Sustained Subconjunctival Delivery of Infliximab Protects the Cornea and Retina Following Alkali Burn to the Eye

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PURPOSE. Tumor necrosis factor (TNF)-α is upregulated in eyes following corneal alkali injury and contributes to corneal and also retinal damage. Prompt TNF-α inhibition by systemic infliximab ameliorates retinal damage and improves corneal wound healing. However, systemic administration of TNF-α inhibitors carries risk of significant complications, whereas topical eye-drop delivery is hindered by poor ocular bioavailability and the need for patient adherence. This study investigates the efficacy of subconjunctival delivery of TNF-α antibodies using a polymer-based drug delivery system (DDS).

METHODS. The drug delivery system was prepared using porous polydimethylsiloxane/polyvinyl alcohol composite fabrication and loaded with 85 μg of infliximab. Six Dutch-belted pigmented rabbits received ocular alkali burn with NaOH. Immediately after the burn, subconjunctival implantation of anti-TNF-α DDS was performed in three rabbits while another three received sham DDS (without antibody). Rabbits were followed with photography for 3 months.

RESULTS. After 3 months, the device was found to be well tolerated by the host and the eyes exhibited less corneal damage as compared to eyes implanted with a sham DDS without drug. The low dose treatment suppressed CD45 and TNF-α expression in the burned cornea and inhibited retinal ganglion cell apoptosis and optic nerve degeneration, as compared to the sham DDS treated eyes. Immunolocalization revealed drug penetration in the conjunctiva, cornea, iris, and choroid, with residual infliximab in the DDS 3 months after implantation.

CONCLUSIONS. This reduced-risk biologic DDS improves corneal wound healing and provides retinal neuroprotection, and may be applicable not only to alkali burns but also to other inflammatory surgical procedures such as penetrating keratoplasty and keratoprosthesis implantation.

Keywords: polydimethylsiloxane, tumor necrosis factor alpha, drug delivery system, antibody therapy, corneal wound healing, retinal protection, burn

Severe chemical burns of the cornea, even if promptly treated, often lead to blindness. Smoldering inflammation of the anterior segment results in corneal opacity, poor epithelial healing, sometimes ulceration and perforation, neovascularization and eventual scarring.1 Rehabilitation is difficult because of extensive loss of limbal stem cells2,3 and the fact that vessel ingrowth causes loss of immune privilege,4 resulting in poor outcome of standard keratoplasty.5,6 An artificial cornea, such as the Boston keratoprosthesis, is an alternative approach for these severe cases, but sterile melting of the cornea carrier graft tissue can occur in burned eyes and may affect keratoprosthesis retention.7 It is also well known that ocular alkali burned patients have increased risk of glaucoma and subsequent irreversible vision loss.8–10 Therefore, early suppression of inflammation and angiogenesis may improve the ocular healing processes and also help retain a keratoprosthesis.

The inflammation and neovascularization following a corneal chemical burn can be attributed to upregulation of angiogenic and proinflammatory factors. One of the most potent inflammatory cytokines is tumor necrosis factor (TNF)α, which has been shown to cause corneal inflammatory injury.11 In mice, TNF-α is highly upregulated within 24 hours after corneal alkali burn and later mediates neovascularization and scarring.12 Prompt inhibition with an anti-TNF-α antibody (infliximab) after alkali burn has been shown to protect the cornea and promote healing.12,13 This effect has also been demonstrated in animals with experimental keratoprosthesis14 and in other settings.15,16 Clinically, infliximab has been found to very effectively suppress inflammation after keratoprosthesis surgery in autoimmune diseases,17,18 as well as in corneal ulceration.19–21

More recently, it has become clear that alkali burns can also adversely and irreversibly affect the retina and optic nerve. In...
the most severe clinical cases, retinal scarring can later be observed if media are clear enough or through a keratoprosthesis. More often, the anatomical signs are subtler but just as functionally impairing. It has been shown in animals that alkali can cause substantial apoptosis of retinal ganglion cells, as well as optic nerve changes, which would be expected to result in glaucoma. The effect of the alkali is not a direct one—the pH of the posterior eye segment remains normal and the alkali seems to be effectively buffered before reaching the retina (data submitted for publication). Rather, the damage to the retina comes from cytokines, which can reach the retina within 24 hours. Tumor necrosis factor-α is quite likely a main offender and systemically administered TNF-α inhibitor (infliximab, a humanized chimeric monoclonal anti-TNF-α antibody [Remicade, Jansen Biotech, NJ, USA]) can prevent retinal ganglion cell apoptosis to a considerable degree. Thus, infliximab in clinically acceptable doses seems strongly neuroprotective and modes of delivery to the retina deserve development of severe uveitis in a large proportion of cases. Infliximab in humans has been associated with the development of severe uveitis in a large proportion of cases (37.5%). Although intravitreal infliximab appears to benefit certain cases, these local safety concerns are a serious barrier to further pursue this method of drug administration.

With the objective of overcoming some of these limitations, we recently developed a drug delivery system (DDS) for local administration of anti-TNF-α antibody to the eye. The drug delivery system is made of a porous polydimethylsiloxane (PDMS) scaffold loaded with a polyvinyl alcohol (PVA) hydrogel containing the drug. We have performed drug stability, release, and in vivo safety evaluations of the DDS loaded with infliximab. The drug has remained stable after sterilization with γ radiation and exposure to room temperature for 1 year. After an initial burst, sustained zero-order release of anti-TNF-α antibody was achieved for 1 month in vitro. Here, the device was implanted subconjunctivally in rabbits with ocular alkali burns and the effect of infliximab elution on the cornea and retina was evaluated for 3 months.

Materials and Methods

Rabbit Alkali Burn Model

All rabbits were treated in accordance with the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Vision Research, and the experimental protocol was approved by the Animal Care Committee of the Massachusetts Eye and Ear Infirmary. All experiments were carried out on the OD eyes under a surgical microscope and general anesthesia. Six Dutch-Belted female rabbits (Covance, Dedham, MA, USA) weighing between 2 and 2.5 kg were used. Rabbits were anesthetized by intramuscular injection of ketamine hydrochloride INJ, USP (35 mg/kg; Ketavet, VEDCO, St. Joseph, MO, USA) and xylazine (5 mg/kg; Anased, LLOYD, Shenandoah, IA, USA). Topical anesthesia (0.5% proparacaine hydrochloride, Bausch & Lomb, 2.5 kg were used. Rabbits were anesthetized by intramuscular injection of ketamine hydrochloride (20 mg/kg) and xylazine (5 mg/kg) and topical anesthetic 0.5% proparacaine hydrochloride was applied to the operative eyes. All treated and control eyes were photographed using a digital SLR camera (Nikon, Tokyo, Japan) attached to a surgical microscope (S21; Carl Zeiss, Jena, Germany) at standard magnifications. Photographs were analyzed using ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health [NIH], Bethesda, MD, USA). The resolution of each image was 4288 × 2848 pixels. Corneal epithelial defects were stained with fluorescein and imaged using a portable slit-lamp (Keeler 3010-P, 2001, PA) equipped with cobalt blue filter and a mounted digital camera at 10× magnification. Ocular lubricant (GenTeal, Alcon, Fort Worth, TX, USA) was applied as needed during these procedures. Reversal of anesthesia was obtained through yohimbine (0.1 mg/kg) IV administration in a marginal ear vein.

Quantification of corneal neovascularization (CNV) area and epithelial defect area was performed using ImageJ software (NIH). The areas of corneal vasculature and fluorescein stain were outlined with the polygon selection tool and calculated using the ImageJ software (NIH). Each area measurement (pixel²) was normalized by the relative whole cornea area (pixel²) in the same image to eliminate the small variation in camera magnification, yielding the CNV or epithelial defect area / whole cornea ratio (%).

Subjective assessments of CNV, central corneal, and peripheral corneal opacity were performed by three indepen-
dent scientists (MR, FL, VK) using photographs in a single masked fashion to minimize observation bias. To differentiate corneal opacification due to immediate alkali reactions (e.g., saponification) seen in the central cornea, from secondary inflammatory cell-mediated remodeling manifested in the peripheral cornea, the central and peripheral corneas were scored separately for opacity. Central and peripheral corneal opacity was scored in 0.5 increments on a scale of 0 to 4, where 0 = completely clear; 1 = slightly hazy, iris/pupil easily visible; 2 = slightly opaque, iris/pupil still detectable; 3 = opaque, iris/pupil hardly detectable; and 4 = completely opaque with no view of the iris/pupil.

Corneal neovascularization was scored based on the intensity of the vessels in the cornea (Int.V), where 0 = no visible vessel, 1 = faint thin vessels, 2 = mild thickened vessels, 3 = moderate thickened vessels, and 4 = thick vessels. The length of vessel (Lth.V) invading into the cornea was scored using the following grade system: 0 = no corneal vessel, 1 = from limbus to far periphery, 2 = from limbus to mid periphery, and 3 = from limbus to central cornea. The clock hours (CHs; 30 degrees = 1 CH) involved in the CNV region were also estimated. Again, the images were scored in 0.5-unit increments. An overall CNV score was derived from the above three assessments (overall CNV score = Int.V + Lth.V + CHs/3).

Because the range in CHs was 0 to 12 hours, the number was divided by 3 to provide normalization to the scale 0 to 4, in order to match the scale of Int.V and Lth.V. Agreement between the three raters was statistically assessed using the intraclass correlation coefficient (ICC) test.

Histologic and Immunohistochemical Examinations

At the end of the follow-up, rabbits were euthanized using Fatal Plus intravenously (Sodium pentobarbital; 100 mg/kg, Vortech, Dearborn, MI, USA). Both eyes and the lower lid with the DDS implant were harvested and fixed in 4% paraformaldehyde (PFA) overnight at 4°C. The retinal nerve fiber layer and number of cells in the retinal GCL of rabbits were analyzed in histologic sections using β3-tubulin monoclonal antibody (1:100, MA1118, Thermo Scientific) and DAPI. β3-tubulin+ DAPI+ cells in GCL were manually counted and normalized to the total measured retinal length. A minimum of three different nonconsecutive tissue sections per eye was analyzed and three rabbits per sample. To assess GCL cell loss in the burned eyes, the contralateral nonburned eye of each rabbit was used as internal control (reference of normal cell count). Data were presented in percentages of the remaining cells, with 100% representing the number of cells in the contralateral nonburned eye (β3-tubulin+ cell density in burned eye/β3-tubulin+ cell density in contralateral eye*100).

Statistics

Quantitative results were reported as means ± standard deviations. The normality of data was assessed by Shapiro-Wilk test. Depending on the normality, Student’s t-test or Mann-Whitney U test was performed to compare the means between the anti-TNF-α DDS group and the sham DDS group. One-way

fluorescence microscope with 20x dry and 63x oil immersion objective lenses. The total number of cells expressing TNF-α or CD45 in a whole cornea section was counted using the “Analyze Particles” tool in NIH ImageJ software. The mean values obtained from three tissue section samples are reported.
and 2-way ANOVA were performed in datasets containing multiple variables, followed with Holm-Sidak pairwise multiple comparison correction test. Analyses were performed using R Studio (Boston, MA, USA). Interrater agreement was assessed with the ICC test for absolute agreement. Intraclass correlation coefficient scores between 0.8 and 0.9 assumed “good agreement” and between 0.9 and 0.99 “excellent agreement.” Intraclass correlation coefficient measurements were provided with 95% confidence interval. Mixed ANOVA was performed in datasets containing dependent variables (e.g., CNV opacity scores, and corneal defect area) with fixed variables being time and treatment. Analyses were performed using the Statistical Package of Social Sciences (SPSS, IBM, NY, USA). Linear and second order polynomial functions were generated in GraphPad Prism Version 6.0 (GraphPad, La Jolla, CA, USA) to fit data points.

**RESULTS**

**Safety of the DDS and Infliximab Stability**

A predominantly granulomatous local response to the polymer implants with (Fig. 1A) and without (Fig. 1C) infliximab was seen following DDS placement in the subepithelial tissues of the conjunctival fornix. A spectrum of granulomatous inflammation was seen in both groups. The majority of the inflammatory cells were mononucleated epithelioid cells (Fig. 1B) in the lumen engulfing remnants of the implant with occasional giant cells (Figs. 1B, 1D). There was minimal to no inflammation noted in the adjacent pseudocapsule and connective tissues. While one rabbit exhibited occasional aggregates of mucus near the DDS implantation site, the subconjunctival DDS implantation appeared to be safe at the ocular surface with no overt sign of toxicity. The small incision in the conjunctival tissue created for inserting the DDS strip healed within 7 days (Fig. 1G). A photograph of the DDS demonstrated its shape and porous texture of the DDS (Fig. 1H).

Antitumor necrosis factor-α DDS showed positive immunoreactivity with a secondary antibody against human IgG 3 months after implantation (Fig. 1E), whereas none of sham DDS showed immunoreactivity to IgG (Fig. 1F). Infliximab antibodies were not completely depleted from the DDS by the end of 3 months. Eyes implanted with anti-TNF-α DDS also showed immunoreactivity to anti-human IgG secondary antibody (Supplementary Fig. S1). Positive human IgG signal was found around and within small vessels in the cornea, conjunctiva, iris, and choroid 3 months after implantation of the DDS. Conversely, eyes implanted with sham DDS had no infliximab signal in any of the aforementioned tissue. The conjunctival tissue harboring the anti-TNF-α DDS also showed marked levels of human IgG in a diffusion gradient pattern (Supplementary Fig. S1). Infliximab presence in ocular tissue 3 months after DDS implantation suggests slow and continuous diffusion of antibody from the DDS.

**Effect of Anti-TNFα DDS Treatment in Corneal Neovascularization After Corneal Alkali Burn**

Although all rabbits developed CNV after alkali burn (Figs. 2A–F), the anti-TNF-α DDS group exhibited lower mean percentage of CNV area and overall CNV score compared to the sham DDS group. The relative CNV area in the anti-TNF-α DDS group 92 days after burn was 13 ± 5%, whereas in the sham DDS group was 51 ± 14%. However, no statistically significant difference was present between the two groups (P = 0.228) likely due to the considerable variability in the sham DDS group (Fig. 2G).

The corneal neovascularization score in the anti-TNF-α DDS group at 92 days was 6.4 ± 2.6, whereas in the sham DDS
group was 8.4 ± 0.7 but no statistically significant difference (Fig. 2H, \( P = 0.131 \)). The scores from all masked raters were in agreement (ICC central corneal opacity: 0.886, \( P < 0.0001 \) [0.835–0.923, confidence interval (CI): 95%], ICC peripheral corneal opacity: 0.889, \( P < 0.0001 \) [0.838–0.925, CI: 95%]).

One rabbit in the sham DDS group (Fig. 2E) developed severe central corneal necrosis that significantly and artificially reduced the mean central CNV area in this group.

**Effect of Anti-TNF-α DDS Treatment in Corneal Opacity After Corneal Alkali Burn**

All rabbits treated with anti-TNF-α DDS exhibited continuous decrease in the central and peripheral corneal opacity, during the 3-months evaluation period, as compared to the sham DDS group (Figs. 2I, 2J). Both groups had similar central corneal opacity within the studied time period (\( P = 0.235 \); mixed ANOVA; Fig. 2I), but the anti-TNF-α DDS group had significantly lowered peripheral corneal opacity than the sham DDS group (\( P < 0.05 \); mixed ANOVA; Fig. 2J). The scores from the three masked raters were in agreement (ICC_{CNV}: 0.892, \( P < 0.0001 \), CI: 95%: 0.762–0.943).

**Effect of Anti-TNF-α DDS Treatment on Corneal Epithelial Wound Healing After Corneal Alkali Burn**

Rabbits treated with anti-TNF-α DDS had significantly reduced area of epithelial defect as compared to sham DDS treated within the studied time frame (Fig. 3G, \( P = 0.04 \), mixed ANOVA), except for a short period of time (36–42 days) where both groups had similar defect area. Rabbits treated with the anti-TNF-α DDS exhibited faster re-epithelialization of the cornea and complete corneal epithelial wound closure 64 ± 8 days after the burn. Conversely, all sham DDS treated eyes exhibited incomplete epithelial wound closure by the end of the study. In fact, at 92 days, the corneal epithelial defect area in the sham DDS group accounted for 6.3 ± 4.7% of the total cornea (\( n = 3 \), \( P < 0.05 \), Figs. 3C, CF). Two linear regressions...
were fitted to the two datasets. The slope of the best-fitted line for anti-TNF-α DDS group was −0.02023, R² = 0.47 and the slope of sham DDS group was −0.0349, R² = 0.0190.

Effect of Anti-TNFα DDS Treatment in TNF-α Expression and Leukocyte Infiltration

Immunohistochemistry of rabbit cornea sections showed that anti-TNF-α DDS suppressed CD45⁺ cell infiltration and TNF-α expression in the burned corneas as compared to the sham DDS group. Antitumor necrosis factor-α DDS treated rabbits had significantly less CD45⁺ cells in the cornea (Fig. 3H) at 3 months as compared to sham DDS treated eyes (K). H–K ×20 with tiling. Scale bar: 500 μm. (L) Numbers of CD45⁺ leukocytes/cornea section in the burned eyes. n = 3 rabbits/group. (M) Numbers of TNF-α expressing cells/cornea section in the burned eyes. n = 3 rabbits/group.

Ocular Pathology

Preservation of the corneal endothelial mosaic and anterior segment structure was seen in all of the eyes treated with anti-TNF-α DDS (Fig. 4A). In eyes with sham DDS implants, all anterior segments were abnormal to varying degrees. These eyes demonstrated epithelial ulceration with bullae formation, subjacent collagen denaturation, chronic anterior stromal...
keratitis, and endothelial cell attenuation (Fig. 4B). Retrocorneal fibrous membrane formation (Fig. 4C) and peripheral anterior synechiae (Fig. 4D) were other anterior segment findings observed in the sham DDS treated eyes but not in the anti-TNF-α DDS treated eyes. Ocular phthisis and disorganization of intraocular structures was developed in one eye treated with sham DDS. No evidence of inflammation was detected in the posterior segment (retina, vitreous, and choroid) of eyes from both groups.

**Retinal and Optic Nerve Degeneration**

This study demonstrated marked retinal and optic nerve degeneration following corneal alkali burn. Retinal neurodegeneration was inhibited using the anti-TNF-α DDS treatment, but not by the sham DDS. Antitumor necrosis factor-α treated eyes exhibited a 4.3% mean reduction of retinal GCL cell count as compared to the corresponding contralateral nonburned eye. Conversely, sham DDS treated eyes exhibited a
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significant 38.1% mean reduction in GCL cell count ($P < 0.05$, Student’s $t$-test; Figs. 4E, 4F). Likewise, burned eyes treated with anti-TNF-α DDS showed no reduction in optic nerve axon density as compared to the optic nerves from the corresponding contralateral nonburned eye. However, sham DDS treated eyes exhibited a significant 24.5% loss in optic nerve axons, as compared to the contralateral nonburned eye. Burned eyes treated with anti-TNF-α DDS had significantly higher optic nerve density as compared to burned sham DDS treated eyes ($P < 0.05$, unpaired Student’s $t$-test; Figs. 4G, 4H).

**Discussion**

Our results confirm that TNF-α is a major mediator of inflammation in the cornea and, perhaps even more importantly, in the retina following ocular alkali burn. The upregulation of TNF-α expression in burned corneas was positively correlated with large corneal infiltration of leukocytes, delayed corneal wound healing, endothelial cell loss, ulceration, corneal opacity, and neovascularization, as well as with retinal ganglion cell loss and optic nerve degeneration. Conversely, prompt treatment with anti-TNF-α antibody (infliximab) significantly suppressed complications of the burned eye. The infliximab-loaded DDS delivered the drug with considerable therapeutic effect, not only to the cornea but also to the retina.

It can be questioned whether the retinal and optic nerve alterations have been mediated by intraocular pressure elevation due to anterior peripheral synechiae. Peripheral corneal inflammation, which was markedly increased in the sham DDS treated eyes, may have contributed to angle closure and subsequent intraocular pressure elevation. Alternatively, and perhaps more likely, severe anterior segment inflammation in the early stages after the burn may have had a direct inflammatory effect on the posterior structures. Of importance here is that etanercept (another antibody of TNF-α) was noted in an eye with anti-TNF-α DDS showed no reduction in optic nerve axon density, whereas sham DDS treated eyes exhibited a significant ~30% reduction. These findings may be clinically important. If a TNF-α inhibitor can be administered to the retina in sufficient doses by any safe and efficient route soon after an alkali burn—ideally in the emergency room immediately following the lavage—it is likely that some damage to the eye can be prevented. Since corneal transparency can now be restored with a keratoprosthesis in even severe alkali burns, it can be argued that protection of the retina and the optic nerve should be given primary attention.

Since damage to these structures is irreversible, dosage and route of administration of infliximab should be chosen with priority to retinal neuroprotection.

Thus the efficacy, safety, and practicality of the various modes of delivery to the eye must be compared: systemic infusion, subcutaneous injection, local drops, gels or DDS, subconjunctival or subtenon injection or DDS, or intravitreal injection. Toxicity and pharmacokinetic studies are clearly warranted. Previous studies with infliximab drops in mouse and rabbit models focused on the early biological responses following injury, where the studied time frame was within 10 days. The infliximab was shown to penetrate into the anterior stroma of the injured corneas only in the absence of the epithelium. However, efficacy is expected to be reduced following re-epithelialization or conjunctivalization of the cornea in the later healing stage. It has not been demonstrated whether infliximab in drop form can protect the retina. Subconjunctival administration of infliximab, on the other hand, appears to bypass the barrier of the epithelium quite effectively and it has already been shown that a single subconjunctival injection of infliximab results in drug infiltration into the cornea and other anterior chamber tissues but, again, any effect on the retina was not described.

It remains to be determined whether subconjunctival implantation of an infliximab-loaded DDS is therapeutically superior to a single subconjunctival injection. Except for the strong initial burst release of infliximab, the DDS has been shown to have a nearly zero-order release kinetics over 1 month in vitro. In this study, eyes with anti-TNF-α DDS showed presence of infliximab antibody around and within small vessels in the cornea, conjunctiva, iris, and choroid 3 months after implantation of the DDS (Supplementary Fig. S1). This suggests that the anti-TNF-α antibody is continuously released by the DDS for at least 3 months and the antibody finds its way to various ocular tissues. The therapeutic effect of sustained anti-TNF-α delivery was also observed in one rabbit with early DDS extrusion (42 days) due to loose conjunctival sutures. This rabbit exhibited increased infiltration of leukocytes in the cornea and increased loss of RGCs as compared to the rabbits that retained the anti-TNF-α DDS for 3 months (Supplementary Fig. S2). Even though this finding is based on only one rabbit, it may suggest that the effect of prolonged release of anti-TNF-α antibody to the eye may be therapeutically important and warrants further investigation. Although more complex in insertion and removal, the bioavailability and sustainability of infliximab delivery to both the anterior and posterior segments of the eye are possibly enhanced compared to a single subconjunctival injection. The effect achieved in our rabbit model with a very small dose of infliximab (85 μg in the...
current DDS compared to that of standard systemic route (2-10 mg/kg) is striking. This means that the systemic effect of the subconjunctival DDS-delivered dose should be trivial in a human compared to that of the standard intravenous dose. It can be speculated that the DDS can be modified to fit into the lower lid fornix (cul-de-sac) to give therapeutic effect at least to the cornea. This modality does not require implantation, the dose is adjustable, and most importantly reversible by removing the DDS.

These results confirm that TNF-α is a major mediator of inflammation in the eye following ocular surface burn with alkali and that TNF-α inhibition may protect the eye from extensive damage to the cornea, retina, and optic nerve, and may even improve the prognosis of a subsequent corneal transplant. The finding that a low dose of local infliximab delivered via the subconjunctival space can result in substantial retinal neoprotection should have applications beyond alkali burns. For example, in keratoprosthesis surgery where systemic delivery of infliximab has been shown to be protective, or in surgical procedures of the eye that induce ocular inflammation, infliximab prophylaxis may be beneficial. The ability of the DDS to deliver various biologic agents to the retina, such as anti-VEGF or combination anti-TNF-α/anti-VEGF agents is an intriguing concept that requires future attention.

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