephritis is associated with poor renal prognosis if left untreated, and requires aggressive therapy. Cyclophosphamide in combination with corticosteroids has improved renal survival compared with steroids alone, and has become the standard for treatment of lupus nephritis. It is, however, very toxic. Many strategies to lower exposure to cyclophosphamide in patients who are predominantly young and female, and in whom infertility is a major worry, have been tried, one of them being the search for alternative non-alkylating drugs, like MPA. MPA has been used for induction of remission instead of oral or intravenous cyclophosphamide, and for maintenance therapy instead of cyclophosphamide or azathioprine.

Data from only a few prospective, controlled studies on induction of remission in patients with refractory focal or diffuse proliferative (classes III and IV) lupus nephritis with limited follow-up are currently available (details provided in Table 1). The first study examined the value of MMF, combined with prednisolone, as induction therapy in 42 Chinese patients with diffuse proliferative lupus nephritis [5]. Treatment with MMF...
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<th>Design, N, Patients</th>
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<td>[5]</td>
<td>RCT 42 Chinese</td>
<td>Class IV</td>
<td>MMF 2 g/day 12 months</td>
<td>CYC 2.5 mg/kg/day</td>
<td>CR 81 vs 76% PR both groups 14% Relapse 15 vs 11%</td>
<td>12 months</td>
<td>CR: prot. &lt; 0.3 g/day, normal sed. and alb., Creat. &lt;115% of baseline PR: prot. &lt; 2.9 g/day, alb. &gt; 3.0 g/dl, stable renal function</td>
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<td></td>
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<td>Creat. &lt; 300 μmol/l</td>
<td>(half dose after 6). After 12 months: AZA 1 mg/kg/day Pred. 0.8 mg/kg/day</td>
<td>po, 6 months. Thereafter: AZA 1.5 mg/kg/day Pred. 0.8 mg/kg/day</td>
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<td></td>
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<td>Prot. &gt; 1 g/day</td>
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<td>[6]</td>
<td>Prospective, part follow-up of former study [5] 64 Chinese</td>
<td>Class IV</td>
<td>MMF 2 g/day 24 months</td>
<td>CYC 2.5 mg/kg/day</td>
<td>CR 73 vs 74% PR 24 vs 23% Relapse 34 vs 30%</td>
<td>63 months</td>
<td>CR: prot. &lt; 0.3 g/day, normal sed. and alb. stable renal function PR: prot. reduction &gt; 50%, &lt;2.9 g/day, alb. &gt; 3.0 g/dl, stable renal function</td>
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<td>Creat. &lt; 400 μmol/l</td>
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<td>po, 6 months. Thereafter: AZA 1.5–2 mg/kg, 18 months Pred. 0.8 mg/kg/day</td>
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<td>[7]</td>
<td>Prospective, MMF group = CYC failure 46 Chinese</td>
<td>Class IV</td>
<td>MMF 1–1.5 g/day, after 3–6 months: 0.5–1 g/day Pred 0.8 mg/kg/day</td>
<td>CYC i.v. pulse 0.75–1 g/m²/month, thereafter: every 3 months for 1 year. Methylpred 2–3 g, thereafter: Pred. 0.8 mg/kg/day</td>
<td>Reduction in prot. &gt; 50%; 70 vs 48%. Reduction in erythrocyturia: 91 vs 65%</td>
<td>6 months</td>
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<td>Prot. &gt; 2 g/day</td>
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<td>[8]</td>
<td>RCT, multi-centre 44 Malaysian</td>
<td>Classes III, IV</td>
<td>MMF 2 g/day 6 months Pred. 60 mg/day, maintenance 5–10 mg/day</td>
<td>CYC i.v. pulse 0.75–1 g/m²/month, 6 months Pred. 60 mg/day, maintenance 5–10 mg</td>
<td>CR: 26 vs 12% PR: 23 vs 36% Renal survival 3 years: 94 vs 92%</td>
<td>37.8 ± 7 months</td>
<td>CR: creat. &lt; 120% of baseline, erythrocyturia &lt; 10 hpf, prot. &lt; 0.3 g/day PR: creat. &lt; 120%, erythrocyturia &lt; 10 hpf and prot. &lt; 3 g/day or reduction &gt;50%</td>
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<td></td>
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<td>Creat. &lt; 200 μmol/l</td>
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<td>[9]</td>
<td>RCT, multi-centre 140 White (17%), remaining Black, Asian or Hispanic</td>
<td>Classes III, IV</td>
<td>MMF 3 g/day 6 months Pred. 1 mg/kg/day</td>
<td>CYC i.v. pulse 0.5–1 g/m²/month, 6 months Pred. 1 mg/kg</td>
<td>CR 23 vs 6% PR: 30 vs 25%</td>
<td>24 weeks</td>
<td>CR: creat. prot. and sed. &lt;110% of normal PR: 50% improvement of abnormal renal measurements</td>
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<td>V Creat. &lt; 265 μmol/l</td>
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<td>Prot. &gt; 0.5 g/day</td>
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RCT, randomized controlled study; Creat(cl), creatinine(clearance), Prot., proteinuria; MMF, mycophenolate mofetil; CYC, cyclophosphamide; AZA, azathioprine; Pred., prednisolone; po, per os; i.v., intravenous; CR, complete remission; PR, partial remission; sed., sediment; alb., albumin; hpf, high-power field.
was compared with oral cyclophosphamide, both combined with prednisolone and followed by azathioprine. These two regimens turned out to be equally effective at 1 year of follow-up (complete remission: 81% MMF vs 76% cyclophosphamide). In another study by the same group, comparing cyclophosphamide with MMF in a group of 64 patients (including 42 patients from their earlier study [5]), no differences in relapse rate and renal function could be found after 5 years [6]. In addition, fewer infections had occurred in the MMF group. Another prospective Chinese study on 46 patients compared 6 months of MMF with pulses of intravenous cyclophosphamide [7]. The study was not randomized; the MMF group consisted of patients who had either failed to respond to or relapsed after treatment with cyclophosphamide. Despite this difference between the treatment groups, superior efficacy of MMF in reducing proteinuria, erythrocyturia and levels of anti-double-stranded DNA antibodies was seen. In a subgroup of 27 patients with repeated renal biopsies, more improvement of pathological parameters was observed in 15 patients of the MMF group than in 12 patients of the cyclophosphamide group. The follow-up in this study was only 6 months. The same two treatment regimens were compared in a recent multi-centre, randomized open study on 44 Malaysian patients with focal and diffuse proliferative lupus nephritis [8]. Again, both therapies were equally effective in inducing remission. Likewise, renal survival after 3 years was comparable. The most recent controlled study on 140 patients compared MMF with a relatively low dose of intravenous cyclophosphamide (0.5 g/m²) [9]. Neither treatment regimens were very successful, but MMF was more effective than cyclophosphamide, with complete remission being achieved in 23% in the MMF group, and in only 6% in the cyclophosphamide group. Strict criteria to define complete and partial remission were used in this study (provided in Table 1). Unfortunately, follow-up in this study was only 24 weeks. Of note, 16% of the patients (MMF 10%, cyclophosphamide 22%) were lost to follow-up and considered as treatment failures, which may have influenced the results. Furthermore, 20% of the patients had membranous lupus nephritis, for which treatment is still controversial.

With respect to maintenance therapy with MMF, only one randomized study has been reported [10]. A total of 59 patients with focal or diffuse proliferative or membranous (class III, IV and one patient with stage Vb) nephritis were treated with the same remission induction regimen, consisting of monthly pulses of intravenous cyclophosphamide and oral corticosteroids. After remission was established, patients were treated with either 3-monthly pulses of cyclophosphamide, azathioprine (1–3 mg/kg) or MMF (500–3000 mg/day). Follow-up was 31, 39 and 37 months in the cyclophosphamide, azathioprine and MMF groups, respectively. Both azathioprine and MMF led to a better patient survival than cyclophosphamide. In addition, the MMF group had less renal flares than the cyclophosphamide group, although renal survival was the same in all three groups. A randomized controlled study, in which MMF is compared with azathioprine for maintenance of remission, is underway (MAINTAIN study; NIH study number: NCT00204022).

Finally, pre-emptive therapy with MMF following a rise in anti-double-stranded DNA antibody levels to prevent relapses has been studied, in an open pilot in 10 patients [11]. This pre-emptive therapy prevented clinical relapse in all 10 patients during a follow-up of 6 months.

In conclusion, MMF seems effective both for remission induction and for maintenance therapy in proliferative lupus nephritis, as described in the above-mentioned studies. In addition, MMF was well tolerated, and caused less adverse events than cyclophosphamide. Introducing MMF as standard therapy for lupus nephritis at this time would, however, not be based on very solid evidence. The major problems with the available studies are their small sample size, limited follow-up and methodological shortcomings. Another important problem is the lack of use of uniform definitions of remission and relapse [12]. Furthermore, four studies were performed in Asian patients only [5–8], and two in predominantly black and Hispanic patients [9,10]. As racial differences in the course and response to treatment of lupus nephritis are well known, patient selection makes it difficult to extrapolate the results. Finally, at this time, no patients with severe renal dysfunction (creatinine clearance <30 ml/min) have been studied. Potentially, treatment with MPA can become the first-line treatment for proliferative lupus nephritis, once adequately powered long-term studies confirm the present data with respect to both patient and renal survival.

Membranous lupus nephritis

In contrast to proliferative lupus nephritis, treatment of membranous lupus nephropathy (class V) remains controversial. As monotherapy with steroids is not very effective (complete remission achieved in only 6% [13]), it has been suggested that combining steroids with immunosuppressive drugs will lead to better results. In a pilot-study, 13 patients were treated with MMF, steroids and renoprotective therapy, including ACE inhibitors, antihypertensive drugs and statins [14]. After a follow-up of 16 months, 12 of these 13 patients had responded. Ten patients showed complete response (urine protein/creatinine ratio <0.44 g/10 mmol) and two patients a partial response (50% reduction in proteinuria). Another 10 patients, resistant to or intolerant of other immunosuppressive drugs, were treated in the same way [15]. Proteinuria was significantly reduced in all patients. A recent prospective, but not controlled, study on another 20 patients (12 biopsy proven), showed reduction of proteinuria of >50% in all patients and induction of complete remission (proteinuria <0.3 g/day) in 55%
after 18 months of follow-up [16]. In the study by Ginzler et al. [9], 20% of the active lupus nephritis patients had membranous nephropathy. Unfortunately, no data on the responses of these patients broken down to histological diagnosis were provided. Finally, in a small recent case series, an interesting observation was made [17]. The combination of MMF with hydroxychloroquine led to a higher complete remission rate (64%) than treatment with MMF only, after 1 year of follow-up.

Though these results seem promising, the value of MMF in membranous lupus nephropathy has yet to be determined, especially as no long-term data on the preservation of renal function are available. Whether combining MMF with hydroxychloroquine will improve the outcome of the patients should be investigated.

IgA nephropathy

IgA nephropathy leads to end-stage renal disease in 20–50% of the patients during long-term follow-up. Generally, conservative treatment aiming at reducing blood pressure and proteinuria with ACE inhibitors is used. However, studies on patients at high risk for progressive disease have shown that immunosuppressive therapy with corticosteroids alone, or in combination with cyclophosphamide, stabilizes renal function and reduces proteinuria and erytrocyturia (reviewed in [18]). Successful experience with MMF in some patients with IgA nephropathy [19,20] has led to a few small controlled studies. One of these showed no benefit of MMF compared with placebo in 21 patients with high risk of progressive disease (inulin clearance of 20–70 ml/min, hypertension, proteinuria >1 g/day or certain histological changes), after 3 years of follow-up [21]. Likewise, another placebo-controlled randomized study showed the same lack of improvement in 17 high-risk patients after 2 years [22]. In contrast, treatment with MMF for 24 weeks (n = 20) significantly decreased proteinuria (>1 g/day), as compared with patients randomized to conservative therapy only (n = 15) [23].

All of these controlled studies had a small sample size and limited follow-up and were, therefore, not powered enough to show differences between treatment groups in renal outcome. However, larger randomized American (NIH study number: NCT00318474) and Italian studies are currently underway [24].

Idiopathic (or primary) membranous glomerulopathy

Patients with primary membranous glomerulopathy are at risk of developing end-stage renal disease (10–40% in a period of 10–15 years following diagnosis). These high-risk patients, i.e. patients with renal insufficiency at diagnosis, deterioration of renal function during follow-up or persistent nephrotic range proteinuria, are usually treated with cytotoxic therapy, including cyclophosphamide, steroids and ciclosporin. There are no controlled studies that compare MMF with cytotoxic therapy. Four small uncontrolled studies on 54 patients have been published [20,25–27]. In these studies, the majority of patients who were treated with MMF were resistant to cyclophosphamide [20,25,26], and follow-up was short, ranging from 6 to 25 months. These showed that MMF reduced proteinuria, though MMF did not induce complete remission (proteinuria <0.3 g/day) in any of the patients. Furthermore, MMF stabilized renal function in two studies [20,25], while in two other studies improvement of renal function was seen [26,27], though in one study this improvement was not significant [26]. In only one study the effect of MMF in 13 patients with a nephrotic syndrome was compared with a (historical) control group (n = 13) who had been treated with cyclophosphamide [27]. In this study with 12 months of follow-up, the reduction of proteinuria from 13.2 (3.6–30.8) to 2 (0–12.2) g/day and improvement of renal function in the MMF group, as evidenced by a decrease of serum creatinine from 158 (117–386) to 113 (88–289) µmol/l, were comparable with those seen in the cyclophosphamide group.

These four studies have used different treatment protocols with and without steroids, have limited follow-up and included small, heterogeneous patient populations. Outcomes with respect to proteinuria varied widely, while follow-up was too short to assess renal function outcome. Moreover, control groups were absent in some studies. Despite these drawbacks, MMF seems promising and should be studied as an alternative for cyclophosphamide.

Minimal change nephropathy

A total of 20 patients, who were steroid-dependent or who had previously been treated with cytotoxic drugs, have been treated with MMF [20,28–31]. In 19 of these patients, complete or partial remission was reached, and steroids were withdrawn or reduced. Three of these 20 patients relapsed. Follow-up was short (3–20 months, median 6). Additionally, in four patients with frequently relapsing steroid-responsive minimal change disease, MMF was able to sustain remission for 19–42 months and steroids could be tapered to 5–10 mg daily in three patients, and stopped in one patient [32].

In contrast to the situation in adults, more experience is available with MPA in children with steroid-dependent or frequently relapsing nephrotic syndrome (usually minimal change disease). In several uncontrolled studies, relapse rates decreased significantly (in one study from 6.6 to 2 episodes per year [33]) and steroid dependency decreased [33,34]. Moreover, MMF was well tolerated. Whether MMF can replace ciclosporin as maintenance therapy or can obviate the use of cyclophosphamide in children with
steroid-dependent or frequently relapsing nephrotic syndrome should be studied in prospective controlled studies. Despite the uncontrolled nature of the studies that have been performed, some authors advocate using MMF in children with steroid-dependent and frequently relapsing nephrotic syndrome before starting ciclosporin [35]. Very few data are available on the treatment with MPA of steroid resistant minimal change disease, and it is unclear whether MPA is an option in this subgroup of difficult-to-treat patients [34,35].

Focal segmental glomerulosclerosis

Patients with focal segmental glomerulosclerosis and impaired renal function and/or persistent nephrotic proteinuria are likely to progress to end-stage renal disease. These patients are usually treated with corticosteroids, sometimes combined with ciclosporin or cyclophosphamide. Once complete or even partial remission is accomplished, either spontaneously or using immunosuppressive therapy, prognosis improves substantially. The efficacy of MPA as a treatment for this disease has been studied in case-series only. One study on 18 patients, who were steroid resistant and, in some cases, ciclosporin dependent or who had progressive renal insufficiency, showed remission (two complete, six partial) in eight patients and reduction of proteinuria in 16 [20]. Renal function stabilized in 9 of 12 patients with renal insufficiency during 9 months (range: 4–24) of follow-up. The most recent study showed that 8 out of 18 patients who failed to respond to cytotoxic drugs or calcineurin inhibitors, responded to MMF, with a reduction of proteinuria of >50% [36]. No deterioration of renal function was seen in all 18 patients after a follow-up of 6 months. Though these studies are not controlled and follow-up is short, it seems that MMF can be useful in patients who do not respond to other therapies. A randomized controlled study in which ciclosporin is compared with MMF, both combined with dexamethasone, is underway (NIH study number: NCT00135811).

Other renal diseases

Eight patients with acute, or acute-on-chronic interstitial nephritis, who were refractory to or intolerant of steroids were treated with MMF, as reported in one abstract [37]. In six of these patients, renal function improved or stabilized, with only one patient still in need of steroids. A child with interstitial nephritis due to presumed renal limited sarcoidosis, which led to renal failure, was successfully treated with MMF after induction of remission with high doses of steroids [38]. Remission was sustained for 1 year, while steroids could be stopped. Five patients with idiopathic membranoproliferative glomerulonephritis were treated with MMF (and prednisolone) and compared with six patients who received no immunosuppressive therapy [39]. After 18 months of follow-up, reduction in proteinuria and stabilization of renal function were seen in the MMF group, but not in the control group.

ANCA associated vasculitis

In patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (Wegener’s granulomatosis, Churg Strauss syndrome, microscopic polyangiitis and renal limited vasculitis), MMF is used both for remission induction, as an alternative to cyclophosphamide, and for remission maintenance therapy, as an alternative to azathioprine. Controlled studies testing the efficacy of MPA in inducing remission are lacking. However, in three uncontrolled studies on 55 patients, complete remission could be induced in 50% [40] to 86% [41] of patients who were intolerant or not responding to standard therapy with cyclophosphamide [40–42]. In this group of patients who were difficult to treat, the relapse rate was high, varying between 38% [42] and 56% [41] after a relatively short period of follow-up (12.2 and 24 months, respectively). At the moment, a multi-centre prospective controlled study in The Netherlands compares MMF with cyclophosphamide for induction of remission (NIH study number: NCT00103792).

MMF has also been used as maintenance therapy in one uncontrolled prospective study [43]. After a follow-up of 18 months, 43% of 14 patients relapsed after remission had been induced with cyclophosphamide. A high relapse rate (48%) was also seen in a retrospective study on 29 patients with 24 months of follow-up [41]. In three small case-series on a total of 21 patients, the relapse rate was 0% [19,44] to 9% [45], after 7–10, 11 and 9 months of follow-up, respectively. Currently, a multi-centre controlled study is being performed in Europe, comparing MMF with azathioprine as maintenance therapy after induction of remission with cyclophosphamide and steroids (IMPROVE trial; www.vasculitis.org).

Other forms of vasculitis

MPA has also been used in patients with vasculitides other than ANCA-associated vasculitis. Three patients with Takayasu arteritis, not responding to high doses of steroids, responded well to MMF [46]. Another patient with urticarial vasculitis successfully used MMF as maintenance therapy [47].

Goodpasture’s syndrome

One case report describes induction of remission of relapsing Goodpasture’s syndrome using MMF, in a patient who failed to achieve remission with plasma exchange, methylprednisolone and
cyclophosphamide [48]. After remission had been induced, anti-GMB antibodies could not be demonstrated during 1 year of follow-up.

**Adverse effects**

There are no long-term data about the adverse effects of MMF or EC-MPS when used in renal diseases. However, in transplantation medicine, more experience with especially MMF and, to a lesser extent, EC-MPS, usually in combination with calcineurin inhibitors and steroids, is available [1,49]. In addition, there is long-term experience with MPA in patients with psoriasis [50].

In general, MPA is well tolerated. The most frequently encountered adverse effects are gastrointestinal complaints. About 30% of patients experience diarrhoea, abdominal pain, nausea or vomiting [49]. Leucocytopenia (30%), anaemia (25%) and thrombocytopenia (9%) also occur frequently. Usually, these gastrointestinal and haematological adverse effects resolve after (temporary) dose reduction. In addition, more infections, like invasive cytomegalovirus, herpes simplex and herpes zoster virus infections are seen [50]. Furthermore, the risk of developing lymphoma increases, in contrast to the incidence of other malignancies [50].

**Conclusion**

Many case reports, case series, uncontrolled studies and a few controlled studies show that MPA can not only be used to prevent rejection after transplantation, but may also be efficacious in the treatment of many immunologically mediated renal diseases. In addition to the immune modulating effects, the anti-fibrotic and anti-proliferative effects of MPA can be especially valuable in these renal diseases. As MPA may offer an alternative for cytotoxic alkylating therapies, it is more and more used in patients, in whom these alkylating drugs are preferentially avoided or not tolerated.

However, before MPA can be advocated as first-line therapy in diseases like proliferative lupus nephritis or steroid-dependent nephrotic syndrome, well-designed prospective controlled studies with adequate follow-up must be performed. The available controlled studies are small, not uniformly designed and have limited follow-up. We, like others [12], strongly recommend the use of uniform patient selection and response criteria, uniform treatment protocols and sufficient follow-up. At this moment though, it is safe to say that MPA offers an alternative treatment to patients who do not respond or are intolerant to current standard therapy. We cannot recommend the widespread use of MPA before more controlled studies have been performed.

**Conflict of interest statements.** None declared.

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Received for publication: 31.8.06
Accepted in revised form: 27.12.06