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.

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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.3-6

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 oral 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.10 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 AD11 and was modified in 1997.12 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).11 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 data satisfied the normality test and were analyzed using 1-way analysis of variance with the Tukey multiple comparison test using statistical software (InStat version 3.00 for Windows 95; GraphPad Software, San Diego, Calif). Data are given as mean±SD; P.<.05 is considered statistically significant.

Ten patients with moderate-severe AD were included in the study (initial subjective SCORAD index, 49.2±13.8). These patients did not respond to conventional topical treatment or to systemic treatment with oral glucocorticoids, phototherapy, or cyclosporine. Treatment with mycophenolate significantly reduced the severity of AD within 4 weeks in all patients (SCORAD index, 27.5±11.7; range, 16-53; P<.05) (Figure 1). After 4 weeks, 7 of 10 patients had cleared completely. Two patients primarily responded well to mycophenolate therapy, but after 5 to 6 weeks of treatment we observed a relapse of AD, although mycophenolate therapy was continued. One patient had to stop mycophenolate therapy after 4 weeks because of the development of herpes retinitis. Six of the 7 responders had lasting remission during 20-week follow-up (for a clinical example see Figure 2), and only 1 patient experienced a partial relapse, with an increase in the SCORAD index from 12 (at week 8) to 24 (at week 20). Nevertheless, in the 7 patients who completed the study, the SCORAD index at week 20 (11.4±5.9; range, 6-24) was reduced by 74% compared with the initial index (44.0±7.8; range, 38-60) (P<.001) (Figure 1).

Overall, mycophenolate therapy was well tolerated in all but 1 patient, who experienced herpes retinitis at week 4. Routine laboratory tests, including blood cell counts, liver and renal function tests, and electrolyte levels, were performed before the study and at biweekly intervals. Test results remained unremarkable throughout the study in all patients. In particular, leukopenia, anemia, and changes in liver function were not observed.

COMMENT

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. 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. However, patients in the transplant studies were receiving other immunosuppressive agents concomitantly. 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, 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 pro-
file, causing only moderate adverse effects. Compared with the unwanted adverse effects of systemic glucocorti-
coid, 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 con-
sidered 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 treat-
ment (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 effect-
iveness 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.

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REFERENCES

1. Larsen FS. Atopic dermatitis: a genetic-epidemiologic study in a population-

2. Salek MS, Finlay AV, Luscombe DK, et al. Cyclosporin greatly improves quality of
life of adults with severe atopic dermatitis: a randomized, double blind, pla-

linoethylester of mycophenolic acid (RS-61445) in rat and nonhuman primate


dotheial prostaglandin E2 in response to allogeneic T cells or cytokines. Trans-

7. Erik AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris.

8. Nousiari OH, Lynch W, Anhalt GJ. The effectiveness of mycophenolate mofetil in

1999;141:175-177.

10. Hanifin JM, Rajka G. Diagnostik features of atopic dermatitis. Acta Derm Vene-
real (Stockh). 1980;92(suppl):S44-S47.

dermatitis by SCORAD using a training atlas by investigators from different dis-

SCORAD index: consensus report of the European Task Force on Atopic Derma-

lic acid: a review of its mechanism, side effects, and potential uses. J Am Acad

mofetil markedly potentiates the antiviral activities of acyclovir, ganciclovir,

15. Neyts J, De Cierq E. Mycophenolate mofetil strongly potentiates the anti-