Original Article

Single-Session Prophylactic Pan-retinal Photocoagulation in Moderate Nonproliferative Diabetic Retinopathy in Low-Resource Settings

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Abstract

Purpose: To study patient's acceptability and safety of offering a prophylactic early single session of pan-retinal photocoagulation (PRP) for moderate nonproliferative diabetic retinopathy (NPDR) in selected patients. **Settings and Design:** Mixed observational and interventional study. **Patients and Methods:** The observational study included 82 eyes of 68 patients presenting with proliferative diabetic retinopathy (PDR) or its complications and the interventional study included 48 eyes of 48 patients with moderate NPDR who were offered a single session PRP because they were unlikely to comply with the follow-up protocol and were at higher risk of diabetic retinopathy (DR) progression. **Results:** The observational study showed that nearly 51% of patients had no idea about the DR screening protocols, 47.5% of included eyes presented with vitreous hemorrhage, 30.5% with tractional retinal detachment, and 22% with retinal neovascularization. The interventional study showed that minor patients' complaints were reported such as night vision problems, flashes, and peripheral field defects. There was no significant change in the mean preoperative logarithm of the minimum angle of resolution (logMAR) corrected distance visual acuity (CDVA) over time throughout the study ($P = 0.951$). At the end of follow-up, 89.5% of included eyes showed no loss of any lines of their preoperative logMAR CDVA and 10.5% lost only one line. All eyes remained in the same stage of moderate NPDR with no signs of progression to severe or very severe NPDR or proliferative DR. **Conclusion:** Prophylactic early PRP is an acceptable, safe, and satisfactory procedure for patients with moderate NPDR in low-resource settings.

Keywords: Diabetic retinopathy, low-resource settings, pan-retinal photocoagulation, vision loss

Introduction

Diabetic retinopathy (DR) is a major challenge to ophthalmic practice in communities with poor socioeconomic development and low coverage of health services. DR is one of the leading causes of vision loss worldwide, estimated to account for 1.25% of moderate-to-severe visual impairment and 1.07% of blindness.[1] Despite the promise of new immunologic-derived pharmaceutical agents, pan-retinal photocoagulation (PRP) remains the gold standard treatment for preventing visual loss in proliferative diabetic retinopathy (PDR).[2] Scatter photocoagulation is not recommended for eyes with mild or moderate non-PDR (NPDR) provided that careful follow-up can be maintained. When retinopathy is more severe, scatter photocoagulation should be considered and should not be delayed if the eye has reached the high-risk proliferative stage.[3] As many as 27% of patients with moderate NPDR are estimated to progress to PDR in 1 year; therefore, they should be seen every 4–8 months.[4] This ideal is not what ophthalmic practice has to deal with in communities of low-resource settings, where screening protocols are not followed and patients often seek medical advice due to visual complaints from the complications of PDR without being diagnosed in the nonproliferative stage. It is this documented situation in

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our community and the challenge to our service that provides the rationale for the early interventional study.

The current study had two main goals – the first one was to highlight the challenge to ophthalmic practice in low-resource settings in having to deal with patients who present with PDR or its complications without being aware of or complying with earlier screening protocols. Second, to study the acceptability, feasibility, and safety of offering and performing early single session of PRP in moderate NPDR in selected patients who were considered unlikely to comply with the follow-up screening protocol and those who were at higher risk for disease progression.

Patients and Methods

Ethical approval

A written informed consent was obtained from all participants in the study. The study was conducted under the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of the Faculty of Medicine (IRB: 17300819).

Trial registration

Clinical trials Government: NCT 05543564.

Study design

This was mixed observational and interventional study.

The observational study

This part of the study included 68 patients who presented with PDR or its complications. We recorded the patient characteristics, clinical condition, and intervention needed. Patients were asked about the cause of delay in ophthalmic medical consultation whether it was related to a patient factor or the health service.

The prospective interventional study

This part of the study included 48 eyes of 48 patients presenting with visual or nonvisual complaints who were diagnosed with moderate non-PDR whose Glycosylated Hemoglobin (HbA1c) is 8% or more and who may not regularly check the HbA1c., were less likely to be able to comply with the screening follow-up protocol, and were considered more likely to have the disease progressing. Patients were informed about the benefits and risks of early PRP at this stage of their disease. This was clarified to the patients and, whenever appropriate, to their relatives. The possible complications of PRP were stated. Patients were made aware of the expected pain during and after the procedure.

After informed consent, patients were offered and accepted a single session of early prophylactic PRP. In Patients with bilateral moderate NPDR (4 eyes), PRP was done in the more severe eye.

Patient selection

Patients with moderate NPDR who met the inclusion criteria summarized in Table 1 were enrolled.

Moderate NPDR was diagnosed according to the International Clinical Disease Severity Scale for DR.[5] The scale is based on the findings of the Wisconsin Epidemiologic Study of DR and the Early Treatment DR Study (ETDRS).[6]

Table 1: Inclusion criteria for the interventional study population

Patients at high risk	Patients with poor compliance with follow-up protocol
PDR or severe NPDR in the other eye	Restricted mobility because of neurological or orthopedic conditions
Early cataract	Dependent on others, including old age
Renal dialysis or impaired renal function	Women in rural areas dependent on the accompaniment of a male relative

PDR: Proliferative diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy

Exclusion criteria included patients who or whose relatives confirmed their attendance for regular follow-up in addition to patients with clinically significant macular edema (CSME). All patients were subjected to routine ophthalmic examination including corrected distance visual acuity (CDVA) using Snellen's chart converted to logarithm of the minimum angle of resolution (logMAR), anterior segment examination using the slit lamp, intraocular pressure using applanation tonometer and posterior segment examination using Volk + 90 double aspheric fundus lens.

Pan-retinal photocoagulation procedure

PRP was usually done in a single session except if the patient complained of severe pain where the session was divided into 2 or 3 parts accomplished on the same day. Topical anesthesia (benoxinate hydrochloride 0.4%) was administered before PRP. We used argon green laser. The equipment in all eyes was (Integre®Pro 532/670 nm slit lamp laser (Ellex by Lumibird) using Volk quadraspheric fundus contact lens (Volk Optical Inc. Mentor, OH, USA.) Laser power was started at 100 Mw and increased till the desired greyish/white reaction was observed. The duration of exposure ranges between 70 and 100 ms. We aimed for 1500 laser applications with a spot size of 150–200 μm and a spacing of one spot size. Patients were asked about pain during and after the procedure. Pain perceived by the patients was classified as mild, moderate, or severe. For mild pain, the patient did not complain during the procedure. For moderate pain, the patient complained but did not ask for discontinuation of the session. Severe pain was enough to discontinue the procedure and continue after some time during the same day.

Postpan-retinal photocoagulation treatment and follow-up

Patients were prescribed topical steroids (prednisolone acetate 1%) four times daily and a cycloplegic (cyclopentolate 1%) twice daily for 5 days after the procedure. They were also instructed to immediately contact us if they felt severe pain or diminution of vision. Patients were strictly advised to report for follow-up every 6 months. We strongly persuaded the patients and their relatives.

Outcome measures

The main outcome measures assessed at each follow-up visit were patient complaints, logMAR CDVA, and progression of DR.

Patients were asked about any symptoms after PRP, including diminution of vision, night vision problems, peripheral field defects, decreased contrast sensitivity, reduced color vision, and problems with driving especially at night for those who used to drive. The assessment of logMAR CDVA was done under the same preoperative settings. A Fundus examination was performed to detect any changes in the fundus such as signs of progression to the proliferative stage which would require additional laser augmentation.

Statistical analysis

Data were verified, coded by the researcher, and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics: Means, standard errors, medians, inter-quartile range, and percentages were calculated. Shapiro–Wilk/Kolmogorov–Smirnov was used to testing the normality of continuous variables. For continuous variables with more than two categories, Kruskal–Wallis test was used to compare the difference in means and *post hoc* test with Tukey's correction was used for pairwise comparisons. A $P < 0.05$ was considered statistically significant.

Results

The observational study

Eighty-two eyes of 68 patients were included in the observational study. The clinical presentations were retinal neovascularization in 18 eyes (neovascularization of the disc [NVDs] in 9 eyes, neovascularization elsewhere [NVEs] in 8 eyes, both NVDs and NVEs in one eye), vitreous hemorrhage in 39 eye and tractional retinal detachment in 25 eyes. PRP had never been performed for any of those patients.

Table 2 documents the baseline characteristics, clinical presentations, and routes of management of the observational study population.

When asked about the cause for delayed presentation, 35 patients (51%) stated that they had no idea about the screening protocol for DR and were not advised by the internist to follow up their eyes; 13 patients (19%) stated that they had visited ophthalmic clinics for other symptoms and were not advised by doctors to follow-up at regular intervals; 20 patients (30%) stated that they were aware of the screening protocol but they did not follow it as they did not complain from their vision.

The prospective interventional study

Forty-eight eyes of 48 patients were included in the interventional study. The baseline and clinical characteristics of the interventional study population are summarized in Table 3. Only 13 patients (27%) were aware of DR screening protocols. Fundus examination using the Volk double-aspheric plus 90 lenses revealed signs of moderate NPDR in all eyes with at least retinal hemorrhages in two quadrants as shown in Figure 1. Regarding the condition of the other eye, PDR was present in 32 eyes, severe NPDR in 12 eyes and moderate NPDR in 4 eyes.

The pain was perceived as mild by 6 patients, moderate by 26, and severe by 16. No patient required the administration of posterior sub-Tenon's or peribulbar anesthesia. One patient suffered from a vasovagal attack immediately after the procedure, which was adequately managed. No patient contacted us immediately after the procedure for decreased vision or severe ocular pain.

Compliance with follow-up

Twenty-four patients presented for follow-up at 6–12 months. Thirty-seven patients presented for follow-up after 1–2 years; these included 21 of the 24 who presented for the previous

Table 2: Baseline characteristics, clinical presentations and routes of management of the descriptive study population

Variable	Category	Value (patients *n*=68/ eyes *n*=82), *n* (%)
Age (years)	Mean±SD	51±12.7
	Median (range)	52 (5)
Sex	Male	23 (34)
	Female	45 (66)
DM duration/ years	Mean±SD	14.37±6.53
	Median (range)	14 (12)
Type of DM	IDDM	30 (44)
	NIDDM	38 (56)
logMAR CDVA	Mean±SD	1.6±0.2
Clinical presentation (eyes)	Retinal neovascularization	18 (22)
	Vitreous hemorrhage	39 (47.5)
	Tractional retinal detachment	25 (30.5)
Management (eyes)	Conservative	9 (11)
	PRP/anti-VEGF injection	11 (13.5)
	PPV	51 (62)
	Refusal	11 (13.5)

DM: Diabetes mellitus, IDDM: Insulin dependent diabetes mellitus, NIDDM: Non-IDDM, logMAR CDVA: Logarithm of the minimum angle resolution corrected distance visual acuity, PRP: Pan-retinal photocoagulation, VEGF: Vascular endothelial growth factor, PPV: Pars plana vitrectomy, SD: Standard deviation

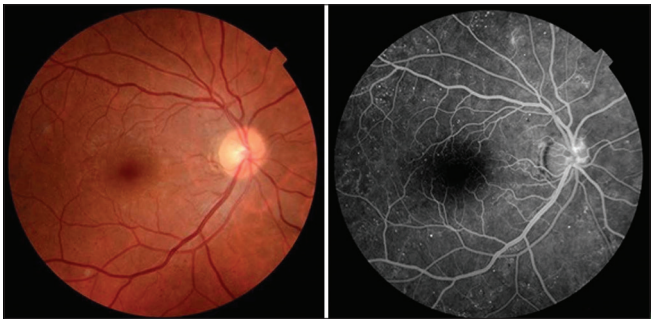

Figure 1: Prelaser moderate nonproliferative diabetic retinopathy of the right eye (Colored fundus and fluorescein angiography photographs)

follow-up and 16 who attended for the first time. Eleven patients did not present for any of the follow-up visits, and we attempted tracing them. We failed to contact 7 patients, while 4 patients stated that they did not present for the follow-up because they had no visual complaints.

Postpan-retinal photocoagulation outcomes (6–12 months follow-up)

Twenty-four patients completed the 1 year follow-up. No complaints were reported by 75% (n = 18) of the patients. Flashes were reported by 8% (n = 2), whereas night vision problems were reported by 17% (n = 4). Of the 8 patients who drove, only one had problems with night driving compared with before driving. None of the patients complained of decreased contrast sensitivity or field defects.

There were no statistically significant differences between the mean pre-and post-PRP logMAR CDVA (P = 0.842) as shown in Table 4. Two eyes of two patients lost one line on Snellen's chart. All the eyes had moderate non-PDR, and no eye had progression to severe or very severe nonproliferative DR as shown in Figure 2. No eye showed epiretinal membranes, NVDs, NVEs, tractional retinal detachment, and vitreous or subhyaloid hemorrhage. CSME was detected in one of 24 (1.2%) eyes at 6 months.

Postpan-retinal photocoagulation outcomes (1–2 years follow-up)

Twenty-one patients completed 2-year follow-up. We did not find statistically significant differences between the mean pre-and post-PRP logMAR CDVA after 1–2 years follow up [P = 0.881, Table 4]. All eyes remained in the same stage of moderate NPDR with no progression to severe or very severe NPDR. CSME was detected only in the same affected eye during the previous follow-up.

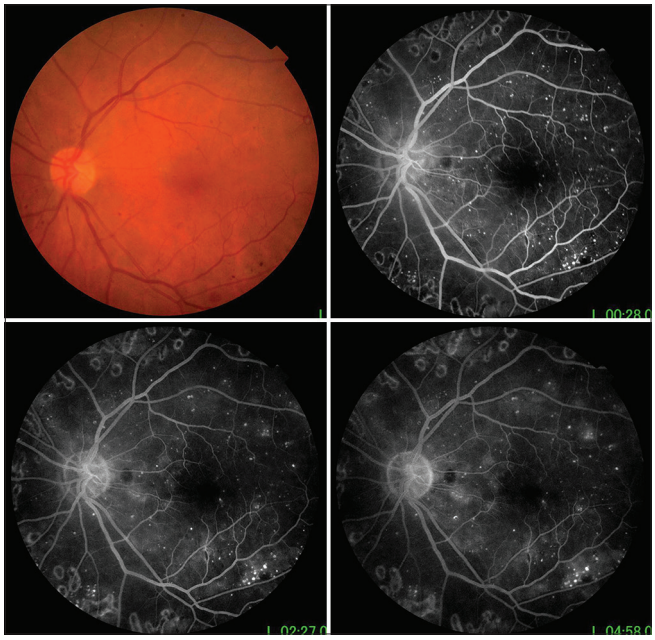

Figure 2: Postlaser fluorescein angiography photograph of the left eye of a 53-year-old patient 1 year after pan-retinal photocoagulation top left: Color fundus photograph, top right: Arteriovenous phase, bottom left: Venous phase, bottom right: Late recirculation phase

Table 3: Baseline and clinical characteristics of the interventional study population

Variable	Category	Value (n=48), n (%)
Age/years	Mean±SD	54.42±9.1
	Median (range)	55 (6)
Sex	Male	19 (39.6)
	Female	29 (60.4)
Educational level	Illiterate	13 (27.1)
	Low education	19 (39.6)
	High education	16 (33.3)
HPT	Yes	19 (39.6)
Renal impairment	Yes	25 (52.1)
$HbA1_C$ (mmol/L)	Mean±SD	9.79±0.7
	Median (range)	9.5 (3)
DM duration/years	Mean±SD	13.35±7.5
	Median (range)	12 (5)
Difficult immobilization	Yes	13 (27.1)
Type of DM	IDDM	22 (45.8)
	NIDDM	26 (54.2)
Reason for not doing FFA	Allergy	3 (12)
	Fainting	2 (8)
	Refusal	12 (48)
	Renal	8 (32)
Condition of the other eye	PDR	32 (66.7)
	Sever NPDR	12 (25)
	Moderate NPDR	4 (8.3)
Cataract	Yes	15 (31.3)
IOP	Mean±SD	14.54±3.1
Preoperative logMAR CDVA	Mean±SD	0.34±0.1

FFA: Fundus fluorescein angiography, DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin, HPT: Hypertension, IDDM: Insulin dependent diabetes mellitus, NIDDM: Non-IDDM, PDR: Proliferative diabetic retinopathy, PPV: Pars plana vitrectomy, PRP: Pan retinal photocoagulation, IOP: Intraocular pressure, logMAR CDVA: Logarithm of the minimum angle resolution corrected distance visual acuity, SD: Standard deviation, NPDR: Non-PDR

Table 4: Corrected distance visual acuity before and after pan-retinal photocoagulation

Variable	Category	LogMAR CDVA	P=0.951*
LogMAR CDVA			
Baseline[a]	Mean±SD	0.34±0.1	[a]versus[b]=0.842[†]
	Median (range)	0.3 (0.1)	
6-12 months follow-up[b]	Mean±SD	0.35±0.1	[b]versus[c]=0.753[†]
	Median (range)	0.3 (0.1)	
1-2 years follow-up[c]	Mean±SD	0.33±0.1	[a]versus[c]=0.881[†]
	Median (range)	0.3 (0.1)	

*Kruskal-Wallis test was used to compare the difference in medians, [†]*Post hoc* test with Tukey's correction was used for pairwise comparisons. logMAR CDVA: Logarithm of the minimum angle of resolution corrected distance visual acuity, SD: Standard deviation, P [a]versus[b]: Baseline vs 6-12 months follow-up, P [b]versus[c]: 6-12 months vs 1-2 years follow-up, P [a]versus[c]: Baseline vs 1-2 years follow-up

Discussion

Our observational study highlights how in our community proliferative DR presents a challenge to ophthalmic practice. Lack of compliance with the recommended screening protocol results in patients first presenting with advanced retinopathy or its complication.

The rationale for a selective approach for prophylactic PRP for cases of moderate NPDR has to be discussed in the light of the following considerations: The probability of progression from one stage to the next, risk factors that accelerate such progression, expected adherence of patients to screening follow-up protocols, possible complications and cost of the prophylactic procedure, and findings from other reported studies.

The probability and risk factors of progression to proliferative diabetic retinopathy

Chen *et al*.[4] estimated that the probability of progression of moderate non-PDR to PDR was 5% (3.29–8.26) within 1 year, 24.1% (18.62–32.58) within 4 years, and 43.6% (35.02–54.08) within 7 years. Several risk factors have been reported to increase the rate of progression. Poor glycemic control, which is indicated by increased hemoglobin A1c (HbA1c), is considered to be a significant risk factor associated with the progression of NPDR to PDR.[7] Harris Nwanyanwu *et al*.[7] reported that a patient who has mild NPDR with an HbA1c level of 7% is expected to progress to moderate NPDR in 5.9 years, while a patient with mild NPDR and an HbA1c of 8% is expected to progress to moderate NPDR in 5.4 years. A 5-year prospective study in China suggested that DR progression was the most rapid when the baseline HbA1c increased from 5.2% to 6.4%.[8] In our intervention study, the mean HbA1c was 9.79% ±0.7%. This high HbA1c is an indication of poor glycemic control and a high risk of progression of DR. Other reported risk factors to include diabetes duration, systemic hypertension, dyslipidemia, and microalbuminuria. It has also been reported that cataract surgery for diabetic patients may lead to a relatively rapid progression of DR.[9] For these reasons, we decided to perform early PRP for patients with moderate non-PDR who had developed even visually insignificant cataract.

The impact of socioeconomic development and awareness of the screening protocols

The early photocoagulation for DR study, 1991 concluded that provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate NPDR.[3] Commitment to follow-up protocols is thus crucial in the prevention and timely management of complications of DR. It has been estimated that the prevalence of blindness from untreated severe PDR can be reduced by as much as 90% through early detection and prompt treatment.[10] However, socioeconomic factors affect the rate of compliance with screening protocols. Hudson *et al*.[11] found differences between the compliance of English and Spanish speakers in the USA. Ohlhausen *et al*.[12] reported the effects of delayed treatment on visual outcomes and characterized the medical and socioeconomic factors that contributed to it. They concluded that a delay in PRP treatment beyond 31 days was associated with worse visual outcomes than earlier treatment. The practical reality is different for our community. A large-sample study by Macky *et al*.[13] in Cairo University hospitals found DR in 20.5% of patients attending diabetic clinics, and 82% were not aware of the hazards of diabetes mellitus on the eyes. Vengadesan *et al*.[14] reported on delayed follow-up in patients with DR in South India and the impact of social factors on disease progression. They concluded that although there have been significant improvements in diagnosis and treatment of DR, poor adherence to treatment and follow-up recommendations remains a significant barrier. Peavey *et al*.[15] studied the impact of socioeconomic disadvantage and DR severity on poor ophthalmic follow-up in rural Vermont and New York and reported that disadvantaged patients had 1.96 times greater odds of poor follow-up than nondisadvantaged patients.

COVID-19 pandemic lockdown had been associated with lost follow-up visits, and, in addition, glycemic control got deranged with a significant increase of mean HbA1c immediate postlockdown period, which may significantly increase the annual incidence of complications related to diabetes.[16] Öncül *et al*.[17] reporting on DR treatment and management during the COVID-19 pandemic, stated that there has been a serious decrease in hospital visits partly due to government lock-down measures and partly due to anxiety of patients fearful of contracting the infection. In our community, nearly all low-pay governmental public hospitals and health centers were working only on emergency cases and used for isolation and treatment of patients.

The complications and cost of the prophylactic laser procedure

PRP could also be less painful and with fewer complications, if done early in the nonproliferative stage.[18] Most patients in our study were able to tolerate the PRP easily. Shortening the laser pulse duration, specifically avoiding the long posterior ciliary nerves at the 3 and 9 o'clock positions, helps in minimizing pain. We used a pulse duration of 70–100 ms. PRP damages retinal tissue and this can lead to symptoms due to the loss of function in burned areas, including peripheral visual field defects, reduced color or night vision, and decreased contrast sensitivity.[19-23]

This usually depends on the intensity of PRP. However, it does help preserve the more important central vision.[24] The lower incidence of visual complaints in our cases may be due to the use of a single session of PRP. More aggressive laser is needed in more advanced stages of PDR, and this may carry a higher risk of adverse effects such as macular edema, angle closure, and exudative retinal detachment.[18,25,26]

Findings from other reported studies

A number of studies addressed the clinical and cost-effectiveness of prophylactic early PRP for NPDR versus waiting for the

development of PDR to start treatment.[27,28] The ETDRS, published in 1991, reported that PRP in all stages of NPDR reduces the risk of severe visual loss, but the difference between absolute risk reduction and the risk of deferring treatment was minimal. Therefore, the study concluded that PRP should be deferred until patients develop PDR.[3] Mistry *et al*.[28] using an economic model, concluded that administering PRP at an earlier stage of retinopathy (severe NPDR) could be more cost-effective than delaying PRP until the high-risk stage. Royle *et al*.[24] noting that PDR is treated by PRP to preserve vision once the retinopathy progresses to an advanced stage, performed a systematic review on whether earlier laser treatment would be better than waiting until high-risk PDR develops. They noted that most of the evidence on earlier-stage treatment came from trials using older lasers. Because considerable uncertainties remain, the authors highlighted the need for a high-quality trial of modern laser treatment at an earlier stage before PDR develops. Arabi *et al*.[29] suggested in an updated review that there may be a paradigm shift toward early management of NPDR without diabetic macular edema.

All the studies on early versus later PRP did not highlight the need to tailor intervention to the characteristics of individual patients and their different levels of risk. More importantly, they seem to assume that patients will regularly follow screening monitoring protocol, an assumption not justified in ophthalmic practice particularly in low-resource settings.

Limitations of the study

One of the main limitations of our study is the short follow-up that didn't include all patients. However, this was expected in view of the condition in our community, to which may be added the constraint caused by the COVID-19 pandemic. In fact, one of the selection criteria of our cases was less likelihood to comply with follow-up.

Conclusion

While there is a continued need to raise awareness among patients and primary health care physicians of the screening protocol for DR and the importance of complying with regular follow-up in low-resource settings, Ophthalmic practice of management of PDR may not be and is not necessary to the same in different communities and setups, patients with moderate NPDR who are less likely to comply with follow-up screening protocol and who are at higher risk to progress to PDR may be offered prophylactic early PRP.

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Conflicts of interest

There are no conflicts of interest.

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