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Review Article

Mycophenolate mofetil: a new therapeutic option in dermatology

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Abstract Mycophenolic acid (MPA) was introduced in the 1970s as a treatment for psoriasis, it has since been reformulated as mycophenolate mofetil (MMF). With an improved side effect profile and enhanced bioavailability, MMF is a promising drug for immune-mediated skin diseases. It is currently approved for the prevention of organ rejection. Its list of dermatological indications continues to grow. As a noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), MMF inhibits *de novo* purine synthesis. Its relative lack of hepatonephrotoxicity and perhaps low risk of carcinogenicity offer important therapeutic advantages. This new formulation showed enhanced bioavailability, tolerability and efficacy. No doubt case reports and case series of MMF therapy dominate the dermatologic literature; preliminary results are sufficiently promising to warrant larger, randomized clinical trials with this emerging therapy.

Key words
Mycophenolate mofetil, inosine monophosphate dehydrogenase, dermatology.

Background

In the past two decades, an increasing number of immunosuppressive agents have been developed to prevent allograft rejection in organ transplantation. A number of these medications have shown therapeutic efficacy in inflammatory skin diseases. Mycophenolic acid (MPA) was first recognized as a lipid soluble weak organic acid, isolated from cultures of *Penicillium stoloniferum*.[1] It was later shown to have antibacterial, antiviral, antifungal, antitumoral and immunosuppressive properties.[2-7] In 1975, MPA demonstrated therapeutic efficacy in psoriasis.[8]

In 1995, MMF received FDA approval for prevention of acute renal allograft rejection and was recognized as an effective treatment option for immune-mediated skin diseases.

Structure

Mycophenolate mofetil is the semi-synthetic 2-morpholinoethyl ester of MPA. The chemical name for MMF is 2-morpholinoethyl (E)-6-(1, 3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (**Figure 1**). It has an empirical formula of $C_{23}H_{31}NO_7$.[9]

Mechanism of action

Mycophenolate mofetil selectively and noncompetitively inhibits inosine

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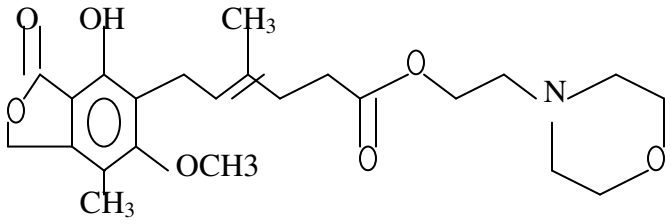

Figure 1 Chemical structure of mycophenolate mofetil.

monophosphate dehydrogenase (IMPDH) in the *de novo* purine synthesis pathway. This enzyme facilitates the conversion of inosine monophosphate to xanthine monophosphate, an intermediate metabolite in the production of guanosine triphosphate. Mycophenolate mofetil results in the depletion of guanosine nucleotides so it impairs RNA, DNA and protein synthesis.[10]

The purine bases, adenosine and guanosine are synthesized through two pathways: the *de novo* purine synthesis pathway and the hypoxanthine-guanine phosphoribosyl transferase salvage pathway. It selectively inhibits lymphocyte proliferation and antibody formation. Mycophenolate mofetil blocks type II isoform of IMPDH, predominantly located on lymphocytes. It also has potent cytostatic effects on T and B cells.[10]

Mycophenolate mofetil also prevents the glycosylation of lymphocytes and monocyte glycoprotein that are involved in adhesion to endothelial cells. It further inhibits the recruitment of leukocytes to sites of inflammation and impairs antigen presentation.[11] It does not inhibit early events in the activation of human peripheral blood mononuclear cells (IL-1 and IL-2 production), but blocks the coupling of these events to DNA synthesis and proliferation.[10]

Pharmacokinetics

After ingestion, MMF is hydrolyzed to its parent compound, MPA by plasma esterases. Mycophenolic acid predominantly binds to albumen; it has a bioavailability of 94%.[12] The peak concentration is obtained within 60-90 minutes after oral administration. After systemic absorption, MPA undergoes effective conjugation to its inactive glucuronide form (MPAG).

Approximately 87% of the drug is excreted through the kidneys, 6% in the feces and the remainder undergoes enterohepatic recirculation. Beta-glucuronidase, found within the epidermis and gastrointestinal tract, can convert MPAG to the active MPA form.[12]

Therapeutic indications

Potential indications are listed in **Table 1**, and selected dermatoses are reviewed below.

Psoriasis

Multiple case reports suggest that MMF is an effective treatment option for psoriasis.[13-17] In a study of 11 patients with stable plaque type psoriasis, the efficacy of MMF was measured using the psoriasis area and severity index (PASI) score.[18] Patients initially received MMF 1g twice daily for 3 weeks followed by 0.5g twice daily. Within 3 weeks of therapy, there was a reduction in

Table 1 Potential dermatologic uses of mycophenolate mofetil.

Psoriasis
Lichen planus
Dermatitis
• Atopic dermatitis
• Dyshidrotic dermatitis
• Chronic actinic dermatitis
Immunobullous diseases
• Pemphigus vulgaris
• Pemphigus foliaceus
• Bullous pemphigoid
• Mucous membrane pemphigoid
• Linear IgA disease
• Epidermolysis bullosa acquisita
Connective tissue diseases
• Systemic lupus erythematosus
• Subacute cutaneous lupus Erythematosus
• Chronic discoid lupus erythematosus
• Chilblains/lupus perniosis
• Dermatomyositis
• Scleroderma
• Urticarial vasculitis
• Takayasu's arteritis
• Microscopic polyangiitis
• Polyarteritis nodosa
• Behcet's disease
• Wegener's granulomatosis
Pyoderma gangrenosum
Graft-versus-host disease
Recurrent erythema multiforme
Cutaneous Crohn's disease
Sarcoidosis

PASI of between 40% and 70% in seven of the 11 patients. Only one patient achieved a reduction in PASI of <25% from baseline. After 6 weeks there was further improvement in 6 patients. However, PASI worsened in 4 patients when MMF was tapered to a lower dosage.

In a two-centre prospective open-label clinical trial, 23 patients with moderate to severe psoriasis were treated with MMF 2-3g/day for 12 weeks.[19] In the 18 patients who completed the study, the PASI was reduced by 24% (p<0.001) at 6 weeks and by 47% (p<0.001) at 12 weeks. The drug appeared to have a beneficial effect on patients suffering from psoriatic arthritis. The treatment was well tolerated. Thus mycophenolate mofetil appears to be an effective treatment for patients with moderate to severe psoriasis.

Atopic dermatitis

In a pilot study of 10 patients with severe refractory atopic dermatitis, MMF was given in a dose of 2g/day.[20] After 12 weeks of therapy the median scores for disease severity (SCORAD index) improved by 68%. The findings were associated with significant decrease in serum IgE and a shift in the T-helper (Th)-1 to Th2 cytokine ratio. In a study of 10 patients with moderate to severe atopic dermatitis, MMF was administered at 2g/day for a month and tapered to 1g/day.[21] In a 20 weeks follow up period there was a 74% reduction in the SCORAD index as compared with baseline (p<0.01). Dyshidrotic eczema and chronic actinic dermatitis have also responded to MMF therapy.[20,21]

Immunobullous diseases

Multiple studies have documented the efficacy of MMF as steroid sparing agent in the autoimmune mucocutaneous blistering diseases. Mimouni *et al*.[22] studied 42 patients with pemphigus who were recalcitrant to standard therapies. Of these patients, 31 were diagnosed with pemphigus vulgaris (PV) and 11 with pemphigus foliaceus (PF). A complete remission was obtained in 22 (71%) and 5 (45%) of PV and PF patients, respectively. The treatment was administered for an average of 22 months, and the median time to achieve remission was 9 months. In two patients, MMF was

discontinued for nausea and symptomatic reversible neutropenia. Some have demonstrated similar success with MMF in treating patients with PV, PF, paraneoplastic pemphigus, bullous pemphigoid, mucus membrane pemphigoid, linear IgA disease and epidermolysis bullosa acquisita.[23-29]

Connective tissue diseases

Cutaneous lesions of subacute cutaneous lupus erythematosus, chronic discoid lupus and lupus perniosis have shown response to MMF therapy. Clinical improvement has also been demonstrated in other connective tissue diseases such as dermatomyositis, scleroderma, urticarial vasculitis, Takayasu's arteritis, microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa and Behcet's disease.[6, 7]

Other dermatological diseases

Mycophenolate mofetil has been shown to benefit other dermatologic conditions like lichen planus, pyoderma gangrenosum, graft-versus-host disease, recurrent erythema multiforme, Steven-Johnson syndrome, sarcoidosis and cutaneous Crohn's disease.[6,7]

Dosage schedule

The usual dose of MMF in adults ranges from 2-3g/day.[7] In the pediatric population the MMF should be administered as 600mg/m^2 per dose every 12 hours.[7] Renal insufficiency has no consistent effect on the pharmacokinetics of MPA, but dose reduction should be considered in patients with severe renal impairment.[7] In order to prevent disease flare, the dose of MMF should be tapered slowly.

Mycophenolate mofetil is currently available as 250mg capsules, 500mg tablets, a powder for oral suspension and a lyophilized sterile powder for intravenous administration.

Side effects

Mycophenolate mofetil is generally well tolerated at therapeutic doses. As compared to other immunosuppressants, such as methotrexate, azathioprine and cyclosporine, the lack of hepatonephrotoxicity with MMF offers an important therapeutic advantage. The most common side effects are gastrointestinal (i.e. nausea, diarrhea, abdominal cramps, constipation, vomiting, and anorexia) and genitourinary (i.e. urgency, frequency, dysuria, hematuria and occasionally, sterile pyuria). These occur in 36% and 40% of patients, respectively. Other adverse events include neurologic (headache, tinnitus and insomnia), Cutaneous (exanthematous eruptions, acne and pedal edema), cardiorespiratory (dyspnoea, cough, chest pain, palpitations and hypertension) and metabolic (hypercholesterolemia, hyperglycemia, hypophosphatemia and hypo/hyperkalemia) reactions. Unlike azathioprine, use of MMF does not put patients with an inherited deficiency of thiopurine methyltransferase at risk.[30]

Opportunistic infections occur in up to 40% of transplant patients treated with MMF. The majority of these patients are also treated with other immunosuppressive agents.[31] The patients are at increased risk for bacterial, viral and fungal infections such as herpes simplex, herpes zoster, cytomegalovirus, candidiasis, cryptococcosis, aspergillosis, mucormycosis

Table 2 Drug interactions with mycophenolate mofetil.

Drug	*Mechanism of drug interaction*	*Effect on MP Levels*
Cholestyramine	Inhibit enterohepatic recirculation of MP	Decrease
Antacids (Al, Mg)	Decrease absorption of MP	Decrease
Divalent cations (Ca, Fe)	Decrease absorption of MP	Decrease
Metronidazole	Decrease bioavailability of MP	Decrease
Fluoroquinolones	Decrease absorption of MP	Decrease
Probenecid	Inhibit tubular secretion of MP	Increase
Acyclovir	Inhibit tubular secretion of MP	Increase
Ganciclovir	Inhibit tubular secretion of MP	Increase
Salicylates	Increase free fraction	Increase
Azathioprine	Not studied	Not studied

MP=mycophenolate, Al=aluminium, Mg=magnesium, Ca=calcium, and Fe= iron.

and *Pneumocystis carinii* pneumonia.[31]

The long term risk of carcinogenicity with MMF remains controversial. Lymphoproliferative disease or lymphoma developed in 0.4%-1% of patients receiving MMF with other immunosuppressive agents for renal, cardiac and hepatic transplantation.[31] These patients were followed for > 1 year. Non melanoma skin cancer occurred in 1.6%-4.2% of patients, while other types of malignancies appeared in 0.7%-2.1% of patients.[31] Three-year safety data in renal and cardiac transplant patients failed to reveal any changes in the incidence of malignancy.[31]

As a noncompetitive inhibitor of purine synthesis, MMF fails to initiate chromosomal breaks, which makes it less carcinogenic.[32]

Contraindications

There are no adequate studies on MMF in pregnant women; the drug has been shown to be teratogenic in animals. Therefore, MMF should be avoided during pregnancy unless the potential benefits justify the potential risk to the fetus (pregnancy risk C).[32]

Drug interactions

Possible drug interactions with MMF are shown in **Table 2**.

Conclusion

Mycophenolate mofetil has been successfully used both in combinations with systemic steroids and as monotherapy in a variety of inflammatory skin disorders. Early reports on efficacy and tolerability show that MMF offer hope to patients with immune-mediated skin diseases. Its safety profile appears reassuring. Randomized clinical trials with long surveillance periods are warranted to validate the efficacy and safety of MMF in the treatment of dermatologic diseases.

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Erratum

In the Original article entitled '*Long-pulsed Nd:YAG laser and intense pulse light therapy for idiopathic facial hirsutism. A comparative study'* by Tahir Kamal published in the October-December 2006 issue of *the Journal of Pakistan Association of Dermatologists* (*JPAD* 2006; **16**: 205-9.), it is clarified by the author that out of 100 patients included in the study, 23 were recruited from the out-patient clinic of dermatology department of Jinnah Hospital, Lahore; however, all were treated with laser or intense pulse light at a private clinic.