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Research Article

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A Retrospective Analysis of Real Life Medication Regimens for Adults with Atopic Dermatitis on Immunosuppressive Medication (Ramadil) In a Single Third Line Center in Belgium

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Abstract

Few Belgian data are available on the treatment of severe atopic dermatitis in adults. As in most other countries, only cyclosporine A is registered for the systemic treatment of atopic dermatitis. Although treatment periods are restricted, side effects may occur, and response failure is possible. Small trials with other immunosuppressive drugs (azathioprine, mofetylmycophenolate, and methotrexate) have indicated they may improve atopic dermatitis, although their effect is slower than with cyclosporine. In the future, treatment of atopic dermatitis may drastically change as the therapeutic effects of new biologicals are promising. This RAMADIL study, from a third line referral center in Belgium, was conducted in order to collect information about the way AD is treated in this pre-biological era.

Keywords: Atopic Dermatitis, Immunosuppressive Drugs, Real Life Database, Systemic Therapy

Abbreviations

AD - Atopic Dermatitis
CsA - Cyclosporine A
MTX - Methotrexate
AZA - Azathioprine
MYC - Mofetyl Mycophenolate

Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease with a high impact on quality of life [1]. Although it is more prevalent in children, the disease may persist in at least 5% during adulthood, and about 50% have moderate to severe disease [2, 3]. Pathogenesis is complex, the primary event remains elusive either driven by genetically based barrier dysfunction and/or alterations in immune response, and it is possible it differs from one patient to another[4,5]. Environmental factors, as well as skin microbiome, contribute to the inflammatory reaction typical of atopic dermatitis [6]. Treatment is based on avoidance of triggers (both irritant and allergic), application of emollients to restore skin barrier, and topical corticosteroids and calcineurin inhibitors for inflammatory lesions [7]. Moderately severe AD may benefit from UV therapy. Flares can be treated with short courses of corticosteroids, but long term side effects make them inappropriate for long term use. Interferon gamma has been used in the past, mainly in the US, but has not redeemed its promises [8]. In patients with chronic severe AD immunosuppressive drugs are used [9]. In Europe, cyclosporine A (CsA) is the only approved drug. However methotrexate (MTX), azathioprine (AZA) and mofetyl mycophenolate(MYC) are increasingly used in recent years [10].

Despite these different treatments AD remains badly controlled in some patients. Biologicals are a promising new strategy in the treatment of severe uncontrollable atopic dermatitis [11]. The aim of the Ramadil study was to collect data on the different immunosuppressive treatments of Atopic dermatitis, used in the pre-biological era.

Methods

This is a retrospective analysis of patients, registered in the database of atopic dermatitis of a third line hospital in Belgium, since 2010 (date systematic registration started). All adult (> 18y) patients treated with immunosuppressive drugs were retrieved from the database. The files of these patients treated with either cyclosporine, azathioprine, mofetyl mycophenolate or methotrexate were analyzed in detail, and data on dosage, duration, result of treatment (analysis of IGA: investigator's global assessment scores) and side effects, were recorded. Topical treatments used were also recorded. However, as this is the mainstay of treatment in atopic dermatitis, they were not further analyzed. The use of systemic corticosteroids was recorded as well, but few data about dosage were available because this was mainly given before attending our hospital; therefore no further analysis was possible. Severity of atopic dermatitis was registered

with IGA scores by qualified dermatologists (0 no AD, 1 almost clear, 2 mild, 3 moderate, 4 severe, 5 very severe if erythrodermic). The study has been approved by the ethical commission of UZ Leuven (S59907).

Results

In total 885 adult patients with atopic dermatitis were treated from 2010 until December 2016. Of these 56 (6,3%) received an immunosuppressive treatment. Most of these patients had severe or very severe atopic dermatitis, 5 had moderate AD. The majority (29/56; 52%) had high levels of IgE (> 5000 kU/L); only 6/56 had levels < 120 kU/L (10%), which is considered the normal range in our laboratory. Of this group 20 (36%) patients needed 34 in hospital treatments with a mean duration of 12,7 days (median 14 days, range from 3 days to 23 days). Most of them (at least 32/56 are registered in our database) already received systemic corticosteroids, some for long periods with adrenal insufficiency and in 1 patient with pathological ruptures of tendons and fractures as side effect. In 4 patients immunosuppressive treatment was either not started or stopped after the first dosage, mostly because they were reluctant to take the medication. They were not further analyzed.

Most (44/56 (78%)) patients were treated with cyclosporine in our hospital. Usual starting dosage was 2,5 - 3 mg/kg/day and if necessary, dose was uptitrated (maximum dosage 5mg/kg/day) until adequate response, 2w to 2 months after start. Of these patients 31 were also treated with systemic corticosteroids in the past. Fourteen patients needed at least one in hospital treatment; 2 periods for 2 patients and 5 periods for 1 patient. In total 20 in hospital treatments, with a mean duration of hospitalization of 11,6 days (median 10,5 days; range from 3 to 22 days). Mean age at start was 35 years (median 35 years; range from 19-62 years). One patient was also treated even because of erythroderma due to AD. Before start the AD was scored as severe in most patients (55%), with the exception of 34% as very severe, and 11% as moderate atopic dermatitis (missing data for 13 cyclosporine courses). Reasons to give cyclosporine to moderate AD were severe impact on quality of life, adverse reactions of topical corticosteroids and severe facial lesions. Mean dosage was 221,9 mg/day (median 200 mg). Mean duration of treatment per cycle was 68,72 w (median 40w). 32 (78%) patients had one course of cyclosporine, but 5 (11%) patients had 2 courses, 4 (9%) had 3 courses and 3 (7%) had 4 courses. In total 66 courses of cyclosporine were given. Results of treatment were fast, mostly seen within 2 weeks; mean improvement was 1.725 points on IGA scale (median 2 points; range 0-3). During 12 courses (18%) a sustained improvement equal or better than moderate AD was not obtained. In 9 (14%) courses treatment was stopped because of lack of final improvement. A sustained IGA 0 or 1 was reached during 12 courses (18%). After the first course of cyclosporine, it was possible to maintain control of disease with the standard topical treatment in 55%, however 45% of the patients needed another course of immunosuppressive treatment or in hospital treatment. In 10 patients subsequently methotrexate was given for a later flare of disease. Reasons for switch were side effects in 5 patients (difficult to treat hypertension in 2, kidney function deterioration in 1, intercurrent malignancies which were possibly unrelated to cyclosporine treatment (multiple squamous cell carcinoma and T-cell lymphoma each in one) and insufficient response or flare during tapering dose, or as a direct result of stopping cyclosporine in 5 patients. Adverse reactions were seen in 10/44 patients (23%): hypertension in 5 patients (11%) -in most patients this was controlled with calcium channel antagonists- kidney dysfunction, convulsions, severe tiredness and arthralgia, gastro-intestinal disturbances and headache (patient started at 5 mg/kg/day) and skin lesions (actinic keratosis and squamous cell carcinoma) each in 1 patient.

Methotrexate was given in 17 patients. Analysis of data was not possible in one patient, who was followed elsewhere after starting treatment in our clinic. Ten patients were treated previously with cyclosporine (see earlier). Five other patients received it with insufficient response in a private practice. In 2 patients methotrexate was the first immunosuppressive given, because of poorly controlled hypertension despite treatment. Of these patients 11/17 (65%) were also treated with systemic corticosteroids in the past and 10 (59%) needed in hospital treatment (6 once, 2 twice, 1 three and 1, 5 times) (in total 18 hospital stays) with a mean duration of hospitalization of 13 days (median 10,5 days; range from 3 days to 23 days). One patient was already treated with systemic corticosteroids for flares, Cyclosporine (with insufficient effect), azathioprine (stopped because of malaise and low leucocytes) and mycophenolate (stopped because of gastro-intestinal intolerance). Mean age of the 16 patients at start of treatment was 45 years (mean 48 years; range from 25 to 57 years). Mean dosage of methotrexate during the whole period was 10, 95 mg/week (median: 12.5 mg/w). Most patients needed 15 mg/w to control the AD, some 17,5 mg/week although maintenance was possible with lower dosages in most (minimum 7,5 mg/w). Mean duration of treatment was 88,16 weeks (median 71,5 weeks). Most patients were treated with one course (10 patients (62,5%), but 5 (31%) received a second and 1 a third course (in total 25 courses). Improvement of AD was slower than with cyclosporine, mostly only seen after the first month of treatment and maximal effect was seen after 3 months. Mean improvement was 1,875 points on IGA scale (median 2 points, range from 0 to 4). Sustained IGA 0 or 1 was seen in 2 patients (8%). However during 5 courses (20%) no sustained improvement better than moderate AD was achieved. Treatment with methotrexate is still ongoing in 10 patients. 2 patients stopped methotrexate and were included in a trial with experimental drugs. Two were treated with IgE specific immunoadsorption. After stopping treatment 4 (25%) patients did not have a relapse until now. Two patients had adverse reactions: liver function alterations in 1 patient, and severe fatigue in 1.

Only 1 patient was treated with azathioprine and 2 with mofetyl mycophenolate. The patient on azathioprine stopped the treatment because of diarrhea and erythema exsudativa multiforme, soon after starting treatment with 150 mg per day (normal TPMT with genetic screening). The patients treated with mofetyl mycophenolate were started with 1000 mg per day and in one dosage it was uptitrated to 1500 mg. Treatment duration was between 24 and 26 weeks, gastro-intestinal problems were reported in both patients.

Table 1: Overview of treatments given at our hospital (total number 56 patients, 4 patients did not start or stopped immediately)

	cyclosporin	methotrexate	azathioprine	mycophenolate
First given IS (number, %)	44(6 more received it in another practice)	7 (in 5 earlier CyA elsewhere)	1 (received CyA elsewhere)	
Next order given IS		2nd in 9 (-4 4rd in 1)	2nd	3rd in 2
Previously used systemic cs	31 (70%)	11/16 (69%)		
Number of hospitalisations	14 needed in hospital treatment, 11 once, 2twice and 1 5 times	10 needed in hospital treatment (6 once, 2 twice 1 three and 1 5 times)		
Mean age at start	35y	45y		
Mean dosage	221,9 mg/day	10,95 mg/ week		
Median dosage	200 mg/d	12.5 mg/w	150 mg	150 mg
Mean duration	68,42w	88,16 weeks		
Median duration	40w	71,5 weeks		
Mean IGA improvement	1,725	1,875		
Number of treatment periods	1 in 32 (78%) 2 in 5 (11%) 3 in 4 (9%) 4 in 3 (7%)	One course (10 patients (62,5%), 2 courses (5 patients 31%) 3 courses in 1		1
Median	2	2		
Side-effects	hypertension in 5 patients (11%), kidney dysfunction, convulsions, severe tiredness and arthralgia, gastro-intestinal disturbances and atypical skin lesions (actinic keratosis and squamous cell carcinoma)	liver function alterations in 1 patient severe fatigue in 1 patient		

Table 2: Order of subsequent treatments with immunosuppressive drugs

CyA	1. Mtx	2. CyA 3. Mtx	1 CyA 2 MTX 3 Myco	1 CyA 2 Aza 3 Myco 4 Mtx
35	2	12 (of which 5 before attending our hospital)	1	1

Table 3: Drug survival for different immunosuppressive drugs

	CyAn = 356	MTX n= 89	AZA n=94	Enteric coated Myco n=84
Drug survival after 1 year/ 2 years	34%/18%	41%/34%	44%/26%	45%/36%
Median overall drug survival	356 days (12,4% still treated)	223 days (39% still treated)	201 days (25% still treated)	322 days (26% still treated)
Stop due to controlled AD	26,4%	MD	11%	11%
Stop due to side-effects	22,2%	25%	36%	14%
Stop due to ineffectiveness	16,3%	15%	19%	38%
Stop due to side-effectsplus ineffectiveness	6,2%	MD	2%	4%
Stop due to other reasons	11%	MD	6%	4%

Discussion

Severe atopic dermatitis in adults is difficult to treat, as the disease may suddenly flare without obvious reasons and the itch frequently provokes loss of sleep and leads to a low quality of life of AD sufferers. Guidelines for treatment of AD have been put forward by different expert groups [7,12]. This retrospective review gives a picture of the actual immunosuppressive treatments in real life in a third line referral center in Belgium.

Only 6, 3% of the adults with AD seen were treated with immunosuppressive drugs, which is low compared to estimations in literature, considering that mostly severe patients are referred by our colleagues [13]. In many of them it was possible to reduce the severity of their eczema by education on skin care, avoidance of triggers and immediate treatment of eczema flares with topical treatment, which still remains the basis of any treatment [7,8]. Although this is time- consuming it is possible that it kept some patients away from more potent treatments [14]. Nevertheless this approach may fail. 36% of our patients, ultimately treated with immunosuppressive drugs, needed at least one period of hospitalization, which is only done for the most severe patients as this is discouraged in Belgium.

Most patients were treated with systemic corticosteroids before attending our hospital. Because of the risk of flares after stopping and adverse effects if used for longer periods, systemic treatment with corticosteroids should be avoided. This was the case in one of our patients who had several tendon ruptures as a result of long-term systemic steroids. As in other inflammatory diseases immunosuppressive treatments are a valid alternative to suppress the inflammation [7,12,14].

Placebo controlled studies have been conducted at the end of last century with cyclosporine (for a review see) [15]. Cyclosporine is the only drug registered for the treatment of AD in Belgium and was given as first choice, except in 2 patients because of contra-indication (difficult to control hypertension). In other countries too this is the first choice [16,17]. The guideline is to give cyclosporine in courses of a few months and no longer than 1 year [8]. However, despite attempts to lower dosage and stop, mean duration of treatment in our patients was more than one year. In 11% of our patients multiple courses of cyclosporine were given.

More recently other well-known immunosuppressive drugs like methotrexate, azathioprine and mycophenolate have been tried in small studies [13]. Roekevisch et al. advise AZA as second line immunosuppressive after cyclosporine. However this advice is largely based on the availability of well-designed trials (Table 2).

Like in France our second choice treatment was methotrexate [17]. In an open label study its effect was demonstrated [18]. In a head to head trial comparing methotrexate (10-22,5 mg/w) to azathioprine 1,5 to 2,5 mg/kg/d for 12 w with follow up of 12 w both drugs had similar reduction of different severity scores for AD, idiosyncratic responses with neutropenia or lung-fibrosis are rare side effects [19]. On the long term methotrexate may be noxious to the liver, but monitoring is possible.

The mean treatment duration with methotrexate was longer than with cyclosporine, probably because it was mostly given as second line treatment in patients who failed to have long term control with cyclosporine. Azathioprin has been evaluated in 2 randomized controlled trials. It was superior to placebo with mean improvements of 26 and 37% on clinical outcome scores after 3 months [20, 21].

Mycophenolate has been tested in a head- to- head trial with cyclosporine after control of AD had been reached with cyclosporine, and was equally effective on the long term [22]. We only used azathioprine and mycophenolate in a few patients. The former because our previous experience in a few patients was discouraging. The latter because of the high costs before it became available as a generic drug. In about 1 in 5 patients we could not improve atopic dermatitis better than moderate disease, which we consider insufficient, considering the potential side effects of immunosuppressives. This has also been reported in other real life studies.

Drug survival studies have been performed for cyclosporine (356 patients), azathioprine (94 patients), enteric coated mycophenolate (84 patients) and one time metothrexate (89 patients) in two tertiary referral centers in the Netherlands [23-25]. Drug survival after two years was highest with Myco (36 %) and Mtx (34%) much lower for Aza 26% and CyA 18%. The highest rate of discontinuation due to controlled AD was for CyA, for adverse reactions for AZA and for ineffectiveness for Myc.

In our series 55% of patients treated with cyclosporine could be maintained on topical treatment after one course of CyA, but follow-up is less than 5 years. In the Netherlands the positive finding of stopping the treatment due to controlled AD, was also the highest with treatment with CyA. However, as CyA is a second line medication -the only one registered to treat AD in adults- these results have to be interpreted with caution. The other medication is third line and hence in a number of cases will have been used in patients who failed on CyA. Only about a quarter of the patients was stopped in the Netherlands. We probably stopped more patients considering potential long term side effects. For CyA an intermediate-to-high starting dose (> 3,5 - 5mg mg /kg/day) was associated with an increased drug survival, because it has a better balance between effectiveness and side effects. However we agree with Roeckevisch that starting with a lower dosage has to be tried considering more side-effects are seen with higher dosages.

Decreased drug survival of CyA was seen in older patients due to adverse effects. This could argument to start these patients immediately on third line or at least monitor them thoroughly.

Our data are comparable with data from literature that current therapies are able to control atopic dermatitis in an important number of patients with atopic dermatitis, however are ineffective or stopped due to adverse events in a significant number of them. Moreover, only in a few of them complete remission or minimal disease is reached. New more potent and safe treatments are therefore welcome and the hope is that upcoming biologicals will be a real breakthrough in the treatment of AD soon [11].

Conclusion

Immunosuppressive drugs are useful in severe atopic dermatitis and can be given where adequately performed topical treatments and/or phototherapy fail.

In our third-line hospital first choice was CsA, mainly because this is the only immunosuppressive with a registered indication for severe atopic dermatitis. Second choice was methotrexate. CsA was given for shorter periods, methotrexate if long term treatment

was preferred. Azathioprine and mycophenolate have been used less in our hospital, but, according to literature show equal efficacy as methotrexate.

Authors' contributions

"CM analyzed and interpreted the patient data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

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"All authors had full access to all of the data in this study and take complete responsibility for the Integrity of the data and accuracy of the data analysis."

"All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published."

"All procedures followed were in accordance with the ethical standards of the responsible Committee on human experimentation (institutional and national) and with the Helsinki Declaration Of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study."

"Drawbacks of this study were the retrospective nature, and dependency on accuracy of patient files."

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