

Review

Use of Mycophenolate Mofetil in Dermatology

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Abstract

Background: In the past two decades, many new small molecules with immunosuppressive properties have been developed to prevent allograft rejection to be used particularly after organ transplantation. During clinical investigation in these conditions some of these substances have been observed to provide therapeutic efficacy in inflammatory skin disorders, as well. Recently, mycophenolate mofetil which is derived from mycophenolic acid has been proven to be available in various inflammatory and autoimmune disorders of the skin because of its antitumoral, antibacterial and immunosuppressive properties.

In the past two decades, an increasing number of immunosuppressive new agents have been developed to prevent allograft rejection in organ transplantation. Some of these agents have been used in dermatology, because they have also been observed to provide therapeutic efficacy in inflammatory skin disorders. One of these agents is mycophenolate mofetil.

Mycophenolate mofetil is a morpholino ester derived of an old drug, mycophenolic acid, which had been isolated from cultures of "Penicillium stoloniferum". Mycophenolic acid, which is a lipid-soluble, weak organic acid, was shown to have antibacterial, antiviral, antifungal, antitumoral and immunosuppressive properties [1].

In 1975, mycophenolic acid was used in treatment of psoriatic patients in dermatology. These studies have no longer been available because of its long term risk of carcinogenicity and gastrointestinal adverse

effects whereas mycophenolate mofetil, a derivative of mycophenolic acid has been introduced. This new formulation showed enhanced bioavailability, tolerability and efficacy [1, 2]. By 1995, MMF received US FDA approval for the prevention of acute renal allograft rejection and soon became recognized as an effective treatment option for immune-mediated skin diseases.

Mechanism of Action

Mycophenolate mofetil selectively and non-competitively inhibits inosine monophosphate dehydrogenase in *de novo* pathway of purine synthesis. This enzyme facilitates the conversion of inosine monophosphate to xanthine monophosphate, an intermediate metabolite which takes place in the production of guanosine triphosphate. As mycophenolate mofetil results in the depletion of the guanosine nucleotides, it impairs RNA, DNA and protein synthesis [1].

The purine bases, adenosine and guanosine, may be synthesized through two pathways: *De novo* purine synthesis pathway, or hypoxanthine-guanine phosphoribosyl transferase salvage pathway. As the lymphocytes lack the salvage pathway, mycophenolate mofetil may selectively inhibit lymphocyte proliferation and antibody formation. Consequently the other cells were not influenced by mycophenolate mofetil.

Mycophenolate mofetil also prevents glycosylation of lymphocyte and monocyte glycoproteins that are involved in adhesion to endothelial cells. It may also inhibit the recruitment of leukocytes to sites of inflammation and impair antigen presentation [1].

Pharmacokinetics

After oral ingestion, mycophenolate mofetil is hydrolyzed to its active metabolite, mycophenolic acid, by plasma esterases. Predominantly bound to albumin, mycophenolic acid has a bioavailability that approaches 94%. The peak concentration of the active metabolite that is obtained within 60-90 minutes after oral administration, undergoes hepatic conjugation to its inactive glucuronide form. Approximately 87% of the drug is excreted by urine, 6% by feces and the remainder undergoes enterohepatic recirculation. Beta glucuronidase, found within the epidermis and gastrointestinal tract, can convert inactive glucuronide form to active form [1].

Safety

MMF is generally well tolerated. Compared to other immunosuppressants, such as methotrexate, azathioprine and cyclosporine, the lack of hepatonephrotoxicity with mycophenolate mofetil offers an important therapeutic advantage. The most common side-effects involve gastrointestinal (nausea, diarrhea, abdominal cramps, constipation, vomiting and anorexia) and genitourinary symptoms (urgency, frequency, dysuria, hematuria and sterile pyuria). These occur in up to 36% and 40% of cases. Other reported adverse events include neurologic (headache, tinnitus and insomnia), cutaneous (exanthematous eruptions, acne and pedal edema), cardiorespiratory (dyspnea, cough, chest pain, palpitations and hypertension) and metabolic (hypercholesterolemia, hyperglycemia, hypophos-

phatemia and hypo/hyperkalemia) reactions. Severe leukopenia has been reported to occur in less than 3% of patients treated with mycophenolate mofetil.

Infection rates with mycophenolate mofetil therapy are difficult to quantify in the dermatologic literature. Opportunistic infections occur in up to 40% of transplant patients treated with mycophenolate mofetil; however, the majority of these patients are also treated with other immunosuppressive agents. In addition to common bacterial and viral infections, patients are at increased risk for herpes simplex, herpes zoster, cytomegalovirus, candidiasis, cryptococcosis, aspergillosis, mucormycosis and *Pneumocystis carinii* pneumonia.

The long-term risk of carcinogenicity with mycophenolate mofetil remains controversial. In the dermatologic literature, few malignancies have been reported in patients receiving mycophenolate mofetil or its pro-drug, mycophenolic acid. Lymphoproliferative disease or lymphoma developed in 0.4%-1% of patients receiving mycophenolate mofetil. Non-melanoma skin cancer occurred in 1.6%-4.2% of patients, while other types of malignancy appeared in 0.7%-2.1% of patients.

While there are no adequate studies on mycophenolate mofetil in pregnant women, the drug has been shown to be teratogenic in animals. Therefore, mycophenolate mofetil should be avoided during pregnancy (pregnancy risk C) [1].

Dosage

The usual dose of mycophenolate mofetil ranges from 2-3g/day in adults. Mycophenolate mofetil should be administered as 600mg/m² per dose every 12 hours in the pediatric population. In order to prevent a disease flare, many clinicians would consider tapering MMF slowly. Dose of MMF reductions should be considered in patients with severe renal impairment [1].

Clinical Uses

There exist a considerable number of reports and concerning the availability of mycophenolate mofetil in various dermatological disorders. These conditions are demonstrated in **Table 1**.

Table 1. Dermatological Disorders in which Mycophenolate Mofetil may Exert Beneficial Effects

<p>Psoriasis</p> <p>Immunobullous diseases</p> <ul style="list-style-type: none"> • Pemphigus vulgaris • Pemphigus foliaceus • Paraneoplastic pemphigus • Bullous pemphigoid • Epidermolysis bullosa acquisita • Linear IgA disease <p>Connective tissue disease</p> <ul style="list-style-type: none"> • Systemic lupus erythematosus • Discoid lupus erythematosus • Dermatomyositis • Wegener's granulomatosis • Urticarial vasculitis • Microscopic polyangiitis • Takayasu's arteritis <p>Lichen planus</p> <p>Pyoderma gangrenosum</p> <p>Idiopathic lobular panniculitis</p> <p>Dermatitis</p> <ul style="list-style-type: none"> • Atopic dermatitis • Dyshidrotic dermatitis • Chronic actinic dermatitis <p>Graft-versus-host disease</p> <p>Sarcoidosis</p> <p>Cutaneous Crohn's disease</p> <p>Cutaneous lymphoma</p>
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PSORIASIS

Mycophenolate mofetil has been used in the treatment of psoriasis, since it suppressed pro-inflammatory cytokines and cytokines which stimulate keratinocyte proliferation and ICAM-1 (intercellular adhesion molecule-1) expression all of which are thought to be involved in the pathogenesis of psoriasis. Mycophenolate mofetil have been found more efficient especially in patients with chronic plaque psoriasis and erythrodermic psoriasis, while studies concerning results of treatment in pustular psoriasis are still lacking [2].

Mycophenolate mofetil was assessed in a clinical trial with 11 patients suffering from severe psoriasis. Oral mycophenolate mofetil was administered in doses of 1 g twice daily for 3 weeks and 0.5 g twice daily for 3 weeks. The clinical end point was a reduction in the psoriasis area and severity index (PASI). There was a reduction in PASI of 40% to 70% in 7 patients and of 25% to 39% in 3 patients within 3 weeks. After 6 weeks, there was a further improvement in

6 patients. The only side effect observed was muscle pain in 1 patient, which led to withdrawal from the study. The treatment was tolerated in all other patients without clinical and laboratory side effects. Thus, oral administration of 2 g mycophenolate mofetil per day has been shown to be safe and effective in the treatment of psoriasis [3, 4, 5, 6].

Because mycophenolate mofetil has been shown to provide therapeutic benefit in the treatment of rheumatoid arthritis, the drug was suggested to offer an alternative in the treatment of psoriatic arthritis. In a recent 10-week study, mycophenolate mofetil monotherapy (2 x 1 g daily) showed good tolerance and improvement in patients suffering from psoriatic arthritis [2, 3, 4].

Because adverse effects of cyclosporin, eight patients who had severe psoriasis were treated with mycophenolate mofetil where it has not been found as effective as cyclosporin, but suggested to be an alternative therapy in patients who could not tolerate cyclosporin because of its nephrotoxicity [2, 7].

To summarize, mycophenolate mofetil is effective in the treatment of severe psoriasis, but more studies are still needed.

IMMUNOBULLOUS DISEASES

Oral mycophenolate mofetil was administered in 12 patients with pemphigus vulgaris, which had relapsed while they underwent treatment with azathioprine (1.5–2 mg/kg daily) and prednisolone (2 mg/kg daily). The patients received a combination therapy with mycophenolate mofetil (2 x1 g daily) and prednisolone (2 mg/kg daily). Eleven patients responded to the therapy and did not show any relapse of their disease, even after tapering the steroid dose. During the period of 9 to 12 months, none of the 11 patients showed recurrence of blistering lesions. Only 5 patients had mild gastrointestinal symptoms and 9 patients had mild lymphopenia [3].

In a patient with pemphigus vulgaris, mycophenolate mofetil (2 x1 g daily) led to a complete remission of skin lesions within 8 weeks, followed by a disease-free interval of 8 months during maintenance treatment [2, 3].

In 1996, the first report who has bullous pemphigoid that was treated with oral my-

cophenolate mofetil successfully has been demonstrated. After a 1-week treatment with 80 mg prednisolone daily, mycophenolate mofetil (2 x 1 g daily) was combined with prednisolone for 6 weeks and along with gradually tapered doses of prednisolone for a further 4 weeks, started as monotherapy for 10 months. During this treatment schedule no relapses occurred [1].

Successful monotherapy with mycophenolate mofetil in bullous pemphigoid has been reported in two patients receiving 1 g mycophenolate mofetil twice daily. Resolution of the blisters was attained after 10 and 11 weeks, respectively, and there was no recurrence of blisters during 6 to 8 months of maintenance therapy [2, 3].

A patient with epidermolysis bullosa acquisita was successfully treated with mycophenolate mofetil. She received 1.5 g daily during the first week, 1 g daily for another 5 weeks, and 0.5 g for another 4 weeks. Thereafter, she was given 0.5 g mycophenolate mofetil every second day and remained without relapse of the disease for 6 months [3].

All these studies point out that mycophenolate mofetil is an effective agent and may be used in the treatment of immunobullous diseases.

CONNECTIVE TISSUE DISEASES

The efficacy of MMF in systemic lupus erythematosus has been clearly validated. Moreover, the cutaneous lesions of subacute cutaneous lupus erythematosus, chronic discoid lupus erythematosus and lupus perniosis have responded to MMF therapy. In a study evaluating effectiveness of MMF in 10 patients who had systemic lupus erythematosus by Gaubitz *et al*, mycophenolate mofetil was given 1.5-2 gr daily to all patients and at the end of the study clinical healing have been achieved. Goya *et al*. have reported two patients who had palmoplantar discoid lupus erythematosus and were treated with mycophenolate mofetil successfully [2, 10].

Schanz *et al*. have reported two patients that had subacute cutaneous lupus erythematosus and were resistant to conventional therapy, but responded well to mycophenolate mofetil 2 gr/day [11].

Recently it has been reported to be effective

in dermatomyositis, especially erythema and heliotropic rash improved with mycophenolate mofetil.² Other connective tissue disorders in which variable beneficial effects have been recorded are scleroderma, urticarial vasculitis, Takayasu's arteritis, microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa and Behçet's disease [1].

LICHEN PLANUS

Mycophenolate mofetil has been used in some patients with lichen planus, since diffuse, hypertrophic, bullous and erosive forms of lichen planus are resistant to conventional therapy. 2gr daily mycophenolate mofetil was given to 2 patients with lichen planus that had diffuse and severely pruritic lesions and complete remission was achieved within 20 weeks [2].

PYODERMA GANGRENOSUM

The management of pyoderma gangrenosum may be difficult and require prolonged treatment with systemic corticosteroids and/or other systemic immunosuppressants. There are some reports that have been shown that mycophenolate mofetil might be an effective treatment choice in pyoderma gangrenosum.

Mycophenolate mofetil 2 g daily was given in combination with prednisolone and cyclosporine (200 mg daily) in a 68-year-old female patient suffering from severe and resistant ulcers due to pyoderma gangrenosum on the calves. This condition was controlled to some degree and additional topical treatment with autologous thrombocytic growth factor led to improvement of granulation and complete healing after 12 weeks. The patient was still disease-free after 12 months [3].

In a 17-year-old male patient with severe recalcitrant pyoderma gangrenosum, healing was achieved with a combination of mycophenolate mofetil 2 g daily and cyclosporine (10 mg/kg daily), accompanied by negative-pressure dressings and split-skin grafts after 7 months of therapy. Complete remission was achieved after 10 months, and the doses of mycophenolate mofetil (2 x0.5 mg daily) and cyclosporine (150 mg daily) could be reduced [3, 12].

These case reports suggest that mycophenolate

nolate mofetil is an alternative as part of a immunosuppressive combination therapy with cyclosporine and corticosteroid or cyclosporine alone in severe recalcitrant pyoderma gangrenosum.

ERYTHEMA NODOSUM

A case with erythema nodosum who had not responded to potassium iodide, azathioprine and indomethacine was reported to improve with mycophenolate mofetil 1g / day. Complete remission was achieved within 3 months [2].

IDIOPATHIC LOBULAR PANNICULITIS

Idiopathic lobular panniculitis often requires prolonged treatment with high doses of systemic corticosteroids and/or immunosuppressants, such as cyclosporine, cyclophosphamide, methotrexate, or azathioprine. Mycophenolate mofetil (2 x1 g daily) was given in combination with prednisolone (2 mg/kg daily) in three patients who had not responded to a combination of prednisolone (2 mg/kg daily) with azathioprine (1.5 mg/kg daily) or to methotrexate (50 mg daily). Resolution of lesions and normalization of inflammatory blood parameters were achieved within 2 weeks. After discontinuation of the steroid treatment and reduction of mycophenolate mofetil to 2 x0.5 g daily, there was no relapse observed during the follow-up of 6 to 10 months [3].

DERMATITIS

Two patients with severe atopic eczema who had not responded to conventional topical treatment or to systemic treatment with oral steroids, psoralen plus ultraviolet A (PUVA) photochemotherapy, or cyclosporine were treated with mycophenolate mofetil (1 g b.i.d) monotherapy. Clinical healing was reached within 2 to 4 weeks. The treatment was continued for another 4 weeks and was tolerated without side effects. During a follow-up of 12 weeks, no relapse was seen [2, 3].

In another study, 10 patients with severe atopic eczema were treated with oral mycophenolate mofetil at an initial dose of 2x0.5 g daily during the first week and 1g. b.i.d within 11 weeks. Compared with the baseline, the median scores for disease severity (SCORAD index) improved by 68% during treatment with mycophenolate mofetil. The median serum immunoglobulin E level de-

creased significantly after 12 weeks [3].

In another study mycophenolate mofetil 2x1 g /day was given to 10 patients with atopic eczema in a month and then 0.5g b.i.d mycophenolate mofetil was given within 20 weeks. Compared with the baseline, the median scores for disease severity (SCORAD index) improved by 74% during treatment with mycophenolate mofetil [1, 13]. But in some of the studies, mycophenolate mofetil has not been found effective in the treatment of atopic eczema [14].

A patient with relapsing dyshidrotic eczema within corticosteroid therapy and was resistant to other therapeutic modalities including PUVA was treated with mycophenolate mofetil (1.5 mg b.i.d). Complete improvement was achieved within 4 weeks. The dose was reduced to 2 g/day and maintained for 12 months without recurrence of the eczema and therapy-related side effects [2, 3].

URTICARIA

Since mycophenolate mofetil has been found to be effective in some patients with atopic eczema, 9 patients with urticaria who were resistant to antihistaminic agents and oral steroid, were treated with mycophenolate mofetil 2 g daily and pruritus was reduced and lesions were cleaned within 12 weeks. As a result, it has been concluded that mycophenolate mofetil may be used in patients with chronic idiopathic urticaria that is resistant to other conventional treatment, but more controlled studies are needed [15].

CHRONIC ACTINIC DERMATITIS

Two patients with chronic actinic dermatitis who did not respond to conventional therapies including topical steroids, prednisolone, PUVA, azathioprine and cyclosporin and developed side effects, were treated with mycophenolate mofetil 1 and 2 g daily. After 6 weeks clinical improvement was observed. Consequently mycophenolate mofetil should be considered as an alternative treatment to conventional therapies for refractory chronic actinic dermatitis [2, 16].

GRAFT-VERSUS-HOST DISEASE (GVHD)

Especially in pediatric ages, mycophenolate mofetil is an agent that can be selected in the treatment of GVHD. It is reported that mycophenolate mofetil and UVA-1 combina-

tion therapy is an alternative therapy in GVHD [2].

SARCOIDOSIS

Kouba *et al.* have reported a patient with sarcoidosis who was treated with mycophenolate mofetil, hydroxychloroquin and prednisolone combination therapy. It is thought that mycophenolate mofetil could be an effective agent with other immunosuppressive agents in the treatment of sarcoidosis [2, 17].

CUTANEOUS CROHN'S DISEASE

Mycophenolate mofetil 1 g daily and thalidomide 200 mg daily combination therapy were given in a patient with perineal and metastatic cutaneous Crohn's disease that was resistant to azathioprine, methotrexate, prednisolone and FK-506, and reduction of lesions were achieved [2].

There is a variety of inflammatory skin disorders that have been shown to respond to oral mycophenolate mofetil either as monotherapy or in combination with systemic steroids and other immunosuppressants as steroid-sparing agents. Other systemic conditions with inflammatory or autoimmune pathogenesis which have cutaneous manifestations such as Behçet's disease or lymphoproliferative disorders may be targeted for future studies.

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