Mycophenolate Mofetil Is Effective in the Treatment of Atopic Dermatitis

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Objective: To evaluate whether mycophenolate mofetil, a new immunosuppressive agent, is effective for treating moderate-severe atopic dermatitis (AD).

Design: In an open-label pilot study, mycophenolate mofetil, 1 g, was given orally twice daily for 4 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.

Setting: University hospital dermatology department.

Patients: Ten consecutive patients with moderate-severe AD nonresponsive to standard therapy.

Main Outcome Measure: Severity of AD as measured using the subjective SCORAD [SCORing Atopic Dermatitis] index.

Results: Clinical efficacy was measured every 2 weeks using the subjective SCORAD index. Treatment with mycophenolate notably reduced the severity of AD within 4 weeks in all patients (P<.05), and after 8 weeks the mean±SD SCORAD index dropped from the pretreatment value of 49.2±13.8 to 21.9±26.5 (P<.01). One patient had to discontinue mycophenolate therapy after 4 weeks because of the development of herpes retinitis. Except for this event, mycophenolate was tolerated well in all patients. Six of 7 patients who had responded to mycophenolate monotherapy had no relapse of disease during 20-week follow-up. In the 7 patients who finished the study, the SCORAD index was reduced by 74%, from 44.0±7.8 before treatment to 11.4±5.9 at 20-week follow-up.

Conclusions: Mycophenolate is a highly effective drug for treating moderate-severe AD, with no serious adverse effects occurring in any patients. Thus, mycophenolate might develop into a promising alternative in the therapy of moderate-severe AD.

Arch Dermatol. 2001;137:870-873

Although atopic dermatitis (AD) is a common inflammatory skin disease, there are no entirely satisfactory treatments. Potent glucocorticoids, although frequently effective, cannot be used continuously because of significant adverse effects. Newer modalities, such as oral cyclosporine, are likewise effective but often are limited by severe unwanted effects.1,2

Mycophenolate mofetil is a new entry into the field of immunosuppressive agents. Mycophenolate is the 2-morpholinoethyl ester of mycophenolic acid and is rapidly absorbed after oral administration. Mycophenolate is then hydrolyzed to its active metabolite mycophenolic acid, which is supposed to potently, selectively, and reversibly inhibit inosine monophosphate dehydrogenase and therefore suppress the de novo pathway of purine synthesis in T and B cells. Unlike most other cells, lymphocytes rely on the de novo pathway more than the salvage pathway for purine biosynthesis. Because mycophenolic acid specifically inhibits the de novo pathway, lymphocytes are the primary target of mycophenolic acid action in vivo, thus minimizing unwanted effects on other cell types.

Mycophenolic acid also exerts its immunomodulatory effects through inhibiting the leukocyte recruitment and glycosylation of lymphocytic glycoproteins involved in their adhesion to endothelial cells. Recently it has been shown that mycophenolate has an inhibitory effect on endothelial prostaglandin E2 production, which might lower the benefits of the prostaglandin E2–triggered immune response after organ transplantation.3,4

Mycophenolate has been approved for treating acute renal graft rejection and has been used to treat vasculitis, blistering autoimmune diseases, and pyoderma gan-
PATIENTS AND METHODS

Ten patients with moderate-severe AD (mean SCORAD [SCORing Atopic Dermatitis] index, 49.2; range, 38-80) who had not responded to conventional topical treatment or to systemic treatment with topical glucocorticoids, phototherapy, or cyclosporine were included in the 8-week study after giving oral informed consent (Table). Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka. A 2-week washout period of systemically applied immunosuppressive agents was required before starting therapy with mycophenolate. Severity of AD was measured using the subjective SCORAD index at treatment weeks 0, 2, 4, 6, and 8 and at follow-up week 20. The subjective SCORAD index was developed in 1993 by the European Task Force on Atopic Dermatitis to create a standardized assessment method for AD and was modified in 1997. The subjective scoring index combines the extent (rule of 9) and severity of 5 intensity items (erythema, edema and papulation, oozing and crusts, excoriation, and lichenification) and the subjective symptoms (daytime pruritus and sleep loss). All patients were given 1 g of mycophenolate mofetil orally twice daily during weeks 1 to 4; during weeks 5 to 8 the dosage was reduced to 500 mg twice daily. During the first 2 weeks, treatment with topical glucocorticoids was permitted; beginning with week 3, only emollient ointment was permitted.

Mycophenolate therapy was discontinued after 8 weeks, at which time each patient was followed up for 20 weeks. During follow-up, use of class 2 to 3 topical glucocorticoids was permitted if necessary.

All patients were given prednisone (44.0±7.8; range, 38-60) who had not responded to conventional topical treatment or to systemic treatment with oral glucocorticoids, phototherapy, or cyclosporine.

The results of this pilot study demonstrate that mycophenolate is highly effective in the treatment of moderate-severe AD. Because of the effectiveness of mycophenolate therapy in patients who relapsed while receiving conventional treatment with systemic glucocorticoids or cyclosporine, one may conclude that mycophenolate might be superior for treating...
moderate-severe AD. Adverse effects observed in patients undergoing transplantation treated with mycophenolate include gastrointestinal tract symptoms, leukopenia, and anemia. The actual risk of an increased incidence of viral and bacterial infection due to treatment with mycophenolate has been a matter of controversial discussion.12 Recent studies of mycophenolate therapy for blistering autoimmune diseases do not report an increase in the incidence of infections, as has been reported for patients receiving a transplant.7,13 However, patients in the transplant studies were receiving other immunosuppressive agents concomitantly.13 One of our patients had to discontinue mycophenolate therapy because he developed herpes retinitis, which resolved quickly after treatment with acyclovir. Although there is no direct evidence of mycophenolate being a major cause of herpes retinitis, in this patient it seems likely that this might be due to immunosuppression resulting from mycophenolate therapy. However, to our knowledge, it has not been reported until now that mycophenolate monotherapy is associated with a significant increased risk of bacterial or viral infection such as herpes infection. Therefore, we have no evidence that regular antiviral therapy is necessary before starting mycophenolate therapy. In addition, it has been shown that mycophenolate strongly potentiates the antiviral activity of acyclovir, ganciclovir, and penciclovir in vitro and in vivo,14,15 suggesting that it is sufficient to start antiviral therapy when clinical signs of herpes infection occur.

The results of this pilot study in 10 patients demonstrate that the adverse effects of mycophenolate therapy are acceptable, with no serious adverse effects occurring in any patients. In addition to being a highly effec-

Figure 1. Significant reduction in the SCORAD [SCORing Atopic Dermatitis] index in response to mycophenolate mofetil therapy.

Figure 2. Patient 6 before (A) and after (B) mycophenolate mofetil therapy.
tive drug in the treatment of moderate-severe AD, mycophenolate is also characterized by a low toxicity profile, causing only moderate adverse effects. Compared with the unwanted adverse effects of systemic glucocorticoid, azathioprine, or cyclosporine use, mycophenolate seems to have an improved risk-benefit ratio. In 6 of 10 patients, lasting remission for 20 weeks was observed. After the end of mycophenolate monotherapy (week 8), patients were allowed to use class 2 to 3 topical glucocorticoids in localized areas if necessary. This was considered a significant improvement by patients and dermatologists because before mycophenolate therapy, AD in all patients had been resistant to potent topical glucocorticoids and systemic immunosuppressive treatment (Table). Thus, mycophenolate might develop into a promising alternative for treating AD.

These promising initial results warrant initiation of controlled clinical trials comparing the safety and effectiveness of mycophenolate with that of conventional immunosuppressive agents. Because of the long-lasting remission in responders to mycophenolate therapy, intermittent mycophenolate modalities should be evaluated.

Accepted for publication February 8, 2001.

Part of this work was supported by Hoffmann-La Roche, Grenzach-Whylen, Germany; Paul und Ursula Klein-Stiftung; and August Scheidel-Stiftung.

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REFERENCES