Author’s response to reviews

Title: Evaluation the ocular surface characteristics and Demodex Infestation in Paediatric and Adult Blepharokeratoconjunctivitis

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Author’s response to reviews:

Dear editors and reviewers,

Thank you very much for your letter and for the reviewers’ comments concerning our manuscript entitled “Evaluation the ocular surface characteristics and Demodex Infestation in Paediatric and Adult Blepharokeratoconjunctivitis” (BOPH-D-18-00497R1). Those comments are all valuable and very helpful for revising and improving our paper. We have studied all the commands carefully and have made some revisions which we hope could meet with approval. Revised portion are marked in highlight in the manuscript. The main corrections in the paper and the response to the reviewers’ comments are as following:

Reviewer reports:

Aleksandra Sędzikowska, Ph.D. (Reviewer 1): The article is clear, groups are well-characterised and selected (subjects with other ocular disease were excluded). Paediatric patients with BKC and delayed diagnosis are important information. Tables are easy to read.

Only in same places the word "Demodex" is write with small letter, the genus name should be write with capital letter.

Answer: Thank you very much for your thoroughgoing review. We really appreciate your positive comments which give us encouragement for our further study in this field. We have revised all the words into “Demodex”.
Hong Liang, MD, PhD (Reviewer 2): This study evaluated the ocular surface characteristics and Demodex Infestation in Paediatric and Adult Blepharokeratoconjunctivitis (BKC). However, some points are not clear in the design of the study. The actual study seemed like an accumulation of datas without any scientific approaches. The implication of demodex of BKC is already reported by many previous studies. The comparison of paediatric/adult forms of BKC did not have many results presented in the actual version.

Answer: Thank you very much for taking time on our work and really appreciate your valuable comments. Although the implication of Demodex was reported in blepharitis, chalazia and Meibomian gland dysfunction, it remains unclear whether Demodex play a role in corneal changes in BKC. In this study, we found that Demodex was associated with corneal fluorescence staining. The comparison of paediatric and adult patients with BKC revealed that paediatric patients suffered a more severe corneal involvement with a similar lid margin inflammation, indicating a potential different physiopathology in cornea lesion. The different physiopathology and potential specific treatment can be explored in future study. We believe this point has been noticed by some ocular surface experts just like you, but the understand on BKC is still far more enough. We have carefully revised the manuscript according to your comments and hope it can reach your requirement. The point to point answer is showing below:

1. The criteria for patients included for BKC is not clear. Even though BKC included a large spectrum of clinical manifestations, for a study, the author might offer his included criteria.

Answer: Thank you for your advice. We notice we didn’t fully represent our inclusion and exclusion criteria in the manuscript. In the revised version we represented the inclusion criteria for BKC more clearly, and also we supplement some exclusion criteria which we did in the clinical work but we didn’t represent. We have detailed the included criteria as “(1) subjective symptoms, including tearing, photophobia, recurrent episodes of red eye; and (2) eyelid involvement, including anterior and/or posterior blepharitis (lid hyperemia, lid scaling or crusting, and lid margin hypertrophy), chalazia and meibomitis; and (3) conjunctiva and cornea involvement, including conjunctivitis (conjunctival hyperemia, conjunctival chemosis, and conjunctival discharge), keratitis (superficial punctate keratopathy, corneal infiltration or ulceration), corneal vascularization, thinning, scarring or perforation.” (in Line 61-67). For the exclusion criteria we emphasis the history of atopy, vernal keratoconjunctivitis, or perennial allergic conjunctivitis.(in Line 67-69)

2. How to define 16 years as the limits of the paediatric/Adult forms? I don't understand the interes of comparing the two populations, because the physiopathology is different. The reliability of paediatric exams was not persuasive.

Answer: According to the “General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products”, the Food and Drug Administration (FDA) of USA suggested the limit age of paediatric population is 16 years old. Many studies about BKC in children took the cut-off of 16 years old (ref.2,3,5,21 in Manuscript). So, we also included patients with age ≤ 16 in the paediatric group. As to the comparison of paediatric and adult patients with BKC,
because we want to explore the potential differences in paediatric and adult patients with BKC, especially in corneal changes. Although there were many studies focusing on the corneal involvement in paediatric BKC, to our best knowledge, no paper compared the paediatric and adult patients with BKC. We found paediatric patients suffered a more severe corneal involvement, which may be caused by a longer delay diagnosis or different corneal physiopathology. We believe the difference of clinical signs between paediatric and adult BKC has been noticed by some ocular surface experts just like you, but the study to unclear the difference and possible mechanism is still not enough. Some discussion has been added in Line 240-247. Although the corneal lesion scoring is objective, the reliability of meibomian glands evaluation is limited considering the less cooperativity in children. We have added some sentences about the limitation of reliability of paediatric exams in Line 288-290.

3. The eyelashes-removed demodex method has too many limits, for it can miss the demodex accumulated at the follicles of eyelashes.

Answer: Thank you for your good advice. Recently, in vivo confocal microscopy (IVCM) has been used for a complete examination of the follicles with detecting the Demodex. However, the value of IVCM in diagnosing Demodex still needs to be confirmed and the cooperativity of IVCM examination in children is also challenging. So, lash sampling and microscopic examination still provide a reliable way to identify the Demodex in the lashes with cylindrical dandruff. Many studies also applied the eyelash-removed method. We also applied the fluorescein dye in the eyelash examination, which was demonstrated can improve the proficiency of detecting mites embedded in cylindrical dandruff (ref.20 in Manuscript). In order to be rigorous, we have added some statement in Discussion considering the limitation of eyelash-removed method in Line 284-288.

4. Anti-virus treatment had the relationship with BKC?

Answer: It was reported that the most frequent misdiagnosis is herpes simplex virus (HSV) keratitis in patients with BKC (ref.11 in Manuscript). Here we just wanted to report the percentage of patients with BKC who were treated with anti-virus eye drops before and misdiagnosed as HSV keratitis. It is a consensus that long term and frequent use of anti-virus eye drops could destroy the ocular surface, so the anti-virus treatment might further destroy the ocular surface of BKC which need to pay attention. We have added some statement to make this point clear in Line 225-231.

5. The analysis of tear of impression cytology could be practiced in order to enhance the study, not just by simple slit lamp analysis.

Answer: Thank you very much for your valuable advice. The analysis of tear of impression cytology is a good way to explore the physiopathology of ocular surface disease. Just because it is hard to perform on the children, we didn’t do it in current study. But in our future BKC study, we will try this method. We have added this information in Discussion in Line 290-293.