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Mycophenolate in non-transplant disorders

(Includes review of therapeutic equivalence of mycophenolate formulations)

A Position Statement of the NSW Therapeutic Advisory Group Inc.

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Executive summary

There are published reports in the literature describing use of mycophenolate mofetil with varying degrees of success in a wide-range of non-transplant conditions, particularly auto-immune disorders (e.g. psoriasis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, granulomatosis and uveitis). Individual case reports and case series make up a large proportion of current available evidence, with only a limited number of randomised controlled studies published in the literature.

There have been no published trials investigating the use of mycophenolate sodium in non-renal transplant diseases. However therapeutic equivalence between mycophenolate mofetil and mycophenolate sodium has been established in renal transplant patients when used in combination with cyclosporin and oral corticosteroids. Early pharmacokinetic/dynamic studies have demonstrated bioequivalent mycophenolic acid (MPA) exposure and similar pharmacodynamic responses for mycophenolate sodium and mycophenolate mofetil. Higher systemic MPA exposure and maximal MPA concentrations with mycophenolate sodium were reported in one trial investigating mycophenolate sodium *vs* mycophenolate mofetil in renal transplant patients. However this higher exposure did not demonstrate any significant improvement in clinical efficacy (protection against allograft rejection) or increase in adverse effects.

Almost all published papers investigating the use of mycophenolate in non-transplant indications conclude that there is a need for randomised controlled trials to confirm or reject current findings. The overall incidence of auto-immune diseases is rare and hence the likelihood of large, randomised controlled studies in these indications is unlikely. This should not necessarily preclude the use of mycophenolate in these conditions, provided the decision to treat is carefully considered in light of the available evidence about mycophenolate and other treatment options.

Since use of mycophenolate in non-transplant indications is not currently approved by the Therapeutic Goods Administration, use of mycophenolate in these indications should follow normal procedures for 'off-label' use of medicines. Further guidance about off-label use of drugs in hospitals is available from NSW TAG: 'Off-Label Use of Registered Medicines and Use of Medicines under the Personal Importation Scheme in NSW Public Hospitals'.

Randomised, controlled trials are currently underway overseas in patients with myasthenia gravis and Wegener's granulomatosis, IgA nephropathy, pemphigus vulgaris, lupus nephritis and focal segmental glomerulosclerosis.

In the meantime, current evidence suggests that mycophenolate use should be restricted to patients with auto-immune disorders in whom standard treatment has failed or is contraindicated.

Summary of Evidence in Non-transplant Conditions

1. Skin conditions

1.1 Psoriasis

Early open and placebo-controlled studies reported that mycophenolic acid (MPA) was effective in patients with moderate-to-severe psoriasis, including those with severe refractory disease or intolerance to conventional therapy.[1-3] Concerns were reported regarding the toxicity of the drug (e.g. immunosuppressant effects, carcinogenic potential, gastrointestinal effects). Nevertheless MMF has continued to be trialed in patients with psoriasis.[4-12]

MMF was found to be an effective and safe treatment in severe psoriasis, according to the results of a study involving 11 patients.[11] Patients received MMF 1 g twice daily for three weeks then 0.5 g twice daily for three weeks. Within three weeks there was a reduction in the Psoriasis Area and Severity Index (PASI) of between 40% and 70% in seven of 11 patients, with only one patient achieving a reduction in PASI of less than 25% from baseline (no statistical analysis reported). Reducing MMF from 2 g daily to 1 g daily led to further, although only slight, improvement in six of 11 patients during the following 3 weeks. In four of 11 patients, the PASI increased at this lower dosage, and in one patient the drug was withdrawn because of muscle pain which reversed within a few days after stopping the drug. No gastrointestinal or haematological adverse events were reported.

A twelve week prospective open label clinical trial evaluated MMF, 2-3 g/day, in 23 patients with moderate to severe psoriasis.[13] The following results are based on the 18 patients who completed the study (one patient withdrew due to angioedema, three due to lack of response and the other due to unrelated causes). At week 6 the PASI was reduced by 24% ($p< 0.001$) and by 47% at week 12 ($p<0.001$). At the end of the 12 week period 14 patients (77%) achieved a in the PASI of $\geq$ 37% (range 37-98%), while 4 patients (22%) did not respond. Five patients reported mild nausea and one patient each had peri-orbital oedema and pruritis. One patient had transient leukopenia.

A single case report also demonstrated a marked reduction in the PASI (22.0 vs 11.4) after 5 weeks of MMF in a patient with severe psoriasis.[9]

MMF has also been used in combination with cyclosporin to manage severe psoriasis.[10] Nine patients received MMF (maximum dose 3 g daily) with low-dose cyclosporin (mean dose 2.5 mg/kg per day). All patients had either previously been intolerant of higher doses of cyclosporin alone or were refractory to cyclosporin. After the addition of MMF good clinical improvement was observed in three patients and moderate disease control in a further four patients after a follow-up period of 3-11 months, with no additional evidence of toxicity at the doses used. The authors concluded that MMF may be useful in patients with psoriasis unresponsive to, or intolerant of, other treatments, or who are at risk of developing nephrotoxicity at higher doses of cyclosporin.

In a study of 11 patients with refractory moderate to severe psoriasis and psoriatic arthritis, only patients with moderate psoriasis and psoriatic arthritis improved with MMF therapy. Patients

with severe psoriasis did not clinically respond to MMF.[14] In this 10-week study patients were treated with 2 g per day and MMF was well tolerated in all patients.

A case series of 8 patients with severe psoriasis demonstrated MMF to be less effective than cyclosporin.[15] After switching from cyclosporin to MMF an increase in the PASI was seen in all 8 patients at five weeks. However, three patients were reported as having 'reasonable' disease control and a statistically significant improvement in renal function was noted at 5 weeks after switching from cyclosporin to MMF (150.5 *vs* 121.3 micromoles/L) ($p < 0.01$). The authors stated that MMF may have a place in therapy for patients unable to take cyclosporin due to renal toxicity.

A case of severe, transient arthralgia related to MMF treatment in a patient with erythrodermal psoriasis has been reported.[16]

Topical MMF (2%) cream has been found effective in plaque-type psoriasis in three patients.[17] However, no difference was detected between 0.1% betamethasone-17-valerate cream and the MMF cream. The authors stated that a double-blind, randomised, placebo-controlled comparison of topical 2% MMF and 2% mycophenolic acid (MPA) in an amphiphilic cream is currently underway. Results of this trial have not been published to date. Despite a previous study of MPA being unsuccessful,[18] some animal data[19] have suggested that topical MPA may show potential in skin disorders.

1.2 Atopic dermatitis

Positive results for MMF treatment in atopic dermatitis have been reported in a number of open studies, as well as at least one report of treatment failure in 5 patients.

In one open study all 10 patients with severe atopic eczema responded to MMF treatment.[20] There was a significant reduction in the median Scoring Atopic Dermatitis (SCORAD) index at 12 weeks compared to baseline (22·0 *vs* 68·3 respectively)($p<0.007$). The initial dose of MMF was 1 g daily during the first week and 2 g daily for a further 11 weeks.

In a second study, seven of 10 patients with moderate-severe atopic dermatitis improved, demonstrated by a significant reduction in the SCORAD index at 8 weeks compared to baseline (21.9 *vs* 49.2)($p<0.01$).[21] Patients received MMF 1 g twice daily for four weeks; at week 5 the dosage was reduced to 500 mg twice daily until study end (week 8). Patients were followed up for 20 weeks. One patient had to discontinue MMF therapy after four weeks due to the development of herpes retinitis.

Six of 7 patients with moderate to severe atopic dermatitis completed another open study involving treatment with MMF 2 g daily for 6 weeks and followed up for another 6 weeks.[22] A significant reduction in the SCORAD index was reported at 6 weeks compared to baseline (28.7 *vs* 67.2 respectively)($p<0.01$). No serious side effects were reported.

Other case reports indicating efficacy for MMF in atopic dermatitis have also been published.[23, 24]

However, there have been some reports of lack of efficacy and/or severe side effects in a small number of patients. MMF 1-1.25 g twice daily was considered unsuccessful in all five patients

with atopic dermatitis in an open trial.[25] *Staphylococcus aureus* septicaemia and endocarditis after five months of MMF treatment for atopic dermatitis has been reported in a single case study.[26] A case of severe, transient arthralgia related to MMF treatment in a patient with erythrodermal psoriasis has also been reported.[16]

1.3 Blistering auto-immune skin diseases

Pemphigus
Several uncontrolled trials demonstrating favourable results for MMF in the treatment of pemphigus have been published.

In an open trial involving 42 patients, remission was achieved in 22 (71%) and 5 (45%) of patients with pemphigus vulgaris and pemphigus foliaceus, respectively.[27] Partial remission was achieved in a further 1 (3%) and 4 (36%) patients, respectively. The MMF dosage was 35 to 45 mg/kg per day. The median time to achieve complete remission was nine months. MMF was administered for a median of 22 months and the median follow-up period was 22 months. 77% of patients had no adverse effects. Two patients withdrew from the trial due to severe side effects - one with symptomatic but reversible neutropenia, the other with nausea. The authors considered MMF an effective and safe adjuvant in the treatment of both pemphigus vulgaris and pemphigus foliaceus.

Benefit in 12/17 patients with severe, refractory pemphigus was also reported from MMF treatment in a recent study.[28] MMF was considered well tolerated and there were no withdrawals due to safety concerns. At 18 months the average daily prednisolone requirement had reduced to 7mg, compared to 33mg at baseline.

Eleven of 12 patients responded to MMF treatment (1 g twice a day initially with prednisolone 2 mg/kg per day) in another study in pemphigus vulgaris. The responding patients showed no relapse of their disease even after tapering of their steroid dose.[29] Toxicity was considered low with mild gastrointestinal symptoms in five patients and mild lymphopenia in nine.

In a French open trial, 9/10 patients with resistant pemphigus vulgaris showed complete clearance of lesions within six to 16 weeks of treatment with MMF 2 g per day and systemic steroids.[30] At the end of six months, the daily dose of prednisolone was significantly lower (36mg vs 18mg)($p = 0.003$). Nausea and constipation were observed in 2 patients. No abnormality in blood tests was noted. The authors considered that, to induce long lasting remission, MMF had to be administrated for more than six months.

A patient with paraneoplastic pemphigus was reported free of skin and oral lesions following MMF monotherapy for ten months.[31] MMF had originally been introduced to an ongoing multiple drug regimen. However, it proved possible to gradually discontinue other medications. The patient's MMF dose was 1g per day, although 2g per day had been given during the prednisone taper. After the addition of MMF to her therapy, the patient developed mild thrombocytopenia which persisted.

According to another case report, skin lesions improved gradually in a patient with paraneoplastic pemphigus after cyclosporin and MMF treatment.[32]

However, the disease was fatal in another patient, despite maximal therapy with plasmapheresis, corticosteroids, MMF and subsequent addition of cyclophosphamide and cyclosporin.[33]

Pemphigoid

A number of case reports have recorded success for MMF in pemphigoid.[34-38] An observational study conducted in 14 patients with cicatricial pemphigoid (CP), ranging from mild-severe relapsing disease (3), severe disease currently managed with intravenous cyclophosphamide (7) and disease refractory to dapsone (4) reported some success.[39] MMF, administered at a dose of 1.5 – 2g per day, was reported to be 'efficient' in obtaining or maintaining disease control in 10/14 patients. The authors concluded that MMF may be of use in mild-severe CP but should not replace IV cyclophosphamide in severe sight or life-threatening forms of CP. However other reports have demonstrated efficacy in ocular CP (see Eye disorders).

1.4 Other skin conditions

In **severe recalcitrant pyoderma gangrenosum**, case reports have suggested that MMF, dosed at 1 – 2g per day, is a promising alternative as part of an immunosuppressive regimen or as monotherapy.[40-42] There have also been case reports of MMF either as monotherapy or with steroids in **idiopathic nodular panniculitis (Pfeifer-Weber-Christian disease)**.[43] One case report suggests efficacy for MMF in **dyshidrotic eczema**.[44] However, in a liver transplant patient, MMF treatment was associated with dyshidrotic eczema.[45] In this patient, allergy skin testing with MMF reproduced the lesions. Some promising results have been reported for MMF in **chronic actinic dermatitis**.[46] A small number of case reports suggest efficacy for MMF in **cutaneous lupus erythematosus**,[47-49] **acquired bullosa epidermolysis**[50] and **bullous lichen planus**.[51]

2. Eye disorders

MMF (average 2 g per day) has been found to help reduce or resolve uveitis, particularly in patients whose disease is unresponsive to or intolerant of other immunosuppressants.[52-56] The total response rate from these studies was 78% (73/93 patients). MMF was given either as monotherapy, or with prednisolone, cyclosporin or methotrexate. Side effects included diarrhoea, other gastrointestinal problems, fatigue, allergic reaction, low white cell count, and alopecia. It is of interest to note that in a dose optimisation study conducted in 2004, with use of therapeutic drug monitoring, investigators suggested that MMF dosages in the range of 0.5-1.5g/day may be sufficient for patients with uveitis.[57]

Long term efficacy of MMF in the management of refractory uveitis has been demonstrated in small number of patients.[58] A retrospective review of 14 patients with refractory uveitis treated with MMF, 1g twice daily, for a median period of 33 months demonstrated intraocular inflammation being under control in 10 patients, unchanged in three and deteriorated in one patient.[58]

Case reports of MMF use in **ocular pemphigoid** have also been published.[59, 60]

3. Renal conditions

Early reports indicated potential for MMF in various glomerulonephritides.[61, 62] Since that time further case reports and studies in specific renal disorders have been published. Efficacy for

MMF in glomerulonephritis after renal transplantation has been noted[63] (for reports of MMF use in **lupus nephritis** see Systemic lupus erythematosus).

3.1 Nephrotic syndrome

The use of MMF in nephrotic syndrome caused by lupus, membranous nephropathy (MN), minimal change disease (MCD) and glomerulonephritis has been described in the literature. The reports are based on small patient numbers and often include small subsets of patients with the different causes of nephrotic syndrome listed above.[64, 65]

3.2 Membranous nephropathy

A small number of case series have been reported, with varying results. The author of a recent review concluded that MMF's role as mono- or adjunctive therapy in the treatment of idiopathic MN needs more rigorous evaluation.[66]

Some encouraging results have been reported for MMF in a study involving 17 patients with MN.[67] All patients were steroid dependent, or were resistant/intolerant of conventional therapy (steroids and cyclosporin). MMF was initiated at 0.5 to 0.75 g twice a day and increased as appropriate up to 1.5 g twice a day. Dosages were carefully titrated in patients with marked reductions in glomerular filtration rate. A decrease in median 24-hour urine protein to creatinine ratio from 7.3 to 1.5 ($p=0.001$) was noted. However, no significant change in median serum creatinine was detected during treatment. Progressive steroid withdrawal and cyclosporin withdrawal was achieved in 93% of patients with steroid or cyclosporin dependency. MMF was discontinued in three patients. One patient developed severe erosive gastritis, one pneumonia and one squamous cell cancer.

MMF therapy reduced proteinuria in some patients with idiopathic MN resistant to steroids, cytotoxic agents or cyclosporin according to the results of a small study published in 2000.[68] The urine protein excretion rate was reduced by 50% in 6 out of 16 patients after a mean duration of six months MMF treatment. Partial remission occurred in two patients. Over the course of the study here were no significant changes in the mean values of serum creatinine, serum albumin, or the urinary protein excretion rate. Side effects of MMF were infrequent and generally mild.

The results of a recent study in eight patients also reported some success for MMF in MN (2 g per day for nine months).[69]

A retrospective review of 18 patients with lupus nephritis, including 6 patients with MN, treated with MMF and oral steroids reported complete remission in 10 (56%) patients and partial remission in another four (22%).[70] However, the remaining 4 patients who failed therapy all had MN. There was no significant improvement in serum creatinine, creatinine clearance, proteinuria or active urinary sediment at 12 months in the 6 patients with MN. The authors concluded that the role of MMF in MN was unclear.

3.3 IgA nephropathy

In a randomised controlled trial of 62 patients with severe IgA nephropathy, MMF was more effective in reducing proteinuria and serum lipids than corticosteroid therapy.[71] Partial and total remission rates were in the MMF group than in the control group (44.4% vs 19.1% and 88.9% vs 61.9%, respectively)($p< 0.05$). The authors reported less adverse effects with MMF than with prednisone. The dosage of MMF was initially 1 to 1.5 g per day depending on bodyweight. Dosage was reduced after six months treatment. The maintenance dosage was approximately

0.75 g per day after 12 months. Three patients in the MMF group were reported to have slight diarrhoea, one nausea in the first weeks and one herpes zoster.

A smaller randomised controlled trial reported conflicting results.[72] Thiry four patients were randomised to either an angiotensin converting enzyme inhibitor (ACEI) + salt restriction + MMF 2g per day or ACEI + salt restriction + placebo. Three year data demonstrated that MMF treatment provided no beneficial effect over placebo. There was no difference between groups in the percentage of patients with a decrease of 25% or more in inulin clearance or with a serum creatinine increase of 50% or more over 3 years. No significant difference was noted between groups for inulin clearance, serum creatinine, proteinuria, blood pressure, or other parameters of renal function.

Isolated reports of reduction in serum creatinine and reduction or resolution of proteinuria after administration of MMF combined with prednisone and/or cyclosporin have been published.[73] Preliminary data also suggested that MMF may reduce the risk of recurrent IgA nephropathy in renal allografts and there are ongoing randomised controlled trials testing the effectiveness of this treatment.[74]

There is an ongoing RCT, involving 100 patients, evaluating the efficacy of MMF + ACEI + fish oil supplements *vs* placebo + ACEI + fish oil supplements.[75] No results have been published to date.

3.4 Focal segmental glomerulosclerosis

The authors of a recent review concluded that, from preliminary experience, it was difficult to draw any conclusion regarding the role of MMF in focal segmental glomerulosclerosis (FSGS).[76] These authors noted there was an impression that patients may obtain a short-term benefit from MMF therapy, which may reduce proteinuria and the cumulative dosage of steroids. They commented that none of the available studies were controlled and they were all based on short-term treatment. Well-designed randomised trials were considered necessary to assess the role of MMF in FSGS.

Other reviewers have noted MMF that has been used with some success in a small number of high-risk patients with FSGS resistant to or intolerant of other therapies.[77, 78] In one review,[79] authors concluded that patients who are resistant to corticosteroid therapy may benefit from the use of a cytotoxic agent, cyclosporin or mycophenolate.

Decrease in median 24-hour urine protein to creatinine ratio from 2.7 to 0.8 ($p=0.001$) was reported in a study of 18 patients with FSGS.[67] No significant change in median serum creatinine was detected. MMF was initiated at 0.5 to 0.75 g twice a day and increased as appropriate. One patient received 1.5 g twice a day. The MMF dose was decreased by 25 to 33% for persistent or moderately severe gastrointestinal symptoms.

A marked reduction in proteinuria from 6.8 to 5.7 g per day was reported in a study in eleven patients with FSGS and nephrotic syndrome. The mean MMF dose was 1.275mg per day for a mean period of 28 weeks.[80] This was considered of little clinical relevance.[76]

Another report indicated partial or complete remission in a small number of patients with treatment-resistant FSGS.[64] MMF was administered at a dose of 1 g twice daily, together with a reducing dose of corticosteroids.

One report involved nine children and young adults with steroid-resistant FSGS suggested some benefit from combined MMF and angiotensin blockade.[81] After six months of the combined therapy, the urine protein/creatinine ratio was 72% below baseline ($p<0.01$). This level was maintained for a minimum of 24 months of observation. Similarly, hyperlipidemia improved significantly with the treatment. The dose of MMF in these patients was 250-500 mg/m^2 per day.

3.5 Minimal change disease

Clinical remission was noted in all five patients with minimal change disease (MCD), according to one recent report.[65] Combined MMF and prednisone therapy was used for six months with an initial MMF dose of 1 to 2 g per day and a prednisone dose of 20-60 mg per day. Both drugs were tapered gradually. In another report complete steroid withdrawal was accomplished in 5/6 steroid dependent patients with MCD.[67] A case report of four patients with refractory minimal change disease demonstrated completed remission in all four patients after commencement of MMF (1-1.5g/day).[82] At the final assessment (19-42 months), MMF therapy was ongoing at a dose of 1g – 1.5g/day and daily oral prednisone requirements were reduced by at least 66%.

4. Systemic lupus erythematosus (SLE)

4.1 Lupus nephritis

MMF has gained widespread favour as an alternative immunosuppressive in SLE[83] following the publication of a number of controlled trials in patients with diffuse proliferative lupus nephritis (DPLN).[84-86] A number of published reviews have stated that MMF appears to be an effective alternative for the induction and maintenance of lupus nephritis, particularly for patients who are refractory or intolerant of conventional therapy.[87-89]

In a controlled trial by Chan et al 2000,[84] MMF with prednisolone was as effective as cyclophosphamide (CYP) and prednisolone followed by azathioprine (AZA) and prednisolone. This 12-month trial involved 42 patients. MMF was started at a dose of 1 g twice a day, then halved at six months. 81% of the 21 patients in the MMF/prednisolone group had a complete remission and 14% a partial remission, compared with 76% and 14%, respectively, in the other group. Toxicity was considered similar in the two groups. Data out to 32 months demonstrated a higher cumulative relapse rate in the MMF arm.[89] The authors have since noted that the data on relapse from the 32 month analysis was non-conclusive due to lack of power within the study design to detect a difference between the two arms.[90] An extension of the initial 12 month trial by Chan et al,[84] has recently been published.[91] Data collected out to 5 years demonstrated comparable long-term efficacy of MMF and prednisolone vs CYP-AZA and prednisolone therapy. The MMF and prednisolone arm was associated with a significantly lower number of patients with an infection requiring antibiotic therapy or infection requiring hospitalisation. The authors concluded that MMF is the preferred agent in induction treatment, and MMF in combination with low-dose corticosteroid presents an appropriate maintenance regimen for patients with DPLN.

MMF has been compared to intravenous CYP pulse therapy in patients with DPLN in at least two controlled trials. In one study twenty three patients received MMF 1 -1.5g per day plus supplemental steroids, and the other 23 patients received intermittent cyclophosphamide pulse therapy.[85] The groups were matched for age, sex and severity of renal damage. At six months a 50% reduction in proteinuria was achieved in 69.6% patients receiving MMF vs 47.8% of

patients on CYP. Similarly at six months a 50% reduction in urinary red blood cell excretion was achieved in 91.3% of MMF patients *vs* 65.2% for CYP. Adverse events in the MMF arm were less frequent compared to the CYP arm: gastrointestinal (26% *vs* 43%) and infection (17% *vs* 30%). No statistical scores of significance were provided by the authors. The second trial, recruiting 140 patients, randomised 71 patients to MMF 1g/day escalating up to 3g/day as tolerated and 69 patients to monthly intravenous cyclophosphamide, with a treatment duration of 24 weeks.[87] There was a significantly higher number of cases of remission reported in the MMF arm (14 in MMF vs 4 in CYP)($p = 0.014$). Combined complete and partial remissions were also higher in the MMF arm (21 vs 14 respectively)($p = 0.034$).

Sequential management of DPLN has been investigated in a trial involving 59 patients.[86] In this study all patients received induction therapy of monthly intravenous CYP for seven months. Patients were then randomly assigned to CYP infusion (0.5 -1.0g/m^2 every three months) or oral AZA (1-3mg/kg/day) or oral MMF (500 -3000mg/day) for one to three years. The 72 month event-free survival rate for the composite end point of death or chronic renal failure was higher in the MMF and AZA arms compared to the CYC arm ($p = 0.05$ and $p= 0.009$ respectively). The rate of relapse-free survival was higher for MMF compared to CYC therapy. ($p = 0.02$). Although the authors concluded that MMF and AZA might be superior to CYC as maintenance therapy, the study was not powered to demonstrate superiority.

In another study,[92] MMF significantly reduced the rate of decline of renal function, and steroid dosage was reduced in 80% of patients. In this study, 13 patients were treated with MMF for up to 37 months. All patients had relapsed on conventional treatment or there had been pressing reasons to minimise steroid dosage or avoid alkylating agents. MMF (mean dose 1 g per day) was generally well tolerated. Infections occurred in three patients.

A number of other reports have indicated that MMF may be helpful in lupus nephritis refractory to conventional therapy, including cyclophosphamide, corticosteroids and azathioprine,[70, 93-96] and paediatric-onset lupus erythematosus where a steroid-sparing effect is needed.[97]

4.2 Extra-renal disease

MMF appeared a safe and effective alternative immunosuppressant for extra-renal as well as renal disease in SLE not responding to conventional immunosuppressive treatment, according to the results of an open trial.[98] The maximum MMF dose was 2 g per day. This study involved 21 patients with SLE, most of whom had previously received courses of cyclophosphamide therapy and had also received courses of azathioprine or methotrexate. Indications for treatment included uncontrolled disease activity and worsening renal involvement.

Administered after a rise in antibodies to double stranded DNA in ten patients, MMF (2 g per day for six months) appeared to prevent clinical relapse of SLE and was well tolerated.[99] Concomitant drugs were left unchanged during the whole study period with the exception of AZA which was discontinued.

Case reports of MMF efficacy in glucocorticoid-refractory immune thrombocytopenia in and pulmonary haemorrhage in SLE have also been published.[100, 101] MMF has also been used with some success in cutaneous lupus (see skin conditions).

5. Vasculitis

Although a number of reports have indicated that MMF may be effective in severe vasculitis, including Takayasu's arteritis, it has been reported that "a definite recommendation cannot be made at the present time, particularly in view of recent reports of infection with cytomegalovirus and rapid recurrence of anti-neutrophilic cytoplasmic antibody-negative vasculitis in transplanted patients".[74] Another group reported renal vasculitis occurring in a patient being treated with MMF for pyoderma gangrenosum-like skin lesions.[102]

The authors of a 2001 review of therapies for ANCA vasculitis reported on several studies evaluating MMF.[103] Remission was reported in 13/20 patients, MMF was found ineffective in 3/20 patients and the drug was stopped due to gastrointestinal side-effects in 4/20 patients.

An increased rate of side effects was noted in five patients with end-stage renal disease being treated for ANCA-associated vasculitis.[104] MMF had been initiated as a remission maintenance therapy, at a dose of 1 g per day. The aim was to increase the MMF dose to 2 g per day. Four patients developed severe anaemia, one patient developed leukopenia. Gastrointestinal symptoms led to a dose reduction to 1 g per day in two patients and cessation of treatment in one. Three patients remained on MMF treatment; however, the daily dose did not exceed 1g.

6. Rheumatoid arthritis

MMF has been reported to be potentially effective and fairly well tolerated in rheumatoid arthritis.[105, 106]

In one of the earlier published studies, improvement was said to be seen in many patients who had been refractory to several disease-modifying anti-rheumatic drugs.[105] MMF was shown to reduce titres of rheumatoid factor, immunoglobulin levels and the total number of T-cells (CD62 +) in peripheral blood.

A randomised, placebo-controlled, double-blinded trial demonstrated MMF 1 g twice a day to be as effective as 2 g twice a day, with the lower dose having fewer gastrointestinal side effects.[106] This study, involving 153 patients, reported marked efficacy at week 4, with a peak effect around weeks 8 to 12, which was sustained to week 36.

7. Myositis

Clinical improvement has been reported in case reports or small case series in polymyositis,[107] dermatomyositis[108, 109] and inclusion body myositis.[110] The doses ranged from 1 to 3 g per day.

8. Myaesthenia gravis

Efficacy of MMF in the treatment of myaesthenia gravis has been reported in at least 100 patients (case reports or small studies).[110-118] A double-blind, placebo-controlled pilot study involving 18 patients demonstrated efficacy for MMF compared to placebo.[119] The most frequently used dosage in these patients was 1 g twice a day.

9. Wegener's granulomatosis

A number of reports of potential efficacy for MMF in this condition have been published.[120-124] However, there have also been case reports of cytomegalovirus colitis occurring during treatment [124, 125] and an acute inflammatory syndrome, characterised by fever, arthralgias and muscle pain.[126]

All 13 patients with active Wegener's granulomatosis responded to MMF treatment according to one report, but relapses occurred in 3/13 patients after 5-10 months of follow-up treatment.[120] The other ten patients were in complete remission during a median follow-up of 14 months. The dosage of MMF was 2 g per day given with prednisone 0.5-1.0 mg/kg per day with successive tapering of the steroid dose. All 13 patients had been intolerant of cyclophosphamide, and most had been receiving azathioprine and corticosteroids at the time of relapse.

Successful maintenance therapy with MMF (2 g per day) and tapering doses of oral corticosteroids, after induction with cyclophosphamide, has been reported in two separate case series[123, 124] Eleven patients in one study remained in remission over a period of 15 months with MMF maintenance therapy.[124] Possible drug-related adverse effects reported in this study included abdominal pain, respiratory infection, diarrhoea, leukopenia, and, as referred to above, cytomegalovirus-colitis in one patient (successfully treated with ganciclovir). Langford et al reported effective maintenance of remission in 8/14 patients over a median period of 27 months.[123] MMF was well tolerated in this patient group, with no reports of gastro-intestinal upsets. Two cases of leukopenia were reported but resolved upon reduction of MMF dose. One case of severe bacterial pneumonia was also reported.

10. Scleroderma

From the results of one pilot study, combination antithymocyte globulin with MMF therapy appeared to alleviate some symptoms of scleroderma, but with considerable adverse events.[127] The combined treatment was undertaken for 12 months in 13 patients with diffuse scleroderma. The MMF dose was 2 g per day. Skin scores improved over the duration of treatment. Five cases of serum sickness were attributed to the antithymocyte globulin. Of the 13 patients treated, one developed severe fibrosing alveolitis, one pulmonary hypertension and two renal crisis. The disease manifestations were thought to have stabilised in the remaining patients.

11. Inflammatory bowel disease

A number of positive reports for MMF in refractory ulcerative colitis or Crohn's disease have been published.[128, 129] However, it has been noted that the beneficial effects may be of relatively brief duration and the side effect profile not favourable.[130] The promise of earlier reports has also been disputed in other publications.[131, 132] At least two studies have suggested that MMF is not as efficacious as other immunosuppressants, such as AZA, in either Crohn's disease or chronic ulcerative colitis.[133, 134] A large, multicentre, international RCT of MMF in active refractory Crohn's disease was terminated in 1999, due to registration of 'new innovative medicines' and 'slow recruitment into the trial'.[135]

MMF may have a role in AZA refractory disease or as an alternative for patients in whom AZA is contraindicated. A randomised trial (70 patients) of MMF *vs* AZA for the treatment of chronic active Crohn's disease found MMF to be effective and well tolerated.[128] MMF was shown to be equally effective as AZA in moderately active disease, and resulted in an earlier reduction in the

Crohn's disease activity index in patients with highly active disease compared to AZA. Investigators concluded that MMF should be considered in patients in whom AZA is contraindicated or proven ineffective. Similar conclusions were made in a retrospective review of 39 patients diagnosed with inflammatory bowel disease.[129] 40% of patients went into remission and complete steroid withdrawal was achieved in all these patients. Almost all patients included in the review had been intolerant of, or had not responded to AZA.[129]

Skelly et al reviewed the results of their own and past studies.[132] They noted that, since patients with ulcerative colitis may be unduly prone to colonic injury, MMF may not be a suitable drug for its treatment. They concluded that further use of MMF as therapy in inflammatory bowel disease should be confined to clinical trials.

12. Behçet's syndrome

A study in 30 patients with Behçet's syndrome was interrupted due to inefficacy of MMF after the intermediate evaluation of the first six patients (as required by the ethical committee).[136] These authors concluded that MMF (2 to 3 g per day) was unable to control the signs of mucocutaneous Behçet's disease. Although an improvement of the disease activity index from a mean of 5.2 to 1.3 had been found after the first month of combination treatment, withdrawal of prednisolone led to quick relapses with an index increase. Introduction of interferon alpha (2a) (3 x 9 million IU 3x/week s.c.) in three patients decreased the activity index from a mean of 4.0 to 0.0.

13. HIV infection

Several studies have investigated MMF use in HIV infection, both *in vitro* and in *vivo*, with varying results. Its clinical role in HIV infection remains unclear.[137] Further studies are ongoing to determine the safety and efficacy profile of MMF in HIV-infected patients.[138]

14. Other conditions

From scant case reports in the literature, MMF has been reported to be effective in a number of other conditions such as autoimmune haemolytic anaemia, sarcoidosis, retroperitoneal fibrosis, idiopathic thrombocytopenic purpura, multiple sclerosis, biliary cirrhosis and primary sclerosing cholangitis.

Recommendations

Current evidence suggests that use of mycophenolate in non-transplant disorders should be restricted to patients with auto-immune disorders in whom standard treatment has failed or is contraindicated.

Almost all published papers investigating the use of mycophenolate in non-transplant indications conclude that there is a need for randomised controlled trials to confirm or reject current findings. This should not necessarily preclude the use of mycophenolate in these conditions, provided the decision to treat is carefully considered in light of the available evidence about mycophenolate and other treatment options.

Since use of mycophenolate in non-transplant indications is not currently approved by the Therapeutic Goods Administration, use of mycophenolate in these indications should follow normal procedures for 'off-label' use of medicines. Further guidance about off-label use of drugs in hospitals is available from NSW TAG: 'Off-Label Use of Registered Medicines and Use of Medicines under the Personal Importation Scheme in NSW Public Hospitals'.

Mycophenolate formulations: Are they therapeutically equivalent?

Summary
No significant differences in efficacy and gastrointestinal (GI) tolerability have been reported between mycophenolate sodium enteric coated (MS EC) and mycophenolate mofetil (MMF) in either newly transplanted *(de novo)* or maintenance renal transplant patients*.

There have been no published studies investigating the use of MS EC in patients treated with MMF for other transplant or non-transplant indications.

MS EC 720mg has been found to be therapeutically equivalent to MMF 1g*.

MMF is listed under Section 100 of the Pharmaceutical Benefits Scheme for prevention of rejection in renal and cardiac transplant patients and Section 85 for maintenance therapy in renal and cardiac transplant patients. MS EC is listed under Section 100 of the PBS for the prevention of rejection in renal transplant patients and Section 85 for maintenance therapy in renal transplant patients.

**Used in combination with cyclosporin and corticosteroids.*

Introduction
Mycophenolate sodium enteric coated (MS EC), delivers mycophenolic acid (MPA), the active moiety, to the systemic circulation. This is the same compound delivered by the ester pro-drug mycophenolate mofetil (MMF). MS EC was designed to allow the delayed release of the active agent into the small intestine, unlike MMF which releases MPA into the stomach. The predicted benefit of MS EC was to enhance the therapeutic efficacy of MPA through increased tolerability (particularly aimed at reducing gastrointestinal related side effects) relative to systemic exposure.

Efficacy and adverse events
Two phase-III, multicentre, randomised, double-blind, parallel group studies comparing MS EC with MMF have been conducted in renal transplant patients. The first study was conducted in newly transplanted patients (*de novo*) and the results at 6 and 12 months have been reported.[139] In the second study, maintenance renal transplant patients were randomised to remain either on MMF or be switched to MS EC (Myfortic®). Results out to 12 months have been published.[140] Interim results of a multicentre prospective study investigating the switch from MMF to MS EC have also been reported.[141] There have been no published studies investigating the use of MS EC for indications other than renal transplant.

De novo renal transplant patients
A total of 423 patients were randomised within 48 hours of renal transplantation, 213 to MS EC (720 mg twice daily) and 210 to MMF (1 g twice daily) as part of triple immunosuppressive therapy with cyclosporin and steroids.[139]

The results showed that 720 mg of MS EC administered twice daily was therapeutically equivalent to 1 g of MMF administered twice daily. For MS EC and MMF respectively, overall efficacy failure (biopsy-proven acute rejection {BPAR}, graft loss, death or loss to follow up) was 25.8% vs 26.2% at 6 months (ns) and 26.3% vs 28.1% at 12 months (ns), demonstrating therapeutic equivalence. BPAR alone was seen in 22.5% vs 24.3% of patients (MS EC *vs* MMF) {ns}. Among patients with BPAR, the incidence of severe acute infection was 2.1% vs 9.8%

(MS EC *vs* MMF)(ns). Patients in the MS EC arm of the study were noted to be potentially disadvantaged with respect to graft cold ischaemic time >24 hours and panel reactive antibody titres (p=0.051 and p=0.019 respective difference *vs* MMF). However these differences did not appear to affect the results of the study.

The safety profile and incidence of gastrointestinal adverse events were similar for both groups. There was no observed difference in the incidence of GI drug related adverse events between the MS EC and the MMF arms over the 12 month study period. The authors note in their discussion that the study was not powered to detect statistically significant differences between treatment groups in terms of GI tolerability. The overall incidence of serious infections was similar in both arms (MS EC 22.1% vs MMF 27.1%)(ns), however the incidence of serious pneumonia (the definition of serious was not provided by the authors) was lower in the MS EC arm, 0.5% vs 4.3% for MMF (p = 0.01).

Maintenance renal transplant patients

Stable maintenance renal transplant patients at least 6 months post-transplant were enrolled in this study (n = 322).[140] All patients received open-label MMF (1g bd) plus cyclosporin with or without corticosteroids (according to local guidelines) for 2 weeks prior to randomisation. Patients were then randomised to receive either 720 mg of MS EC twice daily or 1 g MMF twice daily; the cyclosporin +/- corticosteroids continued. The primary endpoints of the study were the incidence and severity of GI adverse events at 3 months and incidence of neutropenia (absolute neutrophil count < 1500 cells/mm^3) in the first 3 months. Secondary endpoints included evaluation of adverse events, laboratory data and efficacy failure out to 12 months.

No significant difference in incidence of GI adverse events was found between the two groups at 3 months (26% for MS EC *vs* 21% for MMF)(ns) and 12 months (30% *vs* 25% respectively) (ns).[140] The occurrence of neutropenia within the first 3 months of therapy was similar (MS EC 0.6% *vs* MMF 3.1%; 95% CI: {-6.74, + 0.80}) and remained unchanged at 12 months (12 month figures not reported by the authors).[140]

The overall incidence of serious infections was 8.8% for MS EC vs 16.0% for MMF ($p<0.05$).[140] The definition of 'serious' infection was not provided by the investigators. No significant difference was noted between the two arms with respect to efficacy failure at 12 months (2.5% for MS EC and 6.1% for MMF)(ns) and the incidence of biopsy-proven chronic rejection was also comparable (3.8% for MS EC and 4.9% for MMF)(ns).[140]

A 3-month interim analyses from an open label, multicentre observational study (*myPROMS*) suggested that in the maintenance of renal transplant patients conversion from MMF to MS EC was well tolerated.[141] The incidence of efficacy failure was low in the two sub-studies included in the analyses, with only one patient out of the 150 patients reporting BPAR and no reports of chronic rejection, graft loss or death following the conversion from MMF to MS EC at three months.[141]

Bioavailability and pharmacokinetic studies

An early bioavailability study in 24 stable renal transplant patients determined that 720 mg of MS EC (Myfortic®) delivered bioequivalent MPA exposure to 1 g MMF.[142] A pharmacokinetic/pharmacodynamic (PK/PD) study of 14 stable renal transplant patients demonstrated identical drug exposure and similar PD-response, despite minor differences in

PK[143] A single dose, cross over trial, was reported to show that systemic MPA exposure from MS EC (Myfortic®) was linear and increased proportionally with dose.[144]

A PK analysis of a subset of 48 patients in the '*de novo*' trial was conducted, demonstrating substantially and consistently higher systemic MPA exposure and maximal MPA concentrations for MS EC than for MMF.[144] The mean increase in systemic MPA exposure associated with the MS EC formulation relative to MMF was 32% ($p = 0.004$).[144] However this higher exposure did not demonstrate any significant improvement in clinical efficacy (protection against allograft rejection) or increase in adverse effects in the *'de novo'* trial.[139]

References

1. Jones E, Epinette W, Hackney V, Frost P. Treatment of psoriasis with oral mycophenolic acid. Journal of Investigative Dermatology 1975; 65:537-42.
2. Lynch W, Roenigk HJ. Mycophenolic acid for psoriasis. Archives of Dermatology 1977; 113:1203-8.
3. Epinette W, Parker C, Jones E, Greist M. Mycophenolic acid for psoriasis. A review of pharmacology, long-term efficacy, and safety. Journal of the American Academy of Dermatology 1987; 17:962-71.
4. Geilen, Tebbe, Bartels G, Krengel, Orfanos. Successful treatment of erythrodermic psoriasis with mycophenolate mofetil. British Journal of Dermatology 1998; 138:1101-1102.
5. Tong DW, Walder BK. Widespread plaque psoriasis responsive to mycophenolate mofetil. Australasian Journal of Dermatology 1999; 40:135-137.
6. Gomez E, Menendez L, Frost P. Efficacy of mycophenolic acid for the treatment of psoriasis. Journal of the American Academy of Dermatology 1979; 1:531-7.
7. Spatz S, Rudnicka A, McDonald C. Mycophenolic acid in psoriasis. British Journal of Dermatology 1978; 98:429-35.
8. Kirby B, Yates V. Mycophenolate mofetil for psoriasis. British Journal of Dermatology 1998; 139:357.
9. Haufs, Beissert, Grabbe, Schutte, Luger. Psoriasis vulgaris treated successfully with mycophenolate mofetil. British Journal of Dermatology 1998; 138:179-181.
10. Ameen M, Smith H, Barker J. Combined mycophenolate mofetil and cyclosporin therapy for severe recalcitrant psoriasis. Clinical and Experimental Dermatology 2001; 26:480-3.
11. Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. British Journal of Dermatology 2001; 144:583-586.
12. Marinari R, Fleischmajer R, Schragger A, Rosenthal A. Mycophenolic acid in the treatment of psoriasis: long term administration. Archives of Dermatology 1977; 133:930-2.
13. Zhou Y, Rosenthal D, Dutz J, Ho V. Mycophenolate mofetil (CellCept) for psoriasis: A two-centre, prospective open-label clinical trial. Journal of Cutaneous Medicine and Surgery 2003; 7:193-197.
14. Grundmann-Kollmann M, Mooser G, Schraeder P, et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. Journal of the American Academy of Dermatology 2000; 42:835-837.
15. Davison SC, Morris-Jones R, Powles AV, Fry L. Change of treatment from cyclosporin to mycophenolate mofetil in severe psoriasis. British Journal of Dermatology 2000; 143:405-407.
16. Mahe E, Meyer O, Descamps V, Picard-Dahan C, Crickx B. Early, severe and transient arthralgia induced by mycophenolate mofetil in a patient with erythrodermal psoriasis. [French]. Annales de Dermatologie et de Venereologie 2002; 129:1054-5.
17. Wohlrab J, Jahn K, Plaetzer M, Neubert R, Marsch WC. Topical application of mycophenolate mofetil in plaque-type psoriasis. British Journal of Dermatology 2001; 144:1263-1264.
18. Geilen C, Mrowietz U. Lack of efficacy of topical mycophenolic acid in psoriasis vulgaris. Journal of the American Academy of Dermatology 2000; 42:837-40.
19. Shoji Y, Fukumura T, Kudo M, Yanagawa A, Shimada J, Mizushima Y. Effect of topical preparation of mycophenolic acid on experimental allergic contact dermatitis of guinea-

pigs induced by dinitrofluorobenzene. Journal of Pharmacy and Pharmacology 1994; 46:643-6.
20. Neuber K, Schwartz I, Itschert G, Dieck At. Treatment of atopic eczema with oral mycophenolate mofetil. British Journal of Dermatology 2000; 143:385-391.
21. Grundmann-Kollmann M, Podda M, Ochsendorf F, Boehncke W-H, Kaufmann R, Zollner T. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. Archives of Dermatology 2001; 137:870-3.
22. Lee S, Park Y, Kim H, Kim C. Therapeutic efficacy of mycophenolate mofetil in atopic dermatitis. [Korean]. Korean Journal of Dermatology 2002; 40:908-913.
23. Grundmann-Kollmann, Korting, Behrens, et al. Successful treatment of severe refractory atopic dermatitis with mycophenolate mofetil. British Journal of Dermatology 1999; 141:175-176.
24. Benez A, Fierlbeck G. Successful long-term treatment of severe atopic dermatitis with mycophenolate mofetil. British Journal of Dermatology 2001; 144:638-639.
25. Hansen ER, Buus S, Deleuran M, Andersen KE. Treatment of atopic dermatitis with mycophenolate mofetil. British Journal of Dermatology 2000; 143:1324-1326.
26. Satchell AC, Barnetson RSC. Staphylococcal septicaemia complicating treatment of atopic dermatitis with mycophenolate. British Journal of Dermatology 2000; 143:202-203.
27. Mimouni D, Anhlat G, Cummins D, Kouba D, Thorne J, Nousari H. Treatment of pemphigus vulgaris and pemphigus foliaceus with mycophenolate mofetil. Archives of Dermatology 2003; 139:739-42.
28. Powell AM, Albert S, Al Fares S, et al. An evaluation of the usefulness of mycophenolate mofetil in pemphigus. British Journal of Dermatology 2003; 149:138-145.
29. Enk AH, Knop J. Mycophenolate Is effective in the treatment of pemphigus vulgaris. Archives of Dermatology 1999; 135:54-56.
30. Chams-Davatchi C, Azar R, Daneshpazooh M, et al. Open trial of mycophenolate mofetil in the treatment of resistant pemphigus vulgaris [French]. Annales de Dermatologie et de Venereologie 2002; 129:23-25.
31. Williams JV, Marks JR. JG, Billingsley EM. Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. British Journal of Dermatology 2000; 142:506-508.
32. Hsiao C-J, Hsu Mm-L, Lee Jy-Y, Chen W-C, Hsieh WC. Paraneoplastic pemphigus in association with a retroperitoneal Castleman's disease presenting with a lichen planus pemphigoides-like eruption. A case report and review of literature. British Journal of Dermatology 2001; 144:372-376.
33. Ng P, Rencic A, Nousari H. Paraneoplastic pemphigus: a refractory autoimmune mucocutaneous disease. Journal of Cutaneous Medicine and Surgery 2002; 6:434-7.
34. Schmidt E, Sitaru C, Schubert B, et al. Subacute prurigo variant of bullous pemphigoid: Autoantibodies show the same specificity compared with classic bullous pemphigoid. Journal of the American Academy of Dermatology 2002; 47:133-136.
35. Ratnam K. Adjuvant therapy of bullous pemphigoid with mycophenolate mofetil: old drug, new use. Singapore Medical Journal 2001; 42:482-4.
36. Grundmann-Kollmann M, Korting H, Behrens S, et al. Mycophenolate mofetil: A new therapeutic option in the treatment of blistering autoimmune diseases. Journal of the American Academy of Dermatology 1999; 40:957-960.
37. Nousari H, Sragovich A, Kimyai-Asadi A, Orlinsky D, Anhalt G. Mycophenolate mofetil in autoimmune and inflammatory skin disorders. Journal of the American Academy of Dermatology 1999; 40:265-268.

38. Bohm M, Beissert S, Schwarz T, Metze D, Luger T. Bullous pemphigoid treated with mycophenolate mofetil. Lancet 1997; 349:22.
39. Ingen-Housz-Oro S, Prost-Squarcioni C, Pascal F, et al. Cicatricial pemphigoid: treatment with mycophenolate mofetil [French]. Annales de Dermatologie et de Venereologie 2005; 132:13-16.
40. Assmann T, Ruzicka T. New immunosuppressive drugs in dermatology (mycophenolate mofetil, tacrolimus): unapproved uses, dosages, or indications. Clinics in Dermatology 2002; 20:505-14.
41. Daniels NH, Callen JP. Mycophenolate mofetil is an effective treatment for peristomal pyoderma gangrenosum. Archives of Dermatology 2004; 140:1427-1429.
42. Lee M, Cooper A. Mycophenolate mofetil in pyoderma gangrenosum. Journal of Dermatological Treatment 2004; 15:303-307.
43. Baskan E, Saricaoglu H, Tunali S, Tolunay S. Effective treatment of relapsing idiopathic nodular panniculitis (Pfeifer-Weber-Christian disease) with mycophenolate mofetil. Journal of Dermatological Treatment 2003; 14:57-60.
44. Pickenacker A, Luger TA, Schwarz T. Dyshidrotic eczema treated with mycophenolate mofetil. Archives of Dermatology 1998; 134:378-379.
45. Semhoun-Ducloux S, Ducloux D, Miguet J-P. Mycophenolate mofetil-induced dyshidrotic eczema. Annals of Internal Medicine 2000; 132:417.
46. Nousari HC, Anhalt GJ, Morison WL. Mycophenolate in psoralen-UV-A desensitization therapy for chronic actinic dermatitis. Archives of Dermatology 1999; 135:1128-1129.
47. Boehm I, Bieber T. Chilblain lupus erythematosus hutchinson: successful treatment with mycophenolate mofetil. Archives of Dermatology 2001; 137:235-236.
48. Hanjani NM, Nousari CH. Mycophenolate Mofetil for the treatment of cutaneous lupus erythematosus with smouldering systemic involvement. Archives of Dermatology 2002; 138:1616-1618.
49. Goyal S, Nousari H. Treatment of resistant discoid lupus erythematosus of the palms and soles with mycophenolate mofetil. Journal of the American Academy of Dermatology 2001; 45:142-144.
50. Trebing D, Ziemer A. Acquired epidermolysis bullosa with a highly varied clinical picture and successful treatment with mycophenolate mofetil [German]. Hautarzt 2001; 52:717-21.
51. Nousari HC, Goyal S, Anhalt GJ. Successful treatment of resistant hypertrophic and bullous lichen planus with mycophenolate mofetil. Archives of Dermatology 1999; 135:1420-1421.
52. Baltatzis S, Tufail F, Yu E, Vredeveld C, Foster C. Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. Ophthalmology 2003; 110:1061-5.
53. Greiner L, Varikkara M, Santiago C, Forrester J. [Efficiency of mycophenolate mofetil in the treatment pf intermediate and posterior uveitis]. Ophthalmologe 2002; 99:691-4.
54. Zierhut M, Stubiger N, Aboalchamat W, Landenberger H, Bialasiewicz A, Angelmann K. [Immunosuppressive therapy with mycophenolate mofetil (CellCept) in the treatment of uveitis]. Ophthalmologe 2001; 98:647-51.
55. Larkin G, Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. Ophthalmology 1999; 106:370-4.
56. Kilmartin D, Fletcher Z, Almeida J, Liversidge J, Forrester J, Dick A. CD69 expression on peripheral CD4+ T cells parallels disease activity and is reduced by mycophenolate mofetil in uveitis. Investigative Ophthalmology and Visual Science 2001; 42:1285-92.

57. Llinares-Tello F, Hernandez-Prats C, Munoz-Ruiz C, Selva-Otaolaurruchi J, Ordovas-Bains J. Monitoring trough plasma concentrations of mycophenolate mofetil in patients with uveitis. Journal of Clinical Pharmacy and Therapeutics 2004; 29:53-58.
58. Lau CS, Comer M, Lightman S. Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation. Clinical and Experimental Ophthalmology 2003; 31:487-491.
59. Zurdel J, Aboalchamat B, Zierhut M, Stubiger N, Bialasiewicz A, Engelmann K. [Early clinical results with mycophenolate mofetil in immunosuppressive therapy of ocular pemphigoid]. Klinische Monatsblatter fur Augenheilkunde 2001; 218:222-8.
60. Reis A, Reinhard T, Sundmacher R, Althaus C, Voiculescu A, Kutkuhn B. [Mycophenolate mofetil in ocular immunological disorders. A survey of the literature with 3 case reports]. Klinische Monatsblatter fur Augenheilkunde 1998; 213:257-61.
61. Briggs W, Choi M, Scheel Jr. P. Successful mycophenolate mofetil treatment of glomerular disease. American Journal of Kidney Diseases 1998; 31:213-7.
62. Briggs W, Choi M, Scheel Jr. P. Follow-up on mycophenolate treatment of glomerular disease. American Journal of Kidney Diseases 1998; 31:898-9.
63. Harzallah K, Badid C, Fouque D, Lefrancois N, Touraine J, Laville M. Efficacy of mycophenolate mofetil on recurrent glomerulonephritis after renal transplantation. Clinical Nephrology 2003.
64. Day C, Cockwell P, Lipkin G, Savage C, Howie A, Adu D. Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. Nephrology Dialysis Transplantation 2002; 17:2011-2013.
65. Zhao M, Chen X, Chen Y. Clinical observations of mycophenolate mofetil therapy in refractory primary nephrotic syndrome. Nephrology 2003; 8:105-109.
66. Cattran D. Mycophenolate mofetil and cyclosporine therapy in membranous nephropathy. Seminars in Nephrology 2003; 23:272-7.
67. Choi MJ, Eustace JA, Gimenez LF, et al. Mycophenolate mofetil treatment for primary glomerular diseases. Kidney International 2002; 61:1098-1114.
68. Miller G, Zimmerman I, Radhakrishnan J, Appel G. Use of mycophenolate mofetil in resistant membranous nephropathy. American Journal of Kidney Diseases 2000; 36:205-256.
69. Polenakovic M, Grcevska L, Dzikova S. Mycophenolate mofetil in the treatment of idiopathic stages III/IV membranous nephropathy. Nephrology Dialysis Transplantation 2003; 18:1233-1234.
70. Kapitsinou P, Boletis J, Skopouli K, Boki K, Moutspopoulos H. Lupus nephritis: treatment with mycophenolate. Rheumatology 2004; 43:377-380.
71. Chen X, Chen P, Cai G, et al. [A randomised control trial of mycophenolate mofetil treatment in severe IgA nephropathy]. Chinese Medical Journal 2002; 82:796-801.
72. Maes BD, Oyen R, Claes K, et al. Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study. Kidney International 2004; 65:1842-1849.
73. Nowack R, Brirck R, Van der Woude F. Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. Lancet 1997; 349:774.
74. Quiroz W, Herrera-ACosta J, Johnson R, Rodrigues-Iturbe B. Mycophenolate mofetil treatment in conditions different from organ transplantation. Transplantation Proceedings 2002; 34:2523-2526.
75. Hogg R, Wyatt R, Scientific Planning Committee of the North American IgA Nephropathy Study. A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy [ISRCTN62574616]. BMC Nephrology 2004; 5:3.

76. Ponticelli C, Passerini P. Other immunosuppressive agents for focal segmental glomerulosclerosis. Seminars in Nephrology 2003; 23:242-248.
77. Kveder R. Therapy-resistant focal and segmental glomerulosclerosis. Nephrology Dialysis Transplantation 2003; 18:v34-v37.
78. Benchimol C. Focal segmental glomerulosclerosis: Pathogenesis and treatment. Current Opinion in Paediatrics 2003; 15:171-180.
79. Granata A, Nardo A, Cordaro S, et al. Therapeutic update for primary focal and segmental glomerulosclerosis. [Italian]. Rivista Italiana di Biologia e Medicina 2002; 22:24-28.
80. Matalon A, Valeri A, Appel G. Treatment of focal segmental glomerulosclerosis. Seminars in Nephrology 2000; 20:309-317.
81. Montane B, Abitbol C, Chandar J, Strauss J, Zilleruelo G. Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. Paediatric Nephrology 2003; 18:772-777.
82. Pesavento T, Bay W, Agarwal G, Hernandez R, Herbet L. Mycophenolate therapy in frequently relapsing minimal change disease that has failed cyclophosphamide therapy. American Journal of Kidney Diseases 2004; 43:e3-10.
83. Riskalla M, Somers E, Fatica R, McCune W. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. Journal of Rheumatology 2003; 30:1508-1512.
84. Chan TM, Li FK, Tang CSO, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. New England Journal of Medicine 2000; 343:1156-1162.
85. Hu W, LIU Z, Chen H, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chinese Medical Journal 2002; 115:705-9.
86. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. New England Journal of Medicine 2004; 350:971-980.
87. Ginzler E, Aranow C. Mycophenolate in lupus nephritis. Lupus 2005; 14:59-64.
88. Mok C, Lai K. Mycophenolate mofetil in lupus glomerulonephritis. American Journal of Kidney Diseases 2002; 40:447-457.
89. Mok C, Wong R, Lai K. Treatment of severe proliferative lupus nephritis: the current state. Annals of the Rheumatic Diseases 2003; 62:799-804.
90. Chan T. Lupus nephritis: induction therapy. Lupus 2005; 14:s27-s32.
91. Chan T, Tsi K, Tang C, Mok M, Li F. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. Journal of the American Society of Nephrology 2005; 16:1076-1084.
92. Kingdon E, Mclean A, Psimenou E, et al. The safety and efficacy of MF in lupus nephritis: a pilot study. Lupus 2001; 10:606-11.
93. Fu Y, Liu G. Mycophenolate mofetil therapy for children with lupus nephritis refractory to both intravenous cyclophosphamide and cyclosporine. Clinical Nephrology 2001; 55:318-21.
94. Glicklich D, Acharya A. Mycophenolate mofetil therapy for lupus nephritis refractory to intravenous cyclophosphamide. American Journal of Kidney Diseases 1998; 32:318-322.
95. Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. Journal of the American Society of Nephrology 1999; 10:833-839.
96. Gaubitz M, Schorat A, Schotte H, Kern P, Domschke W. Mycophenolate mofetil for the treatment of systemic lupus erythematosus; an open pilot trial. Lupus 1999; 8:731-736.

97. Buratti S, Szer IS, Spencer C, Bartosh S, Reiff A. Mycophenolate mofetil treatment of severe renal disease in paediatric onset systemic lupus erythematosus. Journal of Rheumatology 2001; 28:2103-8.
98. Karim MY, Alba P, Cuadrado M-J, et al. Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. Rheumatology 2002; 41:876-882.
99. Bijl M, Horst G, Bootsma H, Limburg P, Kallenberg C. Mycophenolate mofetil prevents a clinical relapse in patients with systemic lupus erythematosus at risk. Annals of the Rheumatic Diseases 2003; 62:534-9.
100. Vasoo S, Thumboo J, Fong K. Refractory immune thrombocytopenia in systemic lupus erythematosus: Response to mycophenolate mofetil. Lupus 2003; 12:630-632.
101. Samad A, Lindsley C. Treatment of pulmonary haemorrhage in childhood systemic lupus erythematosus with mycophenolate mofetil. Southern Medical Journal 2003; 96:705-7.
102. Manz B, Rytter M, Mittag M, Seidel W, Nenoff P. ANCA-positive vasculitis of the skin and kidneys associated with acne conglobata [German]. Hautarzt 2002; 53:730-4.
103. Tervaert J, Stegeman C, Kallenberg C. Novel therapies for anti-neutrophil cytoplasmic antibody-associated vasculitis. Current Opinion in Nephrology and Hypertension 2001; 10:211-7.
104. Haubitz M, de Groot K. Tolerance of mycophenolate mofetil in end-stage renal disease patients with ANCA-associated vasculitis. Clinical Nephrology 2002; 57:421-4.
105. Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. Clinical and Experimental Rheumatology 1993; 11:s117-9.
106. Schiff M, Leishman B. CellCept(R) (mycophenolate mofetil-MMF), a new treatment for RA: A 12-week, double blind, randomized, placebo-controlled withdrawal trial. Arthritis and Rheumatism 1998; 41:s364.
107. Schneider C, Gold R, Schafers M, Toyka K. Mycophenolate mofetil in the therapy of polymyositis associated with a polyautoimmune syndrome. Muscle and Nerve 2002; 25:286-8.
108. Gelber A, Nousari CH, Wigley F. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. Journal of Rheumatology 2000; 27:1542-5.
109. Tausche A, Meurer M. Mycophenolate mofetil for dermatomyositis. Dermatology 2001; 202:341-3.
110. Mowzoon N, Sussman A, Bradley W. Mycophenolate (CellCept) treatment of myasthenia gravis, chronic inflammatory polyneuropathy and inclusion body myositis. Journal of the Neurological Sciences 2001; 185:119-22.
111. Kotani A, Takahashi A, Koga H, et al. Myasthenia gravis after allogeneic bone marrow transplantation treated with mycophenolate mofetil monitored by peripheral blood OX40+ CD4+ T cells. European Journal of Haematology 2002; 69:318-320.
112. Schneider C, Gold R, Reiners K, Toyka K. Mycophenolate mofetil in the therapy of severe myasthenia gravis. European Neurology 2001; 46:79-82.
113. Caponnetto C, Rossi E, Primavera A. Mycophenolate mofetil: a new immunosuppressive approach. Successful treatment in a case of myasthenia gravis associated with incomplete lupus erythematosus syndrome and hepatitis C virus infection. European Neurology 2001; 46:53-4.
114. Chaudhry V, Cornblath D, Griffin J, O'Brien R, Drachman D. Mycophenolate mofetil: a safe and promising immunosuppressant in neuromuscular diseases. Neurology 2001; 56:94-6.

115. Ciafaloni E, Massey J, Tucker-Lipscomb B, Sanders D. Mycophenolate mofetil for myasthenia gravis: an open label pilot study. Neurology 2001; 56:97-9.
116. Hauser R, Malek A, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. Neurology 1998; 51:912-3.
117. Meriggioli MN, Rowin J. Treatment of myasthenia gravis with mycophenolate mofetil: a case report. Muscle and Nerve 2000; 23:1287-9.
118. Meriggioli MN, Ciafaloni E, Al-Hayk KA, et al. Mycophenolate mofetil for myasthenia gravis: An analysis of efficacy, safety, and tolerability. Neurology 2003; 61:1438-1440.
119. Meriggioli MN, Rowin J, Richman J, Leurgans S. Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. Annals of the New York Academy of Sciences 2003; 998:494-9.
120. Stegeman C, Cohen Tervaset J. Mycophenolate mofetil for remission induction in patients with active Wegner's granulomatosis intolerant to cyclophosphamide.[Abstract]. Journal of the American Society of Nephrology 2000; 11:98A.
121. Le Hello C, Bonte I, Mora J-J, Verneuil L, Noel L-H, Guillevin L. Pyoderma gangrenosum associated with Wegener's granulomatosis: partial response to mycophenolate mofetil. Rheumatology 2002; 41:236-237.
122. Lin S, Shan L, Mingcai Q. A case of Wegener's granulomatosis treated with mycophenolate mofetil. Nephron 2002; 92:959.
123. Langford C, Talar-Williams C, Sneller M. Mycophenolate mofetil for remission maintenance in the treatment of Wegner's granulomatosis. Arthritis and Rheumatism 2004; 51:278-283.
124. Nowack R, Gobel U, Klooker P, Hergesell O, Andrassy K, Van der Woude F. Mycophenolate mofetil for maintenance therapy of Wegner's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. Journal of the American Society of Nephrology 1999; 10:1965-71.
125. Woywodt A, Choi M, Schneider W, Kettritz R, Gobel U. Cytomegalovirus colitis during mycophenolate mofetil therapy for Wegner's granulomatosis. American Journal of Nephrology 2000; 20:468-72.
126. Maes B, Oellerich M, Ceuppens JL, et al. A new acute inflammatory syndrome related to the introduction of mycophenolate mofetil in patients with Wegener's granulomatosis. Nephrology, Dialysis and Transplantation. 2002; 17:923-926.
127. Stratton RJ, Wilson H, Black CM. Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. Rheumatology 2001; 40:84-88.
128. Neurath MF, Wanitschke R, Peters M, Krummenauer F, Buschenfelde K-HM, Schlaak JF. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. Gut 1999; 44:625-628.
129. Ford AC, Towler RJ, Moayyedi P, Chalmers DM, Axon ATR. Mycophenolate mofetil in refractory inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2003; 17:1365-1369.
130. Forbes A. Alternative immunomodulators. European Journal of Gastroenterology & Hepatology. 2003; 15:245-8.
131. Fellermann, Steffen, Stein, et al. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2000; 14:171-176.
132. Skelley M, Logan R, Jenkins D, Mahida Y, Hawkey C. Toxicity of mycophenolate mofetil in patients with inflammatory bowel disease. Inflammatory Bowel Diseases 3003; 8:93-7.

133. Hassard P, Vasiliauskas E, Kam L, Targan S, Abreu M. Efficacy of mycophenolate mofetil in patients failing 6-mercaptopurine or azathioprine therapy for Crohn's disease. Inflammatory Bowel Diseases 2000; 6:16-20.
134. Orth T, Peters M, Schlaak J, et al. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. American Journal of Gastroenterology 2000; 95:1201-7.
135. Rampton D, Neurath M, Almer S, D'Haens G, Petritsch W, Stange E. Mycophenolate mofetil in Crohn's disease. Lancet 2000; 356:163-4.
136. Adler Y, Mansmann U, Zouboulis C. Mycophenolate is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease. Dermatology 2001; 203:322-4.
137. Schlapfer A, Fischer M, Ott P, Speck R. Anti-HIV-1 activity of leflunomide: a comparison with mycophenolic acid and hydroxyurea. AIDS 2003; 17:1613-20.
138. Press N, Kimel G, Harris M, Yip B, Craib K, Montaner J. Case series assessing the safety of mycophenolate as part of multidrug rescue treatment regimens. HIV Clinical Trials 2002; 3:17-20.
139. Salvadori M, Holzer H, Mattos Ad, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. American Journal of Transplantation 2004; 4:231-236.
140. Budde K, Curtis J, Knoll G, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: Results of a 1-year study. American Journal of Transplantation 2004; 4:237-243.
141. Nashan B, Ivens K, Suwelack B, Arns W, Abbud Filho M. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant patients: preliminary results from the Myfortic Prospective Multicentre Study. Transplantation Proceedings 2004; 36:S521-S523.
142. Arns W, Breuer S, Choudhury S, et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clinical Transplantation 2005; 19:199-206.
143. Budde K, Glander U, Hahn H, et al. Pharmacokinetic and pharmacodynamic comparison of mycophenolate mofetil and enteric-coated mycophenolate sodium in maintenance renal transplant patients [Abstract]. American Journal of Transplantation 2002; 2:399.
144. Granger DK. Enteric-coated mycophenolate sodium: results of two pivotal global multicentre trials. Transplantation Proceedings 2001; 33:3241-3244.