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CHEMICAL BURNS OF THE EYE:

The Role of Retinal Injury and New Therapeutic Possibilities

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Severe chemical burns, especially from alkali, still carry a grim prognosis for final visual outcome – witness the large number of patients blind from chemical burns worldwide – often young people with bilateral injury. The exact number is unknown but the vast majority of patients are living in developing countries[1,2]. Lavage as promptly as possible after the accident (tap water, borate buffer, or amphoteric substances[3]), as well as subsequent corticosteroid treatment, have only moderate effect – but should still be routinely employed. Conventional keratoplasty usually has poor long term results[4] but, for unilateral burns, limbal autograft transplantation can be successful[5] and further possibilities of replacing injured epithelium with stem cells are being explored[6,7]. (For more complete reviews of chemical trauma, and traditional treatment, see Pfister[8] or Wagoner, et al[9]). Following advances and more widespread use of artificial corneas (e.g. the Boston Keratoprosthesis[10]), implanted in a later quiescent stage after chemical burns, it has been found that such devices are fairly well retained over the years and that media usually end up transparent[11,12]. However, the now clear image of the posterior segment has often revealed a cupped and pale optic nerve head, with corresponding glaucomatous field defects[12,13]. The postoperative course has also frequently been marked by further glaucomatous deterioration – or new onset glaucoma – often in spite of normal intraocular pressure[14]. In one series of 28 eyes with blindness from severe chemical burn (light perception to finger counting, and 75% with preoperative glaucoma), a Boston Keratoprosthesis restored vision to a remarkable

CHD, FC, CVR, CZ, FL, AC, MH-D, M-CR, GNP, DC, JVA, EKA, KCS, DJD, LW, LQS, MG-A, JC, CSF, RP, KAC, JBC, DGV, RD and EIP are, or have been, full-time employed by the Massachusetts Eye and Ear Infirmary, the manufacturer of the Boston Keratoprosthesis.

level of 20/300 – 20/20 in 86% (24/28) of the eyes. However, complications from progressive glaucoma (or retinal detachment) eventually reduced vision over several years in many of them, with 6 eyes losing light perception completely[12]. Thus, although corneal complications after keratoprosthesis surgery have gradually been brought under reasonable control over the last two decades, this favorable trend has in turn revealed the need for greater attention to damage to the posterior segment --- particularly the ganglion cell layer and the optic nerve[15]. A cornea damaged from chemical burn can now fairly reliably be made transparent again by keratoprosthesis surgery but significant damage to the optic nerve is obviously irreversible. Our search to improve the long term visual prognosis after keratoprosthesis has – unexpectedly – brought the biological response of the whole eye into focus. We can now – for the first time – visualize how the posterior segment is affected by anterior burn, and begin to test new strategies to prevent further damage from inflammation and glaucoma.

We started with the question about the linkage between corneal damage and advanced glaucoma and a pale nerve. In extreme cases, even scar formation in the retina can occur[16]. Does the alkali diffuse posteriorly to directly damage the retina by elevated pH? In such case, should protective attempts include prompt injection of a buffer into the vitreous, or similar? The answer to these questions is no because, surprisingly, repeated recent experiments in rabbits have shown that the pH in the vitreous, the suprachoroidal space and in the retina remains normal even after a severe alkali burn[17,18]. Alkali seems to be effectively buffered in the anterior segment at the iris-lens level.

If not pH (and thus not direct chemical injury), what exactly is injuring the retina? It has been shown earlier in mice that inflammatory cytokines like IL-1α, IL-1β and IL-6 become elevated not only in the corneas but also in the retinas after alkali burns and they would be expected to contribute to the inflammatory response.[19,20] Also, an IL-1 receptor antagonist has been demonstrated to substantially reduce inflammation of the cornea after such burns, resulting in a less vascularized and more transparent tissue.[21] Meanwhile, another inflammatory cytokine, TNF-α, may be relevant based on clinical experience in patients with autoimmune diseases who have had implantation of a Boston keratoprosthesis. In a few such cases, postoperative treatment with the TNF-α antibody infliximab, a biologic antibody-based antagonist of TNF-α, resulted in a dramatic protection against inflammatory corneal necrosis surrounding the device[22–24]. These outcomes stimulated further animal research on TNF-α, as well as on experimental treatment with infliximab, using an alkali burn model.

It turns out that the retinal ganglion cells show marked apoptosis as early as 24 hours after a burn, which suggests that inflammatory substances, generated anteriorly, rapidly diffuse posteriorly and damage the retina[17,15,18]. In more detailed mechanistic investigations, oxygen and redox changes were found to be restricted to the anterior segment, along with subsequent inflammation. Importantly, these events occurred in the absence of elevated IOP[18]. TNF-α elevation was a major feature of the observed inflammatory responses. Disruption of the blood-retinal barrier and invasion of blood-derived monocytes followed, along with added activation of retinal glial cells, again within 24 hours of injury[25]. In turn, these events aggravate the inflammatory process that injures the retina and causes glaucoma.

The most important outcome of these animal studies is the protective effect of infliximab on the retina, as has been repeatedly demonstrated by our investigators[17,18]. This biologic markedly reduces inflammation in the anterior segment of the burned eye, if given promptly enough[26,17], and it can be assumed that less TNF-α will therefore be available to diffuse posteriorly. TNF-α reaching the retina, as well as what is generated locally in this layer, should be further blocked by the systemically administrated infliximab. The net result is a neuroprotective effect manifested by significantly lowering the degree of apoptosis in the ganglion cell layer and thereby reducing axonal degeneration in the optic nerve[17,18]. The importance of TNF-α blockade in chemical burns is also supported by similar anti-inflammatory and neuroprotective effects seen in TNF-α receptor 1 and 2 gene knockout animals[18]. Because local TNF-α inhibition is preferential to systemic treatment, experiments were also performed using a drug-eluting device loaded with a low dose of infliximab[27], placed subconjunctivally in rabbits. This study demonstrated that after an initial burst and with subsequently less than 1 μg of the drug released per day over a month, significant neuroprotective effects were still observed[28].

These findings open up very interesting possibilities for systemic and/or local (e.g. subconjunctival or even topical) protective treatment of acute chemical burn patients in emergency care settings, as promptly as possible following an accident. A rabbit study to fine-tune recommendations for optimal drug dose, mode of application and pharmacokinetics for use by first responders and in emergency rooms is presently under way. Other TNF-α blockers, as well as antibodies against different inflammatory cytokines, may be candidates as well. Etanercept, another TNF-α inhibitor, has been shown to prevent retinal ganglion cell loss in a rat model of glaucoma [29]. It should be emphasized that the above information on neuroprotection of the retina has been learned from animals only, not from humans. For clinical relevance in patients, a human study on the prompt use of cytokine inhibitors following chemical burns is presently being organized but may be slow to finalize because of the vast spectrum of severity of such burns. However, experience from using anti-TNF-α biologic agents in patients with ocular manifestations of rheumatologic disorders might be insightful[30].

Why has post-burn treatment with standard anti-inflammatory corticosteroids, in widespread use, not had more effect in preventing ocular destruction? One reason seems to be the well-known complications of this class of drugs that set an upper limit to their use. It also seems that corticosteroids are, for unknown reasons, not very effective in the burn setting and this has also been demonstrated in animal experimentation[18]. It is likely that pertinent biologics with their low toxicity will allow much more effective doses. In general, given the suspected complexity of inflammation biology, it seems reasonable to try to concentrate on applying the few regimens that have proven effect.

Switching to a different mechanism of neuroprotection after chemical burns and after keratoprosthesis surgery, it has become clinically well documented that reduction of the intraocular pressure is of extreme importance for the long term health of such eyes[12–14]. The fact that trauma and chronic inflammation can lead to rapid profound glaucomatous damage is often underestimated by clinicians and makes close collaboration with a glaucoma specialist mandatory. Pressure spikes immediately post-burn can sometimes occur,

presumably resulting from inflammatory blockage of trabecular tissue and episcleral veins. Such elevation of IOP may be missed however, because of difficulty in registering accurate tonometer measurements on burned corneas.

Even if the IOP remains consistently in the normal range after a burn in patients, the above cited animal experiments indicate that it may be prudent to try lower the pressure anyway as much as is possible and safe. Inflammatory damage to the posterior segment may very well be aggravated even by normal pressure (cf beneficial effect of pressure reduction in "normal tension glaucoma"[31]). Prophylactic pressure lowering to the lowest safe level should therefore be instituted promptly after a chemical injury. Systemic carbonic anhydrase inhibitors are preferable to local drops in the early phase after injury since anti-glaucoma drops may be both ineffectual and further irritating. Thus, oral acetazolamide treatment (starting with at least 250 mg twice daily and increasing to 500 mg twice daily in the adult – with pressure monitoring), should be initiated immediately after a chemical injury as prophylaxis, and continued for as long as intraocular inflammation is suspected (consultation with the patient's primary care physician for contraindications is recommended when used long term). It may be that such treatment will have to continue for a lifetime, and certainly after keratoprosthesis surgery. If the IOP is determined to be above normal despite pharmacotherapy, prompt implantation of an Ahmed valve shunt or cyclophotocoagulation must be considered[32,33].

Finally – restoration of vision. Unilateral ocular burns usually pose less threat to an individual's subsequent overall best visual acuity and they are often, as mentioned, treatable with transplantation of healthy limbal corneal epithelium from the unaffected eye[5]. It is of course the bilateral severe burns, where a suitable source of corneal epithelium for autotransplantation is usually not available, which constitute the major challenge. Enough time, usually several months after the burn, should be allowed for the inflammation to be brought under control by standard treatment and most likely by continuing cytokine inhibition systemically. Eventually, with the inflammation under control and cornea scarring finalized, and the IOP lowered, surgery in the worst eye might be indicated if bilateral vision is approximately 20/200 or less (if one eye has better vision than that, no operation may be indicated, only pressure control).

Standard penetrating keratoplasty is not recommended since the risk for graft failure is very high[4] and we prefer a Boston Keratoprosthesis, which has better potential for long-term vision recovery. Surgical technique and postoperative management have been repeatedly described[34]. If glaucoma has been diagnosed preoperatively, an Ahmed shunt should be implanted concurrently, if not done before[32]. Thus, clinical outcomes have clearly demonstrated the great importance of reducing the intraocular pressure to the lowest safe level, indefinitely. Accurate measurement of the IOP is difficult but finger palpation, however crude, may still give a gross estimation and is therefore recommended at every visit, although significantly scarred eyelids reduce accuracy even further. An implantable transducer device (into the sulcus, behind the iris) that can register IOP by radiowave telemetry is presently being evaluated by FDA[35]. Also, a new Boston Keratoprosthesis design which will allow more exact direct IOP measurements in vivo by fiber optics is presently under development. With pressure lowering accomplished, and adhering to

additional standard postoperative regimens with appropriate patient compliance, prognosis for good vision over many years should now be much more favorable.

Summary of progress:

- In eyes blinded by chemical burns, excellent vision can be restored for short and intermediate terms with the help of a keratoprosthesis. However, earlier, immediate post burn damage to the retina and the optic nerve (particularly glaucoma) frequently reduces long-term level of vision.
- Recent animal studies have shown that within 24 hours following a chemical burn to the cornea, inflammatory cytokines (TNF-α, etc.) are generated in the anterior segment and diffuse rapidly to the retina, causing ganglion cell apoptosis, etc. Major pH changes, on the other hand, seem to be well buffered anteriorly and do not reach the retina.
- The TNF-α biologic inhibitor infliximab, given in animals locally to the eye or systemically, starting 15 minutes after a chemical burn, can be strongly neuroprotective in the retina.
- Infliximab can have an immediate and long-term role after keratoprosthesis surgery as well and possibly after any other necessary surgery in potentially inflamed eyes. (Further studies evaluating other TNF-α inhibitors may similarly demonstrate both anti-inflammatory and neuroprotective effects. Adalimumab is a fully humanized monoclonal antibody that may prove to be superior to infliximab for control of these inflammatory responses, both due to the higher binding affinity for TNF-α and the lack of immune response against the medication (as this is a fully humanized product)[36]. Moreover, in June of 2016, adalimumab became the first and only FDA-approved non-corticosteroid therapy for non-infectious intermediate, posterior and panuveitis. There are also currently available FDA approved medications that specifically target IL-1β (Canakinumab) and IL-6 (Tocilizumab) but therapeutic efficacy of these agents in ocular chemical burns is unknown).
- Further neuroprotection by prophylactically lowering the intraocular pressure to the lowest safe level, usually with oral carbonic anhydrase inhibitors, is indicated immediately following a chemical burn, as well as after any subsequent eye surgery. Such treatment should possibly be sustained for life – as indicated by persuasive clinical evidence.

Beyond the standard accepted treatment of chemical burns [8,9], we feel that recent research in combination with strong clinical evidence is promising marked improvement of outcomes. The specific timeline for such revised treatment might be:

1. At the scene of the accident, en route to the hospital, and/or in the emergency room, standard treatment with lavage, etc. is mandatory, but with added local and/or systemic delivery of an anti-inflammatory biologic for neuroprotection of the retina – as promptly as possible. It can be argued that since only a brief time window is available for such protective treatment, the strong neuroprotection of

infliximab already shown in animals combined with the well-known efficacy and low risk in many human inflammatory disorders, makes immediate adoption of this treatment principle reasonable. Thus, intravenous infusion over 3 hours with 5–10 mg/kg infliximab might be started on the patient's arrival to the emergency room. Local drug delivery to the eye, on the other hand, will have to await further guidelines. Consultation with a rheumatologist may provide guidance for prolonged treatment, lab tests, etc. Also, prophylactic pressure-lowering medication should be started promptly.

2. For the recovery period (months), standard prophylactic antibiotics and moderate-dose corticosteroids should be continued, but IOP should be lowered to the maximal safe level and anti-inflammatory biologics most likely continued as well.

3. In the quiet stage, keratoprosthesis surgery with standard postoperative management for rehabilitation, when visually indicated. Long-term anti-inflammatory treatment and life-time IOP lowering might be mandatory in severe cases.

Applying such a "triple" combination of new therapeutic principles, treatment and rehabilitation of severe bilateral chemical burns might be entering a new era.

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Bibliography

1. Saini JS, Sharma A. Ocular chemical burns – clinical and demographic profile. Burns 1993; 19:67–69. [PubMed: 8435120]
2. White ML, Chodosh J, Jang J, et al. Incidence of Stevens-Johnson Syndrome and chemical burns to the eye. Cornea 2015; 34:1527–1533. [PubMed: 26488629]
3. Rihawi S, Frentz M, Reim M, et al. Rinsing with isotonic saline solution for eye burns should be avoided. Burns 2008; 34:1027. [PubMed: 18485603]
4. Abel R Jr., Binder PS, Polack FM, et al. The results of penetrating keratoplasty after chemical burns. Trans Am Acad Ophthalmol Otolaryngol 1975; 79:584–595.
5. Kenyon KR, Tseng SCG. Limbal autograft transplantation for ocular surface disorders. Ophthalmology 1989; 96:709–723. [PubMed: 2748125]
6. Deng SX, Sejpal KD, Tang Q, et al. Characterization of limbal stem cell deficiency by in vivo laser scanning confocal microscopy: A microstructural approach. Arch Ophthalmol 2012; 130:440–445. [PubMed: 22159172]
7. Katikireddy KR, Dana R, Jurkunas UV. Differentiation potential of limbal fibroblasts and bone marrow mesenchymal stem cells to corneal epithelial cells. Stem Cells 2014; 32:717–729. [PubMed: 24022965]
8. Pfister RR. Chemical trauma. In: Foster CS, Azar DT, Dohlman CH (eds) Smolin and Thoft's The Cornea. Scientific Foundations and Clinical Practice – 4th ed. Lippincott, Williams & Wilkins, Philadelphia 2005:781.th
9. Wagoner MD, Al-Swailem S, Al-Jastan S, et al. Chemical injuries of the eye. In Albert DM, Miller JW, Azar DT, Blodi BA (Eds): Albert & Jakobiec's Principles and Practice of Ophthalmology 3rd ed., Elsevier 2008:761–772.rd

10. Dohlman CH, Cruzat A, White M. The Boston keratoprosthesis 2014 – a step in the evolution of artificial corneas. Spektrum der Augenheilk 2014; 28:226–233.
11. Harissi-Dagher M, Dohlman CH. The Boston keratoprosthesis in severe ocular trauma. Can J Ophthalmol 2008; 43:165–169. [PubMed: 18347618]
12. Cade F, Grosskreutz CL, Tauber A, et al. Glaucoma in eyes with severe chemical burn, before and after keratoprosthesis. Cornea 2011; 30:1322–1327. [PubMed: 22001817]
13. Netland PA, Terada H, Dohlman CH. Glaucoma associated with keratoprosthesis. Ophthalmology 1998; 105:751–757. [PubMed: 9544652]
14. Crnej A, Paschalis EI, Salvador-Culla B, et al. Glaucoma progression and timing of glaucoma surgery in patients with Boston keratoprosthesis. Cornea 2014; 33:349–354. [PubMed: 24531120]
15. Crnej A, Omoto M, Dohlman TH, et al. Effect of penetrating keratoplasty and keratoprosthesis implantation on the posterior segment of the eye. An animal study. Invest Ophthalmol Vis Sci 2016; 57:1643–1648. [PubMed: 27054516]
16. Smith RE, Conway B. Alkali retinopathy. Arch Ophthalmol 1976; 94:81–84. [PubMed: 1247413]
17. Cade F, Paschalis EI, Regatieri CV, et al. Alkali burn to the eye: protection using TNF-α inhibition. Cornea 2014; 33:382–389. [PubMed: 24488127]
18. Paschalis EI, Zhou C, Lei F, et al. Mechanism of retinal damage following ocular alkali burns. Am J Pathol, in press.
19. Sotozono C, He J, Matsumoto Y, et al. Cytokine expression in the alkali-burned cornea. Curr Eye Res 1997; 16:670–676. [PubMed: 9222084]
20. Miyamoto F, Sotozono C, Ikeda T, et al. Retinal cytokine response in mouse alkali-burned eye. Ophthalmic Res 1998; 30:168–171. [PubMed: 9618720]
21. Yamada J, Dana MR, Sotozono C, et al. Local suppression of IL-1 by receptor antagonist in the rat model of corneal alkali injury. Eye Res 2003:76:161–167.
22. Dohlman CH, Dudenhoefer EJ, Khan BF, et al. Corneal blindness from end-stage Sjögren's Syndrome and graft-versus-host disease. In: Sullivan D ed. Lacrimal gland, tear film and dry eye syndrome III. Advances in Exp Med Biol 2002; Plenum Publishing, New York.
23. Dohlman JG, Foster CS, Dohlman CH. Boston keratoprosthesis in Stevens-Johnson Syndrome: A case of using infliximab to prevent tissue necrosis. Digit J Ophthalmol 2009; 15:1–5. [PubMed: 29276452]
24. Robert MC, Crnej A, Shen L, et al. Infliximab after Boston Keratoprosthesis in Stevens-Johnson syndrome. An update. Ocul Immunol Inflamm 2016 3 25: 1–5.[Epub ahead of print].
25. Paschalis EI, Lei F, Zhou C, et al. Immune and glial cell activation in the retina following alkali burn to the ocular surface. Submitted to Proc Nat Acad Sci.
26. Ferrari G, Bignami F, Giaconnini C, et al. Safety and efficacy of topical infliximab in a mouse model of ocular surface scarring. Invest Ophthalmol Vis Sci 2013; 54:1680–1688. [PubMed: 23404121]
27. Robert M-C, Zhou C, Frenette M, et al. A drug delivery system for administration of anti-TNF-α antibody. Trans Vis Sci Tech 2016; 5:1–11.
28. Zhou C, Robert M-C, Kapoulea V, et al. Sustained subconjunctival delivery of infliximab protects the corneal and retina following ocular alkali burn to the eye. Invest Ophthalmol Vis Sci 2017; 58:96–105. [PubMed: 28114570]
29. Roh M, Zhang Y, Murakami Y, et al. Etanercept, a widely used inhibitor of tumor necrosis factor-α (TNF-α), prevents retinal ganglion cell loss in a rat model of glaucoma [published online ahead of print July 3, 2012]. PLoS one 2012;7(7):e40065. doi:10.1371/journal.pone.0040065. [PubMed: 22802951]
30. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014; 121:785–796. [PubMed: 24359625]
31. Collaborative Normal-Tension Glaucoma Study Group: Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998; 126:487–497. [PubMed: 9780093]

32. Law SK, Huang JS, Nassiri N, et al. Technique of combined glaucoma tube shunt and keratoprosthesis implantation. J Glaucoma 2014; 23:23:501–507. [PubMed: 25275831]

33. Rivier D, Paula JS, Kim E, et al. Glaucoma and keratoprosthesis surgery: the role of adjunctive cyclophotocoagulation. Glaucoma 2009; 18:321–324.

34. Dohlman CH, Nouri M. Keratoprosthesis surgery. In Foster CS, Azar DT, Dohlman CH (eds). In: Smolin and Thoft's The Cornea. Scientific Foundations and Clinical Practice – 4th ed. Lippincott, Williams & Wilkins, Philadelphia 2005: 1085.th

35. Todani A, Behlau I, Fava M, et al. Intraocular pressure measurement by radiowave telemetry. Invest Ophthalmol Vis Sci 2011; 52:9573–9580. [PubMed: 22039243]

36. Hu S1, Liang S, Guo H, et al. Comparison of the inhibition mechanisms of adalimumab and infliximab in treating tumor necrosis factor α-associated diseases from a molecular view. J Biol Chem 2013; 288(38):27059–67. [PubMed: 23943614]