Author's response to reviews

Title: Topical Clobetasol for the Treatment of Toxic Epidermal Necrolysis: Study Protocol for a Phase II Split-Body Randomized Placebo-Controlled Trial

Authors:

Reason Wilken (reason.wilken@gmail.com)
Chin-Shang Li (cssli@ucdavis.edu)
Victoria R Sharon (Victoria.sharon@ucdmc.ucdavis.edu)
Falin B Patel (Falin.patel@gmail.com)
Forum Patel (patelforumb@gmail.com)
Emanual Maverakis (emaverakis@ucdavis.edu)

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Author's response to reviews: see over
Dear Trials,

Thank you very much for your detailed and insightful review of our proposed clinical trial protocol “Topical clobetasol for the treatment of toxic epidermal necrolysis: study protocol for a Phase IIa split-body randomized placebo-controlled trial” (MS # 1149667164138970) that was submitted in January 2015. We have received the reviewer comments from the journal and our point by point responses are provided below:

1. **Blinding:** The reviewer expressed concern as to issues keeping the study personnel blinded to the areas treated with topical clobetasol 0.05% and placebo petrolatum ointment due to the vasoconstrictive properties of topical corticosteroids. While vasoconstriction is a property of topical steroid preparations, to date the clinical studies of vasoconstriction have been performed on healthy, intact skin. In the setting of toxic epidermal necrolysis (TEN) with extensive erythema, inflammation and desquamation of the skin it may be difficult to predict the extent of the blanching effect from topical steroid application and whether it could be a confounding factor in the blinding of the study. To increase the validity of the study with respect to evaluating the effect of topical steroids on cutaneous disease progression in TEN, we would like to maintain the blinded design of the study if at all possible. We feel that maintaining blinding will minimize any bias or discrepancy that could confound the results of the study.

Furthermore, multiple randomized, blinded split-body trials comparing steroids to emollients or other non-steroidal topical preparations have been successfully performed and published in the dermatologic literature, namely comparing topical steroids to emollients for treatment of atopic dermatitis (AD), several of which are listed below. In addition, the last trial listed (Sugarman et al) provided sufficient evidence to the U.S. Food and Drug Administration to grant approval for Epiceram (topical emollient) for the treatment of atopic dermatitis. In summary—randomized, blinded split-body trials comparing topical steroids to non-steroidal preparations are commonly utilized in the field of dermatology. None of the below studies commented on blanching of treated skin areas and the trial did not require unblinding at any point due to discernable differences in the sites of treated skin.


3) **Wananukul S et al** “Randomized, double-blind, split-side, comparison study of moisturizer containing licochalcone A (LicA) and 1% hydrocortisone for the treatment of mild to moderate childhood atopic dermatitis”. *J Med Assoc Thai* 2013 Sep;96(9):1135-42.


5) **Jensen JM et al** “Effects of pimecrolimus compared with triamcinolone acetonide cream on skin barrier structure in atopic dermatitis: a randomized, double-blind, right-left arm trial”. *Acta Derm Venerol* 2013;93:515-519


2. **Control Arm**: In addition to the risk of systemic adverse effects from steroid administration (including suppression of the hypothalamic-pituitary axis), the reviewers expressed concern regarding systemic absorption of the topical clobetasol resulting in potential systemic therapeutic effect on the contralateral “control” site and reduced validity of the split-body study design for comparing active and placebo compounds. In response to this, the most important point is comparing the relative concentration of steroid that actually reaches the dermal-epidermal junction. In 2002, a French group led by Joly et al compared the treatment of bullous pemphigoid (BP), another inflammatory dermatosis, with topical (40 grams clobetasol 0.05% ointment per day) versus systemic steroids (0.5 mg/kg oral prednisone for moderate disease and 1 mg/kg for extensive disease per day). This paper found that topical corticosteroids were equivalent to prednisone in terms of overall survival, disease control at three weeks and severe complications for moderate BP (N= 153). However, in the case of extensive BP the group treated with topical steroids (N=93) demonstrated superior disease control and decreased incidence of severe adverse events after three weeks as compared to the oral prednisone group (N=95) receiving 1 mg/kg daily of prednisone.


Similar to BP, TEN is an inflammatory dermatosis in which the target of the inflammatory insult is the dermal-epidermal junction. Topically applied steroids are ideal for treatment of superficial inflammatory dermatoses as they deliver a higher concentration of steroid to the target area in the superficial dermis than systemic steroids. Below, we have included a photo of a patient of ours with cutaneous lupus who was initially treated with systemic immunosuppressant agents including prednisone and cyclosporine.

Thus, while varying degrees of systemic absorption of the clobetasol is expected in TEN and may be associated with adverse effects including HPA axis suppression as described...
in our Discussion section, we do not anticipate any significant therapeutic effect to the contralateral control area of skin resulting from systemic clobetasol absorption.

3. **Ethics:** Additional detail on the modified consent procedures for children < 18 years of age and medically incapacitated adults (unable to provide consent due to altered mental status, intubation sedation etc) is provided under the “Informed Consent Process” section. In addition, the protocol for notification of adult patients who were incapacitated at time of enrollment is detailed, with description of the process to inform them about the study and allow them to decide whether they wish to remain enrolled or withdraw from the study once they have recovered and regained ability to make their own medical decisions.

4. **Pediatric Patients:** The reviewer brought to our attention the labeling for clobetasol restricts use to children aged 12 or older. Thus, we have changed the minimum age to 12 years (from 7 years) for enrollment in the study inclusion criteria and throughout the manuscript.

5. **Assessment of Extent of Disease:** The reviewer brought up concerns regarding accurate assessment of disease severity in both the right and left arms, and issues that could arise if the involvement of the arm treatment areas was asymmetric at baseline. This is an excellent point, and in order to minimize the potential confounding effect of different levels of baseline disease severity and ensure that the treatment areas were as equivalent as possible.

   To resolve this issue, we have revised the protocol such that the treatment areas will be selected from areas of skin with comparable involvement on opposite sides of the body, but not limited to the arms. For example, treatment areas may be selected from the right arm and left leg. Each treatment area will be limited to 5% of the body surface area (BSA). By maintaining that the control and treatment areas be selected from opposite sides of the body, any potential local effect from steroid application on an adjacent control site will be minimized. Selection of the sites will be based on areas that are accessible for daily dressing changes and have a comparable extent of disease involvement.

   Altering the protocol in this fashion addresses the reviewer concerns of specifying a minimum percentage of involved arm skin and requirement for bilateral and symmetric arm involvement.

6. **Time to Re-Epithelialization:** The reviewer expressed concern that the 15 day timeline was too short to allow adequate assessment of one of the secondary endpoints of “time to 90% re-epithelialization” as the reviewer stated that the re-epithelialization phase may take up to 2-4 weeks following the onset of the disease.

   Reviewing the published literature on various treatments for toxic epidermal necrolysis (TEN), quantifying time to re-epithelialization is a common outcome measure. In the following articles, time to complete re-epithelialization was quantified and ranged from 7 to 20 days (articles listed below). Thus, the authors feel that 15 days is a reasonable time period in which 90% re-epithelialization may be achieved in some patients and would like to maintain this outcome measure as a secondary endpoint. As the reviewer brought
up, there is certainly a risk that some patients may not meet this endpoint within the 15 day time window and an additional paragraph discussing this possibility was added to the discussion section.

1) Paradisi A et al “Etanercept therapy for toxic epidermal necrolysis”. J Amer Acad Derm 2014 Dec;71(2):278-281 [Time to complete re-epithelialization from 7-20 days]

2) Arevalo JM et al “Treatment of toxic epidermal necrolysis with cyclosporine A”. J Trauma 2000 Mar;48(3):473-478 [Average time to complete re-epithelialization 12 days in cyclosporine group and 17.6 days in cyclophosphamide group]


7. **Multiplicity:** Additional text relating to appropriate analysis of the primary and secondary endpoints was added by our statistician Dr. Kyoungmi Kim to the section “Statistical analysis of primary and secondary endpoints” describing additional testing and validation procedures to minimize issues related to multiplicity of analyses for the secondary endpoints.

8. **Redundancy:** The background and discussion sections have been revised to remove excessive detail relating to the molecular mechanism of action of steroids and changes in gene expression in response to steroid treatment. Multiple areas of redundancy, including repetitive description of study design and procedures in the Background and Methods sections have been addressed. In addition, a paragraph describing major study limitations (including selection of appropriately matched treatment areas and potential variation in the time to re-epithelialization in TEN that may exceed the study window of 15 days) has been added to the discussion section.

9. **Subtitles & Discretionary Corrections:**

   - The section on “Statistical Analyses of primary and secondary end points” was revised with additional details relating to analysis of primary and secondary endpoints as well as managing issues related to multiplicity (addressed in point #7 above).
   - “Clinical Studies” section was retitled “Clinical Assessments” per reviewer recommendation
   - Comment relating to wrapping of arms and performance of daily skin assessments has now been largely addressed as we have modified the study protocol to designate comparably involved areas on opposite sides of the body, as opposed to designating opposite arms. Therefore, many of the issues raised regarding asymmetric arm involvement by TEN and problems in selecting appropriate treatment areas have been addressed by this protocol change.
   - Clarity related to steroid dosing: This area has been rephrased to more clearly outline how the appropriate dose of clobetasol to treat an area comprising 5% of body surface area once daily, based on the previous French study by Joly et al.
-Editorial Requests: We also noted suggestions for editorial requests in the email, however all of these had previously been addressed after initial submission of the manuscript and the current re-submitted version should be in the correct format. However, if any additional corrections are needed please do not hesitate to let us know.

Thank you again for the detailed review of our proposed trial protocol. Attached we have submitted the revised manuscript as well as tables (1-4) for your review. We look forward to hearing any further comments and suggested changes for manuscript revision in order to make it suitable for publication in your esteemed journal.

Sincerely,

Emanual Maverakis, M.D.
University of California, Davis School of Medicine
Department of Dermatology- Associate Professor
3301 C Street, Suite 1400
Sacramento, CA 95816
Telephone (916) 843-7336
Fax (916) 843-9444
eaverakis@ucdavis.edu