Evaluation of Anti-TGF-β2 Antibody as a New Postoperative Anti-scarring Agent in Glaucoma Surgery

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PURPOSE. Postoperative subconjunctival wound healing remains the commonest cause of late bleb failure after glaucoma filtration surgery. This study was undertaken to investigate whether the human monoclonal antibody that neutralizes transforming growth factor-β2 (CAT-152; lerdelimumab) could be used as a postoperative agent to prevent scarring after glaucoma surgery and compared it with 5-fluorouracil (5-FU), to benchmark its potential clinical benefit.

METHODS. In a randomized, controlled, masked-observer study, after modified glaucoma surgery, 48 rabbits were randomly allocated to receive a postoperative course of seven subconjunctival injections of CAT-152 (1 mg/mL), 5-FU (50 mg/mL), or no treatment. Bleb characteristics, the presence of subconjunctival drainage, and local reaction to treatment were assessed. Animals were killed on days 10, 21, and 30. Immunohistochemistry, histologic staining and electron microscopy were performed to demonstrate the mechanism of CAT-152-mediated effects on the extracellular matrix.

RESULTS. CAT-152 significantly improved surgical outcome (log rank test, P < 0.001) and reduced subconjunctival collagen deposition (P < 0.01) compared with 5-FU and control. Median bleb survival was increased in the CAT-152 group (25.5 days) compared with the 5-FU (20 days) and control (16 days) treatment groups. CAT-152 treatment improved bleb morphology (P < 0.05) and was well tolerated. 5-FU prolonged the duration of corneal epitheliopathy (P < 0.01).

CONCLUSIONS. Postoperative administration of CAT-152 significantly improved surgical outcome, reduced subconjunctival scarring, and minimized the risk of corneal side effects compared with the anti-scarring agent 5-FU. These findings suggest that CAT-152 may offer therapeutic benefit as a postoperative agent to prevent subconjunctival scarring after glaucoma filtration surgery. (Invest Ophthalmol Vis Sci. 2003;44:3394–3401)

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The major determinant of the long-term outcome of glaucoma surgery is the wound-healing response. Excessive postoperative scarring at the level of the conjunctiva and sclerostomy sites is associated with poor postoperative pressure control.1–4 The intraoperative use of the antiproliferative agents 5-fluorouracil (5-FU) and mitomycin C (MMC) has increased the success rate of filtration surgery, and this technique has been accepted in clinical practice.5–12 However, despite these intraoperative applications, failure can occur later in the postoperative period. 5-FU has been given subconjunctivally in the postoperative period to treat failing and encysted blebs.13–16 Prevention of a late increase in intraocular pressure may be particularly important in preserving visual function, given the data from the recent Advanced Glaucoma Intervention Study (AGIS) study.17 MMC and 5-FU work by causing widespread cell death and apoptosis and can result in corneal erosions and cystic avascular blebs. They are associated with severe sight-threatening complications.18–22 More physiological anti-scarring agents are therefore needed for postoperative prevention of bleb failure and increased intraocular pressure.

Of all the growth factors involved in the wound-healing cascade, TGF-β has been shown to be one of the most potent stimulators of scarring in the eye and is involved in the pathogenesis of cataract, proliferative vitreoretinopathy, and conjunctival scarring.22–28 TGF-β, the most predominant of the three mammalian isoforms in the eye, is the most potent growth factor in the aqueous at stimulating conjunctival fibroblast function. Elevated levels of this isoform are found in the aqueous of glaucomatous eyes compared with normal eyes.29–34 These findings suggest that neutralizing the effects of TGF-β2 may reduce conjunctival scarring after glaucoma filtration surgery.

CAT-152 (lerdelimumab) is a novel human monoclonal antibody that was isolated and developed in vitro by the technique of antibody phage display. It displays high affinity and specificity for the active form of TGF-β2 and has been designed for therapeutic use. We have demonstrated in vitro that CAT-152 binds to TGF-β2–induced human Tenon’s fibroblast migration and proliferation. Furthermore, in our in vivo model of aggressive conjunctival scarring we have shown that subconjunctival administration of CAT-152 at the time of glaucoma surgery and in the immediate postoperative period successfully improves surgical outcome, reduces subconjunctival fibrosis, and is safe and well tolerated.26 In the first human trial of CAT-152 in patients undergoing trabeculectomy, good tolerance and safety were reported with a treatment regimen of both intra- and postoperative injection.35 A multicenter phase II study is under way.

However to date, we have made no assessment of isolated postoperative application of CAT-152. Using the same model of glaucoma filtration surgery, the present study was designed to determine whether postoperative application alone of CAT-152 can improve bleb survival and to compare the effectiveness of CAT-152 with the currently used postoperative anti-scarring agent 5-FU.

METHODS

Forty-eight New Zealand White rabbits aged between 12 and 14 weeks and weighing 1.5 to 2.2 kg were used in this prospective randomized,
controlled, masked observer study, which was performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Glaucoma filtration surgery was performed on the left eyes of rabbits under general anesthesia (intramuscular muscular ketamine [50 mg/kg] and xylazine [10 mg/kg]) using a technique previously described by Cordeiro et al. A partial-thickness 800 silk corneal traction suture (Ethicon, Edinburgh, UK) was placed at 12 o’clock, to gain exposure to the superior conjunctiva. A fornix-based conjunctival flap was raised, and blunt dissection of the suprachoroidal space was performed to a distance of 15 mm behind the limbus. An MVR blade (Vistech, Warwickshire, UK) was used to fashion a partial-thickness scleral tunnel, starting 4 mm behind the limbus and continuing until the blade was just visible in the anterior cornea stroma. A 22-gauge/25-mm intravenous cannula (Venflon; BD Biosciences, Helsingborg, Sweden) was then passed through the scleral tunnel until the cannula needle was visible in the clear cornea. The cannula needle entered the anterior chamber, the cannula was advanced to the mid-pupillary area, and the needle was withdrawn. Finally, the cannula was trimmed and beveled at its scleral end so that it protruded 1 mm from the insertion point, and a 10-0 nylon suture was used to fix the tube to the scleral surface. The conjunctival incision was closed with two interrupted sutures and a central mattress-type 10-0 nylon suture on a needle (B/V 100-4 needle, Ethicon) to give a watertight closure. One drop of atropine sulfate 1% and betamethasone sodium phosphate 0.1%, neomycin sulphate 0.5% ointment was instilled at the end of surgery. No other adjunctive treatment was given at the time of surgery. The operations were performed by a single surgeon with experience in using this model.

**Postoperative Subconjunctival Administration of CAT-152 after Rabbit Filtration Surgery**

The animals were randomly allocated to receive a postoperative course of seven subconjunctival injections (100 μL) of CAT-152 (1 mg/mL), 5-FU (50 mg/mL), or no treatment. The subconjunctival injections were given on days 2, 3, 4, 7, 9, 11, and 14 after surgery (day 0) under topical anesthesia (proxymetacaine hydrochloride 0.5% eye drops, 1 drop per eye), using a 30-gauge needle (Myjector 100u; Terumo, Tokyo, Japan). CAT-152 was injected 5 mm behind the limbus at the nasal margin of the superior rectus muscle. 5-FU was administered 180° from the site of surgery. The rationale for the injection site selection was in keeping with the method used in the original studies of subconjunctival 5-FU in glaucoma filtration surgery and widespread clinical practice. Injections were given by an independent clinician, because the different injection sites for each treatment precluded masking.

**Clinical Evaluation of Postoperative CAT-152**

Baseline observations were performed before glaucoma filtration surgery. Measurement of intraocular pressure in both eyes was made with a handheld tonometer (Tonopen; Mentor, Norwell, MA) after topical instillation of 0.5% proxymetacaine HCl eye drops, 1 drop per eye, with a mean reading of three recordings being documented per time point. The conjunctival appearance and the drainage area were observed. All animals were examined by a masked observer at set times after surgery. Assessment of both eyes (contralateral untreated eye used as control) was made daily from days 0 to 4 and thereafter at regular periods, at least twice weekly, until death. Bleb characteristics, including length, width, and height, were measured with calipers, and intraocular pressure was recorded. Previous experience with this surgical model has identified a small area of avascularity (<3 mm) that appears in the nasal conjunctiva. This is a transient clinical observation and appears to develop independently of any treatment given. The incidence of avascularity was noted (normal vascularization, 0; avascular region, 1). The drainage bleb vascularity characteristics were assessed independently from this area and were graded by dividing the conjunctival areas into quadrants (superior, nasal, and temporal) and scoring the appearance (0, avascular; +1, normal vascularity; +2, hyperemic; and +3, very hyperemic). Slit lamp examination was performed to identify both anterior chamber activity (0, quiet; 1, cells; 2, fibrin; and 3, hypopyon) and anterior chamber depth, which was recorded as deep (+2), shallow (+1), or flat (0).

An assessment of the duration of corneal epitheliopathy was made after topical installation of lignocaine fluorescein into the left eye and was graded according to the area of the cornea affected (0, nil; 1, <25%; 2, <50%; 3, <75%; 4, <90%; 5, up to 100%).

**Data Evaluation**

Bleb survival was taken as the primary efficacy end point in the analysis of CAT-152 in rabbit filtration surgery. Bleb failure was defined as the appearance of a flat, vascularized, and scarred bleb in the presence of a deep anterior chamber. Kaplan-Meier and log rank statistics were used to compare treatment groups in bleb and intraocular pressure failure (defined as the return of the intraocular pressure in the surgical eye to baseline level). Bleb area and height, anterior chamber depth and activity, and conjunctival vascularity per quadrant were all analyzed with a repeated-measures procedure and the generalized linear model (SPSS; SPSS Inc., Chicago, IL). This allowed comparison of

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**Image 311x117 to 551x505**

**Figure 1.** The effect of CAT-152 (n = 8), 5-FU (n = 8), or no treatment (n = 7) on (A) bleb survival, (B) bleb area, and (C) bleb height. CAT-152 significantly prolonged bleb survival compared with 5-FU and the untreated control group, as shown in the Kaplan-Meier survival curve (P = 0.0009 log rank test). CAT-152 treated eyes had significantly larger blebs (area and height, P < 0.05).
Table 1. Incidence of Bleb Failure and the Percentage of Bleb Survival in Rabbits Undergoing Glaucoma Filtration Surgery: Effect of CAT-152 and 5-FU Treatment Compared to Control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>30</th>
<th>Survival 30 Days/n</th>
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<tbody>
<tr>
<td>CAT-152</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1/8</td>
</tr>
<tr>
<td>% Survival</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>87.5</td>
<td>75</td>
<td>62.5</td>
<td>50</td>
<td>37.5</td>
<td>25</td>
<td>12.5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/8</td>
</tr>
<tr>
<td>% Survival</td>
<td>100</td>
<td>100</td>
<td>87.5</td>
<td>62.5</td>
<td>37.5</td>
<td>12.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/7</td>
</tr>
<tr>
<td>% Survival</td>
<td>100</td>
<td>57.1</td>
<td>42.9</td>
<td>28.6</td>
<td>14.3</td>
<td>0</td>
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Results

Experimental Details

Of the 24 rabbits observed for the duration of the 30-day experimental period, 23 completed the experimental protocol. One animal was observed to be showing signs of developing severe intraocular infection 5 days after surgery. The rabbit was killed and an independent observer (to preserve masking) identified that the animal was in the control group. Observational analysis was therefore performed on eight animals that received CAT-152, eight animals that received 5-FU, and seven untreated control animals.

Effects on Filtration Surgery

CAT-152 significantly improved glaucoma filtration surgery outcome in this animal model of aggressive postsurgical scarring. CAT-152 significantly prolonged bleb survival compared with the 5-FU group and the untreated control group, as shown in the Kaplan-Meier survival curve in Figure 1A (log rank test; P = 0.0009). The rate of bleb failure and percentage survival in each treatment group is shown in Table 1. All the blebs in the control and 5-FU groups had failed by day 22; however, 62.5% of the CAT-152 treatment group had functioning blebs. By day 30 all but one of the operations had failed; the only animal with...
TABLE 2. Duration of Low-Grade Corneal Epitheliopathy or Avascularity after Treatment with CAT-152 or 5-FU Compared with the No-Treatment Control Animals

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>CAT-152</th>
<th>5-FU</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avascularity</td>
<td>1.63 ± 0.53</td>
<td>10.71 ± 1.71*</td>
<td>1.57 ± 0.48</td>
</tr>
<tr>
<td>Corneal Epitheliopathy</td>
<td>9.13 ± 1.33</td>
<td>16.88 ± 5.2</td>
<td>10.57 ± 2.5</td>
</tr>
</tbody>
</table>

Data are the mean ± SE.
* P < 0.01 comparing CAT-152 or 5-FU treatment groups to the no-treatment control group.

a functioning bleb had received CAT-152. The median (range) survival rates were 23.5 (20–30), 20 (16–22), and 16 (14–21) days in the CAT-152, 5-FU, and control groups, respectively. The presence of a well formed bleb is an important indicator of effective filtration. Subconjunctival scarring causes contraction and flattening of the bleb. Figure 2 shows the typical appearances of the filtration blebs on day 21. Treatment with CAT-152 was associated with elevated, diffuse, fleshy looking blebs compared with the flat, scarred blebs in the other groups. Analysis of both bleb area and bleb height using the repeated measures of the generalized linear model, revealed significant differences in both these variables after treatment with CAT-152 compared with the 5-FU or no-treatment regimens (P < 0.005 area, P < 0.001 height; Figs. 1B, 1C).

Analysis of mean intraocular pressure in the surgical eyes showed no significant differences between treatment groups over the entire study period (P > 0.05). Corneal epitheliopathy is a recognized adverse effect associated with the clinical use of 5-FU and is associated with both ocular discomfort and the risk of infection. Given this, a grading system was included in the methods to assess the severity of this variable. In this experiment only mild punctuate staining of the cornea (superficial punctuate keratitis, grade 1) was detected in all treatment groups, and this was a transient finding. The duration of the staining was significantly longer in the 5-FU-treated group (P < 0.001; Figs. 3D–F, Fig. 5). In addition, CAT-152 significantly reduced the population of cells expressing α-smooth muscle actin, indicating less fibroblast differentiation into the myofibroblast phenotype (P = 0.01; Figs. 4, 5). No other significant differences were found between treatment groups in total cellularity, elastic fiber deposition, or proliferating cell nuclear antigen (PCNA) at day 10. By day 30 subconjunctival scarring at the wound site consisted characteristically of densely packed collagen and fibroblasts. In contrast, the only surviving CAT-152–treated bleb showed much looser architecture with visible conjunctival bleb formation (Fig. 6).

One of the features of existing cytotoxic anti-scarring regimens is their production of nonperfused, avascular areas in locally treated tissues. These areas of avascularity are associated with thin-walled, cystic blebs and the attendant risks of leakage and infection. In all the rabbit eyes, a small region of avascularity was noted in the nasal side of the bleb (<3 mm), within the first 7 days. This was transient finding. The duration of the avascular segment tended to be longer in the 5-FU-treated animals, but did not reach statistical significance (P = 0.159). The duration of avascularity in the CAT-152 group was similar to that observed in the no-treatment control group (Table 2).

Local reaction to treatment was assessed by the degree of anterior chamber inflammation and conjunctival vascularity. No significant difference was found between treatment groups for either of these indicators of the inflammatory response (vascularity, superior P = 0.402, temporal P = 0.434, nasal P = 0.668; anterior chamber inflammation P = 0.430).

The depth of the anterior chamber was assessed as an indirect indicator of drainage. On day 1 after surgery the anterior chamber was flat in most of the animals. Over the next 7 days the anterior chamber gradually deepened. No significant difference was found between the treatment groups in the time taken for the anterior chamber to deepen (P = 0.302).

Histologic Effects

CAT-152 treatment reduced scarring at a microscopic level. The greatest histologic difference between treatment groups was seen on day 10 (Fig. 3). At this time point, total scar formation, as judged by the staining characteristics of picrosirius red, was significantly reduced by CAT-152 treatment (P = 0.01, Figs. 3D–F, Fig. 5). In addition, CAT-152 significantly reduced the population of cells expressing α-smooth muscle actin, indicating less fibroblast differentiation into the myofibroblast phenotype (P = 0.01; Figs. 4, 5). No other significant differences were found between treatment groups in total cellularity, elastic fiber deposition, or proliferating cell nuclear antigen (PCNA) at day 10. By day 30 subconjunctival scarring at the wound site consisted characteristically of densely packed collagen and fibroblasts. In contrast, the only surviving CAT-152–treated bleb showed much looser architecture with visible conjunctival bleb formation (Fig. 6).

We compared electron microscopic (EM) characteristics of CAT-152–treated and untreated control animals. Morphologically, scanning EM demonstrated looser subconjunctival bleb architecture with CAT-152 treatment (Figs. 7A, 7C, 7E). At a cellular level, transmission EM showed a corresponding reduction in inflammatory cell infiltrate and collagen fibril formation within the blebs of CAT-152–treated animals (Fig. 7, compare E and F).
Despite current anti-scarring strategies, continued scarring leading to late failure of glaucoma filtration surgery remains a major barrier to long-term intraocular pressure control and arrest of disease progression.2,5–6 We have demonstrated that neutralizing the effects of TGF-β2 in the postoperative period, by subconjunctival administration of a novel antibody (CAT-152), can improve the outcome of glaucoma surgery in an animal model of aggressive scarring. In addition, postoperative use of CAT-152 appears more efficacious than 5-FU and without some of the side effects associated with antiproliferative use.

The anti-metabolites 5-FU and MMC are currently the backbone of anti-scarring treatments. The intraoperative regimen of mitomycin C has gained favor due to the convenience of a single treatment and the delivery of lower intraocular pressure in certain eyes.37 However, even short exposure to MMC results in local irreversible tissue destruction.12,20 The advantage of CAT-152 over MMC and 5-FU lies in its more physiological method of action, potentially providing long-term titratable intraocular pressure control, while maintaining normal tissue architecture in the absence of side effects.

Rabbit models exhibit an exaggerated healing response as compared to human tissue. Demonstration of efficacy in such models is therefore likely to be reproduced in the clinical setting. The surgical model of glaucoma surgery used in this study localizes scarring to the level of the conjunctiva. This is achieved by maintaining a permanent fistula to drain aqueous into the subconjunctival wound site. Experience has shown that intraocular pressure is not a reliable indicator of filtration in this model of glaucoma surgery. Furthermore, in this study no significant differences were detected in IOP between groups. This can be explained by the fact that basal preoperative intraocular pressure in this model of glaucoma filtration surgery is within the normal range (this is a model of subconjunctival scarring, not of glaucoma). Given this, bleb failure rather than intraocular pressure has always been defined as the primary outcome variable representing failure of surgery in this model.

We found that isolated postoperative 5-FU had the same bleb survival end point as the control in this experiment. This model exhibits an extremely aggressive scarring response that may explain this finding. However, conversely, all the treatments that have improved bleb survival in this model have worked in a subsequent clinical setting.12,26 Only a limited number of studies have looked at efficacy of 5-FU as an isolated postoperative agent in animal experiments. Doyle et al.38 compared the effect of five postoperative injections of 5-FU with single intraoperative 5-FU, and combined intra- and postoperative 5-FU in rabbit filtration surgery. Control animals received intraoperative distilled water only. No significant difference was shown in bleb survival between postoperative 5-FU treatment and control in this study. However, what can be seen in the survival curve from Doyle et al. and our data is that postoperative injections of 5-FU appear to shift the survival curve to the right of the control at the early time points, without affecting the final end point.

The landmark Fluorouracil Filtering Surgery Study6 represents the only definitive report in which postoperative injections of 5-FU were shown to improve surgical outcome. In this study, 21 subconjunctival injections were administered: two injections per day on days 1 to 7 after surgery and one injection per day on days 7 to 14 after surgery. If this number of injections had been used, we may well have shown efficacy of postoperative 5-FU in this model. When designing the protocol we chose a postoperative regimen that more closely reflected current clinical subconjunctival 5-FU use.

Anterior chamber depth was included in the observations as an indirect indicator of the drainage of fluid through the tube into the subconjunctival space. The rabbit anterior segment is very crowded with a very large lens and small anterior chamber. Therefore, in practice, this measurement was fairly difficult to grade. In most of the animals, the anterior chamber was flat on day 1 and gradually deepened over the next 7 days. No significant difference was found between the treatments in the time taken for the anterior chamber to deepen. Overall, this observation may not be as true a representation of anterior fluid dynamics as had been originally anticipated.

Ideally all subconjunctival injections would have been given at the same site. In all the preclinical and clinical studies of CAT-152 in glaucoma filtration surgery, the drug has been...
Figure 6. By day 30, only one bleb (CAT-152 treated) was still functioning. In failed blebs, subconjunctival scarring consisted of dense collagen fibers and fibroblasts (B). In contrast, the surviving bleb showed much looser architecture and visible evidence of bleb formation (A). Bar, 100 μm.

Figure 7. Electron microscopy (EM) was performed on CAT-152–treated animals (A, C, E) and untreated control animals (B, D, F). Morphologically, scanning EM (A–D) demonstrated looser subconjunctival bleb architecture with CAT-152 treatment. At a cellular level, transmission EM showed the associated reduction in inflammatory cell infiltrate and collagen fiber deposition in the CAT-152–treated animals. Bars: (A, B) 1 mm; (C, D) 100 μm; (E, F) 10 μm.
administered by subconjunctival injection in the superior nasal quadrant adjacent to the drainage bleb. The same injection site was therefore selected in this study. Clinically, the site of subconjunctival 5-FU administration varies, depending on clinical preference. Some clinicians favor injections adjacent to the bleb and some 90° and others 180° from the operation site. The main concern with injecting 5-FU adjacent to the bleb relates to the possibility of intraocular penetration, because the pH of 5-FU is 9. We decided to base our study protocol on the pioneering studies of 5-FU in glaucoma surgery performed by the Fluorouracil Filtering Surgery Study Group. In this study 5-FU was injected 180° from the site of surgery. Given the different injection sites for the CAT-152 and 5-FU groups a universal injection site for a control vehicle was not possible and therefore the no-treatment control group was introduced.

Aqueous flow bathes the wound and provides a unique and changeable environment that influences postoperative healing. Of all the growth factors in the aqueous TGF-β is the most potent stimulator of human Tenon’s fibroblast activity. Latent TGF-β2 is produced by tissues within the eye (ciliary body and trabecular meshwork) before activation by plasmin and thrombospondin released from blood components. Aqueous humor in glaucomatous eyes contains increased level of TGF-β2. After glaucoma surgery, elevated levels of activated TGF-β2 at the wound site are therefore likely to be related to aqueous concentration, the flow of aqueous, and breakdown of the blood aqueous barrier. In addition TGF-β2 also displays the ability to autoinduce its own production thereby initiating a perpetuating cascade of activation. In a mouse model of conjunctival scarring, peak levels of TGF-β2 have been shown at the wound site at day 7. Without treatment, the rabbit model fails by day 14. We propose that isolated postoperative administration of CAT-152, between days 2 and 14 in this model, can still neutralize subconjunctival TGF-β2 levels at the wound site below a threshold required to mediate downstream effects on the extracellular matrix.

Histologic analysis of the rabbit tissues showed that CAT-152 significantly reduced subconjunctival collagen deposition compared with both the 5-FU and control groups. CAT-152 also significantly reduced the population of cells expressing α-smooth muscle actin, indicating an inhibition of fibroblast differentiation into the myofibroblast phenotype. Myofibroblasts are specialized fibroblasts that play an important role in wound healing. They are present transiently during tissue repair and are thought to generate the contractile force that is integral to normal wound closure. Excessive or abnormal contraction of granulation tissue leads to pathologic scarring. Fibroblast differentiation into the myofibroblast phenotype, characterized by the expression and assembly of α-smooth muscle actin into stress fibers, is modulated by cytokines. TGF-β has been shown to be a direct inducer of the myofibroblast phenotype and is capable of upregulating α-smooth muscle actin, both in vivo and in vitro. We have shown in vitro that CAT-152 significantly inhibits TGF-β2-stimulated collagen contraction. These observations suggest that the beneficial effects of CAT-152 in glaucoma surgery may be mediated by a reduction in TGF-β2-induced collagen production and contraction.

Repeated injections of subconjunctival 5-FU in clinical practice are known to cause corneal epitheliopathy. Similar findings are associated with the use of 5-FU in this study. The more serious complications of avascular bleb formation, bleb-related infection and chronic hypotony reflect the cytotoxic mechanism of action of antiproliferative agents. CAT-152 treatment provides a more physiological alternative. We present evidence that postoperative TGF-β2 inhibition with this novel monoclonal antibody can prevent failure of experimental glaucoma surgery by inhibition of subconjunctival scarring. This represents a potentially useful development in the prevention of late surgical failure and may provide us with a safer therapy to maintain maximal IOP control in the longer term.

References


