Author's response to reviews

Title: Systemic adalimumab induces peripheral corneal infiltrates

Authors:

Alexandre Matet (alexmatet@gmail.com)
Alejandra Daruich (adaruich.matet@gmail.com)
Talal Beydoun (talal.beydoun@hotmail.com)
Jacques Cosnes (jacques.cosnes@sat.aphp.fr)
Jean-Louis Bourges (drbourges@gmail.com)

Version: 4
Date: 21 April 2015

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

We would like to submit the revised version of our manuscript entitled:

« Systemic adalimumab induces peripheral corneal infiltrates »

We are grateful to the reviewers for their comprehensive evaluation of the manuscript and have addressed the issues raised in their comments. As requested, several changes have been made to the text and figures, which we believe have improved the clarity and impact of our report. We also wish to thank the editorial team at BMC Ophthalmology for their assistance along the review process.

Please find below a point-by-point response to the reviewers’ comments.

REVIEWER 1

- Please include pre-injection photographs to show that there were no lesions at all, and no evidence of other confounding diagnoses such as marginal keratitis. If no one examined the patient before the first injection, then we cannot accept that the injections actually caused this clinical picture.

We have added to the text the following sentences:

"Prior to the current episode, the patient had been evaluated biennially for 10 years by her attending ophthalmologist due to the use of contact lenses. At each visit, she had been screened for ocular signs related to her inflammatory bowel disease. Her corneal status was unremarkable at all examinations. In particular, the patient did not have any history of meibomian gland disease or marginal keratitis."
Unfortunately, the attending ophthalmologist did not perform corneal photographs prior to the onset of the corneal disease described herein. Consistently, we would like to stress that it is very unusual to perform any corneal imaging without clinical signs to be recorded.

However, to increase the level of evidence as requested by the reviewer, we have provided as supplementary material corneal photographs of the right and left eyes (Supplementary Figures 2 and 3) showing the resolution of the infiltrates after the first episode, and their recurrence after the next adalimumab injection.

- Please also add photos of each episode as supplementary material to compare.

As stated above we have provided pictures of the second episode, in multi-part images (Supplementary Figures 2 and 3). After the first two episodes, images have no longer been taken at each visit.

- Any other supporting evidence would be useful: confocal microscopy?

Unfortunately, the quality of the confocal microscopy images that we obtained was poor due to the peri-limbal localization of the lesions. In addition, using anterior segment optical coherence tomography we could not detect the lesions due to their small size. We have provided as Supplementary Figure 1 a high-magnification slit-lamp biomicroscopy image showing the localization of an infiltrate in the anterior corneal stroma.

- Several grammatical and spelling errors need amendments.

This revised manuscript has been proofread by a native English-speaking colleague, whom we acknowledge at the end of the manuscript (Dr Kate Hashemi, Cornea and refractive surgery unit, Jules Gonin Eye Hospital, Lausanne, Switzerland).

The following grammar and spelling errors have been corrected:

Abstract

-“such as” instead of “as”

-“bilateral red eyes” instead of “bilateral red eye”

-“After topical corticosteroid therapy” instead of “with topical steroids”

-“…since they respond to topical corticosteroids and do not necessarily prompt the discontinuation of the immunosuppressive therapy.” instead of “…since they respond to topical steroids and do not prompt the discontinuation of treatment”.

-“immune-complex deposition” instead of “immune complex deposition”

-“to search for” instead of “to identify”
Background

-“adverse events” instead of “adverse effects”
-“prescribed” instead of “given”
-“the only ocular adverse event registered in the literature” instead of “the only registered ocular adverse event in the literature”

Case description

-“bilateral red eyes” instead of “bilateral red eye”
-“She had stopped wearing them…” instead of “…which she had stopped using”
-“Thereafter” instead of “afterwards”
-“a switch from oral azathioprine to…” instead of “to switch oral azathioprine to…”
- “The patient did not report any loss of vision.” instead of “…without any vision loss”
-“peri-limbal” instead of “perilimbal”
-“with a diameter of 0.3 mm” instead of “a 0.3 mm-diameter grayish stromal infiltrate…”
-“all signs” instead of “all items”
-“corneal neovascularization” instead of “corneal new vascularization”
-“Symptoms improved” instead of “symptoms amended”
-“ Two weeks later, 24 hours after the next injection of adalimumab, the patient returned with recurrent symptoms.” Instead of “Two weeks later, the patient returned for resurgent symptoms”
-“Clinical findings were identical to the first examination” instead of “Clinical findings reproduced the first examination”
-“For the treatment of the few recurrences that occurred over the following months…” instead of “When needed…”
- “Two months after the first visit, trough serum adalimumab was 7.4 µg/mL, within therapeutic range” instead of “Two months after the first visit, residual serum adalimumab was tested, and resulted in a level of 7.4 µg/mL, within therapeutic range

Discussion

-“In fact, the residual serum level…” instead of “Indeed, the residual serum level…”
- “Ironically” instead of “Remarkably”
- “Yet, ocular adverse events have been rarely described following adalimumab, and the only reported manifestation is acute anterior uveitis” instead of “Yet, ocular adverse effects have been very seldom described following adalimumab, and all are reported as acute anterior uveitis.”
- “Remarkably” instead of “However”
- “United States-based registry analysis of uveitis induced by TNF-α inhibitors” instead of “US-based registry of TNF-α inhibitors-induced uveitis”
- “Regarding its pathogenic mechanism” instead of “Regarding its mechanism”
- “immune-complex” instead of “immune-complexes”
- “circulating anti-adalimumab antibodies” instead of “anti adalimumab antibodies elution”

Conclusion

- “In this report, the patient developed symptomatic, recurrent corneal peripheral infiltrates after repeated subcutaneous administrations of adalimumab, a TNF-α inhibitor” instead of “In this case we report that adalimumab, a TNF-α inhibitor, induced recurrent and symptomatic corneal infiltrates.”
- “paradoxical exacerbation of Crohn’s disease following adalimumab injections” instead of “paradoxical exacerbation of Crohn’s disease by adalimumab, with ocular involvement”
- “under TNF-α inhibitor therapy” instead of “under TNF-α inhibitors therapy”

REVIEWER 2

- How long had the pt been treated with adalimumab before developing this reaction?

The patient had been treated with adalimumab since age 30, four years before developing the reaction, as mentioned in the first version of the manuscript. To emphasize this, we have modified the following sentence in the “Case” paragraph:

“At the age of 30, 4 years before her visit to our emergency department, recurrence of clinical symptoms led to switch oral azathioprine to subcutaneous adalimumab.”

- If the pt was contact lens wearer, what type (soft or hard, daily or extended) and for how long?

We have specified the following point in the “Case” paragraph:

“She had been wearing soft daily-wear contact lenses with monthly replacement schedule for the past 10 years.”
In addition, to improve clarity we have amended the following sentence regarding contact lens use in the Discussion:
“...since they had been discontinued 3 months before the onset of red eye and discomfort." Instead of “...since discontinuation had not been followed by any clinical improvement.”

- **Had the pt undergone any specific genetic testing as part of their crohn's disease?**
  Yes, the patient had been screened for the HLA B27 variant, which proved negative. We have added this data to the Case description:
  “She developed _HLA B27-negative_ ileal Crohn's disease at age 18”

- **Did the pt have any history of meibmian gland disease (styes, marginal keratitis, etc) in the past?**
  No, the patient, did not have any history of meibomian gland disease, which we have also added to the case description:
  “Her corneal status was unremarkable at all examinations. _In particular, the patient did not have any history of meibomian gland disease or marginal keratitis._”

- **Needs some language corrections before being published**
  As stated in the response to Referee 1, several improvements have been made to the text.

As corresponding Author, I had full access to all the data in the manuscript and take responsibility for the integrity of the data as well as the decision to submit for publication. This work received no funding, and the authors have no financial or proprietary interest in it.

We hope that this revised version of the manuscript will reach the standards of BMC Ophthalmology and will be deemed suitable for publication.

Yours sincerely,

Prof. Jean-Louis BOURGES, MD, PhD

Authors’ contribution:

Identifying the case (AM, TB and JLB), follow-up and data collection (AM, AD and JLB), literature review (AD and AM), writing the manuscript (AM), providing critical revisions (JLB and JC). All authors read and approved the final manuscript.