Clinical Considerations in Proinflammatory Cytokine Profiling of Tears from Patients with Dry Eye by Means of Antibody Microarrays

We read with interest the recently published article by Boehm et al. This is an important research area and certainly the findings presented are highly interesting. The authors found that cytokines are elevated in tears from aqueous deficient dry eye (DR Yaq) and dry eye with combined aqueous deficiency and lipid deficiency (DR Yaqlip), but not in lipid deficient dry eye (DR Ylip). This seems to be a reasonable finding since, traditionally, the aqueous deficient dry eye subtype is associated with autoimmune and especially the systemic autoimmune conditions such as Sjögren’s syndrome. However, we feel that the readers should consider a few points when interpreting these data.

After a thorough reading of the data presented, we feel that the controls may have been improperly selected or insufficiently characterized, leading to puzzling findings as well as the apparent discrepancy with a previous study. First, the authors classified subjects as controls based on Schirmer test results of >10 mm and tear break-up times (TBUT) of >10 seconds. It is not clear from the paper if the meibomian gland dysfunction (MGD) score of <18 had to be fulfilled in this group. Without knowledge of the mean and SD of the MGD score, this group is insufficiently characterized. Second, the positions of * and † in Table 1 appear to have been swapped. The text in the Materials and Methods section states the MGD score criterion is mandatory for the DRYlip group rather than the DRYaq group, and vice versa in Table 1. Third, the significant correlations between tear cytokines (IL-6, IL-8, TNFalpha, and IFN gamma) with TBUT in the control subjects (r values 0.80, 0.74, 0.67, and 0.78, respectively), as reported in Supplementary Table 1B, are puzzling. These correlations are of a higher magnitude than that of other correlations reported elsewhere in this study (e.g., between Schirmer test readings and tear cytokine in dry eye). It is difficult to explain the direct and not inverse association of cytokines with TBUT.

Fourth, even if the MGD score of <18 is obligatory in controls, it still encompasses a broad range of clinical MGD severity. MGD is an important consideration because the lipid alterations may have effects other than tear instability. We analyzed seven classes of meibum lipids from people with dry eye and MGD, and found that certain members of lipids are actually elevated in disease. For example, cholesteryl esters 18:0, 20:0, 21:0, and the ceramide d18:1/19:0 were significantly increased in moderate compared with mild dry eye. It may be that some altered lipids play an important role in promoting inflammation; free fatty acids and ceramides have been known to play such roles, including generation of free radicals. Such phenomena may add to the effect of inflammatory tear proteins and, given sufficient time, they may actually elevate tear cytokines such as IFN gamma and IL-8, which were previously observed in MGD-induced dry eye. Because MGD can potentially affect inflammation in a direct way other than just destabilize tears, it should be a primary consideration in the dry eye subtype.

Given that MGD may have effects on tear proteins, it is helpful to report the MGD scores (as a continuous variable) in the control group and, additionally, in each of the dry eye subtypes, rather than using a criterion of ≥18 in the DRYlip group and optionally including it in the DRYaqlip group. To investigate the effect of aqueous deficiency on tear cytokines, the authors can compare groups with similar extents of MGD but different Schirmer test values.

Louis Tong1,2,3
Sze-Yee Lee7
Andrea Petznick5

1Department of Cornea and External Eye Disease, Singapore National Eye Center, Singapore; 2Office of Clinical Sciences, Duke-National University of Singapore Graduate Medical School, Singapore; and 3Singapore Eye Research Institute, Singapore.

E-mail: louis.tong.h.t@ncc.com.sg

Supported by National Medical Research Council (NMRC) Clinician Scientist Award 013/2009 and NMRC/1206/2009.

References


Author Response: Clinical Considerations in Proinflammatory Cytokine Profiling of Tears from Patients with Dry Eye by Means of Antibody Microarrays

We appreciate the response of Tong et al. to our recently published article. First of all, we agree that the positions of * and † in Table 1 have to be swapped. The meibomian gland dysfunction (MGD) score criterion is mandatory for the DRYlip group, as stated in Material and Methods.

Regarding the classification of control (CTRL) patients, the patients included in the CTRL group were classified on the basis of clinical standard parameters, such as the basic secretary test (BST) and tear breakup time (TBUT), and the results of both tests had to be within normal limits. Further, these patients had neither subjective symptoms of dry eye, such as burning or itching, nor any other abnormalities. Thus, they must be classified as healthy. Excluding patients with a meibomian gland dysfunction (MGD) score >18 from this group and