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CLINICAL REPORT

Long-term Use of Systemic Treatments for Moderate-to-Severe Atopic Dermatitis in Adults: A Monocentric Retrospective Study

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Data regarding systemic therapies in the management of atopic dermatitis are limited. The aim of this study was to provide evidence for the efficacy and tolerance of systemic immunosuppressive treatments for moderate-to-severe adult atopic dermatitis. A single-centre retrospective study was conducted. A total of 54 patients were prescribed systemic treatments between 2000 and 2014. Of these, 28 received methotrexate and 55.6% were considered as responders based on Physician's Global Assessment, 17 received azathioprine (37.5% responders), 43 received cyclosporin A (65.9% responders) and 7 received a combination therapy with methotrexate and azathioprine (57.1% responders). These treatments were well-tolerated overall and few adverse events required discontinuation of treatment. Combination therapy associating methotrexate and azathioprine appears to be a promising treatment for patients who fail to respond to conventional monotherapies. ***Key words: atopic dermatitis; systemic treatment; methotrexate; cyclosporin A; azathioprine.***

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Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder that affects approximately 2–5% of the adult population in the western world (1). The disease involves complex combinatorial pathogenic effects, multiple susceptibility genes, environmental triggers and disruption of the epidermal barrier (2). Clinically, AD can result in impairment of skin function, with intense and bothering itching leading to considerable loss of sleep and poor quality of life that is usually associated with disease severity (3, 4). Failure of topical therapies, including potent topical steroids and topical immunomodulators, is frequent and more than approximately 10% of patients with AD require systemic immune-modulatory drugs to control AD. These systemic treatments include, besides oral corticosteroids, other immunosuppressive therapies, such as cyclosporin A (CsA), azathioprine (AZA) and methotrexate (MTX). These treatments have rarely been compared for both side-effects and efficacy (5, 6).

In this context, a single-centre retrospective study was conducted with the aim of comparing long-term efficacy and safety of systemic treatments in adult patients with AD.

PATIENTS AND METHODS

Patients

We reviewed our hospital charts and selected all patients aged over 18 years who had been diagnosed with AD according Hanifin & Rajka's criteria (7). Only patients undergoing systemic therapy with CsA, MTX, AZA or combination therapy with MTX and AZA for moderate-to-severe AD were included in the study. The study was conducted between January 2000 and December 2014 at the Department of Dermatology of the University Hospital Center of Bordeaux, France. All the patients were followed in the outpatient clinic. Age at onset of disease and at initiation of systemic treatment, type, duration and dosage of systemic treatments (CsA, MTX, AZA, or a combination of the latter), Scoring Atopic Dermatitis (SCORAD), duration of follow-up and serum immunoglobulin E (IgE) level were systematically collected when available.

Assessment of response and tolerance to systemic therapy

All patients followed were evaluated for treatment efficiency at 3–6 months of treatment using Physician's Global Assessment (PGA), as previously described (8, 9). PGA is an overall assessment of AD activity, scored from 0 to 5, taking into account the quality and extent of lesions relative to baseline (0: clear (100%), 1: almost clear (90–99% improvement), 2: marked improvement (50–89%), 3: modest improvement (< 50%), 4: no change and 5: worse). Responders were defined by PGA score 0–2 and non-responders by PGA score 3–5.

The second end-point was to evaluate the clinical and biological safety of systemic therapy, based on patient's records. Clinical assessment was made on a regular basis depending on quality of disease control under treatment, from 3 to 6 months, by a senior dermatologist. During follow-up, treatment doses (and route for MTX) were adjusted regarding efficacy and tolerance. In the same way, the systemic therapy used to treat each patient could be switched to another therapy, without a wash-out period, if required by the severity of AD. Treatments were tapered or discontinued in case of adverse events.

Blood pressure was measured at each visit for patients receiving CsA. Blood tests were performed at baseline and on a regular basis, depending on the age, type of drug or drug asso-

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ciation, and side-effects. In general, blood cell count and renal and liver profiles were obtained every 2 months under chronic therapy, except when MTX and AZA were used in combination, when a monthly check was maintained. Ultrasound liver stiffness measurement with Fibroscan was made every year for patients receiving MTX. Thiopurine methyltransferase (TPMT) genetic testing was made prior to AZA treatment to limit the risk of myelotoxicity. Treatments were discontinued after a phase of progressive tapering dosage if AD was controlled or if treatments were ineffective or poorly tolerated.

RESULTS

Study population

A total of 129 patients followed at our dermatology department for AD between January 2000 and December 2014 were identified. Of these, 54 patients with moderate-to-severe AD were prescribed systemic therapies with MTX, AZA, CsA or a combination of MTX and AZA. Patient characteristics at baseline are shown in Table I.

Among the 54 patients, 28 received MTX (51.9%; 9 received MTX as a first-line therapy), with a maximum dose of 15 mg ($n=18$) or 20 mg ($n=9$) weekly (Table II). Five patients out of 22 who were initially prescribed MTX orally were switched to the subcutaneous route to increase efficacy. The mean treatment duration was 20.4 months. Fifteen patients (55.6%) were considered as responders and 12 (44.4%) as non-responders (Table SI[1]). AZA was prescribed in 17 patients (31.5%) with a maximum dose of 1 mg/kg/day ($n=8$), 2 mg/kg/day ($n=7$) or 3 mg/kg/day ($n=1$) according to TPMT genetic testing. Of these, 4 patients received AZA as a first-line therapy. The mean treatment duration was 11.3 months. Six patients (37.5%) were considered as responders and 10 (62.5%) as non-responders. The most commonly used oral immunosuppressive agent was CsA prescribed in 43 patients (79.6%) at a dose of 3 mg/kg/day ($n=12$), 4 mg/kg/day ($n=17$) or 5 mg/kg/day ($n=12$). CsA was used as a first-line therapy in a majority of these patients ($n=41$). The mean treatment duration was 13.2 months. Twenty-seven patients (65.9%) were considered as responders and 14 (34.1%) as non-responders. Finally, 7 patients (13%) received a combination therapy with MTX and AZA. All had previously received MTX as monotherapy and were non-responders, except for one who was considered first as responder for MTX, but dosage needed to be reduced to less than 10 mg/week because of liver cytolysis, leading to loss of efficacy. Four of the 7 patients had also previously received AZA as monotherapy. All were considered as non- or poor responders. Doses ranged from 7.5 to 20 mg weekly for MTX and from 25 to 100 mg daily for AZA. The mean treatment duration was 27.9 months. Four patients (57.1%) were considered as responders and 3 (42.9%) as non-responders. According to the percentages of responders at 3–6 months of treatment, CsA seemed to be more effective, followed by MTX and AZA. The combination therapy with MTX and AZA was effective in 4 patients out of 7 despite the previous failure of these treatments used as monotherapy.

Among patients considered as responders and receiving systemic treatments for more than 6 months, the

Table I. *Patients' characteristics at baseline*

Characteristics	
Patients, *n*	54
Age, years, mean (range)	34.9 (18–76)
Sex, *n* (%)	
Female	17 (31)
Male	37 (69)
Age at onset of atopic dermatitis, *n* (%)	
< 2 years	31 (57.4)
2–15 years	12 (22.2)
> 15 years	11 (20.4)
Presence of other atopic symptoms, *n* (%)	
Yes	49 (91)
No	5 (9)
Family history of atopic disorders, *n* (%)	
Yes	40 (74)
No	7 (13)
Missing data	7 (13)
Contact sensitizations, *n* (%)	
Yes	26 (48)
No	14 (26)
Missing data	14 (26)
Patients with high serum IgE level (> 150 kUI/l), *n* (%)	46 (85.2)
High serum IgE level (> 150 kUI/l), median (range)	6,895.5 (171–99,999)
Baseline SCORAD (0–103), mean (range)	56.7 (15–83)
Follow-up duration after starting systemic therapy, months, mean (median) [range]	57.8 (41) [5–284]

SCORAD: Scoring Atopic Dermatitis.

Table II. *Treatment characteristics*

Methotrexate (MTX), *n*	28
15 mg weekly, *n* (%)	18 (64.3)
20 mg weekly, *n* (%)	9 (32.1)
Missing data, *n* (%)	1 (3.6)
Treatment duration, months, mean (range)	20.4 (3–78)
Azathioprine (AZA), *n*	17
1 mg/kg/day, *n* (%)	8 (47.1)
2 mg/kg/day, *n* (%)	7 (41.2)
3 mg/kg/day, *n* (%)	1 (5.9)
Missing data, *n* (%)	1 (5.9)
Treatment duration, months, mean (range)	11.3 (3–48)
Cyclosporin A (CsA), *n*	43
3 mg/kg/day, *n* (%)	12 (27.9)
4 mg/kg/day, *n* (%)	17 (39.5)
5 mg/kg/day, *n* (%)	12 (27.9)
Missing data, *n* (%)	2 (4.7)
Treatment duration, months, mean (range)	13.2 (3–78)
MTX + AZA, *n*	7
MTX (7.5–20 mg weekly), *n* (%)	7 (100)
AZA (25–100 mg daily), *n* (%)	7 (100)
Missing data, *n* (%)	0 (0)
Treatment duration, months, mean (range)	27.9 (6–67)

For each treatment, indicated doses are the maximum doses received by each patient.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2389

Table III. *Therapeutic follow-ups in patients considered as responders*

	Duration of treatment, months Mean ± SD	Still on systemic therapy *n* (%)	Switch for another systemic therapy *n* (%)	Switch for topical therapy *n* (%)
MTX	35.7 ± 24.4	7 (46.7)	1 (6.7)	7 (46.7)
AZA	21.1 ± 13.7	1 (16.7)	0 (0)	5 (83.3)
Cyclosporin A	42.5 ± 17.9	1 (3.7)	3 (11.1)	23 (85.2)
MTX + AZA	19.1 ± 26.6	1 (25)	1 (25)	2 (50)

MTX: Methotrexate; AZA: Azathioprine.

mean treatment durations were 35.7, 21.1, 42.5 and 19.1 months, respectively, for MTX, AZA, CsA and MTX+AZA (Table III). To date, 46.7%, 16.7%, 3.7% and 25% receiving MTX, AZA, CsA and MTX+AZA, respectively, are still taking these agents. A limited proportion of these patients (6.7%, 0%, 11.1%, 25% under MTX, AZA, CsA and MTX+AZA, respectively) needed to be switched to another systemic agent. Finally, due to the good control of their disease after long-term follow-up, 46.7%, 83.3%, 85.2% and 50% of patients treated with MTX, AZA, CsA and MTX+AZA, respectively, discontinued their treatments and returned to topical therapies with no major flare-up of their disease.

Adverse events

Table SII[1] shows an overview of the safety results. The most common adverse events were lymphopaenia and common infections. Mild lymphopaenia (>500/mm^3) was found in 1 patient receiving MTX (3.6%), 4 patients receiving AZA (23.5%), 1 patient receiving CsA (2.3%) and 1 patient receiving combination therapy with MTX and AZA (14.3%). Only one patient in the MTX group (3.6%) had lymphopaenia <500/mm^3 leading to a reduction in treatment dose. Common infections, such as folliculitis, conjunctivitis or warts occurred in 3 patients (10.7%) in the MTX group, 2 patients (11.8%) in the AZA group and 3 patients (7%) in the CsA group. None of these adverse events required discontinuation of treatment.

Overall, 8 patients experienced serious infections, including 4 cases of eczema herpeticum, 2 of severe folliculitis, one of severe herpetic recurrences and one of abscess of the eye in a patient with keratoconus. In parallel, AD was poorly controlled at the time of occurrence of these serious adverse events.

Other adverse events included high hypertension and/or renal impairment occurring in the CsA group (15 patients, 34.9%), leading to treatment discontinuation in 3 patients (2 for AHT>160/100 mmHg and 1 for renal function impairment). Digestive symptoms, such as abdominal pain, nausea, vomiting and diarrhoea, were found in 2 patients treated with MTX (7.1%), 4 patients treated with CsA (9.3%) and 2 patients treated with the combination therapy (28.6%), including one patient requiring discontinuation of treatment because of nausea and vomiting. Mild hepatic dysfunction (cytolysis and/or cholestasis) was found in 2 patients undergoing MTX (7.1%) and 2 patients undergoing AZA (11.8%). Discontinuation of treatment because of elevation of transaminases occurred in 2 patients under MTX (7.1%) and 1 patient under AZA (5.9%).

DISCUSSION

In general, our results are in line with previous studies of AD for the global efficiency and tolerance of CsA, MTX and AZA, and the combination of MTX and AZA, which were all found to be effective and well-tolerated overall[2]. In our study, grouping of patients (responders vs non-responders) were based on PGA values assessed at 3 and 6 months of therapy.

CsA was the most prescribed immunosuppressive therapy in our study (particularly for relatively young patients and women), as in the recent study of Garritsen et al. (6), and appears to be the most effective with 65.9% of responders. Earlier studies had clearly shown that CsA is efficacious in adult AD (10, 11); however, the use of CsA is limited by its contraindications, side-effects and the fact that a proportion of patients do not respond to the treatment. A recent study analysed drug survival for CsA in daily practice of adults with AD and found drug survival rates of 34% and 18% after 1 and 2 years, respectively. Reasons for discontinuation were side-effects for 22.2% and ineffectiveness for 16.3% of the patients (12). MTX and AZA are 2 other systemic agents that are classically used to treat AD, but prescribed off-label contrary to CsA. AZA and MTX have both shown clinical efficacy in several case series, open-label studies or randomized controlled trials (13–16). In our study, MTX and AZA were efficacious in, respectively, 55.6% and 37.5% of patients. Few randomized controlled trials have been conducted to compare these treatments in AD. In 2011, Schram et al. (5) showed a near similar reduction of SCORAD

[2]The current study has some limitations. It is a retrospective and monocentric study and the quality of the included data depended on the completeness of medical records. Patients were free to use topical corticosteroids or topical calcineurin inhibitors as it is usually recommended in daily practice. However, all patients started systemic therapies because of failure, bad compliance or poor motivation for topical therapies. Systemic steroid treatment was not frequent in our cohort and was mainly occasional, given, in general, outside the hospital by a GP for a short period of time to control disease flares. Patients who were considered as low- or non-responders to a systemic therapy during follow-up were proposed to start a new regimen without wash-out period in order to avoid major flare-up of the disease. This strategy is usual in daily practice, but may have underestimated the efficacy of the following treatment regimen. In our study, 41 patients received first-line treatment of CsA, 9 received MTX and 4 received AZA. Thus, results concerning the effectiveness of MTX and AZA could have been misestimated because they are prescribed more often after CsA.

(42% with MTX and 39% with AZA) at week 12 of treatment in a population of 42 adults with severe AD. El-Khalawany et al. (17) compared MTX and CsA in a series of 40 children with severe AD and showed a comparable efficacy at week 12, with a SCORAD reduction of 45.3% with MTX and 44.3% with CSA.

In our study, 7 patients were prescribed a combination therapy with MTX and AZA, which proved effective in 57.1% of patients. It is important to note that the patients undergoing this combination therapy were considered as non-responders or intolerant when isolated systemic therapies with MTX or AZA were prescribed. However, a discontinuation of combination therapy occurred in 2 patients owing to nausea and vomiting and to an invalidating folliculitis. Overall, adverse events with combination therapy were not much more common than with treatments used separately, probably because the dosing of each drug was reduced and because follow-up visits were more numerous, but the small number of patients precludes definitive statements. To our knowledge, the association has never been described in the literature about treatment of AD, whereas it has been described in rheumatoid arthritis (18). Further studies with a larger sample size are necessary to confirm that the combination of MTX and AZA could be interesting and effective in patients not controlled with one or both treatments used in monotherapy or in patients responding with one of them with too many side-effects.

We chose to evaluate efficacy in our study by using the PGA, an easy-to-use scale, but rarely described until now in AD. This scoring system has shown a high concordance with the Patient Global Assessment (PtGA) in several studies, as in the recent study of Pascoe et al. for psoriasis and acne (8). It is a convenient system that represents a valuable tool for measuring patient's outcomes.

Furthermore, in our study, 7 patients have ocular involvement associated with their AD (keratoconjunctivitis or keratoconus). They represent a subset of patients with AD, usually difficult to treat, some with an ophthalmological disease more severe than that of the skin, which can lead to blindness and requires close collaboration with ophthalmologists.

Previous reported studies indicated an overall good tolerance of immunosuppressive treatments with few severe adverse events. However, patients are often worried about taking such treatments. In our study, CsA and the combination therapy with MTX and AZA had the highest percentage of patients with adverse events with, respectively, 55.8% and 57.1%, followed by AZA (47.1%) and MTX (35.7%). MTX appeared to be well tolerated in our cohort, which is comparable to the results from a recent study analysing drug survival for methotrexate in a daily practice cohort of adult patients with severe AD (19). CsA was associated with hypertension and increased creatinine serum levels with a higher percentage than that observed in previous reports and trials (20, 21). The most logical explanation is probably the fact that patients treated in hospital practice have more comorbidities than patients selected for clinical trials. Hepatic dysfunction was observed in patients treated with MTX or AZA and required discontinuation of treatment in almost half of the cases. Regarding occurrence of infections, in the context of moderate-to-severe AD, it is always difficult to discriminate between infections due to immunosuppressive therapy or due to the severity of the disease itself. For example, eczema herpeticum is a classical severe viral infection developing on affected skin AD lesions. In our present study, patients with serious infections including eczema herpeticum all had uncontrolled disease (22).

Long-term follow-up of patients responders to systemic agents showed high mean treatment durations (35.7, 21.1, 42.5 and 19.1 months for MTX, AZA, CsA and MTX+AZA, respectively), suggesting that the overall good tolerance of systemic agents allows for long-term therapy. For example, despite the risk of renal toxicity in patients taking CsA, some patients received this agent for several years with no adverse events and with good control of their disease. Interestingly, a large proportion of patients responders to systemic agents were able to discontinue their therapies without flare-up of their disease under topical therapies suggesting that a long course of systemic agents could lead to partial remission of the disease.

Another point of interest is the fact that CsA is commonly prescribed for young adult patients with AD. Some of them had been insufficiently treated before: they had not previously applied topical therapies optimally and sometimes refused a short hospitalization to achieve optimal topical treatment and therapeutic education. In these cases, CsA is prescribed as a short-term rescue and ideally patients return to topical treatments after a few months of treatment. Therefore, this subset of patients with moderate-to-severe AD seems to differ from older patients with a long story of topical therapies or phototherapy and may have overestimated CsA efficacy.

Systemic immunomodulating therapies appear to be a promising approach for the treatment of AD (23). A recent randomized, double-blind, placebo-controlled trial proved the efficacy of dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13 (24). However, biologics are very expensive and further studies are needed to determine the best strategy for indication in the management of AD. As for psoriasis, regulatory agencies may ask for the use and documented failure of a conventional immunosuppressive first line. Furthermore, as an alternative for maintenance treatment, factors that could restore the epidermal barrier are presently under study (25, 26).

In conclusion, we report here a retrospective study evaluating in a hospital setting 3 immunosuppressive

treatments often used in AD. Our study confirms, as previously demonstrated, that MTX, AZA and CsA are effective and overall well tolerated in adult severe AD. We report also for the first time in AD our experience of the use of a combination therapy with MTX and AZA. The association, lowering the dose of both drugs, can be effective for patients for whom these treatments have failed used as monotherapy. Further studies are needed to evaluate efficacy and tolerance of this combined approach.

The authors declare no conflict of interest:

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