Conflict of interest

The authors declare no conflict of interest.

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Sir,
Searching for the best blood-derived eye drops

We have read with great interest the article by Than *et al*[1] regarding the use of fingerprick autologous blood (FAB) as an alternative treatment for dry eye syndrome (DES). Sixteen patients diagnosed with DES were treated with FAB, 11 of whom had Sjögren syndrome, obtaining good results for the different clinical variables evaluated. The treatment dosage was four times daily for eight weeks.

We commend the authors' search of a low-cost and readily accessible treatment for this type of syndrome. At the same time, we would like to offer some commentaries and additional perspectives to the study.[1]

First, our experience is that, in order to achieve optimal therapeutic effects, it would be recommended that the concentrations of platelets and growth factors would be greater than those obtained in whole blood. A good example of that is platelet-rich plasma (PRP),[2] a therapy in which platelets are concentrated in a volume of plasma. Furthermore, we speculate that if platelet activation is not completed in FAB, the amount of platelet-derived growth factors would be lower than even autologous serum (AS).

Second, the authors should clarify whether there is platelet activation in the ocular surface, or whether it does not always occur, for example due to the clearance of FAB. The authors state that clots are observed in some patients, but this should be generalized so that the method is reproducible. Recent studies carried out on ocular surface cells show that the biological activity of non-activated PRP is lower than AS or other activated PRPs, such as plasma rich in growth factors (PRGF).[3]

Third, it is important to highlight that most of the patients (11/16) had been diagnosed with Sjögren syndrome, a long-term autoimmune disease in which the already exacerbated inflammatory component of DES is accentuated.[4] An interesting approach for these cases might be to perform an inactivation protocol of immune components in the eye drops, preserving most of the biologically active molecules while reducing immunoglobulin content and complement activity.[5]

Last but not least, there are other issues to be considered, including the drawback of not using a standardized ready-to-use product, the large amount of fingerpricks delivered (448 fingerpricks in 8 weeks), and the variability of capillary blood.[6]

We strongly encourage the authors to further deepen research in the FAB mechanisms of action and product composition in order to optimize the treatment and improve the quality of life of DES patients, thus offering a fully characterized product.

Conflict of interest

The authors declare that EA is the Scientific Director of and GO, RP, and FM are scientists at BTI Biotechnology Institute, a biomedical company that investigates in the fields of oral implantology and PRGF-Endoret technology.

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Sir,
Reply to Anitua *et al*: Searching for the best blood-derived eye drops

We thank Anitua *et al.* for their stimulating comments and welcome further discussion.[1]

We note most of their comments are based on the effect of growth factors on epithelial defects, whereas our study[2] was on treating chronic dry eyes.

We agree that the growth factor concentration in platelet-rich plasma (PRP) is likely greater than in plasma of fresh whole blood. Despite this, our preliminary results suggest fingerprick autologous blood (FAB) efficacy is comparable to that of autologous serum.[3] We propose two possible explanations for this. Firstly, platelet activation may occur in the process of FAB draw and application, and the authors are correct that quantitative characterisation of the degree and reliability to which this occurs requires further study. Additionally, fresh platelets may be able to adhere to areas of the inflamed dry eye anterior surface, allowing for a targeted activation and release of growth factors, as opposed to simply coating the eye momentarily with growth factors from PRP. Secondly, we propose that FAB efficacy might relate to other factors in whole blood, such as fibronectin, vitamins, and other chemicals at physiological level, and their interaction than just growth factors alone. We also note that although Anitua *et al* recommend from their experience higher concentrations of growth factors than blood for optimal therapeutic effect, long-term safety data are lacking. Higher concentrations may induce harmful effects such as corneal neovascularisation from greater epidermal growth factor[4] or impaired epithelial wound healing from high concentrations of transforming growth factor beta.[5] Anitua *et al* rightly mention that non-activated PRP was less effective than its activated counterpart;[6] however, this was a laboratory study only looking at corneal wound healing on rabbit eyes and therefore cannot be directly extrapolated to real-life conditions of human severe dry eye patients. As mentioned in our paper discussion, there may also be release of growth factors by red blood cells,[7] providing an additional source of and possibly different growth factors than just platelet activation. Only fresh blood has the potential to offer an orchestrated response with its additional adaptive cellular composition to the ever-changing ocular surface environment, particularly in dry eyes. The exact mechanisms will need to be elucidated. Speculation on superior efficacy and putative mechanisms of different blood-derived products is limited by a lack of mechanistic studies and direct comparisons between them. We encourage such studies and suggest FAB be included in these comparisons.

The potential variability in cellular composition from drop to drop has been considered by the authors and again further work is suggested to evaluate this.

Anitua *et al* propose an interesting approach of 'inactivation protocol for the immune component of the eye drops' for diseases such as Sjogren's. We agree, but this might affect the antimicrobial properties and any unknown beneficial effect of these inactivated components. The increased use of allogenic serum in Sjogren's patients may give us a better understanding in this area.

The authors note the valid concern regarding viability of long-term compliance in light of repeated fingerpricks during treatment. The subjective improvement noted by these patients has resulted in all continuing treatment after study conclusion (the longest for over 3 years). This would suggest that the discomfort of regular fingerpricks is outweighed by the improvement in quality of life provided by relief from severe dry eye syndrome. We feel a major advantage that FAB presents is not being impeded by many of the barriers experienced by other blood-derived therapies such as cost, repeat venesections, and storage.

Conflict of interest

The authors declare no conflict of interest.

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