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Mycophenolate mofetil therapy in adult patients with recalcitrant atopic dermatitis.

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Abstract:

Patients with severe atopic dermatitis (AD) may require potent immunosuppressive therapy to control their disease. Mycophenolate mofetil (MMF) has been suggested as a safe and effective drug in these cases. We have used oral MMF 2-3gr/day in adult patients with severe recalcitrant AD who failed other major systemic drugs, or where other drugs, including cyclosporine, methotrexate and azathioprine, were contraindicated. Of 9 consecutive adult patients, 4 (44%) responded completely, 2 (22%) had partial response and 3 (33%) did not respond at all. The MMF therapy was continued for 5-36 months (average 21 months) without major side effects. Our results demonstrate that oral MMF may be an effective drug in AD. Due to its good safety profile, it may be recommended as a first line systemic therapy, or successive to cyclosporine in the long term.

Introduction:

Several therapeutic modalities such as topical corticosteroids, topical immunomodulators, and ultraviolet therapy are effective in mild to moderate atopic dermatitis (AD). Patients with severe AD however, may require treatment with potent immunosuppressive drugs to control their disease (1).

Mycophenolate mofetil (MMF) blocks the *de novo* guanine nucleotides synthesis via the inhibition of inosine monophosphate dehydrogenase. Its immunosuppressive effect is achieved due to preferential inhibition of DNA synthesis in B cells and T lymphocytes, which lack purine scavenger mechanisms that compensate for this blockage. Therefore it is selectively and uniquely acting to treat inflammatory disorders. Although MMF is FDA approved solely for the prophylaxis of solid organ transplant rejection, it is well recognized as an off-label systemic therapy in refractory cases of AD (2).

There are few studies regarding the efficacy of MMF in children (3-4) and adults (1, 5-8), but only one study (1) was an observer-blinded randomized controlled trial. Studies are controversial but overall support the use of MMF as an alternative therapy in refractory AD (2, 9-10). We have been using MMF as a “last resort” drug in recalcitrant AD patients in which other major systemic modalities have failed or were contraindicated. The following are the results of this approach.

Patients and methods:

All adult patients with AD as defined by Hanifin et al (11) who were treated by MMF during 2010-2017 in our department were included in the study. The inpatient and outpatient clinical files were thoroughly reviewed and if needed patients were recalled for examination or contacted by a telephone call. The response to therapy was termed “no response” if there was no improvement, “partial response” if there was partial improvement and “complete response” if there was a complete remission.

Results:

The results are presented in Table 1. 9 patients (5 females and 4 males), aged 20-75 yrs (average 37.1 yrs) were included in the study. The duration of disease was 12-75 yrs (average 33.5 yrs). It is notable that in all 9 resistant- to therapy AD patients, the disease begun in childhood, of whom 4 patients had onset in the first year of life. All 9 patients were previously treated with potent topical Corticosteroids, and 5 patients were also treated with local Calcineurin inhibitors. All 9 patients failed narrow-band UVB therapy and one also failed psoralen-UVA (PUVA).

Eight patients were consequently treated with oral cyclosporine 3-5mg/kg/day, 7 of which had complete response and one had partial response. The cyclosporine therapy was discontinued after several months due to concern about the long-term side effects. All 8 patients consequently relapsed.

Six patients were treated by oral methotrexate (MTX) 15-25 mg/week. One responded completely but the therapy was stopped due to elevation of liver enzymes. Four patients

responded partially, but in two of them the therapy was ultimately terminated because of high cumulative MTX doses over 5 grams. The third patient exacerbated after two years while on MTX, and the fourth one stopped the drug due to gastrointestinal complaints. The sixth patient did not respond at all.

Eight patients were treated by oral azathioprine (AZA). Five patients responded partially; 3 of whom stopped therapy due to elevation of liver enzymes or neutropenia, and 2 patients objected to further therapy. The remaining 3 patients did not respond at all.

Altogether, there were 9 adult patients with recalcitrant AD who were ultimately treated by oral MMF 2-3gr/day. Four patients responded completely and the length of remission while on MMF lasted 14-30 months. Three of these patients continue MMF therapy to date, whereas the fourth patient stopped therapy after 24 months and maintains remission using topical emollients only. Two patients responded partially, one of whom stopped therapy after 5 months and is following specific diet modifications with clinical success. The remaining 3 patients did not respond at all (Table 1).

Discussion:

Haeck and colleagues (1) treated 55 adult patients with severe AD with CSA for six weeks. Thereafter, 24 of them were switched to MMF and the rest continued cyclosporine at lower dosage for 30 weeks. The efficacy was equal in both treatment groups, and the side effects were comparable, mild, and temporary. Induction of remission was slower with MMF than with CSA. This suggests that it takes longer for MMF to reach its full effectiveness. On the other

hand, upon discontinuation of the medication, remission lasted longer for MMF-treated patients than CSA treated patients (1).

In a retrospective chart analysis, 17 out of 20 patients with moderate to severe AD responded after only one month of MMF treatment (5). 10 of these patients (50%) achieved disease clearance and were able to discontinue the medication (5).

In an additional prospective study, Neuber et al (6) treated 10 patients with severe atopic eczema (AE) with MMF for 12 weeks. The median score for disease severity (SCORAD index) improved by 68% during the treatment period demonstrating that oral MMF is an effective, safe and well-tolerated immunosuppressive therapy for severe AD in adults (6).

In an open-label pilot study, Grundmann-Kollman et al (7) treated 10 adult patients with severe AD with MMF for 8 weeks. The patients were then followed for 20 weeks, and by that time, 7 of the 10 patients achieved full remission. The authors concluded that MMF might develop into a promising alternative in the therapy of moderate to severe AD (7). Ballester et al (8) also found MMF to be an effective drug in 8 adult patients with AD.

Fewer studies were conducted in pediatric patients with AD. One pediatric case series of 14 AD patients treated with MMF for variable durations showed positive response to MMF with minimal adverse effects (3). Another case series showed significant improvement in two thirds of children on MMF who had previously failed to show response to AZA treatment. MMF was also better tolerated than AZA (4).

Our study is unique in that MMF was administered only to adult patients with severe recalcitrant AD in which all other major oral systemic modalities were failed, or were

contraindicated, including CSA, MTX and AZA. CSA was always effective but ultimately was stopped because of concern about systemic side effects during prolonged therapy. MTX and AZA were stopped in a minority of the cases because of cumulative dose (MTX), elevation of liver enzymes (MTX & AZA), and neutropenia (AZA), and ultimately in the majority of the remaining cases it was terminated due to lack of efficacy. It should be noted, however, that the present study included only patients who ultimately needed MMF therapy, and that they were other cases in our clinic who responded to MTX or AZA in such a way that they did not need to switch to MMF as a “last resort”.

Altogether, 6 of 9 (67%) patients responded to MMF therapy of whom 4 (43%) responded completely. There were no major side effects with MMF treatment in contrast to CSA, MTX and AZA therapies in our series. This indicates that MMF is a safe drug (12,13) and should be considered as a first line oral therapy, or as successive to CSA in the long term. The new drug Dupilumab, may also prove to be an additional safe optional drug for severe AD (14).

Table 1: Results of therapy.

Number/Age/Sex	Duration of disease (yrs.)	Previous therapies	Response to MMF therapy	Length of therapy (months)
1/75/F	75	Topical CS, NB-UVB, CSA, MTX, AZA	partial	36
2/20/F	17	Topical CS, NB-UVB, CSA, AZA	complete	14
3/20/M	17	Topical CS, topical CI, NB-UVB, AZA	complete	18
4/24/M	12	Topical CS, NB-UVB, CSA, MTX, AZA	partial	5
5/49/F	49	Topical CS, topical CI, NB-UVB, CSA, MTX, AZA	failure	4
6/48/F	48	Topical CS, NB-UVB, CSA, MTX, AZA	failure	3
7/28/M	28	Topical CS, topical CI, NB-UVB, CSA	complete	30
8/40/M	30	Topical CS, topical CI, NB-UVB, PUVA, CSA, MTX, AZA	complete	24
9/30/F	26	Topical CS, topical CI, NB-UVB, CSA, MTX, AZA	failure	3

CS: corticosteroids; NB-UVB: narrow band ultraviolet B; CSA: cyclosporine; MTX: methotrexate; AZA: azathioprine; CI: calcineurin inhibitor; PUVA: psoralen ultraviolet A; MMF: mycophenolate mofetil.

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