

First experience with enteric-coated mycophenolate sodium (Myfortic®) in severe recalcitrant adult atopic dermatitis: an open label study

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Summary

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Conflicts of interest

None declared.

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Background Severe atopic dermatitis (AD) is often treated successfully with oral immunosuppressive drugs such as ciclosporin (CsA) or oral corticosteroids. However, some patients develop adverse effects or are unresponsive to these first-choice oral immunosuppressive drugs.

Objectives To evaluate whether enteric-coated mycophenolate sodium (EC-MPS) is an effective treatment in patients with severe, recalcitrant AD.

Methods Ten patients with severe, recalcitrant AD were treated with EC-MPS 720 mg twice daily for 6 months. All patients had to discontinue other oral immunosuppressive drugs due to adverse effects ($n = 8$) or nonresponsiveness ($n = 2$). Disease activity was monitored using the Severity Scoring of Atopic Dermatitis (modified SCORAD) index and the Leicester Sign Score (LSS). Additionally, the level of serum thymus and activation-regulated cytokine (TARC) was measured. During treatment, safety laboratory examination was performed. Total serum immunoglobulin E (IgE) was followed during treatment. Use of topical corticosteroids was recorded before and during treatment.

Results Compared with baseline, the mean scores for disease activity significantly decreased during treatment with EC-MPS [modified SCORAD ($P = 0.04$), LSS severity ($P = 0.01$), LSS extent ($P = 0.01$)]. In addition, serum TARC levels and total serum IgE levels significantly decreased after treatment compared with before ($P = 0.03$; $P = 0.05$). Disease activity decreased after approximately 2 months of treatment and stabilized during the 6-month treatment period. No differences in the amount of topical corticosteroids used in the 6 months prior to treatment compared with the 6-month treatment period were found ($P = 0.4$). None of the patients discontinued use of EC-MPS and only mild adverse effects were seen.

Conclusions In this study EC-MPS at a dose of 720 mg twice daily for 6 months has proven to be an effective and well-tolerated treatment for patients with severe, recalcitrant AD.

Atopic dermatitis (AD) is a common inflammatory skin disease worldwide, with a lifetime prevalence of 10–20% in children and 1–3% in adults.¹ Clinically, AD is characterized by chronically persistent, as well as recurrent, pruritic, erythematous skin lesions and has a profound effect on the quality of life. Although most patients with AD can be treated successfully with topical corticosteroids, topical immunomodulators or ultraviolet (UV) phototherapy, patients with widespread and severe disease often require oral immunosuppressive treatment.

Oral corticosteroids can rapidly reduce disease activity, but long-term use is limited because of side-effects, such as osteoporosis or suppression of adrenal gland function.² Ciclosporin (CsA) has proven to be clinically effective and safe for short- and long-term treatment.^{3–5} However, some patients develop side-effects such as nephrotoxicity or hypertension, which requires dose reduction or discontinuation of therapy. In addition, there is a small group of patients with AD who experience increased disease activity during treatment with

CsA, sometimes accompanied by an increase in total serum immunoglobulin E (IgE).⁶

Mycophenolate mofetil (MMF) has proven to be effective in the treatment of severe AD.^{7,8} In the study of Neuber *et al.* clinical improvement was paralleled by a decrease in total serum IgE.⁹ However, the use of MMF can be limited by gastrointestinal side-effects such as diarrhoea and abdominal pain.¹⁰ The incidence of gastrointestinal side-effects with MMF in patients with a renal transplantation can be up to 45.5%.¹⁰ Literature on gastrointestinal side-effects during MMF therapy for AD patients is scarce. Neuber *et al.*⁹ described transient nausea in the early weeks of treatment in two out of 10 AD patients.

Enteric-coated mycophenolate sodium (EC-MPS) is designed to reduce the incidence of gastrointestinal side-effects of MMF.^{11,12} Both substances contain the same active moiety, mycophenolic acid (MPA), and have the same therapeutic equivalence in *de novo* renal transplant patients.¹³ MPA is a potent, selective and reversible inosine monophosphate dehydrogenase (IMPDH) inhibitor. It interferes with the *de novo* synthesis of purines necessary for the production of precursors for the synthesis of RNA and DNA. This pathway is essential for the clonal expansion of T and B cells.^{14,15}

EC-MPS could be an alternative treatment in patients with severe AD who are unresponsive to first-choice oral immunosuppressive drugs, or in patients who have to discontinue treatment due to side-effects. Finally, EC-MPS could also be of use in patients with AD with pre-existent high levels of total serum IgE.

This study describes the results of treatment with EC-MPS in 10 patients with severe AD during a 6-month treatment period.

Patients and methods

Patients

Ten patients, five men and five women (age range 23–72 years), with severe AD according to the criteria of Hanifin and Rajka,¹⁶ were included between August 2006 and April 2007. The baseline characteristics of the patients are described in Table 1.

Table 1 Baseline clinical characteristics the patients

Patient characteristics	Mean $\pm$ SD at baseline
Age (years)	47 $\pm$ 15
Sex (men/women)	5/5
LSS severity score	32 $\pm$ 7
LSS extent score	47 $\pm$ 17
Modified SCORAD index	39 $\pm$ 9
TARC level (pg mL ⁻¹)	3955 $\pm$ 6702
Total serum IgE (kU L ⁻¹)	12 250 $\pm$ 9665 ^a
History of atopy (n patients)	9

LSS, Leicester sign score; SCORAD, Severity Scoring of Atopic Dermatitis; TARC, thymus and activation-regulated cytokine.
^aSEM.

Intensive treatment with potent topical corticosteroids and/or UV phototherapy was insufficient in controlling disease activity. All patients had previously been treated with oral immunosuppressive drugs, but had to discontinue this treatment due to side-effects or nonresponsiveness (Table 2). None of the patients received oral immunosuppressive treatment or UV therapy in the 3 months prior to starting on EC-MPS. None of the patients were pregnant at the start of therapy. The study was approved by the local medical ethical committee.

Treatment

EC-MPS (Myfortic[®], Novartis, Basel, Switzerland) was given in a standard dose of 720 mg twice daily for 6 months. This dose contains equimolar amounts of MPA when compared with the standard dose of 1000 mg twice daily of MMF.¹⁷ The use of bland emollients and topical corticosteroids (class III) was permitted. The use of topical corticosteroids was monitored for the 6-month period prior to treatment and during the treatment period. The amount of topical corticosteroids used was quantified using pharmacy records.

Parameters of disease activity and total serum IgE

Before and after 2, 4 and 6 months of treatment disease activity was scored using the modified SCORAD¹⁸ index and the LSS score.¹⁹

In addition, the level of serum thymus and activation-regulated cytokine (TARC) was measured as an objective marker for disease activity.²⁰ Furthermore, the total serum IgE was measured before starting and after a treatment period of 3 and 6 months.

Safety

Safety laboratory examination was performed before the start of treatment, after 2 and 4 weeks of treatment and then every 4 weeks during the 6-month treatment period. Blood examination included a full blood count, lymphocyte subsets, total bilirubin, alkaline phosphatase, aminotransferases (ASAT and ALAT), electrolytes, urea, creatinine, total cholesterol, HDL and LDL cholesterol and triglycerides. Furthermore, at each visit patients were asked if they had experienced any subjective adverse effects.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 12, 2003; SPSS Inc., Chicago, IL, U.S.A.). Because the data were not normally distributed, nonparametric tests were used. Changes in modified SCORAD, LSS, serum TARC and total serum IgE within the treatment period were compared with baseline using the Wilcoxon signed rank test. Probability levels of 0.05 and below were considered significant.

Table 2 Use of systemic immunosuppressive therapy before start of EC-MPS

Patient	Duration of CsA treatment	Reason for discontinuation of CsA treatment	Other therapies
1	4 years	Hypertension ^a	Prednisone; UV therapy
2	9 months	Hypertension; ^a hypercholesterolemia	NA
3	9 months	Nephrotoxicity; hypertension ^a	NA
4	4 months	Nephrotoxicity; failure of treatment	NA
5	2 months	Hypomagnesemia; nausea; muscle ache; hypertension ^a	Prednisone
6	NA ^b	NA	Prednisone; UV therapy
7	2 months	Failure of treatment	Prednisone; UV therapy
8	3 months	Hypertension, ^a hypercholesterolemia	Prednisone
9	2 months	Nausea; abdominal discomfort	Prednisone
10	1 month	Nausea; headache	NA

EC-MPS, enteric-coated mycophenolate sodium; NA, not applicable; CsA, ciclosporin; UV, ultraviolet. ^aHypertension is defined as unresponsive to antihypertensive drugs. ^bNo previous treatment with CsA due to pre-existent hypertension.

Results

Parameters of disease activity and total serum IgE

All patients noted gradual improvement in the course of 4–8 weeks of treatment. This improvement remained stable over the 6-month treatment period.

The mean modified SCORAD ($\pm$ SD) decreased from 39 ± 9 to 27 ± 9 ($P = 0.042$) during treatment (Fig. 1a). Mean LSS extent decreased from 47 ± 17 to 24 ± 13 ($\pm$ SD) ($P = 0.012$), and mean LSS severity decreased from 33 ± 7 to 20 ± 6 ($P = 0.012$). Clinical improvement was paralleled by a gradual decrease in serum TARC from 3955 ± 6702 pg mL⁻¹ to 1744 ± 2122 pg mL⁻¹ ($P = 0.028$) (Fig. 1b). A decrease in total serum IgE was seen during treatment from $12\,250 \pm 9665$ to $10\,244 \pm 6843$ ($\pm$ SEM) ($P = 0.05$).

There was no significant difference (651 ± 463 vs. 1019 ± 813 g; $P = 0.39$) in the amount of topical corticosteroids used in the 6 months before the start of treatment and during treatment.

Safety

Safety laboratory examination

During the 6-month treatment period no significant changes were found in white blood cell count, red blood cell count, level of serum creatinine and level of total serum cholesterol. Also, no changes were seen in alkaline phosphatase, aminotransferases (ALAT, ASAT) and electrolytes.

Adverse reactions

Only mild adverse reactions were seen. During the first 2 weeks of treatment two patients reported diarrhoea, one patient reported mild nausea, and one patient reported flatulence. Furthermore, five patients reported mild headache, which was consistent during treatment. The frequency varied from once a week to once a month. Two patients reported

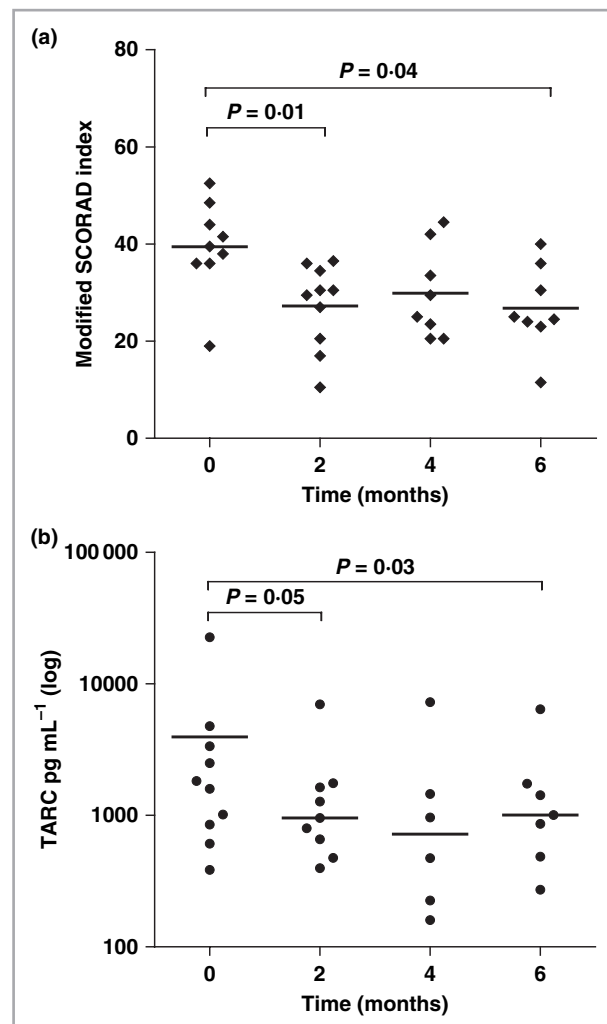


Fig 1. Mean modified Severity Scoring of Atopic Dermatitis (SCORAD) (a) and thymus and activation-regulated cytokine (TARC) (b) levels in patients with atopic dermatitis at baseline and during treatment with enteric-coated mycophenolate sodium. Scatter plots show mean and distribution of data.

Table 3 Adverse events during use of EC-MPS

Organ system	Side-effect	Severity	Number of patients
Gastrointestinal	Diarrhoea	Mild	2/10
	Nausea	Mild	1/10
	Flatulence	Mild	1/10
Neurological	Tiredness	Mild	2/10
	Concentration problems	Mild	1/10
	Headache	Mild	5/10

EC-MPS, enteric-coated mycophenolate sodium.

tiredness, and one patient noted concentration problems during his work (Table 3). In none of the patients was a dose reduction or discontinuation of therapy needed due to side-effects.

Discussion

In this study, treatment with EC-MPS resulted in a significant decrease of disease activity in patients with severe, recalcitrant AD. The mean improvement in disease activity scores was 40% in the 6-month treatment period. After 8 weeks of treatment a significant clinical improvement was observed which remained stable till the end of the 6-month treatment period. No difference in the amount of topical corticosteroids was found during treatment with EC-MPS compared with the 6 months prior to treatment. Thus, clinical improvement could not be attributed to increased use of topical corticosteroids.

Neuber *et al.* described a median improvement of SCORAD of 68% during a 12-week treatment period with MMF.⁹ However, the mean disease activity at the moment of inclusion was more severe compared with our study. End of study scores are comparable.

In severe AD, not responsive to topical steroids and/or UV phototherapy, CsA is the first choice of treatment. After treatment with CsA, a clinical improvement of 55% (95% CI 48–62%) can be reached after 6–8 weeks of treatment.²¹ Although the results of our study show that EC-MPS is also effective in decreasing the disease activity in patients with severe AD, the clinical efficacy seems to be less potent compared with CsA. However, this may also be explained by differences in patient selection: we studied patients with recalcitrant AD in which previous treatment with CsA and/or oral corticosteroids was unsuccessful due to therapy resistance or side-effects.

A limitation, especially, of long-term treatment with CsA is the occurrence of nephrotoxicity in up to 10.9% per month of treatment, and hypertension in 5.8% per month of treatment in patients with AD.²¹ These side-effects often require dose reduction or discontinuation of therapy. In our 6-month study, none of the patients developed nephrotoxicity or hypertension during treatment with EC-MPS. These

findings are in accordance with earlier studies using EC-MPS/MMF.^{7,9}

EC-MPS has been developed with the objective to reduce gastrointestinal side-effects which are observed during treatment with MMF.¹¹ Data from organ transplantation studies suggest that the overall incidence of gastrointestinal side-effects are comparable between renal transplant patients receiving either EC-MPS or MMF. However, the increase in severity of gastrointestinal side-effects during a 12-month treatment period tended to be lower in patients receiving EC-MPS.¹² Furthermore, conversion of MMF to EC-MPS in transplantation patients with gastrointestinal side-effects led to an improvement of gastrointestinal tolerability of 84.2%.²²

The gastrointestinal side-effects in our study were mild, transient and did not lead to a dose reduction or discontinuation of therapy. However, the incidence of gastrointestinal side-effects is comparable to the study of Neuber *et al.*⁹ with MMF. Literature on MMF in the treatment of severe atopic dermatitis is scarce, and only small patient groups are described. This could be an explanation for the low incidence of gastrointestinal side-effects, and for not detecting a difference between treatment with EC-MPS and MMF. However, the number of patients in the MMF study⁹ and our EC-MPS study is too low to draw any conclusions on the incidence of gastrointestinal side-effects.

No bacterial or viral infections occurred during the 6-month treatment with EC-MPS; this is in accordance with earlier studies using treatment with MMF in severe AD.^{7–9,23} However, organ transplant recipients have an increased incidence of bacterial or viral infections during treatment with EC-MPS.²⁴ This might be explained by the fact that, in contrast to patients with AD, organ transplant recipients are treated with multiple immunosuppressive agents.

In our study a small, but significant decrease in total serum IgE was found, in accordance with earlier studies using MMF in AD.⁹ Patients with AD who have been successfully treated with CsA did not show changes in total serum IgE levels.⁴ Some patients may even show an increase of total serum IgE levels.⁶ The decrease in total serum IgE in our study can be explained by the inhibitory effect of EC-MPS on B cells. However, the clinical relevance of this small decrease in total serum IgE is unknown.

Treatment with EC-MPS in this group of patients with severe recalcitrant AD leads to a significant decrease in disease activity after 8 weeks of treatment, which was stable during a 6-month treatment period. The decrease in disease activity was accompanied by a significant decrease in serum TARC and total serum IgE.

These are the first results of treatment with EC-MPS in patients with severe AD. Larger randomized controlled trials are needed to compare the effects of long-term treatment with EC-MPS to CsA and to identify subgroups of patients with severe AD who may especially benefit from treatment with EC-MPS.

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