Choroidal neovascular membrane inhibition in a laser treated rat model with intraocular sustained release triamcinolone acetonide microimplants

T A Ciulla, M H Criswell, R P Danis, M Fronheiser, P Yuan, T A Cox, K G Csaky, M R Robinson

Aim: To determine if intravitreal microimplants containing triamcinolone acetonide (TAAC) inhibit experimental fibrovascular proliferation (FVP) induced by laser trauma in a rat as a model of choroidal neovascular membranes (CNVMs).

Methods: 20 anaesthetised male Brown Norway rats received a series of eight krypton red laser lesions per eye (647 nm, 0.05 s, 50 µm, 150 mW). Three types of sterilised TAAC microimplant designs were evaluated: implant A consisting of 8.62% TAAC/20% polyvinyl alcohol (PVA) matrix (by dry weight); implant B consisting of 3.62% TAAC/20% PVA matrix; and implant C consisting of a dual 8.62% TAAC/20% PVA matrix design combined with a central core (0.5 mm) of compressed TAAC to extend the implant release time. For each animal studied, one eye received one of the three aforementioned TAAC implant designs, while the fellow eye received a control implant consisting of PVA but without TAAC. The animals were sacrificed at day 35 and ocular tissues were processed for histological analysis. Serial histological specimens were methodically assessed in a masked fashion to analyse each laser lesion for the presence or absence of FVP; maximum FVP thickness for each lesion was measured from the choriocapillaris.

Results: All three types of TAAC implants inhibited FVP relative to controls in a statistically significant fashion. In the eyes that received implant A (n = 8), the mean thickness of the recovered lesions (n = 36) measured 32 (SD 22) µm, compared to 52 (30) µm (p <0.005) for the recovered lesions (n = 40) from the fellow control eyes. In the eyes that received implant B (n = 6), the mean thickness of the recovered lesions (n = 31) measured 28 (15) µm, compared to 50 (29) µm (p <0.001) for the lesions (n = 19) recovered from the fellow control eyes. In the eyes that received implant C (n = 6), the mean thickness of the recovered lesions (n = 21) measured 39 (24) µm, compared to 65 (30) µm (p <0.001) for the lesions (n = 39) recovered from the fellow control eyes.

Conclusions: All three of the tested TAAC microimplant designs produced potent inhibition of FVP in a rat model of CNVMs. There were no differences in inhibition of FVP between the three different types of implants evaluated. This study provides evidence that: (1) corroborates previous investigations that propose TAAC as a potential treatment for CNVMs in humans, and (2) demonstrates TAAC can be effectively delivered via long acting sustained release intraocular microimplants. It should be noted, however, that the FVP observed in this rat laser trauma may not reflect the CNVM observed in human with exudative age related macular degeneration (AMD).
A 8.62% TAAC matrix with a 200 μg TAAC central reservoir, far right. The matrix for each design consists of 20% polyvinyl alcohol (PVA).

Implant design

Three TAAC containing microimplant designs were evaluated (Fig 1). Implants A and B were designed to deliver drug at different rates to determine if a dose response could be elicited in the rat laser trauma model. Implant C was designed to deliver drug throughout the entire time period of the model. Implant A was prepared using the following procedure: a 20% polyvinyl alcohol (PVA) weight/volume (w/v) solution was formulated by placing TAAC (Sigma Chemical, St Louis, MO, USA) 1652 mg was added to the PVA and mixed with a spatula for 10 minutes to make a 8.62% w/v suspension. The suspension was poured onto a 12 × 12 cm plate producing a thin film, dried at room temperature for 48 hours, and cut into sections of approximately 1 × 2 mm in size, each section representing one matrix implant. Implant B was made by adding 724 mg TAAC to make a 3.62% w/v suspension and a similar procedure as described above was performed to make matrix implants with similar dimensions. Implant C was constructed using the same matrix design as implant A (PVA 20%, TAAC 8.62% w/v) with the addition of a central reservoir of TAAC to extend the implant release time. The central reservoir was made by compressing TAAC powder into 0.5 mm diameter pellets using a customised pellet press (Parr Instruments, Inc, Moline, IL, USA), each weighing 200 μg. The pellets were embedded in the implants by placing the pellets within the matrix film on the glass plate during the wet phase. After drying at room temperature for 48 hours, sections measuring approximately 1 × 2 × 2 mm were cut from the dry film with the drug core centered within the section, each representing one matrix/reservoir implant (implant C).

Control implants (implants without drug) were made in a similar fashion by omitting the TAAC powder. All implants were sterilised (3 megarads, gamma radiation) before the in vitro assays and use in the animals.

Release rate determination

It was not possible to reliably and serially isolate the limited amount of rat vitreous to perform standard drug extraction and HPLC analysis of release rates. However, HPLC was used to assay in vitro release rates on representative implants of each design. In order to mimic the vitreous environment to some extent, each implant was placed in a vial with a constant volume of phosphate buffered saline (PBS) (pH 7.4) at 37°C and 0.5 ml aliquots were removed for a drug assay every 1–3 days. The PBS was replaced every 24 hours to simulate sink conditions. The drug assays were done using a Hewlett Packard HP1100 HPLC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a diode array detector, an autosampler, a quaternary, and an HP Kayak workstation which controlled the operation of HPLC and analysed the data. A Beckman UltraspHERE C-18 column (5 μm, 250 × 4.6 mm) (Beckman Coulter, Inc, Fullerton, CA, USA), used for separation and detection, was set at 254 nm. The flow rate employed was 1.0 ml/min with a mobile phase of 60% of water and 40% of acetonitrile by volume. The retention time of TAAC was 7.0 minutes and the TAAC detection limit was 10 ng/ml. The release rates were determined by calculating the amount of drug released in a given volume over time and recorded for each implant design in µg/day (plus or minus 1 standard deviation (SD)). The cumulative drug released was calculated by integrating the area under the release rate curve using the trapezoidal rule and recorded separately for each implant design in µg plus or minus 1 SD. The differences in the cumulative release rates between the different implant designs (that is, A − B, A − C, and B − C) at days 7, 14, 21, and 28 were tested in SAS 8.0 Proc Mixed (SAS Institute, Inc, Cary, NC, USA) using a general linear fixed effects model that allowed for correlations between measurements on individual implants. Values were based on two sided statistical tests and error estimates were reported in standard deviations (SD).

Placement of TAAC implants and control implants

In the current study, a TAAC microimplant was placed within the vitreous chamber of the right eye and the left eye received a control implant composed of PVA but containing no TAAC. Eight rats were assessed using the implant A design, six rats were assessed using the implant B design, and six rats were assessed using the implant C design. Oxybuprocaine (proparacaine) hydrochloride (0.5%) was used for topical anaesthesia (in addition to general anaesthesia) during this procedure. Before surgical placement of the implants, 5% povidone was applied to the ocular surface. A single small incision was made in the superior globe, just posterior and parallel to the ora serrata, which allowed the implant to be inserted within the vitreous, followed by a single suture for closure. The posterior segment was evaluated immediately after insertion to confirm proper placement of the implant into the vitreous cavity. All eyes were treated with daily topical bacitracin ointment for the first week. The entire group of 20 rats was treated in this fashion.

Assessment

Fundus photography and fluorescein angiography were not conducted because of the implant, which partially obscured the view of the posterior segment. However, eye examinations were conducted on day(s) 0, 1, 3, 7, 14, 21, 28, and 35 to rule out endophthalmitis and to assess the overall health of the animals.

On day 35, eyes were enucleated immediately after the rats had been sacrificed and eyecup preparations fixed in 4% phosphate buffered paraformaldehyde solution (overnight at room temperature). For each eye, a single square-shaped tissue
block (approximately 1.5 mm/side), containing the optic disc and the eight lesion sites, was hand sectioned from the eyecup preparation. Tissue sections were dehydrated, embedded in paraffin, serially sectioned (6 µm), and stained for light microscopy with haematoxylin and eosin. Each laser lesion site recovered was individually evaluated and photographed. In both treated and untreated eyes, some of the lesion sites were not considered “recoverable” because of (1) the presence of subretinal haemorrhages, produced at the time of laser photocoagulation, (2) the loss of tissue sections during histological processing, and (3) the inability to clearly discern separate lesion sites that resulted from tangential expansion of FVP from one lesion site into the next. All of the histological specimens were methodically assessed in a masked fashion by one reader (MHC) to analyse each laser lesion for the presence or absence of FVP (the combined presence of choriocapillaris/inner scleral, layers. 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Each recovered lesion site was evaluated in its entirety to quantify the fibrovascular response. Maximum FVP thickness was measured from the choriocapillaris, which, at some sites, had expanded distally into the deeper choroidal/inner scleral, layers. Maximal thickness measurements were obtained from masked digital photographs (Nikon CoolPix 990), converted to µm measurements from image of graticule measurements; this technique showed a test-retest reproducibility of plus or minus 2 µm using a random sampling of representative masked lesions. Proximally, the FVP remained subretinal at some lesion sites, while in other instances, continued proximally with infiltration of the retina. Occasionally, individual neovessels from the central FVP mass continued to infiltrate further into the retinal layers; however, this vasculature was not included in the FVP thickness measurements. At TAAC treated lesion sites where complete inhibition had occurred, retinal elements often were drawn into absolute defects in the choroid which were devoid of FVPs. This effect is well depicted in the figures. At these sites, the maximum thickness of the choriocapillaris was obtained, immediately adjacent to the lesion site. As such, measurements of FVP/choriocapillaris thickness by these criteria probably resulted in overly conservative estimates of neovascular inhibition by the TAAC implants. Within each of the three implant design populations tested, the significance of the difference between the mean thickness of the TAAC treated population and the mean thickness of the untreated control population was evaluated by non-directional (two tailed) t test analysis.

RESULTS

Implant in vitro release rates

Implant A (n = 3, mean weight 0.9 (SD 0.17) mg) and implant B (n = 3, mean weight 1.2 (0.1) mg) delivered drug for a total of 29 and 22 days, respectively. The cumulative amount released for implants A and B, estimated from the release rates, was proportional to the square root of time (Fig 2), typical for a matrix implant whose release kinetics is governed by diffusion from dispersed drug. The cumulative release between implants A and B was significantly different (p <0.03) at 14, 21, and 28 days. Implant C (n = 4, mean weight 2.45 (0.37) mg), a combination matrix/reservoir design, delivered an initial bolus of drug over the initial 11 days followed by a steady state release of drug throughout the 7 week assay period. The steady state cumulative release from implant C after day 11, estimated from the release rates, followed zero order kinetics (Fig 3), typical for diffusion controlled reservoir devices. The cumulative release between implants A and C was significantly different (p <0.04) at 7, 14, 21, and 28 days. There were no significant difference between implants B and C in the cumulative release rates at all time points; however, implant C, with its reservoir component, extended the release 13 days after implant B release had expired.

Histopathological analysis

All three types of TAAC microimplants inhibited FVPs relative to controls in a statistically significant fashion (Table 1). A first group of eight rats underwent placement of implant A in one laser treated eye, and implantation of a control implant in the fellow laser treated eye. In the control eyes, histopathology from day 35 revealed FVPs arising through the disrupted RPE and Bruch’s membrane and infiltrating the retina (Fig 4A).

<table>
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<th>Table 1</th>
<th>Comparison of mean FVP thickness in eyes receiving TAAC microimplants versus eyes receiving control implants</th>
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<td>Implant A</td>
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<td>FVP sites [n]</td>
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<td>Mean FVP thickness (µm)</td>
<td>36 [22]</td>
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<td>Significance</td>
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These histological results in the control eyes were comparable to those previously published using this model (Fig 4G). In the fellow eyes treated with implant A, there were prominent defects in the RPE and Bruch’s membrane with inhibition of FVPs, and with the retina typically being drawn into the defect (Fig 4B). In these eyes that underwent placement of implant A, mean FVP thickness at the recovered lesion sites (n = 36) measured 32 (22) µm, compared to 52 (30) µm (p <0.005) for the recovered lesion sites (n = 40) from the fellow control eyes.

A second group of six rats underwent placement of implant B in one laser treated eye and implantation of a control implant in the fellow laser treated eye. The histological findings from this group of animals (Fig 4C, D) were similar to those results from the first group of rats that were treated with implant A; once again TAAC inhibition of FVPs was evident both qualitatively and quantitatively. In these eyes, the mean FVP thickness of the recovered TAAC treated lesion sites (n = 31) measured 28 (22) µm compared to 50 (29) µm (p <0.001) for the lesions sites (n = 19) recovered from the fellow control eyes (see Table 1).

A third group of six rats underwent placement of implant C in one laser treated eye and implantation of a control implant in the fellow laser treated eye. The histological findings (Fig 4E, F) were again similar to those from the previous two implant design groups, and demonstrated inhibition of FVPs. Note, however, in Figure 4F that while the retinal elements were being drawn distally into the choroidal defect on the left side of the lesion, some new choroidal vessels were infiltrating the retina on the right side of the lesion site. In eyes from this
group, the mean FVP thickness of the recovered TAAC treated lesion sites (n = 21) measured 39 (24) µm compared to 65 (30) µm (p < 0.001) for the lesion sites (n = 39) recovered from the fellow control eyes (see Table 1).

DISCUSSION

This investigation demonstrates that triamcinolone acetonide can be delivered intraocularly via long acting sustained release microimplants and further corroborates previous experimental animal studies which indicate that TAAC and other corticosteroids can inhibit initial FVP formation.\(^\text{11-19}\) In this study, three different TAAC microimplant designs were evaluated. Each type of TAAC delivering microimplant significantly inhibited FVP relative to non-TAAC controls; however, no statistically significant differences in efficacy could be demonstrated between the three implant designs at the specific dosage tested and given the length of therapy (35 days). Nevertheless, this study contributes to a growing body of evidence that TAAC may serve as a potential treatment for CNVM development in humans.

The rat laser model that was chosen for use in this investigation has been validated previously by other investigators using intense diode\(^\text{26}\) or krypton\(^\text{27}\) laser photocoagulation to acutely rupture Bruch's membrane, leading to rapid and reproducible FVP. In addition, this particular animal laser model does not exhibit the rapid spontaneous regression of the neovascular process,\(^\text{15} 16\) which occurs in the primate laser model; this is a useful feature when evaluating antiangiogenic/antiproliferative treatments.

The stimulus for neovascularisation in laser models obviously differs from that in AMD, as laser models invoke a traumatic repair process, which may better mimic traumatic CNVM development and not necessarily AMD related CNVMs. Investigators using the primate laser model first postulated that macrophages, involved in the initial response to Bruch's membrane injury, secrete angiogenic growth factors.\(^\text{18}\) This macrophage response may initiate the expression of a cascade of angiogenic growth factors, including basic fibroblast growth factor (bFGF),\(^\text{31-33}\) vascular endothelial growth factor (VEGF),\(^\text{15} 16 19\) and transforming growth factor beta (TGF-\(\beta\)) in the rat laser trauma model. Similarly, these growth factors are probably also mechanistically relevant to human CNVM formation, as surgically excised and postmortem CNVM and RPE cells have shown immunoreactivity for these same growth factors.\(^\text{34-39}\)

Steroid compounds possess antiangiogenic properties through the alteration of extracellular matrix degradation, an important step in angiogenesis,\(^\text{40}\) and possibly through inhibition of leucocytes that release angiogenic growth factors.\(^\text{12} 14\) Intraocular steroid injections potently inhibit experimental preretinal neovascularisation in pigs\(^\text{41}\) and rats,\(^\text{42}\) as well as experimental subretinal neovascularisation in primates\(^\text{43}\) and rats.\(^\text{15} 16\) In humans, oral prednisone or sub-Tenon's injections of depo forms of steroids have been advocated for treatment of CNVM due to presumed occult histoplasmosis syndrome.\(^\text{44-46}\) Although no controlled studies have yet been performed to verify this hypothesis.

Several pilot studies of intravitreal triamcinolone acetonide for AMD related CNVMs have suggested some beneficial effect.\(^\text{47-51}\) These authors have speculated that intravitreal triamcinolone has a beneficial effect on AMD related CNVM development through the inhibition of leucocytes, including macrophages, which release angiogenic factors as noted above.\(^\text{52}\) Therefore, it is possible to speculate that the cellular and molecular mechanisms that elicit FVP in this experimental model could be intrinsically similar to those mechanisms that produce CNVM formation as an integral component of exudative AMD.

The findings of this current TAAC microimplant study also can be compared to a previous study in which one laser treated rat eye underwent acute injection of 0.8 mg TAAC and the fellow laser treated eye underwent acute injection of 20 µl saline.\(^\text{53}\) Representative histopathology is depicted in Figure 4G and H. Note that the lesion sites from the saline injected control eyes (Fig 4G) were essentially identical to those eyes that underwent acute placement of a control implant (Fig 4A, C, E), in that FVP developed at the sites of laser disruption of the choroids and RPE. The treated lesions from both the TAAC injected eyes (Fig 4H) and the TAAC implant eyes (Fig 4B, D, F) were also similar with inhibition of the FVP. At various lesion sites in the TAAC implant eyes, the extent of this effect ranged from partial inhibition to absolute inhibition, whereas FVP inhibition was absolute at all lesion sites in the TAAC injected eyes. This partial dissimilarity in TAAC efficacy between the two methods of drug delivery may have resulted from both a dosing effect and a timing effect. Intuitively, eyes injected with TAAC in solution can be expected to develop much higher initial concentrations of intravitreal TAAC compared to those eyes that undergo placement of the TAAC implants. In addition, microimplants, by their inherent construction, require a finite time period to elapse before initial release of the drug agent is initiated, followed by a refractory time period before maximum dissemination of the agent is achieved. FVPs in this experimental model have been shown to develop aggressively and have been observed within 3 days of lesion induction.\(^\text{54}\) Therefore, the bolus of injected TAAC may have more effectively inhibited FVPs during this initial period than that of the sustained release low doses of TAAC delivered by the microimplants. In addition, some regional variations in the extent of neovascular inhibition were noted within many of the eyes; it can be speculated that this variation could reflect local intravitreal concentration gradients, with those lesion sites located closest to the implants demonstrating the most prominent inhibition of FVPs.

An inherent limitation of the rat experimental model that should be noted is the small volume of the vitreous, which can be estimated at approximately 56 µl (as determined from rat schematic eye dimensions).\(^\text{55}\) as well as the strong attachment by the vitreous to the lens and retina in this species (personal observations). Unfortunately, this makes direct, in vivo measurements of dynamic TAAC concentration levels unfeasible.

In the current study, all three types of TAAC microimplants inhibited FVP compared to their control populations in a statistically significant fashion. However, it should also be noted that this study, by its design, demonstrated inhibition or prevention of FVPs, but not regression of pre-existing FVPs, which would be more relevant to human CNVM development. The rapid development of FVP by this model also prevented subtle comparisons of the effectiveness of the three microimplant designs relative to each other. Further differentiation of these microimplant designs in the delivery of purported antiangiogenic and antiproliferative agents (such as TAAC) will be necessary. Obviously, new methods such as implants, microspheres and liposomes will continue to be developed as alternatives to acute injection for the safe, regulated, and extended delivery of intracocular drug agents.

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CNVM inhibition in a laser treated rat model

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