FOLIA MEDICA CRACOVIENSIA
Vol. LXIII, 1, 2023: 97–108
PL ISSN 0015-5616
DOI: 10.24425/fmc.2023.145433

Clinical aspects of the treatment of atopic dermatitis with topical glucocorticoids and calcineurin inhibitors — a pilot questionnaire study

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Abstract: Atopic dermatitis (AD) is the most common inflammatory skin disease. However, recent reports concerning the simple clinical aspects of treatment with topical glucocorticosteroids (TCS) and calcineurin inhibitors (TCI) are lacking. The objective of this study is providing an update on these characteristics of AD management. A group of 150 adults suffering from AD treated with TCS during last year was asked to fill an anonymous questionnaire. The course of topical treatment was analyzed in the context of the severity of symptoms and the knowledge of the patients about therapy. During the last year, the majority of patients (66%) were treated with class IV TCS; however, in the last two weeks, class I TCS was used the most frequently (35%). Only 11% were familiar with the concept of intermittent therapy and 4% used the fingertip unit (FTU). In total, 77% of them used TCI. Most of the patients used the same class of TCS permanently. Unfortunately, patients are unaware of simple approaches (like intermittent therapy or FTU) that increase both the effectiveness and safety of the treatment. Practicians should be aware of these problems to identify and eliminate them, primarily through the education of patients.

Keywords: atopic dermatitis, topical glucocorticosteroids, topical calcineurin inhibitors, finger tip unit, intermittent therapy.

Submitted: 15-Nov-2022; **Accepted in the final form:** 15-Feb-2023; **Published:** 30-Apr-2023.

Introduction

Atopic dermatitis (AD) is the most common inflammatory dermatosis in the world, affecting up to 20% of children and 10% of adults [1]. The most characteristic features of the disease include: a chronic and recurrent course with the appearance of skin eczema localized in typical age-dependent sites accompanied by itching and dryness of the skin [2]. Chronically persistent eruptions become lichenified due to scratching and inflammation.

AD develops primarily in children, but it should be emphasized that the adult population of AD patients is still growing [1–3]. The strongest known risk factors for AD include: the presence of the disease among first-degree relatives and lifestyle [4]. Some patients are diagnosed with other atopic diseases, often developing in a characteristic sequence referred to as atopic march (i.e., food allergy, conjunctivitis, bronchial asthma, and allergic rhinitis) [5].

Due to persistent itch, the disfiguring appearance of skin lesions, and susceptibility to skin infections, the quality of life in patients with AD drastically decreases [1, 6].

The treatment of AD is prolonged, so the primary objective is to obtain satisfactory control of the disease symptoms. Therefore, the crucial principle of treatment is to achieve cooperation between the patient and the dermatologist, mainly through patient education. Skin moisturizing preparations (emollients) and topical glucocorticosteroids (TCS) are the foundation of topical therapy [3, 7].

The classical mechanism of TCS includes their anti-inflammatory, anti-proliferative, immunosuppressive and vasoconstrictive properties [8]. Unfortunately, the fear (or sometimes the anxiety) of side effects of TCS treatment occur in even 50 to 80% of patients, impairing the compliance [9]. Clear and reliable information obtained from the attending physician is the critical factor that reduces the frequency of these steroid concerns [10]. The statement by Johannes Ring: 'as short as possible, as long as necessary' [11] is considered as the 'golden rule' of TCS therapy.

However, the course of TCS therapy in the population of adult AD patients has not been investigated in recent years. As shown by the previous studies the knowledge about the therapy was incomplete among patients with AD treated with TCS, while their concerns regarding systemic side effects were inadequate to the real risk [12].

In the Polish literature, the last analysis of the practical aspects of the treatment of AD with TCS was carried out in 2015 [13]. It seems appropriate to update the state of knowledge on this aspect of AD therapy, especially in the context of the relationships with other methods of AD topical treatment (i.e., emollient therapy and topical calcineurin inhibitors [TCI]).

The aim of the study is to assess the basic clinical aspects of the TCS and TCI treatment in adult patients with AD and to establish the relationship between the ongoing management and the severity of disease symptoms as well as the adverse drug reactions.

Material and Methods

The study was carried out at the Department of Dermatology (Collegium Medicum, Jagiellonian University) in Krakow. Data were collected with anonymous questionnaires from 150 adult patients with AD, admitted for a follow-up visit, or hospitalized in a dermatology clinic from 2017 to 2019. As the study design was cross-sectional, no follow-up data were collected. The study was conducted with respect to the STROBE

(Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [14]. All participants gave informed consent to participate in the research.

The diagnosis of AD was established by a dermatologist and allergist (A.K.J.) according to the criteria of Hanifin and Rajka [15]. Exclusion criteria from the study were: age over 18 years and coexistence of inflammatory skin diseases other than atopic dermatitis. Based on these criteria, no patient was excluded from the study.

Respondents reported the severity of the disease by providing information on the frequency of exacerbations during the last month and assessing the most severe itch in the last 24 hours using the VAS scale (Visual-Analogue Scale). On this scale, 0 pts. (points) mean no itch, 1 to 3 pts. mild itch, 4 to 6 pts. moderate itch, 7 to 8 pts. severe itch, and 9 to 10 pts. very severe itch [16]. Then, the severity of the cutaneous symptoms of the disease was assessed by a dermatologist and allergist using the TIS (Three Item Severity Score) scale. It covers three features of skin lesions: erythema, excoriations, and edema, the severity of which is assessed on a scale from 0 to 3, and then sums up the results. Result 0 to 2 pts. allows for the diagnosis of mild AD, 3 to 5 pts. moderate AD, and 6 to 9 pts. severe AD [17].

Information on the course of TCS therapy was obtained from the anonymous questionnaire developed by the study authors (P.H., A.K.J.). The main characteristics of the patients concerned demographic characteristics (age, sex, education) and the use of other forms of topical AD treatment (frequency of skin moisturizing and the use of TCI).

Questions concerning TCS treatment covered the use of TCS preparations during the last year and the last 2 weeks, as well as the knowledge of intermittent therapy. Furthermore, a dermatologist and allergist specialist (A.K.J.) collected a detailed interview in terms of awareness of the concept of the FTU (FingerTip Unit) concept and the appearance of steroid dependence, incognito infections, and tachyphylaxis. Then the presence of atrophy, stretch marks, perioral inflammation, hypertrichosis, and skin dyspigmentation was assessed. The requirements of a statistical analysis demanded to assign the TCS used by the respondents to four groups, according to the potency, as defined by European (British) classification. In our study, they were: class IV — hydrocortisone 1.0% (cream); class III — hydrocortisone butyrate 0.1% (cream, ointment), betamethasone valerate 0.1% (cream) or 0.025% (ointment), mometasone furoate 0.1% (cream); class II — betamethasone dipropionate 0.05% (ointment, cream), fluticasone propionate 0.05% (cream), methylprednisolone aceponate 0.1% (cream, ointment); class I — clobetasol propionate 0.05% (cream, ointment) [18].

Each of the respondents participating in the study provided their answers in conditions guaranteeing peace, without the imposed time limit for completing the questionnaire.

Total IgE antibody concentration was measured in a sample of venous blood collected as part of routine laboratory diagnostics using the fluorescent enzyme immunoassay (FEIA) method in the UniCAP100 device (ImmunoCAP-System, Phadia

AB, Sweden), according to the manufacturer's instructions. The values higher than 100 IU/mL were assumed to be above normal.

The study was carried out according to the principles stated in the Declaration of Helsinki of 1975, as revised in 1983. Due to the non-interventional survey setting of the study, ethics approval was not obtained.

Statistical Analysis

It was a pilot study, therefore the sample size was arbitrarily set as 150 participants for the purpose of preliminary evaluation of the results. Data were presented as median and range (min–max) for categorical and interval variables. Comparison of the distribution of nominal variables was performed using the χ^2 test or the two-tailed Fisher test (if the expected values for any group were <5). The Mann–Whitney U test and the nonparametric Kruskal–Wallis ANOVA test were used to compare the groups. Spearman rank correlation was used to determine the strength and direction of the relationship between interval variables. Logistic regression was used to determine the effect of the use of individual TCS on the frequency of side effects and the relationship between the use of different TCS during the last year and in the last two weeks.

If data on a given parameter were missing, cases were not included in the analysis for this parameter. The threshold level for significance was decided to be $\alpha = 0.05$. All statistical analyzes were performed using the Dell Statistica (Data Analysis Software System), version 13.3.

Results

One hundred fifty respondents (F/M = 78/72, 52%/48%) participated in the study. Their median age was 29 years (18 to 80). Generally, the duration of the disease was >20 years (n = 96, 64%). Patients usually declared skin moisturization with a frequency of 2 to 3 times a day (n = 89, 59%) (Table 1).

The highest percentage of respondents used class IV TCS in the last year (n = 99, 66%), while in the last two weeks class IV and class I were used most frequently (n = 41, 27% and n = 53, 35%, respectively). Among the respondents, 16 people (11%) were familiar with the principles of intermittent therapy. Alarmingly low number of patients knew the FTU concept, i.e., 6 (4%) of them (Table 2).

Patients who used class IV TCS most often had a mild severity of skin lesions (TIS — Me: 2, min: 1, max: 9; both for two weeks and the year of use) compared to those who applied TCS of higher potency. Among the respondents who were treated with more potent TCS, symptoms were more severe (median TIS 6 to 8) (Fig. 1). Respondents who did not apply any TCS in the last two weeks had a median TIS 1.5 (min.: 1, max.: 7).

Table 1. Characteristics of patients with AD.

Sex: Female/Male, n (%)	78 (52) / 72 (48)
Age: years, median (min.–max.)	29 (18–80)
Education level: n (%) lower secondary higher	 38 (25) 41 (27) 71 (48)
TIS: points, median (min.–max.)	4 (1–9)
VAS: points, median (min.–max.)	3 (0–10)
Duration of the disease: n (%) <10 years 10–20 years >20 years	 23 (15) 31 (21) 96 (64)
Applications of an emollient per day: n (%) 0–1 2–3 >3	 23 (15) 89 (59) 38 (26)
Exacerbations of AD per month: n (%) ≤5 >5 active lesions persist	 98 (65) 17 (11) 35 (23)
TCI: n (%) tacrolimus pimecrolimus	 78 (52) 38 (25)
total IgE: IU/mL, median (min.–max.)	430 (24–26,000)

Abbreviations: AD — atopic dermatitis; IgE — immunoglobulin E; max. — maximal; min. — minimal; n — number; TCI — topical calcineurin inhibitors.

Table 2. Replies to the questions from the questionnaire.

TCS used in the last year, n (%)	
Class IV	99 (66)
Class III	43 (29)
Class II	67 (45)
Class I	60 (40)
TCS used in the last two weeks, n (%)	
Class IV	41 (27)
Class III	15 (10)
Class II	30 (20)
Class I	53 (35)
None	40 (27)

Table 2. cont.

Information obtained from an medical interview and examination carried out by a dermatologist and allergist:	
Knowledge of intermittent therapy, n (%)	16 (11)
Knowledge of FTU, n (%)	6 (4)
Adverse reactions to TCS treatment, n (%)	89 (70)
skin atrophy	45 (30)
stretch marks	46 (31)
perioral dermatitis	9 (6)
hypertrichosis	10 (7)
discolorations	67 (45)
steroid dependency (in anamnesis)	42 (28)
incognito type infection (in anamnesis)	22 (15)
tachyphylaxis (in anamnesis)	32 (21)

Abbreviations: FTU — finger-tip unit; n — number; TCS — topical glucocorticosteroids.

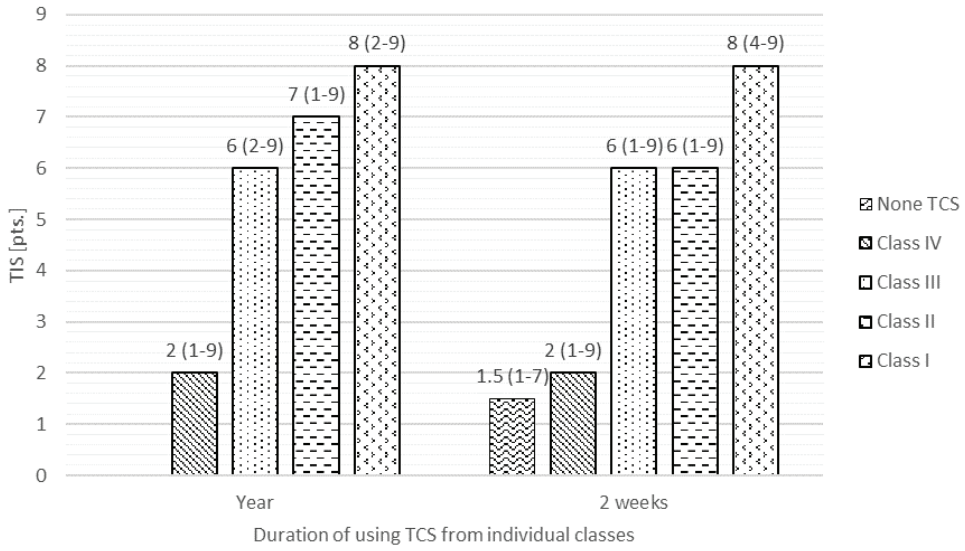

Fig. 1. Graph showing the relationship between the TCS class used during the last two weeks and the last year with the severity of AD symptoms according to the TIS scale. The results are presented as the median and the range of data (min.–max.). To preserve the clarity of the graph, the bars show only the median of TIS, while the range is given above.

Comparable results were observed in the self-assessment of pruritus severity according to the VAS scale. The average severity of pruritus in patients using class IV TCS within the last 2 weeks was estimated at 2 pts. (min.: 0, max.: 10), while in the

case of classes III–II 7 pts. (min.: 1, max.: 10), and for class I it was 8 pts. (min.: 1, max.: 10). Patients that reported no use of TCS during the last two weeks had no or mild AD symptoms (TIS Me: 1, min.: 0, max.: 9).

We found that older patients used more potent TCS throughout the last year (the median age for class I — no: 27 [18 to 60] vs. yes: 34 [18 to 80]; $P = 0.0004$) and two weeks (the median age class I — no: 27 [18 to 60] vs. yes: 34 [18 to 80]; $P = 0.002$) — all the subjects older than 65 years used only class I TCS. However, an analysis of the relationship between the severity of symptoms on the TIS scale and the age of the patients revealed a positive correlation between these variables (Spearman's correlation coefficient r = 0.33, $P < 0.001$). Thus, age is more directly associated with the severity of the disease, while the relationship with the TCS class seems to be only secondary to that.

A total of 116 (77%) respondents used TCI, that is, 78 of them applicated tacrolimus and 38 pimecrolimus (Table 1). Patients with higher level of education used TCI the most frequently. The same trend applies to the each of TCI, i.e., tacrolimus and pimecrolimus ($P_{trend}<0.001$ for both comparisons).

An increased frequency of emollient applications per day was associated with a significantly lower odds of perioral dermatitis as a complication of TCS: 0–1x/d. — 22%, 2–3×/d. — 4%, >3×/d. — 0% ($P = 0.002$, $P_{trend} = 0.017$).

Among the respondents who used class I TCS the following adverse reactions had higher odds of occurring, compared to other subjects: perioral dermatitis (both during the year and in the last two weeks), hypertrichosis (last two weeks) and tachyphylaxis (last year) (Table 3).

Table 3. Results of logistic regression analysis that compares the odds of distinct adverse reactions during the TCS treatment — class I glucocorticosteroids compared to the remaining classes (II–IV). Results are presented as log OR ± 95%CI.

	Class I vs. classes II–IV during last year		Class I vs. classes II–IV during last two weeks	
	log OR ± 95%CI	p-Value	log OR ± 95%CI	p-Value
atrophy	1.4 (–1.1–3.9)	0.3	1.7 (–0.2–3.7)	0.08
stretch marks	1.3 (–0.5–3.1)	0.2	1.9 (–0.8–4.7)	0.2
steroid dependency	1.3 (–0.2–2.9)	0.09	–0.1 (–2.0–1.9)	1.0
perioral dermatitis	9.3 (7.4–11.1)	<0.001	7.4 (5.2–9.5)	<0.001
hypertrichosis	1.1 (–1.5–3.8)	0.4	6.5 (2.9–10.1)	<0.001
discolorations	0.5 (–0.8–1.9)	0.4	1.9 (0.0–3.7)	0.05
tachyphylaxis	9.0 (5.8–12.2)	<0.001	4.1 (–0.5–8.7)	0.08

Abbreviations: CI — confidence interval; OR — odds ratio; TCS — topical glucocorticosteroids.

Most patients who used the particular class of TCS during the last year applicated preparations from this class also during the last two weeks. Consecutively, the odds of choosing a TCS preparation that differed by >1 class of potency were small (Table 4).

The severity of skin lesions assessed with the TIS scale positively correlated with total IgE (Spearman's coefficient r = 0.73, P <0.001).

Table 4. Relationship between the use of distinct TCS classes in the last year and in the last two weeks (or using no TCS in the last two weeks). Results are presented as OR ± 95%CI and p-Value is shown below.

Last two weeks (horizontal) / Last year (vertical)	None TCS	Class IV	Class III	Class II	Class I
Class IV	3.1 (1.3–7.7) 0.01	34 (4–255) 0.0006	0.4 (0.1–1.8) 0.2	0.4 (0.1–1.1) 0.063	0.1 (0.04–0.4) 0.003
Class III	0.4 (0.2–1.1) 0.1	0.6 (0.2–1.4) 0.3	23 (5–106) 0.0001	1.1 (0.5–2.6) 0.9	1.3 (0.6–2.7) 0.5
Class II	0.2 (0.1–0.4) 0.0001	0.5 (0.2–1.0) 0.053	2.0 (0.7–5.9) 0.2	63 (8–476) 0.0001	2.7 (1.4–5.4) 0.005
Class I	(none of patients)	0.2 (0.1–0.5) 0.0008	1.4 (0.5–4.0) 0.6	2.8 (1.2–6.3) 0.015	578 (70–4,756) <0.0001

Abbreviations: CI — confidence interval; OR — odds ratio; TCS — topical glucocorticosteroids.

Discussion

The pioneers who introduced TCS to dermatology in 1952 were Marion Sulzberger and Victor Witten, who published the results of the treatment of selected dermatoses (including AD) with the use of an ointment preparation containing hydrocortisone acetate, 'Compound F' [8, 19]. In the 1950s and 1960s, intensive pharmacological research was conducted, resulting in the synthesis and introduction of novel hydrocortisone derivatives (such as triamcinolone or betamethasone valerate) into dermatological therapy [20, 21].

The principles of TCS treatment in AD have been specified by numerous recommendations of scientific societies [3, 7, 22, 23]. While using simultaneously both TCS and emollients, it seems important to resolve acute inflammation first, what is achieved by TCS application [24]. Since most cases of AD are characterized by persistent dryness of the skin, ointments are highly efficient. To reduce the risk of side effects during TCS treatment, preparations can be applied 2 to 3 times a week (the so-called intermittent therapy), while on other days emollients alone should be used [25].

The group we studied included mainly young adults who have suffered from AD since childhood. The course of the disease was usually mild or medium. Almost the complete lack of awareness about the use of FTU is concerning. This term is defined as the amount of ointment squeezed onto the palmar surface of the distal phalanx (from the tip of the finger to the distal interphalangeal crease) from a tube of 5 mm in diameter. This amount of preparation is expected to cover the skin surface of approximately twice the area of the patient's hand (i.e., about 2% of the body surface) [26]. The concept of FTU was proposed by Long *et al.* already in 1991 [27] and dermatologists rapidly recognized the clinical benefits that it brought. Paterson *et al.* in 2018 were first to objectively establish that patients who are not familiar with FTU apply only ~35% of the recommended amount of TCS (2 mg/cm^2 vs. 9 mg/cm^2). Within the same study, the researchers showed that it took a merely brief explanation of the meaning of this term (<1 minute of conversation) to improve its understanding and enable proper use by the patients [28]. Similarly, only a few of the respondents reported knowledge and use of intermittent therapy, which could be associated with the relatively high frequency of side effects of TCS treatment in the observed group. However, it should be emphasized that the objective evaluation of complications of TCS treatment carried out by experienced dermatologists was an independent factor that contributed to a more reliable assessment (thus, revealing these treatment complications that would be easily underreported). Objective techniques, that is, optical coherence tomography and high-frequency skin ultrasound, showed that the application of TCS only twice a week significantly reduces the risk of adverse effects (thinning and scarring of the skin and telangiectasia), compared to the daily application [29]. Being unfamiliar with the term FTU and failure to introduce the regimen of intermittent therapy were described among most of respondents in a previous Polish report [13].

The data we obtained regarding the relationship between the clinical severity of disease symptoms assessed according to the TIS scale and the class of the TCS preparation used are clear, i.e., patients with more severe skin lesions were treated with stronger TCS. Along with the higher level of education, patients more willingly combined TCS therapy with TCI. Topical therapy with TCI, particularly tacrolimus 0.1%, is a method of similar effectiveness to TCS (of low-to-medium potency) in controlling the severity of skin symptoms in AD, except for acute eruptions or these associated with severe itch (against which TCS are undisputedly of first choice) [3, 30]. It is worth emphasizing that the combination of these two methods of local treatment is of particular significance in case of skin lesions exacerbation and during their resolution [31]. It can be assumed that patients of higher education are more likely to acknowledge the fact that TCI preparations are considered safer [30].

The fundamental aspect of AD therapy is sufficient skin hydration. Although properly performed emollient treatment involves several factors [9], the daily frequency of skin moisturizing remains a simple and objective indicator of the correct

implementation of this element of therapy. The moisturizers are recommended to be applied 2 to 3 times per day [3, 7]. Most of the respondents followed the above principles. Of note, the proper skin hydration was associated with the reduced odds of perioral dermatitis.

The course of TCS treatment in the investigated patients can be summarized that most of the patients were treated chronically with preparations of the same potency class. This behavior suggests that patients are unaware of the differences between the classes of TCS, i.e., their potency and risk of adverse reactions.

An additional observation, consistent with our previous reports [32], is the presence of a strong correlation between the severity of clinical symptoms of AD and the concentration of total IgE in the patients' serum. Moreover, the disease was more severe among the elder respondents (particularly, all the subjects older than 65 years used class I TCS). Multiple factors could contribute to that, including less time for skin care, forgetting some elements of treatment (e.g., application of emollients), or, ultimately, the biological changes resulting from ageing [33].

Our study has some limitations. It was designed as a retrospective, cross-sectional, single-center survey. Therefore, it is not possible to draw certain conclusions about the cause-effect relationships based on our results. The answers given by patients in the questionnaire might have not fully reflected the actual course of their treatment, e.g., due to the forgetting of certain information or the intention to present compliance better than in reality.

The study was conducted on a medium-sized group of adults treated for AD with TCS and other topical preparations. Respondents answered questions about simple and important aspects of therapy that were related to the real-world dermatological practice. The conclusions of the study can be extrapolated to other Polish and European centers.

Summary

Our study revealed several important problems that need to be resolved to improve the quality of dermatological care for patients treated topically for AD, particularly with TCS. The physician who governs the treatment should strive for the use of TCS of the lowest possible strength for the shortest possible time to avoid side effects. The lack of knowledge of the term FTU (and therefore omitting its application) deteriorates the agreement between the actual treatment and that recommended by a dermatologist. A concise verbal explanation and written information for the patient are interventions that are routinely sufficient to significantly augment the effectiveness of therapy [34]. The prominence of these simple recommendations will result in significant improvement in disease control, as well as patient quality of life, abstaining from the implementation of new pharmacological interventions.

Conflict of interest

None declared.

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