

A randomized controlled prospective study to assess the role of subconjunctival bevacizumab in primary pterygium surgery in Indian patients

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Background: Pterygium is an ocular surface disorder with prevalence rates ranges from 0.3% to 29% in different parts of the world. Vascular endothelial growth factor (VEGF) has been detected in increased amounts in pterygium epithelium, compared with normal conjunctiva. Bevacizumab is a recombinant, humanized anti-VEGF antibody suggested as a possible adjunctive therapy for pterygium excision that appears to have a role in prevention of recurrence. We conducted this study to evaluate the role of subconjunctival bevacizumab in primary pterygium surgery in Indian patients. **Methods:** In this randomized prospective clinical study, the patients were randomized into two groups of 30 patients each. Study group received 1.25 mg/0.05 ml subconjunctival bevacizumab 1 week before pterygium surgery with conjunctival autograft. Control group received 1.25 mg (0.05 ml) subconjunctival normal saline 1 week prior to pterygium surgery with conjunctival autograft. Patients were followed up at day 1, day 7, 1 month and 3 months. The main outcome measures were morphology of pterygium after injection, intra-operative ease, recurrence of pterygia, and any complications. **Results:** After giving bevacizumab, there was statistically significant improvement in grade, color intensity, size of pterygium, and symptoms of patients. Intra-operatively, less bleeding was observed by the surgeon. No statistically significant difference regarding reduction in astigmatism, improvement of visual acuity, and complications were observed in two groups. Recurrence was noted in five patients (8.33%) in total study population at the end of 3 months. It was present in two patients (6.67%) in Group A and three patients (10%) in Group B. **Conclusion:** Single preoperative administration of subconjunctival injection bevacizumab given 1 week before the pterygium excision with conjunctival autograft decreases the vascularity of newly formed blood vessels, hence may decrease recurrence rate though not in our study.

Key words: Bevacizumab, pterygium, subconjunctival

Pterygium is a common ocular surface disorder with a wing shaped fibrovascular overgrowth of bulbar conjunctiva onto the cornea and it is often triangular in shape and consists of a head, i.e., the part which rests on the cornea, a neck, and a body.^[1] It is a common conjunctival degenerative condition, which is characterized by elastotic degeneration of collagen and fibrovascular proliferation. Pterygium affects 0.3–29% of the population worldwide and it is reported to occur in males twice as frequently as in females. Patients older than 40 years have the highest prevalence of pterygia while patients aged 20–40 years are reported to have the highest incidence of pterygia.^[2,3] Pterygium occurs as a result of breakdown of the corneoscleral limbal barrier results in subsequent conjunctivalization of the cornea,^[4] as the scattered light might follow alternative optical paths when entering the eye, thus hitting limbal stem cells from their inner surface.^[5]

A number of treatment methods have been described which includes adjunctive medical methods (mitomycin c, 5-fluorouracil, daunorubicin, thiotepa drops, and cyclosporine drops instillation), beta irradiation and surgical methods (conjunctival autograft, amniotic membrane grafts,

conjunctival flaps, bare sclera technique, and excision with lamellar keratoplasty).^[6]

It has been well-established that pterygia are composed of proliferating fibrovascular tissue and the pterygium formation, and progression require neovascularization, many molecules regulate angiogenesis have been identified, suggesting that the vascular endothelial growth factor (VEGF) may be involved directly or indirectly in the pathogenesis of pterygia.^[7]

Various studies have shown that recurrence is high from 30% to 88% after simple excision in pterygium and in excision with bare sclera it may be 32%.^[8] VEGF has been detected in increased amounts in pterygium epithelium, compared with normal conjunctiva by studies employing immunohistochemistry.^[9]

Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) is a recombinant, humanized anti-VEGF antibody that binds all VEGF isoforms and exerts a neutralizing effect by inhibiting the VEGF-receptor interaction. It has been suggested

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as a possible adjunctive therapy for pterygium excision that decreases the vascularity of newly formed blood vessels, hence decreasing the recurrence rate and appears to have a role in prevention of recurrence.^[10]

This study aimed to evaluate the effect of subconjunctival injection of bevacizumab in a single dose followed by surgical excision of pterygium with conjunctival autograft after 1 week.

Methods

This prospective, comparative, triple-blinded, randomized control study was conducted over a period of 18 months (from September 2011 to February 2013). Randomization was performed by simple randomization method using table of random number. This study was approved by the Institutional Ethics Committee no. IEC/VMMC/SJH/Thesis/April-13/321 and was conducted according to Indian Council of Medical Research (ICMR) ethical guidelines on biomedical research and principles of good clinical practices. A total of 60 eyes with primary pterygium of 60 patients were enrolled in this study. Each patient underwent a complete ocular examination including visual acuity, refraction, slit lamp biomicroscopy, fundoscopy and intraocular pressure (IOP) measurement, corneal topography by CT-1000 corneal topographer.

Inclusion criteria were patients >18 years of age, patients with Grade II or III primary pterygium (according to Tan *et al.* grading scheme)^[11] with the apex of the lesion past the limbus, patients willing to participate in the study, patients willing to follow-up. Exclusion criteria included patients with evidence of any ocular disease except refractive errors, prior ocular surgery in the past such as pterygium, squint, trabeculectomy surgery, administration of topical medications for pterygium, patients with recurrent pterygium, hypertrophied or atrophic pterygia, acute or inflamed pterygia, pseudo-ptyerygium, conjunctival intra epithelial neoplasia, history of glaucoma or ocular hypertension in the study eye, systemic conditions in which bevacizumab is contraindicated such as hypertension, proteinuria, bleeding tendencies, previous myorectal infarction or stroke, pregnant and lactating women, inability to follow-up for the duration of the study. The main outcome measures of this study are change in morphology of pterygium, evidence of any adverse events (evaluate safety and tolerability), and pterygium recurrence.

Dimensions of pterygium were measured by taking length in mm (from base to apex) and width in mm at the base and apical areas. Size/area of pterygium was calculated by measuring the width at the apex (L_A) and base (L_B) and length of pterygium. Then area = length $(L_A + L_B)/2$. It was a crude method of the calculating area by comparing pterygium to a trapezoid.

Grading of each pterygium was done according to Tan *et al.*^[11] grading scheme proposed in 1997 given as:

- Grade II: (Intermediate) has partially visible episcleral vessels under the body of pterygium
- Grade III: (Fleshy) has totally obscured episcleral vessels under the body of pterygium.

Grading of color intensity on scale of 0–4 was done according to Teng *et al.*,^[12] (0 = unremarkable, 1 = trace, 2 = mild, 3 = moderate, 4 = diffuse).

After taking the written informed consent, patients were randomized into two groups of 30 eyes each, patient details

were obtained and noted on predesigned proforma. One week preoperatively, Group A received subconjunctival bevacizumab (under topical proparacaine) in a dose of 1.25 mg (0.05 ml) by 26-gauge needle into the body of pterygium by gently lifting with colibri forceps and Group B received subconjunctival normal saline 0.05 ml. Two drops of 0.5% moxifloxacin hydrochloride was subsequently instilled in the eye. After a week, examination of patient for size, vascularity, color intensity, and complications was conducted. This was followed by pterygium excision with conjunctival autografting in all the patients by a single trained surgeon.

Complete sterilization and aseptic measures were taken during surgery. Peribulbar anesthesia using 2% xylocaine + 0.5% bupivacaine was injected. After opening the lids using a rigid speculum, 0.2–0.3 ml injection of 2% xylocaine was given at the site of the pterygium to raise it up to its attachment to the cornea. Using Crescent blade, the pterygium was shaved off the cornea starting 0.5 mm in front of its head. The pterygium attached with the conjunctiva was separated from the scleral surface with tenotomy scissor and excised leaving about 3–4 mm area of the bare sclera. After scrapping the episcleral tissue, the area of bare sclera then was measured horizontally and vertically. A free conjunctival autograft was then taken from the superior limbal region approximately 1 mm larger than the recipient site. Graft was then shifted to the recipient area and stitched limbus to limbus with 10/0 vicryl suture. Any intraoperative complication was noted and was treated accordingly, and the patients were reassured.

All cases were given dexamethasone + moxifloxacin eye drops postoperatively 4 times a day in the 1st week. Dexamethasone was tapered over 4 weeks and moxifloxacin was stopped after 2 weeks of the study. Carboxymethylcellulose (0.5%) eye drops 4 times a day for 2 months. Follow-up was done at day 1, 1 week, 1 month, and 3 months after the surgery. Symptoms such as pain, lacrimation and photophobia, grittiness, and redness were noted at each visit. Best-corrected visual acuity, refraction, clinical photographs, and slit lamp examination for any complications such as ischemia, necrosis, infection, graft dehiscence at surgical site were observed. Average corneal power (ACP) was calculated by taking the mean of horizontal and vertical corneal power obtained by corneal topography. Corneal topography was done at 3 months.

Evidence of recurrence by appearance of surgical bed at 3 months was noted according to Tseng's criteria^[13] (Grade I: Normal appearance, Grade II: Fine episcleral vessels without corneal extension, Grade III: Episcleral vessels and fibrovascular tissue without corneal extension, Grade IV: Fibrovascular tissue extending past the limbus).

Statistical analysis

Statistical analysis was performed using SPSS 19.0 package and STATA 11.2 version (SPSS Inc., Chicago, IL, USA). Quantitative data were analyzed using Student's *t*-test (paired and unpaired) and categorical data by the test of proportion, Chi-square, Fisher's exact test, and McNemar test. Results of the analysis were evaluated under 95% confidence interval. Mean values were shown as mean \pm standard error of mean. The value $P \leq 0.05$ was considered statistically significant.

Results

The age of the patients was between 18 and 64 years with a mean age of 37.33 years. Thirty-four patients (56.67%) were male while 26 patients (43.34%) were females. Male to female ratio was 1.34: 1. The only right eye was involved in 24 patients (40%) and only left eye in 21 patients (35%) and both eyes in 15 patients (25%). There were 50 nasally situated pterygia (83.34%), of which, 36 were unilateral and 14 were bilateral. Ten pterygia were temporally situated (16.67%), of which, 9 were unilateral and 1 was bilateral. No significant difference was observed in demographic pattern of patients in the two groups ($P > 0.05$).

The mean pterygium size in Group A was 60.52 ± 3.90 mm² preoperatively, which decreased to 59.08 ± 3.68 mm² after bevacizumab injection ($P = 0.005$). The mean pterygium grade in Group A was 2.43 ± 0.09 preoperatively, which decreased to 2.13 ± 0.12 after bevacizumab injection ($P = 0.001$). The mean pterygium color intensity in Group A was 3.13 ± 0.13 preoperatively, which decreased to 2.56 ± 0.15 after bevacizumab injection ($P = 0.0007$). No change was observed in size, grade, or color intensity of pterygia for 1 week in Group B [Table 1]. The intergroup comparison between two groups was not significant as shown in Table 2.

Postoperatively, In Group A, there was improvement of 1 line on Snellen’s chart in 30% patients and improvement of two lines in 6.67%. Visual acuity remained same in 63.34% patients. In Group B, improvement of one line was there in 26.67%,

and of two lines in 6.67%. Visual acuity remained same in 66.67% patients. No worsening was noted in any of the groups.

ACP increased in both the groups postoperatively [$P < 0.05$, Table 3]. Mean simK astigmatism decreased significantly after surgery in both groups. The “with the rule” astigmatism was found to be the most common type of astigmatism both before and after surgery (86.67%) in both the groups. The distribution of type of corneal astigmatism did not change by the surgery. Mean IOP did not change significantly in any group [Table 3]. The intergroup comparison between two groups was not significant as shown in Table 4.

In Group A, after injection, there was improvement in all symptoms (redness, irritation, pain, itching, watering, and photophobia) except mass and decreased vision. The change in symptoms after injection was statistically significant ($P < 0.05$). In Group B, after injection, no increase or decrease in symptoms was noted. Subconjunctival hemorrhage was present in two patients (6.67%) in each group after injection. These patients presented as increased redness after injection. There was an apparent subjective benefit in Group A in the form of less bleeding due to less vascularized pterygium as compared to Group B pterygium. However, we did not quantify this effect.

Subconjunctival hemorrhage was present in 6.67% of patients both in Group A and B after injection. Patients were operated without any intra-operative complications.

Graft edema and congestion were present in 6.67% of patients in Group A and in 3.33% of patients in Group B on the

Table 1: Mean size, grade, and color intensity of pterygium within two groups

Parameter (mean±SEM)	Group A			Group B		
	Preoperative	Postinjection	P*	Preoperative	Postinjection	P*
Size	60.52±3.90	59.08±3.68	0.005	54.68±3.12	54.68±3.12	1.000
Grade	2.43±0.09	2.13±0.12	0.001	2.33±0.08	2.33±0.08	1.000
Color intensity	3.13±0.13	2.56±0.15	0.0007	3.16±0.11	3.16±0.11	1.000

*Comparison between before and after treatment in the same group. All values are expressed as mean±SEM. Pre- and post-treatment comparison was done with paired t-test. SEM: Standard error of mean

Table 2: Mean size, grade, and color intensity of pterygium between two groups

Parameter (mean±SEM)	Preoperative			Postoperative		
	Group A	Group B	P*	Group A	Group B	P*
Size	60.52±3.90	54.68±3.12	0.24	59.08±3.68	54.68±3.12	0.42
Grade	2.43±0.09	2.33±0.08	0.44	2.13±0.12	2.33±0.08	0.18
Color intensity	3.13±0.13	3.16±0.11	0.85	2.56±0.15	3.16±0.11	0.007

*Comparison of before and after treatment between two groups. All values are expressed as mean±SEM. Pre- and post-treatment comparison between two groups were done with unpaired t-test. SEM: Standard error of mean

Table 3: Mean ACP, simK astigmatism of pterygium within two groups

Parameters (mean±SEM)	Group A			Group B		
	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*
ACP	42.81±0.30	43.58±0.24	<0.0001	43.00±0.31	43.84±0.25	<0.0001
simK astigmatism	1.66±0.23	0.66±0.11	<0.0001	1.84±0.26	0.79±0.11	<0.0001

*Comparison between before and after treatment in the same group. All values are expressed as mean±SEM. Pre- and post-treatment comparison was done with paired t-test ACP: Average corneal power, SEM: Standard error of mean

Table 4: Mean ACP, simK astigmatism of pterygium between two groups

Parameters (mean±SEM)	Preoperative			Postoperative		
	Group A	Group B	P*	Group A	Group B	P*
ACP	42.81±0.30	43.00±0.31	0.46	43.58±0.24	43.84±0.25	0.66
simK astigmatism	1.66±0.23	1.84±0.26	0.61	0.66±0.11	0.79±0.11	0.41

*Comparison of before and after treatment between two groups. All values are expressed as mean±SEM. Pre- and post-treatment comparison between two groups were done with unpaired t-test. ACP: Average corneal power, SEM: Standard error of mean

first postoperative day. This was resolved in 1–2 weeks period. Conjunctival cyst was reported in 3.33% of patients both in Group A and B. due to its small size no intervention was done, and it resolved on its own within 2 months.

Recurrence [Table 5] was noted in five patients (8.33%) in the total study population at the end of 3 months. It was present in two patients (6.67%) in Group A and three patients (10%) in Group B. There was no statistical difference between two groups ($P > 0.05$). There were 80% recurrences (four patients) below 50 years of age and only 20% recurrences (one patient) occurred above 50 years.

Among all the patients in Group A, Grade II and III recurrence comprised 50% each. There was no Grade IV recurrence seen. They were present only in patients having Grade III and bilateral pterygium.

Among all the patients in Group B, Grade II and III recurrence comprised of 33.34% ($n = 1$) and 66.67% ($n = 2$), respectively. There was no Grade IV recurrence seen. 66.67% recurrences were seen in patients having Grade II pterygium, and 33.34% was seen in patients having Grade III pterygium. Similarly, 66.67% recurrences were in unilateral pterygium and 33.34% in bilateral pterygium [Table 5].

Discussion

Management of pterygium poses a challenge due to the high rate of recurrence after surgery. VEGF plays a major role in angiogenesis and promotes endothelial cell migration and proliferation and a significant role of inflammation in the induction of recurrence after pterygium surgery.^[14] The present aim of our study is to use anti-VEGF therapy in the treatment of pterygium in Indian patients. Because the anti-VEGF therapy induces the regression of blood vessels and decreases the size of pterygium. Blockade of VEGF can result in inhibition of new vessel formation. Hence, anti-VEGF has been suggested as possible adjunct therapy for pterygium excision that appears to play a role in prevention of recurrence. Since, bevacizumab is an anti-VEGF drug, so exploring its role in primary pterygium surgery in Indian patients. Since bevacizumab has a role in decreasing the size and vascularity of pterygium, it can be used preoperatively in highly vascular or large pterygium. Furthermore, it decreases the recurrence rate (though not statistically significant), it can be used in recurrent pterygium.

The first study to demonstrate that increased VEGF level may play a role in pterygium development was reported in 2001 by Lee *et al.*^[9] Thus, inhibiting VEGF by giving anti-VEGF like bevacizumab may reduce fibroblast proliferation and possibly recurrence, which forms the basis of our study. A recurrence rate of 8.3% was reported in our study after a period of 3 months. On comparing both the groups,

Table 5: Number of patients with complications in two groups

Complications (number of patients)	Group A (%)	Group B (%)
Recurrence (3)	2 (6.67)	3 (10.00)
Graft edema (1)	2 (6.67)	1 (3.33)
Subconjunctival hemorrhage (2)	2 (6.67)	2 (6.67)
Conjunctival cyst (4)	1 (3.33)	1 (3.33)

the difference in recurrence rate did not reach statistical significance levels.

In Group A, bevacizumab in the concentration of 1.25 mg/0.05 ml was given. The optimal dosing for the subconjunctival use of bevacizumab is still undetermined, but same concentration has been used in other studies.^[15]

Statistically significant change was observed in the mean size of pterygium in Group A. Similar results were obtained by Fallah Tafti *et al.*^[16] This is also supported by results of Besharati *et al.*,^[17] (size decreased after 3 months of repeated injection). There was statistically significant improvement with respect to mean grade of pterygium in Group A as compared to Group B in which it remained unchanged. A study done by Felipe *et al.*, showed similar improvement of mean grade at 2nd week postinjection.^[18] They inferred that bevacizumab has potential to cause shrinkage and regression in the vascular caliber of pterygium blood vessels.

The change of grade correlated with the change in color intensity in Group A as bevacizumab cause shrinkage of vessels present in pterygium. Mean color intensity in Group A decreased from 3.13 to 2.56 after injection bevacizumab. Decrease in color intensity was noted by Teng *et al.*, in a case report of a patient with inflamed nasal primary pterygium.^[12] Similar results were obtained by Besharati *et al.*^[17] Change in pterygium grade and color intensity among patients of Group A and B are shown in Fig. 1.

Visual acuity remained same or improved postoperatively in both the groups. No worsening of vision was noted. There was a shift of patients from worse to better vision, probably due to a reduction in astigmatism.

Mean simK astigmatism decreased in both groups after 3 months of surgery. Corneal topography revealed mostly “with the rule” astigmatic patterns before and after surgery. Similar results were observed by Cinal *et al.*,^[19] they reported an increase in mean ACP from 42.26D to 43.69D and decrease in mean simK astigmatism from 2.30D to 0.82D after pterygium surgery. Lin and Stern found a significant correlation between the pterygium size and corneal astigmatism; they reported pterygium to induce significant degrees of astigmatism once

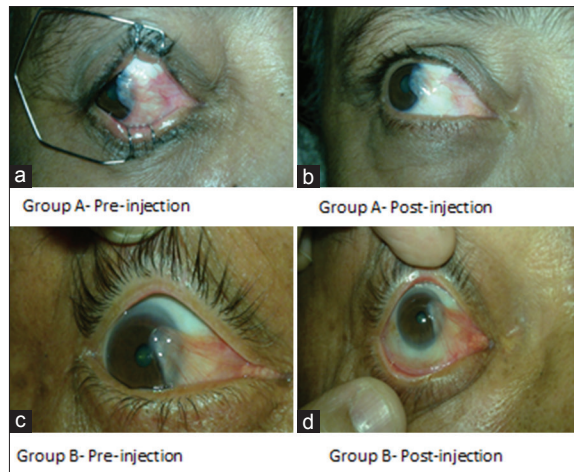


Figure 1: Pre- and post-injection changes observed in Group A and Group B patients. There was more decrease in grade of pterygium and color intensity in Group A patients as compared to Group B. (a) Group A nasal pterygium pre-injection (b) Group A nasal pterygium post-injection (c) Group B nasal pterygium pre-injection (d) Group B nasal pterygium post-injection.

it exceeded $>45\%$ of the radius.^[20] Kampitak reported that 2.25 mm pterygium resulted in astigmatism of 2D, and should be considered in the limits of surgery.^[21]

Majority of patients presented to us with complaints of redness, mass, and itching. In Group A, there was a significant decrease in symptoms after injection ($P = 0.0018$). Pain and photophobia were gone, and there was a decrease in redness, itching, watering, and irritation. In Group B, no change was observed postinjection. Teng *et al.*, also reported considerable decrease in irritation and redness postinjection.^[12]

Intraoperatively, bleeding was observed in some patients in both the groups which were successfully managed by pressure and cauterization. However, it was observed that in Group A, the vascularity of pterygium decreased in majority of patients which led to less bleeding. So, there was subjective ease in doing surgery.

In our study, 3 patients developed graft edema, 4 with subconjunctival hemorrhage, 2 conjunctival cysts and 5 recurrences. No local irritation, allergic reaction, surface epitheliopathy, or uveitis was observed. This is in contrast with a 60% rate of spontaneous loss of epithelial integrity as recently reported by Kim *et al.*, where the investigators used topical bevacizumab at a slightly higher concentration (1.25%) twice daily for a much longer period (3 months), and adverse effects generally appeared during the 2nd month of treatment.^[22]

A study by El Shafie *et al.*, described that the preoperative subconjunctival bevacizumab reduces the recurrence rate of pterygium surgery, as it reduces the vascular element of pterygium.^[23] Another study by Alhammami *et al.*, showed that subconjunctival bevacizumab is useful in patients with recurrent pterygium.^[24,25]

There were five recurrences (8.33%) in our study. In Group A, there was recurrence in 6.67% of cases while in Group B, recurrence was observed in 10% cases. However, no statistically significant difference was observed. In a study, the authors concluded that if pterygium is going to recur, it usually grows back or shows signs of recurrence during first 3 months.^[26]

Therefore, the follow-up period for our study was chosen to be 3 months. In a similar study by Razeghinejad *et al.*, equal numbers of recurrences were observed in both the groups. They concluded that single intra-operative subconjunctival bevacizumab has no effect on recurrence rate of pterygia.^[27]

In a study done by Oguz *et al.*, the recurrence rate was as low as 9.52% by the method of pterygium excision with conjunctival autograft, which is similar to our study.^[28] Fahmi *et al.*, reported recurrence rate of 13.3% with conjunctival autograft.^[29] About 14% recurrence was reported by Allan *et al.*,^[30] 12% by Baig *et al.*,^[31]

We observed that most of the recurrences (in four patients, 80%) were in age group <50 years and only one (20%) was in patient of age >50 years. Our observation was consistent with the observation of Lewallen *et al.*,^[32] Manning *et al.*,^[33] and Figueiredo *et al.*,^[34] who stated that most of the recurrences occurred in patients younger than 50 years in their study.

Recent studies have shown that several factors, such as anti-apoptotic mechanisms, pro-inflammatory cytokines, growth factors, extracellular matrix remodeling, immunological mechanisms, viral infections and the genetic component may be involved in the pathogenesis of the disease. Bevacizumab is directed against all type of VEGF, but not against other growth factors found in pterygium.

Conclusion

The study intends to observe the morphological changes and adverse effects in pterygium after injection apart from observing the recurrence rate. So, from our study, it can be concluded that single preoperative administration of subconjunctival injection of bevacizumab given 1 week before the pterygium excision with conjunctival autograft is useful in the treatment of patients with primary pterygium without local or systemic adverse effects. It provides a promising approach in inducing regression in pterygium size, vascularity, and grade. It decreases the recurrence rate of pterygia, but this decrease was not statistically significant.

Future we need to continue to follow-up our patients in a longer term to see if any differences are observed in the recurrence rate in the two groups in the long run.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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