Correspondence

Comment on: Management of Congenital Aniridia-Associated Keratopathy: Long-term Outcomes From a Tertiary Referral Center

EDITOR:

WE READ WITH GREAT INTEREST THE ARTICLE WRITTEN BY Yazdanpanah and associates on "Management of Congenital Aniridia-Associated Keratopathy: Long-term Outcomes From a Tertiary Referral Center," involving 92 eyes of congenital aniridia in a retrospective case series.[1] Aniridia-associated keratopathy (AAK) is rare but a chronic disabling condition with limited literature on its management strategy. We appreciate the authors for their excellent work on this topic. Stage-related therapy of congenital AAK has been described previously in literature with minimally invasive management strategy for early stages of the disease. However, such long-term outcome of medical and surgical treatment of AAK has not been reported previously.

AAK is characterized by a progressive deterioration in the function of limbal stem cell niche and degradation of palisades of Vogt, leading to corneal epitheliopathy, that is, abnormal differentiation, cell adhesion, increased sensitivity to oxidative stress, and impaired wound healing.[2]

There are a few concerns—rather, doubts—that we would like to comment upon. It is interesting to observe a significant improvement in the visual outcome with a success rate of around 58% with limbal stem cell transplantation (LSCT) even at a long-term follow-up of approximately 6 years in advanced AAK cases. The outcome of LSCT or keratoplasty is usually disappointing in such cases. A progressive deterioration in the microenvironment of stem cell niche that becomes incapable of supporting and sustaining the transplanted stem cells in the long term is often the cause for such poor outcome. Shortt and associates reported a substantial improvement in ocular surface for up to 12 months following allogeneic ex vivo cultivated limbal epithelial transplantation in 10 eyes with AAK.[3] However, signs of limbal stem cell deficiency were recurring by 18 months, and by 24 months had returned to presurgery level. The probability of a sustained benefit beyond 2 years was only 25%.[3] It would be interesting to know the details of the technique of LSCT used in the study (such as the size and site of the allografts used, and whether a limbal pocket in the recipient eye was created or not) so that the technique can be replicated by the readers. Was there any modification in the technique used that could have led to a better survival?

Besides, it would be interesting to know if there was any difference in the success rate between patients undergoing allogenic vs cadaveric LSCT. Titiyal and associates have reported a better visual and anatomic outcome with living-related conjunctival limbal allograft as compared to keratolimbal allograft in 20 patients with ocular surface burns at 6 months follow-up period.[4] Lastly, the regimen and the drug used for immunosuppression in the cases that underwent LSCT have not been mentioned.

The authors have concluded a beneficial effect of surgical therapy only on the basis of visual outcome, whereas anatomical outcome (including ocular surface stability, corneal clarity, conjunctivalization, neovascularization, and epithelial erosions) reported to be graded by the Clinical Outcome Assessment in Surgical Trials of Limbal stem cell deficiency (COASTL) tool has not been considered.[3] This is often considered to be an important predictor of success following a surgical intervention in limbal stem cell deficiency patients. Thus, it would be beneficial to comment upon the anatomic outcome of eyes that underwent LSCT. The authors mention "no significant difference in [best-corrected visual acuity] between the two groups (No surgery and advanced surgery) was found at last follow-up." However, it is not mentioned whether any adjustment for the baseline best-corrected visual acuity was performed since visual acuity might be affected by multiple other factors such as foveal hypoplasia, glaucoma, and cataract, which can be a source of bias for the results.

Table 3 suggests 7 eyes underwent LSCT-KPro. Was it a combined procedure or sequential? The authors could have included the detailed surgical technique in this group of cases and the time duration after which KPro was performed following LSCT in sequential cases. Although it appears that type 1 KPro was performed in all cases, a mention of it would be useful for the readers. They report that 60% of eyes experienced improvement of visual acuity following primary KPro implantation. Shah and associates have reported that 74% of eyes showed a significant improvement in visual acuity at 1-year postoperative period; however, this number reduced to 43.5% at a long-term follow-up of 4.5 years owing to factors like glaucoma progression, toxic optic neuropathy, and retro-prosthetic membrane formation.[5] Thus, it would be appropriate to comment upon any difference in the visual outcome between early and late or long-term follow-up after KPro implantation.

Autologous serum is often used at our center, but we have not used it for cases of AAK.[6] It would be of great interest to know the details of autologous serum therapy used in mild cases, such as the strength, frequency, and duration of therapy, as well as whether any difference was noted in the outcome of patients with and without the use of autologous

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serum drops. In addition, over this long-term follow-up period did the authors notice any progression from early stage 0-2 to advanced stage 3-5 of the disease among the patients that were treated with medical management?

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REFERENCES

1. Yazdanpanah G, Bohm KJ, Hassan OM, et al. Management of congenital aniridia-associated keratopathy: long-term outcomes from a tertiary referral center. *Am J Ophthalmol* 2020; 210:8–18.
2. Ihnatko R, Eden U, Fagerholm P, Lagali N. Congenital aniridia and the ocular surface. *Ocul Surf* 2016;14(2): 196–206.
3. Shortt AJ, Bunce C, Levis HJ, et al. Three-year outcomes of cultured limbal epithelial allografts in aniridia and Stevens-Johnson syndrome evaluated using the Clinical Outcome Assessment in Surgical Trials assessment tool. *Stem Cells Transl Med* 2014;3(2):265–275.
4. Titiyal JS, Sharma N, Agarwal AK, Prakash G, Tandon R, Vajpayee R. Live related versus cadaveric limbal allograft in limbal stem cell deficiency. *Ocul Immunol Inflamm* 2015; 23(3):232–239.
5. Shah KJ, Cheung AY, Holland EJ. Intermediate-term and long-term outcomes with the Boston type 1 keratoprosthesis in aniridia. *Cornea* 2018;37(1):11–14.
6. Mukerji N, Sinha R, Vajpayee RB. Role of autologous serum in persistent epithelial defects. *Br J Ophthalmol* 2002; 86(7):832.

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REPLY

WE THANK DRS SINGHAL, NAGPAL, AND MAHARANA FOR their interest in and comment on our work regarding the management of aniridia-associated keratopathy (AAK). In answer to the question regarding the surgical techniques for limbal stem cell transplantation (LSCT), we have previously published our techniques.[1,2] We refer the authors to those publications for more details and encourage them to directly contact 1 of the corresponding authors for more specific questions. As for the choice of donor tissue, the great majority of LSCTs were cadaveric keratolimbal allograft (KLAL) and only a few cases had undergone living-related LSCT (mentioned in the manuscript); therefore, a direct comparison of outcomes was not possible in this study. Nonetheless, we highly recommend living-related conjunctival limbal allograft (lr-CLAL) when there is an available donor. A recent large series with long-term follow-up (7.2 years) published by Holland and associates has shown lower rejection rate, improved graft survival, and higher best-corrected visual acuity (BCVA) in lr-CLAL compared to KLAL in patients with limbal stem cell deficiency.[3] Our standard immunosuppression regimen is similar to the already published protocol.[4]

As they have indicated, ocular surface stability is an important factor for the success of LSCT, and it is one of the major criteria in the management of AAK patients undergoing LSCT. In this study, we considered BCVA as our primary outcome measure because it made it easier to compare LSCT with Boston keratoprosthesis (KPro), since ocular surface stability is not measurable in KPro patients. Previous reports have demonstrated detailed anatomic surface results of LSCT in patients with aniridia.[5]

Management of other pathologies such as glaucoma and cataract is crucial for improving the visual outcomes in aniridia patients. Either glaucoma or cataract could be a confounding factor or effect-modifier while conducting statistical analysis. In our analysis, however, there was no significant difference between patients with advanced cornea surgery and no surgery in terms of developing cataract, but glaucoma was significantly more common in patients with advanced corneal surgeries. Our preliminary analyses showed that there might be a potential for glaucoma as a confounding factor, but this effect did not significantly affect the final outcome measure (BCVA). Therefore, we found that adjustment for glaucoma and cataract was not necessary in this study and will not affect the result of comparison between advanced corneal surgery and no advanced corneal surgery. Further studies on the management of glaucoma in aniridia patients are necessary.

The advanced corneal surgeries in the study were LSCT, Boston KPro, and combination of these 2 surgeries. Patients were categorized into LSCT, LSCT followed by KPro (LSCT-KPro), and primary KPro. Owing to the retrospective review design of the study and the complexity of management in these patients between various clinical services, it was not possible to evaluate the effect of early or late KPro on the final outcome measure; and future prospective studies are required to address this question. However, all the KPro surgeries were performed separately from LSCT, as a primary procedure or following LSCT failure. The KPro implantation complications and their managements, and visual outcomes following KPro surgeries, are summarized in the paper.

Autologous serum tears (20% applied at least 4 times a day) are prescribed for some patients in stages II and III of AAK. In