Author's response to reviews

Title: Approaches to discontinuing efalizumab: an open-label study of therapies for managing inflammatory recurrence

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

Thank you for considering our manuscript for publication in your journal. We have considered all the reviewers’ comments, which we hope we have addressed thoroughly.

In particular, we have made a focused effort to improve the terminology used so that the reader will be able to make clear distinctions between the terms ‘relapse’, ‘rebound’, ‘flare’ and the study-specific term ‘inflammatory recurrence’. Because this study was exploratory and was designed to mimic routine clinical practice, a few of the requests for further details cannot be provided. For instance, the details of exactly which corticosteroids each investigator was permitted to use were not specified in the study protocol – this was to allow investigators to prescribe treatments based on their own experience as they would in routine practice. However, we feel that the insights that this study provides will be extremely valuable for dermatologists who encounter the scenarios reflected by this study.

We hope that you will consider the revised manuscript favourably (attached) and feel that we have done our best to address the reviewer’s comments – our responses to each of the reviewer’s comments are included in the table below.

Kind regards,

XXX

Reviewer: Dan J Pearce

Comment 1:
One problem with systemic psoriasis therapies is the difficulty in applying clinical trial paradigms to practice. Several references to "rebound" are made without clear definition of the term. Either providing a full explanation of terms such as recurrence, rebound and relapse or speaking more generally will help avoid confusion. Furthermore, these formal terms are defined in PASI terms and PGA was used in this study. --It would also be interesting to comment on the evolution of these terms as a possible consequence of study design with the pivotal efalizumab studies. Ref: J Am Acad Dermatol. 2006 Apr; 54(4 Suppl 1): S171-81.

Response 1:
The terms commonly used in clinical trials of psoriasis treatments (i.e. ‘rebound’, ‘relapse’, ‘recurrence’ and ‘flare’) do not have universally accepted definitions – the US National Psoriasis
Foundation (NPF) and the EMEA have published separate definitions. However, as quite-rightly pointed out, this may cause confusion with the readers. We have therefore, added a table that provides the NPF and EMEA definitions for the terminology used in the manuscript, as well as the term 'inflammatory recurrence' that we adopted in this study to cover two scenarios that may be encountered in routine clinical practice and which should prompt re-initiation of treatment to prevent rebound. The two scenarios for 'inflammatory recurrence' are now described in the Introduction and the Methods sections. We hope that these changes clarify all the terminology used in the manuscript.

We have also added rationale for using PGA rather than PASI in our study – this is a recommendation made by the FDA.

Although the evolution of the terminology used in clinical studies is definitely an interesting topic, we feel that this has been covered in the reference mentioned above. Also, we feel that to do justice to this topic a considerable degree of discussion would be required, which may distract the reader from the key findings of this study.

Comment 2:
The definitions of psoriasis morphologies are not clear to me. Certainly pustular and erythrodermic flares are of concern with d/c of efalizumab. This needs to be emphasized; possibly presentation of these to types together a reboudn group would be clinically useful. This may help to make one of the main points of the paper. I found the morphology data, in particular table 3 difficult and time consuming to understand. Also, I am not familiar with the "inflammatory" variant.

Response 2:
The definitions of morphological variants are not universally accepted. Many of the descriptors were taken from the reports submitted by clinical investigators, many of who did not provide clarification or further delineation of their observations. The introduction of the term ‘inflammatory’ is in response to the NPF definition of rebound.

Comment 3:
I think important to flaring after discontinuing efalizumab is the reason that the therapy was discontinued. Is this data available? Also, was treatment allowed during the 2 months?

Response 3:
Hopefully Response 1 one covers fully the issue of discontinuing treatment due to flaring. Treatment was initiated as soon as inflammatory recurrence had been identified by the investigator. Indeed, some patients were already allocated to one of the study drugs at the time of enrolment into the study. For these patients, baseline data were collected retrospectively, while data were collected prospectively for patients who were prescribed their initial psoriasis treatment at the time of enrolment. As the results were qualitatively similar for the two subgroups, the results are presented only for the two subgroups analysed together.

This information is now provided in the methodology.

Comment 4:
The PGA data is difficult to understand, particularly table 2. I wasn't sure what was meant by first and last treatment. Better perhaps is to analyze according to either the first OR the last treatment and present graphically (this gets back to the intent to treat question)

Response 4:
In order to reflect the fact that investigators (as in routine clinical practice) were free to switch patients between treatments in order to best manage inflammatory recurrence, we needed to analyze the data according to the treatment that was initiated, as well as the treatment that was being received at the end of the study (week 12). We didn't group these data, as this would not have captured PGA outcomes following the switching of patients between treatments.
We have done our best to clarify the meaning of ‘first treatment’ and ‘last treatment’ in both the results section and in Table 2. Hopefully the changes explain the reason for these two analyses to the reader.

The intention-to-treat question is address by Response 6.

Comment 5:
BACKGROUND--All cases of psoriasis are not chronic.

Response 5:
Wording has been changed.

Comment 6:
METHODS--the inclusion criteria are not clear. How was it determined "natural progression" versus related to efalizumab?
---Given that the physician could switch between therapies during the 12 week treatment interval, was an "intent to treat" approach used?
---I assume that the only retinoid was acitretin. Also, there is a major difference in the dosing range allowed for acitretin and corticosteroids (which steroids were used by the way??); a comment in the discussion is appropriate to address these points.
---Again, can you define "inflammatory" psoriasis
---Is recurrence the appropriate term in the last para of the methods?

Response 6:
- Natural disease progression (i.e. a relapse) is now described in the Methods and defined in Table 2.
- As this was an open label study, which did not involve randomization and evaluated potential interventions, an ITT is inappropriate.
- All medications were used within the parameters of a clinical practice – guidelines were intentionally very broad to allow investigator to provide treatment as they would in routine practice. The five treatment regimens listed in the Methods section are worded exactly as in the study protocol.
- ‘Inflammatory recurrence’ terminology has been clarified (Response 1).

Comment 7:
RESULTS--be consistent with spelling out numbers and listing them in numerical form.
---Limitation that only 3 were treated with acitretin???
---P8, 1st para "incidence" is used incorrectly
---P9, 2nd para was "recurrence" the intended term

Response 7:
- All numbers are expressed according to the following convention:
  One–nine are spelled out in full
  10 and higher are written as figures
  EXCEPT where the numbers relate to units (e.g. 2 weeks) or if patient numbers are expressed as proportions (7/20 patients).
  We understand this to be standard practice.
- The low numbers of patients included in each of the treatment groups has been added to the discussion as a limitation.
- The term ‘incidence’ has been changed to ‘prevalence’.
- The term ‘recurrence’ has been changed to ‘inflammatory recurrence’.

Comment 8:
DISCUSSION--another limitation was retrospective nature of a portion.
TABLES-table 2 could be clarified as mentioned above.
---Table 3 is confusing and dilutes the message that pustular and erythrodermic flares post d/c of efalizumab were successfully treated with mtx, cys; also missing is the acitretin patients; did they d/c b/c of AEs?? dose related???

Response 8:
- The retrospective collection of baseline data has been added as a limitation to the discussion.
- Table 3 is designed to follow Table 2. Table 2 shows PGA response to each of the treatments according to first and last treatments received and establishes that responses were similar between patients who switch and those who did not switch. Now that this has been established, the patients are grouped according to the last treatment assigned and the data are stratified according to disease morphology to allow the reader to see how treatment affects each of the disease morphologies. We feel that the table gives the reader useful information in addition to the fact that pustular and erythrodermic flares are successfully treated with mtx and cys – physicians will need to treat patients with all psoriasis morphologies.
- The proportion of patients who experienced at least 1 adverse event and the relationship of adverse events to treatment have been added to the results. The relationships between adverse events at the dose of each treatment administered were not recorded and thus cannot be reported.
Reviewer: Jennifer Cather

Comment 1:
It would be helpful to put this article into perspective--i.e. what is the anticipated rate of inflammatory flare upon discontinuation? A person unfamiliar with the data may mis-interpret the rate of inflammatory flare as 78%, which is not true.

Response 1:
A sentence about the proportion of patients who have a rebound following efalizumab treatment has been added to the introduction and referenced to: Scheinfeld N: Efalizumab: a review of events reported during clinical trials and side effects. Expert Opin Drug Saf 2006, 5(2):197-209.

Comment 2:
On your rescue therapy regimen you mention "clinical improvement" can this be clarified for the readers so they can better understand when to start the tapers?

Response 2:
All medications were used within the parameters of a clinical practice – guidelines were intentionally very broad to allow investigator to provide treatment as they would in routine practice. Clinical improvement was judged based on the investigators experience. The Methodology wording has been adjusted accordingly.

Comment 3:
If the data is available, could you provide the number of patients who were actually tapered off the rescue meds? My experience has been that it is rare to get them off the rescue meds within 12 weeks. We need to make sure the readers understand that getting off systemics is really not the goal--so are you tapering as tolerated? Please reword to clarify.

Response 3:
Tapering was not fixed but was generally done over 8 weeks. However, we are afraid that the data on the number of patients who were tapered off rescue meds is unavailable

Comment 4:
PGA response: CyA most favorable response and yet MTX appears best for "inflammatory Ps". I think it really depends on how you are defining things--please clearly define inflammatory and explain what that actually includes. This is going to be confusing to the readers.

Response 4:
Given the small numbers of patients and the subjective nature of the PGA criteria, no conclusion can be drawn regarding superiority of one treatment over another. It is the impression of the lead author that cyclosporine is the most consistently effective intervention and that treatment for 6–8 weeks is sufficient to abrogate rebound, assuming intervention is initiated sufficiently early in the course of events.