

ORIGINAL ARTICLE

Ten years experience with oral immunosuppressive treatment in adult patients with atopic dermatitis in two academic centres

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Abstract

Background There is a lack of information on the use oral immunosuppressive drugs in atopic dermatitis (AD) daily practice.

Objective A 10-years overview of the use of oral immunosuppressive drugs in patients with severe AD.

Methods Medical charts of patients with AD, who received oral immunosuppressive drugs at the Academic Medical Center Amsterdam and in the University Medical Center Utrecht between January 2001 and January 2011, were analysed. Particular attention was paid to patient characteristics, prior treatment, prescribed oral immunosuppressive drugs, the order of use, doses and treatment durations and reasons for discontinuation of treatment.

Results Of 334 patients [53% male, mean age at start of an oral immunosuppressive drug 36.9 years (SD 13.6)] with AD received oral immunosuppressive treatment of which 102 (31%) participated in clinical trials. Cyclosporine A (CyA) was given in 80% of the patients, mycophenolate mofetil or enteric-coated mycophenolate (MMF/EC-MPS) in 31%, azathioprine (AZA) in 14%, methotrexate (MTX) in 11%, systemic glucocorticosteroids in 7% and systemic tacrolimus in 5%. In these academic centra, CyA was the first choice oral immunosuppressive in 252 patients. Reasons for discontinuation of oral immunosuppressive drugs were controlled AD disease, ineffectiveness and adverse events.

Conclusion Various types of oral immunosuppressive drugs have been used over the past 10 years for the treatment of severe AD with a prominent first choice for CyA. Adverse events and ineffectiveness were frequent reasons for discontinuation. A prospective database of patients using oral immunosuppressive treatments in daily practice will give more insight in the effectiveness and safety and may help to formulate future recommendations.

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Conflicts of interest

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease. The prevalence varies between 2 and 10% in adults and 15–30% in children.^{1,2} A combination of emollients, topical glucocorticosteroids, calcineurin inhibitors, antihistamines and antibiotics, is often used in the management of AD.³ Different forms of phototherapy may also be effective.^{4–6}

In severe AD patients, with insufficient response to topical treatment or needing continuous treatment with mid to high potent corticosteroids, oral immunosuppressive therapy is indi-

cated. Studies show that cyclosporine A (CyA), azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF) and Enteric-Coated MycoPhenolate Sodium (EC-MPS) are effective in the treatment of severe AD patients. Long-term treatment with oral glucocorticosteroids is not recommended.^{7–11}

Guidelines for the use of oral immunosuppressive drugs have been published and include recommendations to support daily practice in the management of patients with AD.^{7,11–18} These guidelines are mostly based on results from clinical trials, preferably randomized clinical trials (RCT). However, patients participating in clinical trials often differ

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from daily practice patients due to the strict in- and exclusion criteria. In addition, patients participating in clinical trials are in general more compliant, probably resulting in better clinical efficacy of the drug. Daily practice data concerning oral immunosuppressive drugs used in AD patients may help to give additional insight in the effectiveness and safety. Therefore, a medical chart review was performed of all 334 AD patients treated with oral immunosuppressive drugs at the dermatology department of the Academic Medical Center Amsterdam (AMC) and University Medical Center Utrecht (UMCU) in the Netherlands over a period of 10 years (from January 2001 till January 2011). The aim of this study was to give an overview of the use of oral immunosuppressive drugs in patients with severe AD, with respect to patient characteristics, prior treatment, prescribed oral immunosuppressive drugs, the order of use, doses and treatment durations and reasons for discontinuation of treatment. Both daily practice data and trial (follow-up) data were evaluated to provide a complete overview of systemic immunosuppressive drug use in AD patients.

Materials and methods

Patient selection

In both centres, AD patients were diagnosed by a dermatologist or validated diagnostic criteria.¹⁹ All patients using oral immunosuppressive drugs for AD between January 2001 and January 2011 were included. For all patients, follow-up ended on January 1st 2011, regardless whether treatment was continued after this date. Patients who started an oral immunosuppressive drug before January 1st 2001 and continued this treatment after this date were included. Only patients born before January 1st 1995, were investigated, excluding young children.

In the AMC all patients diagnosed with AD in the digital registration system using oral immunosuppressive drugs were included. Additionally, patients treated in a RCT performed between July 2009 and December 2010, comparing AZA with MTX were included.⁸

In the UMCU, data of all adult patients diagnosed with AD and treated with oral immunosuppressive drugs from 1996 until now were retrospectively registered into a database. Patients who were treated with oral immunosuppressive drugs between January 2001 and January 2011 were selected. In addition, data from a RCT performed on EC-MPS vs. CyA from November 2005 to November 2007 were included.⁹

Excluded were patients who received oral immunosuppressive drugs as a therapy for a disease other than AD. When patients used the same oral immunosuppressive treatment more than once, only the first treatment episode was evaluated. When patients used different oral immunosuppressive drugs simultaneously, the combination of both treatments was evaluated. In case of monotherapy with systemic glucocorticosteroids, only

patients who were treated for a continuous period of more than 3 months were included.

Data-extraction

Information about patient characteristics, prior oral immunosuppressive drug use and phototherapy were collected. Information about the order in which oral immunosuppressive drugs were prescribed, doses and durations of treatment, the reasons for discontinuation of treatment were collected. Also the manner of discontinuation (acute or stepwise) was investigated.

Study outcome

The primary outcome parameter of this study was the reason for discontinuation of treatment and was subdivided in i) controlled disease, ii) adverse events iii) ineffectiveness, iv) end of study, v) miscellaneous. Controlled disease was defined as improvement of AD (in the opinion of the patient and/or physician) which resulted in discontinuation of the oral immunosuppressive drug. Adverse events leading to discontinuation of treatment included both subjective and objective adverse events, such as laboratory abnormalities. Ineffectiveness was registered as reason for discontinuation when patient and/or physician were not satisfied with the clinical response. Primary (not effective at all) and secondary (initially improvement but a loss of effect after a certain amount of time) ineffectiveness were not specified but the mean number on days on treatment were provided. End of the study was the reason for discontinuation in all patients participating in the RCT performed on EC-MPS vs. CyA as part of the study protocol. Patients participating in the RCT comparing AZA and MTX did not have to discontinue treatment after the trial period. These patients continued treatment with AZA or MTX as in daily practice. Any other reasons for discontinuation were summarized under miscellaneous. More than one reason for discontinuation per patient could be recorded.

This study followed the STROBE guidelines as much as possible.²⁰

Statistical analysis

SPSS version 20 for windows (SPSS, Inc, Chicago, IL, USA) was used to calculate means, medians, standard deviations and interquartile ranges.

Results

Patient characteristics

A total of 334 patients were included (85 from the AMC and 249 from the UMCU). Forty-two (13%) of them participated in the AMC RCT and 60 patients (18%) participated in the UMCU RCT.^{8,9} Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

	N (%) (Total = 334)
Male sex	177 (53)
Mean age	36.89 years (SD 13.64)
Presence of asthma†	180 (54)
Presence of allergic rhinitis†	211 (63)
Presence of food allergy†	146 (44)
Serum IgE determined	217 (65)
Serum IgE increased (>100 kU/L)	204 (61)
Mean number of previous oral immunosuppressive treatment per patient before referral to academic centres	0.60 (SD 0.86)
Patients who used more than one type of oral immunosuppressive treatment in the 10 years period	114 (34)

n, number, †Anamnestic.

Table 2 An overview of prior immunosuppressive or UV interventions

Therapy	N (%) (Total = 262)
Cyclosporin A	98 (37)
Systemic glucocorticosteroids†	68 (26)
Azathioprine	7 (3)
Mycophenolate mofetil/Enteric-Coated MycoPhenolate sodium	4 (2)
Efalizumab	1 (0)
Methotrexate	2 (1)
Neotigason	1 (0)
UVB‡	50 (19)
PUVA‡	18 (7)
UVA‡	13 (5)

†Data include short additional courses of a few days.

‡Data were only collected in the AMC.

UVB, ultraviolet B; UVA, ultraviolet A; PUVA, psoralen plus UVA.

Prior treatment

The mean number of oral immunosuppressive therapies per patient, used before referral to our academic centres, is 0.60 (SD 0.86) (Table 1). CyA was most frequently used (98 times, 37% of all patients) (Table 2), a requirement for starting in the MTX vs. AZA RCT.⁸

Oral immunosuppressive drugs

More than one type of oral immunosuppressive drugs was used by 114 patients (34%) between January 2001 and January 2011. Table 3 shows an overview of the treatment characteristics, reasons for discontinuation and median duration (days) of treatment until discontinuation. In Table 4 the adverse events that caused discontinuation of the different drugs are described in more detail.

Cyclosporin A In total, 267 patients (80%) were treated with CyA. Thirty-seven patients (14%) received CyA in the UMCU RCT.⁹ Fifty-seven patients had more than one treatment episode with CyA, of which only the first episode was evaluated. The median duration of treatment till January 1st 2011 was 258 days (IQR 108–434).

Of the 234 patients that discontinued treatment, 69 patients (29%) stopped because of controlled disease, 57 patients (24%) discontinued treatment because of adverse events. In 35 patients ineffectiveness (15%) was the reason for discontinuation of therapy. Thirty-seven patients (16%) discontinued because of the end of the trial in which they participated. One hundred and ninety-three other miscellaneous reasons caused discontinuation of treatment. Six patients used >3 months of prednisone simultaneously.

Mycophenolate mofetil and Enteric-Coated MycoPhenolate Sodium In total, 104 (31%) patients were treated with MMF and EC-MPS. Twenty-three patients (22%) received EC-MPS in the RCT that was performed in the UMCU.⁹ Four patients had more than one treatment episode with EC-MPS, of which only the first episode was evaluated. The median duration of treatment was 84 days (IQR 31.25–151.75) (MMF) and 212 days (IQR 113.75–380.75) (EC-MPS).

Among the 82 patients (79%) who discontinued treatment before January 1st 2011, 11 patients (13%) stopped because of controlled disease, 18 patients (22%) because of adverse events. In 36 patients (44%) MMF or EC-MPS was ineffective. Twenty-three patients (28%) discontinued because of the end of the trial in which they participated. Thirty-five other miscellaneous reasons caused discontinuation of treatment. Twenty-eight patients used >3 months of prednisone simultaneously.

Azathioprine In total, 46 patients (14%) were treated with AZA. Twenty-three patients (50%) received AZA as part of the AMC RCT.⁸ One patient had more than one treatment episode with AZA of which only the first episode was evaluated. In our 10-year observation period, the median duration of treatment was 208 days (IQR 27.25–340.25). Twenty patients (43%) continued treatment with AZA after January 1st 2011. Of the 26 patients who stopped treatment, five patients (19%) stopped because of controlled disease, ten patients (38%) due to adverse events. In four patients (15%) AZA was ineffective. Twelve other miscellaneous reasons caused discontinuation of treatment. Twelve patients used >3 months of prednisone simultaneously.

Methotrexate Of the 37 patients (11%) who received MTX, 23 patients (62%) started with this therapy as part the AMC RCT.⁸ No patients had more than one treatment episode with MTX. In our 10-year observation period, the median duration of treatment was 298 days (IQR 147–384.5). Twenty

Table 3 An overview of the treatment characteristics, reasons for discontinuation and the median duration (days) of treatment until discontinuation

Therapy	Total patients	Male (%)	Started before January 1st 2001 and continuing after this date (%)	Mean age at start in years (SD)	Mean start dose (SD)	Mean maximum dose (SD)	Median duration of treatment in days (IQR)	Continuing after January 1st 2011 (%)	Discontinuing before January 1st 2011 (%)	Mode of discontinuation	Reasons for discontinuation (%) and median duration (days) of treatment until discontinuation (IQR)
Cyclosporin A	267	146 (55)	18/267 (7)	35.50 (12.90)	4.23 mg/kg/day (0.95)	4.27 mg/kg/day (0.91)	258 (108–434)	33/267 (12)	234/267 (88)	Acute: 108 Stepwise: 94 Unknown: 32	Controlled disease: 294 (184–486) 69/234 (29) Adverse events: 217 (100–512) 57/234 (24) Not effective: 244 (162–512) 35/234 (15) End of trial: 50 (43–267) 37/234 (16) Miscellaneous: 193
Mycophenolate mofetil/Enteric-Coated Mycophenolic Sodium	104	63 (61)	0	42.10 (12.17)	MMF: 1050 mg/day (437.80) EC-MPS: 1371.06 (275.72)	MMF: 1650 mg/day (474.34) EC-MPS: 1371.06 (275.72)	MMF: 84 (31.25–151.75) and EC-MPS: 212 (113.75–380.75)	22/104 (21)	82/104 (79)	Acute: 64 Stepwise: 11 Unknown: 7	Controlled disease: 377 (241–814) 11/82 (13) Adverse events: 177 (70–222) 18/82 (22) Not effective: 114 (80–283) 36/82 (44) End of trial: 217 (207–222) 23/82 (28) Miscellaneous: 35
Azathioprine	46	22 (48)	0	40.24 (14.03)	99.77 mg/day (43.91)	121.56 mg/day (64.09)	208 (27.25–340.25)	20/46 (43)	26/46 (57)	Acute: 14 Stepwise: 2 Unknown: 10	Controlled disease: 270 (194–366) 5/26 (19) Adverse events: 27 (15–128) 10/26 (38) Not effective: 146 (27–214) 4/26 (15) Miscellaneous: 12
Methotrexate	37	19 (51)	0	43.98 (14.42)	8.75 mg/week (2.57)	20.90 mg/week (18.50)	298 (147–384.5)	20/37 (54)	17/37 (46)	Acute: 11 Stepwise: 1 Unknown: 5	Controlled disease: 261 1/17 (6) Adverse events: 96 (11–204) 7/17 (41) Not effective: 175 (11–204) 11/17 (65) Miscellaneous: 3
Systemic glucocorticosteroids	24	14 (58)	3/24 (13)	Prednisone: 44.65 (18.78); Celestone: 36.40 (6.32)	Prednisone: 22.50 mg/day (9.93) Celestone: 1.83 mg/day (0.76)	Prednisone: 23.00 mg/day (9.51); Celestone: 1.50 mg/day (0.5)	Prednisone: 266 (129.25–492) and Celestone: 1363 (258.75–2688.5)	4/24 (17)	20/24 (83)	Acute: 0 Stepwise: 16 Unknown: 4	Controlled disease: 138 (104–409) 4/20 (20) Adverse events: 2930 1/20 (5) Not effective: 323 (118–1574) 4/20 (20) Miscellaneous: 31
Tacrolimus	18	13 (72)	1/18 (6)	38.67 (SD 11.97)	6.53 mg/day (SD 1.81)	6.53 mg/day (SD 1.81)	106.5 (59–556.5)	2/18 (11)	16/18 (89)	Acute: 15 Stepwise: 1 Unknown: 0	Controlled disease: 223 1/16 (6) Adverse events: 77 (33–586) 9/16 (56) Not effective: 91 (77–294) 7/16 (44) Miscellaneous: 9

Table 4 Adverse events that caused discontinuation of therapy

Therapy	Adverse events that caused discontinuation of therapy	
Cyclosporin A	Serum creatinine increase	24/234 (10%)
	Hypertension	17/234 (7%)
	Neurological symptoms†	14/234 (6%)
	Fatigue	9/234 (4%)
	Gastrointestinal symptoms	9/234 (4%)
	Myalgia	7/234 (3%)
	Pitting oedema	5/234 (2%)
	Flu like symptoms	4/234 (2%)
	Hypertrichosis	2/234 (1%)
	Physical condition loss	2/234 (1%)
	Gum hyperplasia	2/234 (1%)
	Rushed feeling/mood changes	2/234 (1%)
	Recurrent viral infection with herpes simplex	1/234 (0%)
	Flushing	1/234 (0%)
	Petechia	1/234 (0%)
	Joint problems	1/234 (0%)
	Anaemia	1/234 (0%)
Mycophenolate mofetil/Enteric-coated MycoPhenolic Sodium	Neurological symptoms†	8/82 (10%)
	Gastro-intestinal symptoms	5/82 (6%)
	Flu like symptoms	3/82 (4%)
	Shortness of breath	3/82 (4%)
	Myalgia	2/82 (2%)
	Fatigue	1/82 (1%)
	Oedema	1/82 (1%)
	Hair loss	1/82 (1%)
Azathioprine	Nausea	7/26 (27%)
	Neurological symptoms†	2/26 (8%)
	Liver dysfunction	2/26 (8%)
	Fatigue	1/26 (4%)
	Flu like symptoms	1/26 (4%)
	Anaemia	1/26 (4%)
	Lymphocytopenia	1/26 (4%)
	Pancytopenia	1/26 (4%)
Methotrexate	Neurological symptoms†	3/17 (18%)
	Nausea	2/17 (12%)
	Fatigue	2/17 (12%)
	Transaminase increase	1/17 (6%)
Systemic corticosteroids	Unknown	1/20 (5%)
Tacrolimus	Gastro-intestinal symptoms	3/16 (19%)
	Serum creatinine increase	3/16 (19%)
	Neurological problems†	2/16 (13%)
	Hypertension	1/16 (6%)

†Including trembling of the hands, visual impairments, tingling of the fingers, jactation, vertiginous, feeling weak and heaviness of the arms.

patients (54%) continued treatment with MTX after January 1st 2011. Of the seventeen patients who stopped treatment, one patient (6%) stopped because of controlled disease. Seven (41%) discontinued because of adverse events. Eleven patients discontinued treatment because of ineffectiveness (65%). Three other miscellaneous reasons caused discontinuation of treat-

ment. Six patients used >3 months of prednisone simultaneously.

Systemic glucocorticosteroids monotherapy Twenty-four patients (7%) were treated with a monotherapy of systemic glucocorticosteroids, of which twenty patients (83%) used pred-

Table 5 Order of use in oral immunosuppressive treatments in steps

Therapy	First step	Second step	Third step	Fourth step	Total
CyA	252	13	2	–	267
Syst cort	16	4	3	1	24
MMF	–	6	3	1	10
AZA	22	8	13	3	46
MTX	21	9	6	1	37
EC-MPS	19	66	9	0	94
Tacrolimus	4	9	3	2	18

Syst cort, systemic corticosteroids.

nisone and four patients (17%) used celestone. Four patients had more than one treatment episode with systemic glucocorticosteroids, of which only the first episode was evaluated. All courses lasted longer than 3 months (inclusion criterium), with a median duration of treatment with prednisone of 266 days (IQR 129.25–492) and 1363 days (IQR 258.75–2688.5) for celestone. The mean starting dose was 22.50 mg/day (SD 9.93) for prednisone and 1.83 mg/day (SD 0.76) for Celestone. The mean maximum dose was 23.00 mg/day (SD 9.51) for prednisone and 1.50 mg/day (SD 0.5) for celestone. Twenty patients (83%) discontinued treatment, of which four patients (20%) discontinued treatment because of controlled disease. One patient discontinued treatment with celestone because of unknown adverse events. In four patients (20%) systemic glucocorticosteroids were ineffective. Thirty-one other miscellaneous reasons caused discontinuation of treatment.

Tacrolimus Eighteen patients (5%) were treated with tacrolimus, with a median duration of treatment of 107 days (IQR 59.0–556.5). One patient had more than one treatment episode with tacrolimus, of which only the first episode was evaluated. Of the sixteen patients (89%) who discontinued treatment, one patient (6%) discontinued because of controlled disease. Nine patients (56%) discontinued treatment because of adverse events. In seven patients (44%), the treatment was not effective (Table 3). Nine other miscellaneous reasons caused discontinuation of treatment.

Order of use

The order of use of the different oral immunosuppressive drugs in the included patients is shown in Table 5. These data include only oral immunosuppressive drugs that were given to the patients in our centres and do not include previous oral immunosuppressive treatments, prescribed by dermatologists of peripheral hospitals or by general practitioners.

First choice a treatment was CyA, given in 252 patients. The absolute number of patients receiving AZA, MTX or EC-MPS in first instance were comparable. Most of them participated in the earlier mentioned clinical trials.

Discussion

The present study provides an overview of oral immunosuppressive drugs used in the treatment of adult AD patients in two academic centres in a time period of 10 years. These data reflect the situation in the Netherlands and may be different from other European countries. CyA was the most commonly used oral immunosuppressive drug, followed by MMF/EC-MPS, AZA, MTX, systemic glucocorticosteroids and tacrolimus. Although long-term treatment with oral glucocorticosteroids is not recommended in guidelines, 27 patients were treated with oral glucocorticosteroids for more than 3 months. These patients were monitored well and only one patient had to discontinue due to unknown side-effects.

The mean amount of 0.60 previous oral immunosuppressive treatments per patient indicates that the use of oral immunosuppressive drugs is not limited to our academic centres. Although the major part of the patients used oral immunosuppressive drugs in a daily practice setting, about 30% of the patients participated in one of the earlier mentioned trials. These patients may have a different profile due to the inclusion and exclusion criteria of the trials.

The aim of the present study was to provide a complete overview of the oral immunosuppressive drugs that were prescribed in AD patients over a period of 10 years. It was not the intention to compare the efficacy of the different oral immunosuppressive drugs, as reliable efficacy measures, such as clinical scores were not available in all patients (only in trial patients) and bias could influence the data. Therefore, we chose the reason for discontinuation of the oral immunosuppressive drug as primary outcome measure. In our opinion this is the most reliable measure in retrospective studies. Still, this outcome has its shortcomings, because no predefined definitions for controlled disease and inefficacy were used.

Discontinuation of treatment may have been influenced by different factors like local differences in treatment strategies and physician's experience. Guidelines and insights have changed during the 10-year evaluation period. For instance in the first part of the evaluation period only CyA and oral steroids were described for severe AD, while the prescription of second-line drugs like MTX, AZA and MMF/MPA started in the last part of the evaluation period. This may partly explain the high number of finished CyA treatment episodes, while relatively more patients on second-line drugs are still under treatment at the moment of datalock.

Adverse events were reported often as a reason for discontinuation of treatment. The lowest percentages were seen in patients treated with systemic glucocorticosteroids (5%), MMF/EC-MPA (22%) and CyA (24%). In CyA-treated patients objective adverse events (serum creatinine rise and hypertension) were the most common reason for discontinuation, while subjective side-effects as a reason for discontinuation were more

prominent in the other treatment modalities. A relatively high percentage of patients discontinued treatment with AZA (38%), MTX (41%) and tacrolimus (56%) due to subjective adverse events, especially gastro-intestinal (AZA and MTX) and neurological (tacrolimus) side-effects. Although these side-effects are reported in clinical trials, the percentage of patients that discontinued treatment in this daily practice population is higher compared to published clinical trials.^{8–10} The most logical explanation is the difference in patients selection and probably compliance between trials and daily practice.

Although AD is a chronic disease, it is in general not the intention to use oral immunosuppressive drugs for many years, despite good clinical efficacy. This in contrast to the treatment with biologicals in for instance psoriasis patients where continuous treatment for many years in stable disease is more common. Therefore, we also focussed on adequate disease control (controlled disease) as a reason for discontinuation of treatment.

Controlled disease was the reason for discontinuation in relatively few patients. The highest number was seen in patients treated with CyA (29%), followed by systemic glucocorticosteroids (20%) and AZA (19%). For MMF/EC-MPS, MTX and tacrolimus the percentages of discontinuation due to controlled disease were 13%, 6% and 6% respectively.

It is important to realize that discontinuation due to controlled disease is not the same as clinical effectiveness, as patients who were still under treatment at the moment of data analysis, probably have a good response to treatment. In the future, these patients may also discontinue their treatment because of controlled AD disease.

In the present study, patients with multiple comorbidities and difficult treatable AD are included. This in contrast to RCTs where guidelines are based on. Due to the strict inclusion criteria, patients participating in RCTs have less comorbidity and are often more motivated and compliant. A recent study of anti-TNF- α in psoriasis patients, showed that patients who received prior anti-TNF- α in a clinical trial setting, had a better drug survival rate afterwards when treated in a daily practice setting compared to patients who had not participated in clinical trials before. Possible explanations could be that former trial patients may be healthier and have fewer comorbidities, or show a better adherence to treatment due to positive experiences in a previous trial.²¹

Another important difference between clinical trials and daily practice is the duration of treatment: in clinical trials treatments are often limited to 3–6 months, while treatment periods in daily practice are much longer.

There is a need for more practical guidelines in the treatment of patients with AD with oral immunosuppressive drugs. A recent published systematic review provided an evidence-based systemic treatment algorithm for patients with moderate-to-severe AD and the recent AAD guideline gives an overview of the existing literature.^{7,11} In children, the TREAT survey gives an

indication on which systemic immunomodulating drugs are used.²²

Data from the present study provide practical information on dosing, order of use and reasons for discontinuation of oral immunosuppressive drugs in adult AD patients, which is valuable for future recommendations in guidelines.

Limitations of this study

In this retrospective study, the quality of the included data depended on the completeness of medical records.

Some patients used prednisolone >3 months simultaneously with other oral immunosuppressive drugs. It was not possible to evaluate these treatments separately. The use of oral steroids was supportive. Therefore, the data of these combinations were described in the evaluation of the main compound. In the result section of the amount, long-term treatment with prednisone is mentioned for each oral immunosuppressive drug.

To provide an extensive complete overview of oral immunosuppressive drugs that were prescribed in the last 10 years, both daily practice and RCT data were included. We were encouraged to do so because the trials were set up as much as possible according to daily standard care. Nevertheless, it should be taken into account that the data of trial patients are influenced by the trial process. Table 5 for instance gives an overview of the order of use of oral immunosuppressive drugs in our centres, but it should be taken in consideration that the order has been influenced by the randomization process that was applied in the AMC and UMCU RCTs.

Finally, we are aware of the fact that these data may not be generalizable for the Netherlands and may show differences with other European academic AD centres.

Recommendations

Besides clinical trial data, observational daily practice data should be taken into account in updating existing guidelines and formulating recommendations.

A prospective database of adults and children with AD using oral immunosuppressive drugs in daily practice, including validated and standardized diagnostic criteria, outcome domains and measurements, could be of great value for further recommendations and is currently being developed.

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