POSITION STATEMENT

Optimization of placebo use in clinical trials with systemic treatments for atopic dermatitis: an International Eczema Council survey-based position statement

Y.A. Leshem,[1,2,*] R. Bissonnette,[3] C. Paul,[4] J.I. Silverberg,[5] A.D. Irvine,[6,7,8] A.S. Paller,[9] M.J. Cork,[10] E. Guttman-Yassky[11]

[1]Department of Dermatology, Beilinson Hospital, Rabin Medical Center, Petach-Tikva, Israel
[2]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[3]Innovaderm Research Inc, Montreal, QC, Canada
[4]Paul Sabatier University, Toulouse, France
[5]Department of Dermatology, Department of Preventive Medicine, and Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[6]Pediatric Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland
[7]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin, Ireland
[8]Clinical Medicine, Trinity College Dublin, Dublin, Ireland
[9]Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine and Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
[10]Sheffield Dermatology Research Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, UK
[11]Icahn School of Medicine at Mount Sinai, New York, NY, USA
*Correspondence: Y.A. Leshem. E-mail: yael.leshem@gmail.com

Abstract

Background As novel systemic therapeutics for patients with atopic dermatitis (AD) are developed, ethical and methodological concerns regarding placebo-controlled-trials (PCT) have surfaced.
Objective To guide the design and implementation of PCT in AD, focusing on trials with systemic medications.
Methods A subgroup of the International Eczema Council (IEC) developed a consensus e-survey, which was disseminated to IEC members.
Results The response rate was 43/82 (52%). Consensus was reached on 24/27 statements and on 3/11 options from multiple-selection statements, including: performing monotherapy studies in proof-of-concept phases; avoiding concomitant topical corticosteroids or calcineurin inhibitors until a predefined timepoint as rescue (borderline consensus); selection of sites and assessors with recognized expertise in AD clinical trials; clear definition and identification of baseline disease severity; minimizing time and proportion of patients on placebo; using daily emollients with several options provided; instigating open-label extension studies for enrolment after a predefined timepoint; and including outcomes which set a higher bar for disease clearance.
Conclusion Conducting PCT in AD requires balancing several, sometimes opposing principles, including ethics, methodology, regulatory requirements and real-world needs. This paper can provide a framework for conducting PCT with systemic medications for patients with AD.
Received: 19 October 2018; Accepted: 4 January 2019

Conflicts of interest

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or nonfinancial interest in the subject matter or materials discussed in this manuscript. Author names: Yael Leshem is a consultant and/or advisory board member for and/or received honoraria or fees from AbbVie Inc., Sanofi and Regeneron Pharmaceuticals Inc., Pfizer, Dexcel Pharma, and Genentech, and an investigator without personal compensation for Eli Lilly and Abbvie. Robert Bissonnette is an investigator, consultant, advisory board member, and/or speaker for and/or received honoraria from Aquinox Pharmaceuticals, AntibioTx, Asana BioSciences, Astellas Pharma US, Inc., Brickell Biotech, Dermavant Sciences, Dermira, Dignity Sciences Ltd, Eli Lilly, Galderma, Glenmark Pharmaceuticals, GlaxoSmithKline-Stiefel, Hoffmann-La Roche, Kiniksa Pharmaceuticals, Leo Pharma, NeoKera, Pfizer, Sanofi and Regeneron

Introduction

With the emergence of novel therapeutics for patients with atopic dermatitis (AD), there is a need to better define the optimal study design for clinical trials. Studies including a placebo arm[1] are the gold standard for studying safety and efficacy of novel therapies at the proof-of-concept stage (phase Ib and IIa), followed by phase IIb and pivotal phase III confirmatory trials for inflammatory skin diseases such as AD. The placebo-controlled trial (PCT) design poses methodological and ethical concerns in AD trials. Recruiting and maintaining patients with moderate-to-severe AD on placebo arms, when effective medications are available, is one challenge. Patients on placebo whose active medications are abruptly stopped weeks before the trials can have a rebound effect, compromising retention in the trial. However, the often-robust response in the placebo group observed in AD when concomitant topical corticosteroids (TCS) and/or calcineurin inhibitors (TCI) are used in a clinical trial setting may reduce the difference between the active and placebo group.[2,3] To address these issues, a group of councilors and associates of the International Eczema Council (IEC), an organization of international experts on AD, conferred to provide practice recommendations for the design and execution of PCT with systemics for AD.

Materials and methods

Authors participated in online discussions to delineate topics of interest and subsequently developed a consensus e-survey, approved by all authors, which was disseminated to the IEC membership between 21 February 2018 and 12 March 2018 (SurveyMonkey Inc., San-Mateo, CA, USA; www.surveymonkey.com). The survey consisted of 27 statements followed by a 5-point Likert response (from 'strongly agree' to 'strongly disagree') and two statements with multiple-check options. Consensus was reached when <30% of voters disagreed (i.e. no more than 30% marked 'strongly disagree' or 'disagree').[4]

Results

The survey response rate was 43/82(52%). Consensus was reached on 24/27 statements and on 3/11 multiple-selection options (Table 1, Appendices S1 and S2). An overview of PCT in AD is presented below, followed by the IEC consensus.

Scientific rationale for placebo controls

Since the first use of a placebo in the 1930s,[5] inclusion of placebos as controls has become the gold standard of comparator trials. PCT are proposed to control for the placebo effect: the effect of receiving treatment, even a biologically inert one. They also control for other factors that can influence study outcomes and are not related to the pharmacologic properties of the study drug, such as regression to the mean and the change in behaviour when people are monitored closely.[6] Specific to dermatology trials, changes in daily skin care routine such as moisturizing can also influence the disease.

Placebo-controlled-trials provide direct evidence for the efficacy of the study drug. This contrasts with active-control trials (ACT), which rely on evidence of the efficacy of the active control from prior studies, to interpret the efficacy of the study drug.[7] PCT also enable measuring the pharmacological effect of a study drug by itself, rather than only the relative effect compared with another treatment.[1]

Ethical considerations

The use of placebo as a comparator in AD has long evoked controversy. Patients randomized to placebo may not receive standard-of-care, effective treatment.[5] Consequently, AD patients with intractable itch, sleep loss and reduced quality of life would be left untreated for extended periods of time.[8–11] The World Medical Association Declaration of Helsinki promotes ACT as the design of choice, with PCT considered only with a robust scientific methodological justification and when patients do not face severe risks, as most would consider is the case of AD.[12]

Regulatory issues

Drug studies are often designed to meet requirements of health authorities worldwide. Guidance and position papers from these agencies place a significant emphasis on the scientific need for placebo controls[6,13] and indeed The US Food and Drug Administration (FDA) and the Japan Pharmaceuticals and Medical Devices currently require placebo controls in AD pivotal trials that support a marketing authorization application. The European Medicines Agency (EMA) presents a similar approach[14] and also often requires either an active control or enrolment of patients who have failed an approved systemic treatment for AD.[15]

Practical considerations

Patients and investigators can be reluctant to participate in studies with a placebo arm. This is particularly important in trials of systemic agents for AD, in which patients may have a considerable symptom burden. Studies regularly require participants to be off medications for a washout period prior to baseline, further prolonging the time off therapy and often profoundly worsening disease severity. As safer and more effective treatments become available, recruitment for PCT in AD could prove difficult. This could lead to selection bias, with preferential recruitment of patients with more severe and recalcitrant disease who have failed numerous prior treatment options. Although these patients may have low placebo responses, they may also display delayed or diminished responses to the study drug, underestimating its efficacy. Alternatively, patients naïve to systemic therapy or with milder disease may be more likely to be recruited, as they may better tolerate placebo treatment or because they failed to qualify for reimbursement for a new therapy for AD. These patients may have enhanced placebo responses.

The placebo effect in atopic dermatitis clinical trials

There are limited data on the actual effect of placebo on outcomes in AD. A meta-analysis of randomized controlled trials (RCT) found a clinically modest but statistically significant placebo effect on itch in patients with AD on systemic medications, although trials with concomitant topical treatments were included.[16] Recent AD RCT offer insights on the placebo effect on other outcomes in AD. Pooled data of 575 patients on placebo from studies of dupilumab in moderate-to-severe AD without concomitant TCS[17–19] demonstrate a 31% improvement from baseline Eczema Area and Severity Index (EASI) and a 13% EASI-75 response at weeks 12–16, much higher than placebo arm responses in studies on biologics for psoriasis (average PASI-75 of 4%).[20] While a plethora of factors contributes to the high placebo responses in AD as compared to psoriasis, an important factor may be that AD is more difficult to quantify clinically. Psoriasis lesions are typically well demarcated and markedly thickened, but AD lesions are often flatter and tend to blend with non-lesional skin.

Drivers and predictors of the placebo response in AD

The placebo response in trials of systemic medications for AD is likely multifactorial. The placebo may offer some true therapeutic properties in AD, more so with outcomes that depend on patient perception, such as itch. Frequent visits and better education about skin care could also play a role in high placebo responses.[21,22] Improvement could reflect the natural history of AD, or that some patients are more prone to participate in a trial when their disease is at its peak.

However, some of the effects observed in the placebo arms of AD RCT are related to the design and implementation of a study, rather than a true placebo effect. It is important to ensure that when a study drug fails to demonstrate superiority to placebo, it means that the drug lacks clinically significant efficacy, rather than that the study was unable to distinguish an effective treatment from placebo.[1] Some factors to consider include:

1 Inclusion of patients with milder disease in studies designed for patients with moderate-to-severe disease can artificially enrich the placebo response. The assessment of patients with AD is complex, as highlighted in a recent IEC consensus

Table 1 Results of the International Eczema Council consensus survey†

Topic	Statement	Proportion (%) of respondents marking 'disagree'/'strongly disagree'
Investigational sites	PCT should be conducted by centres with recognized expertise in dermatology clinical trials	1/43 (2)
	PCT should be conducted by centres with recognized specific expertise in AD clinical trials	3/43 (7)
	Clinical assessments should be performed by (more than one answer can apply)‡	
	Dermatologists with clinical and research expertise in AD	5/43 (12)
	Dermatologists with experience treating AD but no special expertise	22/43 (51)
	Physicians under direct supervision of Dermatologists with clinical and research expertise in AD	22/43 (51)
	Any dermatologist (e.g. Including Dermatologists that do not have a significant medical dermatology practice)	42/43 (98)
	Non-dermatologists	40/43 (93)
Study design	Monotherapy studies (studies where patients receive only one active treatment in addition to emollients) are recommended in proof-of-concept studies	3/43 (7)
	Active comparator studies are recommended following monotherapy phase 3 PCT	1/42 (2)
	Active comparator studies are recommended parallel to monotherapy phase 3 PCT	5/43 (12)
	For moderate-to-severe AD patients the duration of treatment with placebo should be reduced as much as possible	2/43 (5)
	For moderate-to-severe AD patients the proportion of patients receiving placebo should be reduced as much as possible	2/43 (5)
	The interval between assessments should verify that patients with poorly controlled disease are identified	0/42 (0)
	PCT in AD should comply with general principles of PCT to ensure double blinding of placebo vs. drug for patient and study staff members (e.g. similar look, similar taste of placebo and drug if oral; similar feel if placebo and drug are injected)	0/43 (0)
	It is key to educate participants to adhere to the clinical trial protocol and avoid using off-protocol treatments	0/43 (0)
Inclusion/exclusion	Studies requiring failure of TCS/TCI should clearly define and document failure in the study protocol to standardize patient selection	1/43 (2)
	The protocol on TCI/TCS failure requirements should specify: (more than answer can apply)‡	
	Minimal potency of TCS/TCI used	9/43 (21)
	TCS length of use	9/43 (21)
	TCS quantity per unit time such as grams per day or week	22/43 (51)
	Time before flares typically occur upon TCS discontinuation	19/43 (44)
	TCS side effects	24/43 (56)
	No specification necessary	39/43 (91)
Open-label extension	Open-label extension studies following PCT are recommended	0/43 (0)
	PCT should define a minimal time after initiation for dropout after which patients can enter an open-label extension study	2/43 (5)
Emollient use in trials	Emollients should be used in both study and placebo arms daily/twice daily	1/43 (2)
	A choice of several emollients should be provided by company/study to standardize emollient use	5/43 (12)
	Both cream and ointment emollients should be made available for patients to choose	8/43 (19)
	Emollient should be reimbursed by the company	0/43 (0)
	Propylene glycol-free emollients should be available	3/43 (7)
	Fragrance-free emollients should be available	0/43 (0)
	No prescription emollient should be used	9/43 (21)
Concomitant TCS/TCI	Phase 1, 2 and 3 pivotal trials should not allow the use of concomitant TCS/TCI in protocol at all	23/43 (53)
	Phase 1, 2 and 3 pivotal trials should not allow the use of concomitant TCS/TCI in protocol until a predefined timepoint as rescue medications	12/43 (28)
	Phase 1, 2 and 3 pivotal trials should allow concomitant TCS/TCI in protocol at all timepoints	20/43 (47)
	Patients will be considered non-responders after TCS/TCI rescue	19/43 (44)
	If rescue with TCS/TCI is allowed, the amount, potency and frequency of rescue medications used should be monitored and quantified and could be recorded as a secondary end point	0/43 (0)

Table 1 *Continued*

Topic	Statement	Proportion (%) of respondents marking 'disagree'/'strongly disagree'
Outcome measures and analysis	Trials should include outcomes which set a higher bar for disease clearance such as IGA0/1 and EASI-90 to mitigate the placebo response	8/43 (19)
	Analysis should include both change from baseline and proportion of responders	0/43 (0)

[†]Statements reaching consensus are marked in grey (i.e. no more than 30% marked 'strongly disagree' or 'disagree'). [‡]Multiple option questions had 'agree/disagree' options only. The proportion (%) of respondents marking 'agree' is displayed.

statement endorsing a systematic and holistic approach to identifying patients who warrant systemic treatment.[23] Correct identification of patients who are suitable for trials of systemic medications requires AD-related clinical expertise, and may be difficult for sites that are less familiar with AD patients and not well versed with disease assessments. Eligibility creep, described as the tendency for patients to meet eligibility criteria when they are close yet not meeting eligibility,[24] can skew recruitment towards patients with milder disease. Centres which are not specialist dermatology departments may have less access to severe patients, which could promote the latter phenomenon.

2 Concomitant TCS or TCI. Current AD treatment guidelines recommend a step-up approach from trigger avoidance and emollients, to TCS,[25–27] and then to phototherapy and systemic medications.[23] In practice, patients often use topical medications in conjunction with systemic therapy. To make it easier for participating patients, better reflect 'real-world' treatment patterns, and study potential synergistic effects of combination topical and systemic therapy, some trials assess systemic therapy in AD with concomitant use of TCS/TCI. However, such combination therapy studies confer additional layers of complexity for study design and interpretation. TCS/TCI can affect study outcomes at both the clinical and molecular levels.[2,3,28–30] In patients with moderate-to-severe AD, a phase 3 trial of dupilumab vs. placebo with concomitant TCS[29] demonstrated higher responses for both placebo and dupilumab arms than similar phase 3 trials without TCS[17] (Table 2). The absolute difference in efficacy between the placebo and active arms was unchanged by TCS, indicating the power to detect a difference between dupilumab and placebo was preserved in these studies. However, recent studies of lebrikizumab and tralokinumab in moderate-to-severe AD patients with mandated TCS use found much higher placebo responses than the dupilumab studies, up to 60% EASI-50 and 34% EASI-75 responses.[2,3] Detecting drug efficacy with such elevated placebo responses is difficult.

3 The course of AD is impacted by multiple environmental influences.[31–34] Some studies have shown that AD prevalence decreases in geographic locations with increased sun exposure and warmer temperatures,[35,36] although others have

Table 2 Absolute difference and relative improvements (expressed as relative risks; RR) of dupilumab vs. placebo in phase 3 trials

Intervention	EASI50	EASI75	EASI90	IGA0/1
Monotherapy (SOLO 1 & SOLO 2)[17]				
Dupilumab (*n* = 919)	64%	49%	32%	37%
Placebo (*n* = 460)	23%	13%	7%	9%
Absolute difference	41%	36%	25%	28%
RR	2.8	3.7	4.4	4
Concomitant TCS (Chronos)[29]				
Dupilumab (*n* = 425)	79%	65%	42%	39%
Placebo (*n* = 315)	37%	23%	11%	12%
Absolute difference	43%	42%	31%	27%
RR	2.1	2.8	3.8	3.2

demonstrated these factors are associated with poorly controlled AD.[37] The effect of humidity on AD prevalence has also produced conflicting results.[35,36] While the placebo response may be affected by geographical location and seasonality, environmental effects can be difficult to harmonize across studies.

IEC statement on PCT with systemic medications for AD
The IEC recommendations (summarized in Fig. 1) are based on the survey consensus statements (in *italic*) and group discussions.

1 *Monotherapy studies (in which patients receive only one active treatment in addition to emollients) are recommended in proof-of-concept studies.*

2 The inclusion of concomitant TCS/TCI in protocol in phase 1, 2 and 3 pivotal trials was controversial. *Disallowing TCS/TCI until a predefined timepoint as rescue medications* reached borderline consensus with 28% of respondents disagreeing. Even more disagreed with either completely prohibiting TCS/TCI in pivotal studies (53%) or, alternatively, allowing them at all timepoints (47%). This controversy probably reflects two opposing problems: strict and prolonged prohibition of TCS/TCI during trials risks selecting against patients with severe AD, consequently elevating the placebo response. Conversely, permissive TCS/TCI use can also raise the placebo response. Minimizing TCS/TCI washout to 1–2 weeks and allowing
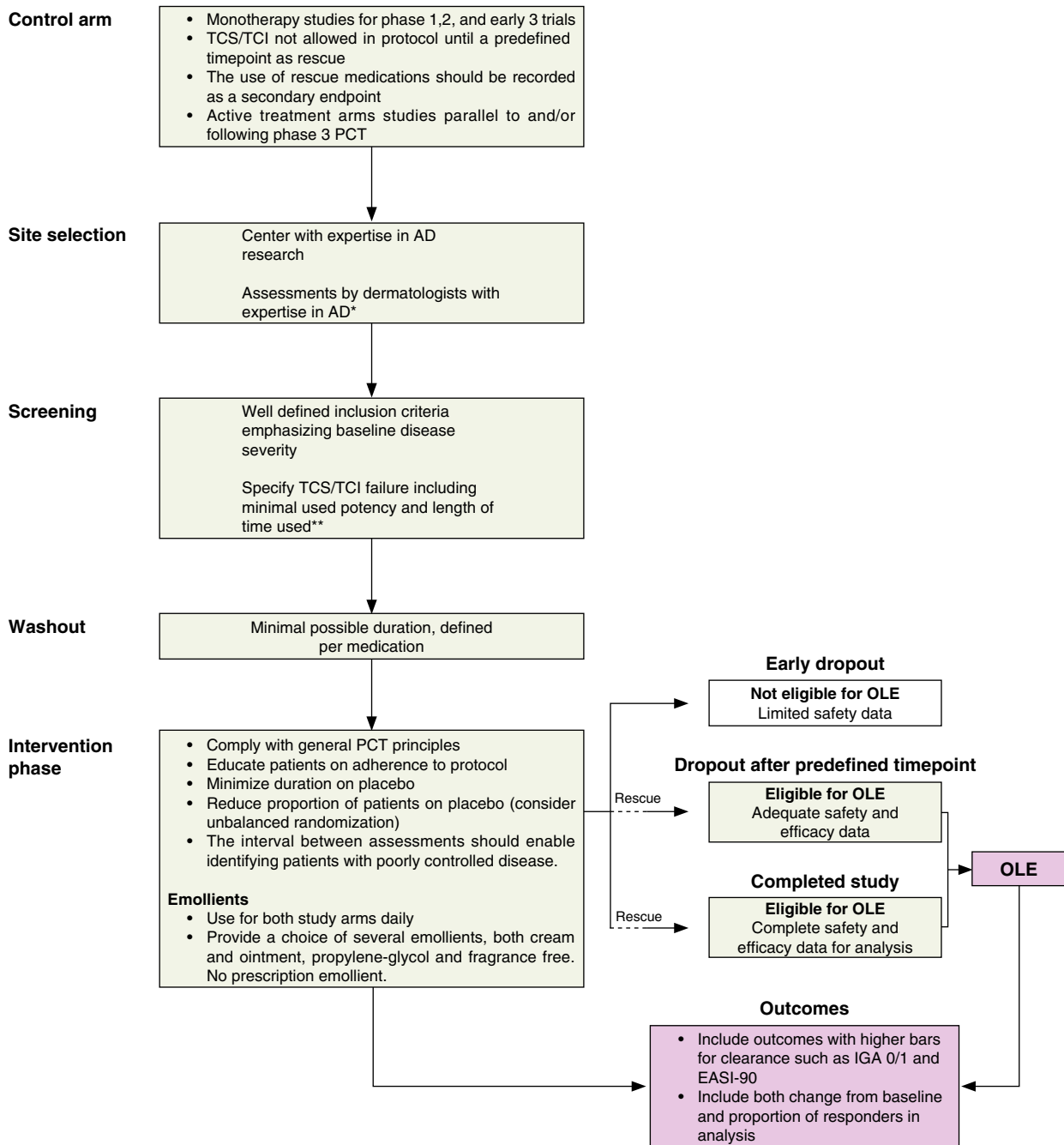
Control arm
- Monotherapy studies for phase 1,2, and early 3 trials
- TCS/TCI not allowed in protocol until a predefined timepoint as rescue
- The use of rescue medications should be recorded as a secondary endpoint
- Active treatment arms studies parallel to and/or following phase 3 PCT

Site selection

Center with expertise in AD research

Assessments by dermatologists with expertise in AD*

Screening

Well defined inclusion criteria emphasizing baseline disease severity

Specify TCS/TCI failure including minimal used potency and length of time used**

Washout

Minimal possible duration, defined per medication

Early dropout

Not eligible for OLE
Limited safety data

Intervention phase
- Comply with general PCT principles
- Educate patients on adherence to protocol
- Minimize duration on placebo
- Reduce proportion of patients on placebo (consider unbalanced randomization)
- The interval between assessments should enable identifying patients with poorly controlled disease.

Emollients
- Use for both study arms daily
- Provide a choice of several emollients, both cream and ointment, propylene-glycol and fragrance free. No prescription emollient.

Rescue

Dropout after predefined timepoint

Eligible for OLE
Adequate safety and efficacy data

Completed study

Eligible for OLE
Complete safety and efficacy data for analysis

Rescue

OLE

Outcomes
- Include outcomes with higher bars for clearance such as IGA 0/1 and EASI-90
- Include both change from baseline and proportion of responders in analysis

Figure 1 The approach to placebo-controlled trials of systemic medications for atopic dermatitis. AD, atopic dermatitis; EASI-90, a 90% improvement from the baseline Eczema Area and Severity Index score; IGA 0/1, Investigator Global Assessment of clear or almost clear; OLE, open label extension; PCT, placebo-controlled trial; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor; *Less favorable options for assessors: Dermatologists with experience treating AD and physicians under the direct supervision of AD experts, **Possibly specify TCS/TCI quantity, time to flare upon TCS/TCI discontinuation and TCS side effects.

rescue TCS/TCI at the earliest timepoint possible, depending on drug mechanism and expected time to effect, can address these concerns in part.

3 *If rescue with TCS/TCI is allowed, the amount, potency and frequency of rescue medications used should be monitored and quantified and could be recorded as a secondary end point.*

4 *Active treatment arms studies are recommended parallel to and/or following phase 3 PCT.*

5 *Selection of sites with recognized expertise in AD management and testing of therapeutics should be encouraged* to assure that the right patients, inclusion criteria and assessments are implemented, as well as having *Dermatologists with clinical and research experience in AD performing clinical assessments.*

6 An emphasis should be placed on correct identification of the participants' baseline disease severity, which should be clearly defined using validated outcomes after a period of adequate treatment, defined individually per treatment.[23,25,38]

7 *Studies requiring TCS/TCI failure for inclusion should clearly define and document failure in the study protocol to standardize patient selection including the minimal potency and length of time used.*

8 *PCT in AD should comply with PCT design principles, e.g.*: the physical qualities of the placebo should be as identical as possible to the study drug.

9 *Educating participants to adhere to the clinical trial protocol and limit placebo arm patients from using active treatment is key to measuring the true placebo effect.*

10 *For moderate-to-severe AD patients, the duration of treatment with placebo and the proportion of patients receiving placebo should be reduced as much as possible.* The washout period prior to intervention should also be as short as possible, defined per medication.

11 *The interval between assessments should verify that patients with poorly controlled disease are identified.*

12 While emollients are much less effective in alleviation of moderate-to-severe AD signs and symptoms than TCS/TCI, they still demonstrate some efficacy.[21,30,39] It is recommended *to provide emollients and encourage all patients to use them daily in clinical trials.* To enhance acceptability *a choice of several emollients and both cream and ointment emollients should be made optional for patients*; minimizing irritants and allergens is recommended, e.g. *providing fragrance-free and propylene glycol-free emollients* (low concentrations of propylene glycol can sometimes be added to enhance penetration of emollient ingredients). It is imperative that the vehicle, frequency, quantity and duration applied are defined and standardized within a study, *avoiding more sophisticated (prescription) emollient formulations*. Some emollients have detrimental effects in AD[40] and should be avoided.

13 *Ensure that patients on placebo are able to enrol in open-label extension (OLE) studies*, even when they drop out in the double-blind component of a study. *A minimal time after initiation for dropout after which patients can enter an OLE should be predefined*, taking into account the onset of action of the experimental treatment. The criteria for dropping out should be well-specified to minimize premature discontinuation with the promise of relief through rescue or open-label administration. Early loss of placebo patients could impair the evaluation of long-term effectiveness in the placebo arm.

14 *Trials should include outcomes which set a higher bar for disease clearance such as IGA0/1 and EASI-90.* Pooling patients from the dupilumab phase 3 studies, we observed that both with and without concomitant TCS, as the bar for efficacy is lowered from IGA 0/1 and EASI-90 towards EASI-50, placebo responses increase proportionally more than the drug arm responses (Table 2). It is possible that inclusion of more stringent definitions of treatment success can mitigate placebo responses, although additional studies need to corroborate this observation. Inclusion of less stringent outcomes is also advised as it allows for a more complete representation of treatment responses.

15 The Harmonizing Outcome Measures in Eczema (HOME) group selected the EASI and the Patient-Oriented Eczema Measure (POEM) as the preferred measures of AD signs and symptoms in clinical trials of AD, and published recommendations on standardized reporting of these measures.[41–43] However, best practices for analysing these outcomes are not clearly established. *We recommend including both change from baseline and proportion of responders in the analysis.*[43]

16 As the placebo response may be increased in patients with moderate vs. severe disease,[44] performing a planned subgroup analysis by disease severity could aid in understanding the differential effect of both study drug and placebo on these patient populations.[45] However, this analysis requires sufficient patients with severe disease.

Limitations

This consensus is limited by the relative lack of research on the predictors of the placebo response in AD. A higher survey response rate would have been preferable, although our 52% rate was similar to other recent IEC surveys. The IEC is composed of experts dedicated to the treatment and research of AD, which could have affected the conclusions regarding the optimal setup for AD clinical studies.

Conclusion

Balancing ethics, scientific rigour, practical and regulatory concerns in PCT with systemic treatments for AD is challenging. Concomitant use of TCS facilitates inclusion of more severely affected AD subjects but raises the placebo rate. On the other hand, long TCS washout periods and avoidance of TCS during trials select for subjects with milder AD and also risks a higher placebo response. This article provides an outline of the multiple considerations involved in the design and implementation of such trials, further stressing the importance of using sites and investigators well versed in AD research and care who are able to enroll a more severe AD population. As the therapeutic landscape

of AD evolves, the balance between these principles may shift, and a dynamic and critical approach when designing PCT is advised. Future work is needed to fill in the gaps highlighted in this paper and to better delineate the placebo effect on different outcomes in AD. This paper can serve as a basis for discussions and research on the use of placebo in other fields in dermatology.

References

1 Choice of Control Group and Related Issues in Clinical Trials: ICH. URL http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/choice-of-control-group-and-related-issues-in-clinical-trials.html (last accessed: 11 September 2017).

2 Simpson EL, Flohr C, Eichenfield LF *et al.* Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol* 2018; **78**: 863–871.e11.

3 Wollenberg A, Howell MD, Guttman-Yassky E *et al.* A phase 2b dose-ranging efficacy and safety study of tralokinumab in adult patients with moderate to severe atopic dermatitis. In: *75th Annual Meeting of the American Academy of Dermatology*. Orlando, Florida; 2017.

4 Schmitt J, Spuls P, Boers M *et al.* Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. *Allergy* 2012; **67**: 1111–1117.

5 Emanuel EJ, Miller FG. The ethics of placebo-controlled trials–a middle ground. *N Engl J Med* 2001; **345**: 915–919.

6 Guidances (Drugs). URL https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (last accessed: 15 April 2017).

7 Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Ann Intern Med* 2000; **133**: 455–463.

8 Drucker AM, Wang AR, Li W-Q, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol* 2017; **137**: 26–30.

9 Chamlin SL, Mattson CL, Frieden IJ *et al.* The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; **159**: 745–750.

10 Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2013; **27**: e239–e242.

11 Siegfried EC, Jaworski JC, Eichenfield LF *et al.* Developing drugs for treatment of atopic dermatitis in children (≥3 months to < 18 years of age): draft guidance for industry. *Pediatr Dermatol* 2018; **35**: 303–322.

12 WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical. Principles for medical research involving human subjects. URL https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed: 14 April 2017).

13 Current Status and Perspectives of Placebo-controlled Studies. The Subcommittee on Placebo-controlled Studies of the Pharmaceuticals and Medical Devices Agency (PMDA) Science Board. URL https://ss.pmda.go.jp Published March 9, 2016 (last accessed: 29 December 2017).

14 EMEA/17424/01 – EMEA/CPMP Position statement on the use of Placebo in Clinical Trials with regard to the Revised Declaration of Helsinki. URL http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/12/WC500017646.pdf (last accessed: 18 September 2017).

15 de Bruin-Weller M, Thaçi D, Smith CH *et al.* Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol* 2018; **178**: 1083–1101.

16 van Laarhoven AIM, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AWM. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. *J Invest Dermatol* 2015; **135**: 1234–1243.

17 Simpson EL, Bieber T, Guttman-Yassky E *et al.* Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**: 2335–2348.

18 Beck LA, Thaçi D, Hamilton JD *et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**: 130–139.

19 Thaçi D, Simpson EL, Beck LA *et al.* Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; **387**: 40–52.

20 Lamel SA, Myer KA, Younes N, Zhou JA, Maibach H, Maibach HI. Placebo response in relation to clinical trial design: a systematic review and meta-analysis of randomized controlled trials for determining biologic efficacy in psoriasis treatment. *Arch Dermatol Res* 2012; **304**: 707–717.

21 van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BW. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev* 2017; **2**: CD012119.

22 Sagransky MJ, Yentzer BA, Williams LL, Clark AR, Taylor SL, Feldman SR. A randomized controlled pilot study of the effects of an extra office visit on adherence and outcomes in atopic dermatitis. *Arch Dermatol* 2010; **146**: 1428–1430.

23 Simpson EL, Bruin-Weller M, Flohr C *et al.* When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017; **77**: 623–633.

24 Hick J, Feldman SR. Eligibility creep: a cause for placebo group improvement in controlled trials of psoriasis treatments. *J Am Acad Dermatol* 2007; **57**: 972–976.

25 Eichenfield LF, Tom WL, Berger TG *et al.* Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; **71**: 116–132.

26 Ring J, Alomar A, Bieber T *et al.* Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; **26**: 1045–1060.

27 Atopic eczema in under 12s: diagnosis and management | Guidance and guidelines | NICE. URL https://www.nice.org.uk/guidance/CG57 (last accessed: 13 April 2018).

28 Brunner PM, Khattri S, Garcet S *et al.* A mild topical steroid leads to progressive anti-inflammatory effects in the skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol* 2016; **138**: 169–178.

29 Blauvelt A, de Bruin-Weller M, Gooderham M *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 2287–2303.

30 Guttman-Yassky E, Ungar B, Malik K *et al.* Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. *J Allergy Clin Immunol* 2017; **140**: 1032–1042.e13.

31 Hidaka T, Ogawa E, Kobayashi EH *et al.* The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. *Nat Immunol* 2017; **18**: 64–73.

32 Thyssen JP, Zirwas MJ, Elias PM. Potential role of reduced environmental UV exposure as a driver of the current epidemic of atopic dermatitis. *J Allergy Clin Immunol* 2015; **136**: 1163–1169.

33 Langan SM, Irvine AD. Childhood eczema and the importance of the physical environment. *J Invest Dermatol* 2013; **133**: 1706–1709.

34 Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol* 2017; **13**: 15–26.

35 Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol* 2013; **133**: 1752–1759.

36 Suárez-Varela MM, García-Marcos Alvarez L, Kogan MD *et al.* Climate and prevalence of atopic eczema in 6- to 7-year-old school children in Spain. ISAAC phase III. *Int J Biometeorol* 2008; **52**: 833–840.

37 Sargen MR, Hoffstad O, Margolis DJ. Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004-2012. *J Invest Dermatol* 2014; **134**: 51–57.

38 Wollenberg A, Oranje A, Deleuran M *et al.* ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016; **30**: 729–747.

39 Czarnowicki T, Malajian D, Khattri S *et al.* Petrolatum: Barrier repair and antimicrobial responses underlying this "inert" moisturizer. *J Allergy Clin Immunol* 2016; **137**: 1091–1102.e7.

40 Danby SG, Al-Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *Br J Dermatol* 2011; **165**: 329–334.

41 Schmitt J, Spuls PI, Thomas KS *et al.* The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014; **134**: 800–807.

42 Spuls PI, Gerbens LAA, Simpson E *et al.* Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol* 2017; **176**: 979–984.

43 Grinich EE, Schmitt J, Küster D *et al.* Standardized reporting of the Eczema Area and Severity Index (EASI) and the Patient-Oriented Eczema Measure (POEM): a recommendation by the Harmonising Outcome Measures for Eczema (HOME) initiative. *Br J Dermatol* 2018; **179**: 540–541.

44 Guttman-Yassky E, Silverberg JI, Nemoto O *et al.* Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2018. [Epub ahead of print] https://doi.org/10.1016/j.jaad.2018.01.018.

45 Thomson J, Wernham AGH, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. *Br J Dermatol* 2018; **178**: 897–902.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Survey results.
Appendix S2. Data reports and statistics.