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Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement

Systemic steroids for atopic dermatitis

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Dr. de Bruin-Weller is a principle investigator for Regeneron/Sanofi /Genzyme, Abbvie, Roche, Novartis, an advisory board member for Regeneron/Sanofi/Genzyme, Abbvie, Anacor and a consultant for Regeneron/Sanofi /Genzyme.

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What's already known about this topic?

- Despite recommendations against their use in practice guidelines, systemic corticosteroids are commonly used for atopic dermatitis.

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What does this study add?

- The International Eczema Council reached consensus on circumstances in which systemic corticosteroids can be used for atopic dermatitis, including a lack of other treatment options, as a bridge to other systemic therapies or phototherapy, during acute flares in need of immediate relief, in anticipation of a major life event or in the most severe cases.
- Clinicians should limit the use of systemic corticosteroids for severe atopic dermatitis to those circumstances.

Keywords

Eczema; atopic dermatitis; systemic corticosteroids; prednisone; consensus; treatment

Abstract

Background: Guidelines discourage the use of systemic corticosteroids for atopic dermatitis but their use remains widespread.

Objective: To reach consensus among an international group of atopic dermatitis experts on the use of systemic corticosteroids for atopic dermatitis.

Methods: A survey consisting of statements accompanied by visual analog scales ranging from "strongly disagree" to "neutral" to "strongly agree" was distributed to the International Eczema Council (IEC). Consensus was reached in agreement on a statement if <30% of respondents marked to the left of "neutral" towards "strongly disagree."

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Results: Sixty of 77 (79%) IEC members participated. Consensus was reached on 12 statements, including that systemic corticosteroids should generally be avoided but can be used rarely for severe atopic dermatitis under certain circumstances, including a lack of other treatment options, as a bridge to other systemic therapies or phototherapy, during acute flares in need of immediate relief, in anticipation of a major life event or in the most severe cases. If used, treatment should be limited to short-term. Most respondents agreed that systemic corticosteroids should never be used in children, but consensus was not reached on that statement. The conclusions of our expert group are limited by a dearth of high-quality published evidence. If more stringent consensus criteria were applied (e.g., requiring <20% of respondents marking towards "strongly disagree," consensus would have been reached on fewer statements.

Conclusions: Based on expert opinion from the IEC, routine use of systemic corticosteroids for atopic dermatitis is generally discouraged and should be reserved for special circumstances.

Introduction

In clinical practice guidelines and position statements concerning the management of atopic dermatitis (AD), the use of systemic corticosteroids (CS), including prednisone, hydrocortisone and celestone, is generally discouraged, with use limited to special circumstances (Table 1).[1-8] While systemic CS can lead to rapid clearing of AD, their side effect profile and the risk of severe rebound flares after discontinuation limit their use.[9]

Evidence of the benefits and risks of systemic CS in AD is scarce.[10] One RCT comparing cyclosporine with prednisolone ended early due to rebound flares occurring in both groups, with 52% of subjects in the prednisolone arm experiencing such a flare.[11] Systemic CS use in children with AD has been studied in two RCTs, but with very small sample sizes.[12,13] The long-term intermittent use of systemic

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CS is well known to cause a multitude of side effects based on their use in other conditions,[14-16] and even use for 30 days or fewer has been associated with increased rates of sepsis, venous thromboembolism and fracture.[17] A recent systematic review of studies in children taking systemic CS for longer than 2 weeks found significant increases in infections, growth delay and obesity.[18]

Despite reasons for caution, systemic CS are still commonly used for patients with moderate-to-severe AD. In a recent clinical trial for adults with moderate-to-severe AD which took place in North America and Europe, 36.1% of participants reported use of systemic CS in the year prior to the trial.[19] Baseline data from a German registry of moderate-to-severe AD revealed that 12.8% of participants had been on systemic CS in the 3 months prior to enrollment,[20] and in another German study, 10% of AD patients had used systemic CS over 2 years.[21] In a survey of 61 UK consultant dermatologists, 42.1% listed systemic CS as their first-line systemic agent for adult moderate-to-severe AD.[22] In surveys of European and North American pediatric dermatologists, oral CS were the first-line systemic agents for severe pediatric AD for 30.7% and 5.2% of respondents, respectively.[23,24]

To address the concern of inappropriate use and overuse of systemic CS for AD in clinical practice and to provide guidance for clinicians as to what circumstances may constitute appropriate use, a consensus process was initiated among the councilors and associates of the International Eczema Council (IEC).

Methods

The IEC (http://www.eczemacouncil.org/), founded in 2014, is a global nonprofit organization whose membership consists of 77 AD experts from 21 countries on 5 continents. All Councilors and Associates are vetted for expertise in the field of AD. In September 2016, an electronic questionnaire

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was sent to the IEC membership regarding their use of systemic CS for AD. On September 29, 2016, a panel discussion among IEC members was held on the topic at the European Academy of Dermatology and Venereology meeting in Vienna, Austria. This informed the design of an electronic consensus survey, developed by a group of IEC members (AMD, KE, MSBW, DFM, ASP, EGY), which all IEC Councilors and Associates were invited to take part in from February 2-March 14 2017. Study data were collected and managed using REDCap electronic data capture tools[25] hosted at Lifespan Health System (Providence, RI). The Brown University Institutional Review Board deemed that this project was exempt from ethics review.

The survey consisted of 26 statements accompanied by visual analog scale (VAS) responses and 6 open-ended questions (the entire questionnaire is available in the online supplement). The VAS represented a continuum from "strongly disagree" to "neutral" to "strongly agree." Participants were asked to indicate with a slider along the VAS whether they agreed or disagreed with a statement. .

Using rules similar to the Harmonizing Outcome Measures for Eczema (HOME) initiative, consensus was reached when less than 30% of voters disagreed[26] (i.e., if no more than 30% of participants marked on the left side of the VAS towards "strongly disagree"). These rules were developed and made known to participants prior to survey completion. Participants' responses were anonymous.

As these consensus criteria are not universal, we conducted post-hoc sensitivity analyses using more stringent consensus criteria: (1) if no more than 20% of participants marked on the left side of the VAS towards strongly disagree; and (2) if no more than 30% of voters marked within the left two-thirds of the VAS (encompassing more of the "neutral" range in addition to "strongly disagree").

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Results

Sixty out of 77 (79%) IEC Councilors and Associates responded to the survey with 52 respondents completing the entire survey. Respondents were from institutions in Australia (2), Austria (1), Brazil (1), Canada (2), China (1), Denmark (3), France (6), Germany (7), India (1), Ireland (1), Israel (2), Italy (2), Japan (5), Korea (3), Netherlands (4), Spain (1), Taiwan (1), Tanzania (1), UK (3) and USA (13).

Consensus was reached on 12 statements related to use of systemic CS in severe AD (Table 2). The percentage of respondents who marked from "neutral" to "strongly agree" to each statement is given in Table 2 and scatter plots of responses to each statement can be found in the online supplementary material.

For each age category (<12, 12-17 years-old, adults), consensus was reached that systemic CS should generally be avoided but can be used rarely for severe AD. For each age category, a substantial majority of respondents disagreed with the statement that systemic CS should be used regularly for severe AD. While consensus was not reached for any age group on the statements that systemic CS should never be used, more than 50% of respondents agreed that systemic CS should never be used in children (57%) and adolescents (54%).

The majority (65%) disagreed that non-response to topical therapy was an indication for systemic CS use. Consensus was reached that among the appropriate circumstances for the use of systemic CS in AD were a lack of other viable treatment options, as a bridge to other systemic therapies or phototherapy, acute flares in need of immediate relief, in anticipation of a major life event or in

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cases that were the most severe. Consensus was reached that, if used, systemic CS treatment of severe AD should be limited to short-term use.

In their responses to the open-ended questions, individual participants qualified their responses in several ways. Some expressed strong support for the use of systemic CS while others expressed strong opposition.

In the sensitivity analysis using <20% disagreement as a more stringent cutoff, only 5 statements would have reached consensus (Supplementary box 1). In the sensitivity analysis in which no more than 30% of voters marked within the left two-thirds of the VAS (counting more of the "neutral" range as disagreement), only 3 statements would have reached consensus (Supplementary box 2).

Discussion

Among a large international group of clinicians and researchers with expertise in AD, we reached consensus on 12 key statements related to the use of systemic CS for severe AD. The results provide a framework for clinicians caring for severe AD patients who are considering systemic CS as a treatment option. Most notably, the group agreed on the statements that, for patients of any age, systemic CS should generally be avoided but may be used rarely, and strongly opposed the statements that systemic CS should be used regularly for severe AD.

While our group agreed that systemic CS use should be limited, consensus was reached on several clinical situations in which systemic CS may be appropriate. These included disease-related factors, such as severe acute flares, as well as patient-related factors such as important life events.

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Additionally, 72% of participants agreed that systemic CS could be considered a bridging treatment to other systemic treatments. While cyclosporine acts rapidly for acute AD flares, it may be contraindicated in some patients. Methotrexate, azathioprine and mycophenolate take several weeks to exert their clinical effects and so, in some circumstances, taking advantage of the systemic CS rapid onset of action while waiting for a safer long-term alternative to work may be appropriate. There are also some circumstances in which other systemic treatment options are not acceptable; for example, a recent diagnosis of cancer along with a history of alcoholism would be a contraindication to the use of cyclosporine, azathioprine and mycophenolate (due to malignancy risk) and methotrexate (due to the risk for liver disease).

We were unable to reach consensus on many issues related to dosing and duration of systemic CS use. However, the clear majority of participants (94%) agreed that the use of systemic CS should be limited to short periods of time. This is in keeping with clinical practice guidelines.[1-7] Our group did not reach consensus on a definition of short-term use. The European Task Force on Atopic Dermatitis (ETFAD)/European Academy of Dermatology and Venerology (EADV) task force position statement on the treatment of AD suggests that a typical regimen of systemic CS might be methylprednisolone 0.5 mg/kg/day for 1–2 weeks tapered over 1 month[3] but there is no RCT evidence for the safety or efficacy of this specific regimen.

Most respondents (but not enough for consensus) agreed that systemic CS should never be used in children. Further, while the circumstances agreed upon for the use of systemic CS in AD can be applied to patients of all ages, they are less likely to be applicable for young children. Most children will have fewer comorbidities complicating the use of immunomodulatory agents such as cyclosporine. As such, while systemic CS should be used rarely for severe AD in general, their use should be even more limited in children, particularly given concerns for infection, growth delay and increased rates of obesity.[18]

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The divergence between guidelines discouraging systemic CS use versus their frequent use in routine clinical practice are a concern. Ease of use, a rapid response in a distressed patient, cost and familiarity of primary care physicians with systemic CS for other conditions are all likely to contribute. The divergence between treatments physicians suggest in guidelines in a hypothetical clinical scenario and decisions they make when dealing with an individual patient in one-to-one consultations has been studied using a behavioral economics approach.[27] Physicians often deviate from agreed best practice when confronted with a distressed patient. Systematic approaches to better understand the implementation gaps between guidelines and practice have been advanced in a recent white paper by the healthcare quality organization Joint Commission International, and may be applicable to systemic CS use for AD.[28]

The major strength of our study is the large, geographically diverse group of International Eczema Council expert AD clinicians and researchers who participated in the consensus process. During the panel discussion preceding the formal consensus survey, it was clear that clinical practice, even among experts, differed significantly from country-to-country. Particularly given the sparsity of randomized controlled trial and high-quality non-randomized study evidence to support any one viewpoint, keeping an open mind to different practices is important. Despite the diversity of respondents, there was over-representation from some countries, including the US, which may have biased the results, and we would have benefited from a higher response rate.

The major limitation of this project is the limited evidence to support the consensus statements. While randomized controlled trial evidence would be ideal, many in the IEC would deem it unethical to subject trial participants to systemic CS at this point. Additionally, RCT follow-up is not likely to be long enough to detect many of the long-term consequences of systemic CS use. The lack of data

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likely also contributed to our inability to reach consensus on specific dosing and duration recommendations for systemic CS. Non-randomized prospective registry studies being planned or currently underway may help to answer some comparative efficacy and safety questions in the AD population.[20,29]

As with any consensus project, our results are influenced by the rules chosen to reach consensus. Using rules chosen *a priori*, we reached consensus on 12 statements. However, if we had used stricter rules, as in our second sensitivity analysis, we would have only reached consensus on 3 statements, limiting the recommendations we could make. Another limitation is the broad age range (0-12 years) used to define the youngest group of children. More precise age categorization may have yielded different results.

In conclusion, it is the consensus of the IEC that systemic CS have a limited role in the treatment of severe AD in children and adults. Clinicians should limit their use to special circumstance and always consider other treatment options. If they are prescribed, they should be limited to short-term use with a long-term treatment plan not involving systemic CS use. We hope that this serves to curb the over-prescription of these medications for patients with AD.

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Abbreviations

AD: Atopic dermatitis

CS: Corticosteroids

IEC: International Eczema Council

RCT: Randomized Controlled Trial

VAS: Visual analog scale

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Table 1. Approach to systemic corticosteroids for atopic dermatitis in various clinical practice guidelines and position papers

Group publishing manuscript	**Reference**	**Selected statements on the use of systemic corticosteroids for atopic dermatitis**
European Task Force on Atopic Dermatitis (ETFAD)/European Academy of Dermatology and Venerology (EADV)	[3]	"[Systemic CS] should only be used for a few weeks for severe acute exacerbations due to the many long-term side-effects. A typical regimen for severe acute exacerbations would be methylprednisolone maximal 0.5 mg/kg/day for 1–2 weeks and tapering over 1 month…In severe chronic cases, starting of another oral immunosuppressive therapy while tapering the [Systemic CS] should be considered. [Systemic CS] must not be used for long periods of time due to significant risk of severe side-effects."
European Dermatology Forum (EDF), EADV, ETFAD, European Federation of Allergy (EFA), the European Society of Pediatric Dermatology (ESPD), and the Global Allergy and Asthma European	[1]	"Systemic steroids have a largely unfavourable risk/benefit ratio for treatment of AE. Short-term (up to 1 week) treatment may be an option to treat an acute flare in exceptional cases of atopic eczema. Restrictive use, largely limited to adult patients with severe atopic eczema, is recommended. The recommended daily dose should be adjusted to body weight. Long term use in AE patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults."

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Network (GA2LEN)		
American Academy of Dermatology (AAD)	[2]	Although systemic steroids are used by some providers to treat AD because they rapidly improve clinical symptoms, caution is warranted to ensure their administration is time-limited and judicious…Thus, although temporarily effective, systemic steroids (oral or parenteral) should generally be avoided in adults and children with AD because the potential short- and long-term adverse effects…largely outweigh the benefits. Systemic steroids may be considered for short-term use in individual cases whereas other systemic or phototherapy regimens are being initiated and/or optimized."
Japanese Dermatological Association	[4]	"Although they are known to be effective, long-term oral corticosteroid therapy induces various serious systemic adverse reactions; therefore, long-term AD control with oral corticosteroids is not recommended. If necessary, administration should be completed in a short period."
Korean Atopic Dermatitis Association (KADA)	[5]	"Although systemic corticosteroids dramatically improve the clinical symptoms of AD, their administration should generally be avoided because of adverse effects and the rebound phenomenon…Once clinical improvement has been achieved, it is very important to taper the dosage gradually over time to minimize the likelihood of a rebound effect…Continuous or chronic intermittent use of systemic corticosteroids in AD is discouraged. However, acute usage may be considered as a

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		transitional therapy in severe, rapidly progressive, or debilitating cases during the initiation of treatment with nonsteroidal systemic immunomodulatory agents that have more favorable side-effect profiles, or phototherapy."
Asia–Pacific Consensus Group for Atopic Dermatitis	[6]	"There was a lack of consensus among the committee members regarding the use of oral corticosteroid therapy. However, some clinicians find it useful to administrate short-term steroid therapy, up to a maximum of 6 weeks, in combination with other standard modalities such as TCS or TCI (e.g. for acute flare). Long-term systemic steroids have little to no value and should be avoided in the management of AD due to adverse effects and rebound flare."
Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), the Joint Council of Allergy, Asthma and Immunology.	[7]	"The use of systemic corticosteroids, such as oral prednisone, might be required in the treatment of severe chronic AD, although there is a paucity of controlled studies, despite widespread use of this therapy…Nevertheless, the PRACTALL consensus report states that in cases of acute flare-up, while patients might benefit from a short course of systemic therapy with corticosteroids, long-term use and use in children should be avoided…If a short course of oral corticosteroid therapy is given for a patient with severe AD, it is important to taper the dosage as it is discontinued. Intensified skin care with topical anti-inflammatory therapy should also be instituted during the corticosteroid taper to suppress rebound flaring of AD."

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Indian Society for Pediatric Dermatology (ISPD) AD treatment Guidelines 2016	[30]	"Systemic corticosteroids are recommended only in adults and as short term bridging therapy while buying time for other immunosuppresssants to act. We do not recommend use of [systemic CS] in children below 18 years for concern of high incidence of rebound flares on discontinuation, immediate and long-term adverse effects."
Dutch Society of Dermatology and Venereology 2014	[8]	Oral corticosteroids are not recommended as prolonged monotherapy in the maintenance treatment of serious atopic dermatitis. Oral corticosteroids can be given shortly as acute intervention therapy for the treatment of exacerbations or as temporary comedication to start up another immunomodulatory agent, such as azathioprine, mycophenolate or methotrexate.*

* Translated from Dutch by Dr. Phyllis Spuls

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Table 2. Results of the International Eczema Council consensus process. If 70% of respondents marked from neutral to strongly agree, consensus was reached. The proportion of respondents who marked from neutral to strongly agree on the visual analog scale for each statement is given.

Statement	**Proportion (%) of respondents who marked from neutral to strongly agree**
Statements reaching consensus	
Children under 12 years-old	
For CHILDREN under the age of 12, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should generally be avoided in the treatment of severe atopic dermatitis.	51/59 (86%)
For CHILDREN under the age of 12, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used rarely for severe atopic dermatitis.	41/58 (71%)
Children 12-17 years-old	
For CHILDREN between 12 and 17 years of age, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should generally be avoided in the treatment of severe atopic dermatitis.	47/56 (84%)
For CHILDREN between 12 and 17 years of age, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used rarely for severe atopic dermatitis.	40/56 (71%)
Adults	
For ADULTS 18 and over, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should generally be avoided in the treatment of severe atopic dermatitis.	43/55 (78%)
For ADULTS 18 and over, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used rarely for severe atopic dermatitis.	44/55 (80%)
Specific circumstances	
Systemic corticosteroids may be used for severe atopic dermatitis when	44/54 (81%)

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there are no other viable treatment options.	
Systemic corticosteroids may be used for severe atopic dermatitis as a bridge to other systemic agents or phototherapy.	39/54 (72%)
Systemic corticosteroids may be used for severe atopic dermatitis in an acute flare in need of immediate relief.	42/54 (78%)
Systemic corticosteroids may be used for severe atopic dermatitis in anticipation of an important life event (eg. wedding).	40/53 (75%)
Systemic corticosteroids may be used for severe atopic dermatitis in cases that are the most severe (eg. erythrodermic).	38/53 (72%)
Dose and timing considerations	
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be limited to short-term use.	50/53 (94%)
Statements not reaching consensus	
Children under 12 years-old	
For CHILDREN under the age of 12, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should never be used in the treatment of severe atopic dermatitis.	33/58 (57%)
For CHILDREN under the age of 12, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used regularly for severe atopic dermatitis.	4/59 (7%)
Children 12-17 years-old	
For CHILDREN between 12 and 17 years of age, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should never be used in the treatment of severe atopic dermatitis.	30/56 (54%)
For CHILDREN between 12 and 17 years of age, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used regularly for severe atopic dermatitis.	4/56 (7%)
Adults	
For ADULTS 18 and over, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids should never be used in the treatment of severe atopic dermatitis.	21/55 (38%)
For ADULTS 18 and over, given concerns of side effects and rebound flares on discontinuation, systemic corticosteroids may be used regularly for	2/55 (4%)

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severe atopic dermatitis.	
Specific circumstances	
Systemic corticosteroids may be used for severe atopic dermatitis not responding to topical therapy.	19/54 (35%)
Systemic corticosteroids may be used for severe atopic dermatitis not responding to other systemic medications or phototherapy.	35/54 (65%)
Systemic corticosteroids may be used for severe atopic dermatitis in pregnancy.	30/53 (57%)
Dose and timing considerations	
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be limited to no more than 2 weeks.	36/52 (69%)
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be limited to no more than 4 weeks.	29/53 (55%)
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be limited to no more than 6 weeks.	25/53 (47%)
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be tapered slowly over weeks.	32/53 (60%)
If used, treatment with systemic corticosteroids for severe atopic dermatitis should be low dose.	22/52 (42%)

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