Special Focus on Anti-VEGF, Original Article

Clinical efficacy and safety of Razumab® (CESAR) study: Our experience with the world's first biosimilar Ranibizumab

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Purpose: The aim of this study was to evaluate the efficacy and safety of Razumab (the biosimilar Ranibizumab by Intas Pharmaceuticals Ltd.) for the treatment of chorioretinal vascular diseases such as diabetic macular edema (DME), choroidal neovascular membrane (CNVM), and macular edema secondary to retinal vein occlusion (RVO). **Methods**: We conducted a single-center, retrospective study, including patients with DME, CNVM, and RVO, who had received treatment with Razumab® between October 2018 and September 2019. Primary outcome measures were the changes in corrected distance visual acuity (CDVA) and central foveal thickness (CFT) from baseline to 1 month and 3 months. Secondary outcome measures included intraocular pressure (IOP) at day 1, any signs of ocular inflammation or systemic adverse events during the follow-up. **Results**: One hundred and fifty-three eyes of 141 patients were analyzed. The indications included DME in 70 (45.8%) eyes, CNVM in 70 (45.8%) eyes, and RVO in 13 (8.4%) eyes. Mean CDVA improved from baseline (0.62 ± 0.44) to month 1 (0.45 ± 0.42) and maintained till 3 months (0.42 ± 0.44; $P < 0.001$). Mean CFT showed significant reduction from baseline (405.68 ± 192.422 µm) to month 1 (286.08 ± 118.36 µm) and month 3 (271 ± 104.24 µm; $P < 0.001$). None of the eyes recorded IOP >20 mmHg on day 1. No evidence of ocular toxicity or systemic adverse event was noted. **Conclusion**: Razumab® showed a rapid improvement in CDVA and CFT in most of the eyes with efficacy observed as early as 1 month and maintained till 3 months. The biosimilar Ranibizumab can be a safe and effective low-cost drug for treating macular diseases.

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Retinal disease management has witnessed revolutionary advances in pharmacotherapy with the development of biological molecules that inhibit vascular endothelial growth factor (VEGF) such as Ranibizumab (Lucentis®; Genentech, South San Francisco, CA, USA/Roche, Basel, Switzerland), Aflibercept (Eylea®; Regeneron, Tarrytown, NY, USA), and less-expensive off-label Bevacizumab (Avastin; Genentech/Roche).[1-17] Low cost and substantial success of Bevacizumab in the management of various retinal diseases including diabetic macular edema (DME), neovascular age-related macular degeneration (AMD), and macular edema due to retinal vein occlusion (RVO) led to the widespread use of this off-label anti-VEGF drug.[17] The efficacy of Ranibizumab for the primary treatment of retinal vascular diseases has been established in several studies.[1-13] However, the high cost of Lucentis® (Ranibizumab) made it less affordable to many patients in developing countries including India.

Biosimilars are defined, according to the World Health Organization (WHO), as biotechnological products that are comparable with an already approved reference product in quality, nonclinical, and clinical evaluation.[18] The world's first biosimilar Ranibizumab, Razumab® was developed by Intas Pharmaceuticals Ltd., Ahmedabad, India, to provide a cost-effective alternative accessible to patients with retinal diseases, and it was approved by the highest Indian regulatory body, the Drug Controller General of India, in 2015. Razumab®, like its biologic reference product Lucentis®, is a recombinant humanized IgG1 monoclonal antibody fragment formulated for intraocular use. It comes in a single-use glass vial with a concentration of 10 mg/mL in 0.23 mL.[19,20]

A prospective pilot study, including 95 patients, has initially demonstrated the efficacy and safety of Razumab® in Indian patients with chorioretinal vascular diseases.[19] In addition to registration clinical trial, Intas also conducted RE-ENACT study (a retrospective pooled analysis) and RE-ENACT 2 study (long-term data) to assess the real-world experience of Razumab® in Indian patients with wet AMD, RVO, and DME.[21-26]

We have conducted the Clinical Efficacy and SAfety of Razumab® (CESAR) study, which is a retrospective study with an independent design as opposed to that conducted by the developers of the biosimilar drug, to evaluate the use of Razumab® in Indian population with chorioretinal vascular diseases such as DME, choroidal neovascular membrane (CNVM), and macular edema secondary to RVO.

Methods

Study design

This single-center, retrospective study analyzed the data of patients who had received treatment with Razumab® at our

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eye hospital, between October 2018 and September 2019. The institutional ethical committee approval was obtained, and the tenets of the Declaration of Helsinki were followed for all study procedures. The confidentiality of patients was maintained throughout at all stages of the data analysis.

Study population

Patients who were administered Razumab® injection, both treatment naïve or previously treated with other anti-VEGF/steroids/laser therapy, for DME, CNVM, or macular edema secondary to RVO, were included in the study. Patients with less than 3 months follow-up, dense cataract or corneal opacity, ocular infection, previous vitrectomy, uncontrolled glaucoma, and a history of myocardial infarction or cerebrovascular accident were excluded.

Pro re nata (PRN; as needed) regimen without mandatory loading doses was followed in all cases. Razumab® injection was discontinued before 3 months if the corrected distance visual acuity (CDVA) has reached 20/20 and central foveal thickness (CFT) was less than 250 μm. Treatment was resumed if CFT exceeded 250 μm and visual acuity dropped.

Intravitreal injection technique

Intravitreal injections were performed under strict aseptic conditions under topical anesthesia in the operating room. 0.5 mg/0.05 mL of Razumab® solution was injected using a 30-gauge needle (1 mL tuberculin syringe; DispoVan) inserted through the pars plana, 4 mm posterior to the limbus in phakic eyes and 3.5 mm in pseudophakic eyes. All patients received topical antibiotic-steroid four times a day for a week after the injection.

Data collection

Demographic data collected from the records of the patients included age, gender, eye laterality, clinical diagnosis, and any previous treatment (anti-VEGF/steroids/laser) for chorioretinal vascular disease. Pre-injection clinical data included CDVA (using Snellen's chart), intraocular pressure (IOP; using non-contact tonometer), and CFT measured by spectral-domain optical coherence tomography (SD-OCT RTVue®, Optovue, Inc., Fremont, CA). Post-injection data included IOP at day 1, CDVA, and CFT at 1 month and 3 months. Any systemic adverse events, anterior segment/posterior segment signs of inflammation throughout the follow-up period were checked.

Outcome measures

The primary outcome measures evaluated the efficacy of the drug, which included the mean change in CDVA and CFT from baseline to 1 month and 3 months. The secondary outcome measures assessed the safety of the drug which included any signs of toxicity or immunogenicity noted on clinical examination such as anterior chamber reaction (cells/flare), posterior segment inflammation (vitritis/snow balls/snow banking/retinitis/retinal vasculitis) or systemic adverse events during any of the follow-up visits. The mean change in IOP on day 1 post-injection was also evaluated.

The CDVA measured by Snellen's visual acuity chart was converted to logarithm of the minimal angle of resolution (logMAR) scale for statistical analysis. CFT was defined as the distance between the internal limiting membrane and the inner border of the RPE.

Statistical analysis

Statistical analysis was performed on the Statistical Package for Social Sciences (SPSS) version 24.0 for Windows. Data were summarized by the mean and standard deviation (SD). Categorical variables were presented as frequency and percentage. The normality of data was tested by the Kolmogorov-Smirnov test. Repeated measures analysis of variance (ANOVA) and paired *t*-test were performed to compare the quantitative variables. *P* value less than 0.05 is considered as significant at 95% confidence level.

Results

One hundred and fifty-three eyes of 141 patients (80 males and 61 females) were analyzed. The mean age was 67.01 ± 14.13 years, ranging from 26 to 86 years. The majority (32.7%) of the patients were in the age group of 71 to 80 years. The indications for injection included DME in 70 (45.8%) eyes, CNVM in 70 (45.8%) eyes, and RVO in 13 (8.4%) eyes. The mean number of biosimilar Ranibizumab injections received was 2.67 ± 0.67 (range 1-3 injections) with 3 monthly injections received by 121 (79.1%) eyes, 2 injections by 14 (9.1%) eyes, and 1 injection by 18 (11.8%) eyes. The majority (79.1%) of the eyes were treatment naïve. In previously treated eyes, the mean interval between the last therapy and biosimilar Ranibizumab administration was 7.59 ± 4.74 months, ranging from 2-12 months. The baseline characteristics of the patients are summarized in Table 1.

The mean logMAR CDVA of all the indications improved significantly from 0.62 ± 0.44 (Median 0.5) to 0.42 ± 0.44 (Median 0.3) at the end of 3 months post-injection ($P < 0.001$) [Fig. 1]. Forty-five (29.4%) eyes had a gain of ≥ 2 lines of visual acuity (Snellen's chart). The CDVA improved in 97 (63.4%) eyes, remained the same in 55 (35.9%) eyes, and worsened in 1 (0.7%) eye. No patients had post-treatment loss of light perception.

A significant decrease in mean CFT was observed from 405.68 ± 192.42 μm at baseline to 271 ± 104.24 μm at the end of 3 months ($P < 0.001$) [Fig. 2]. Ninety-seven (63.4%) eyes had more than 25% reduction in CFT with 69 (45.1%) eyes showing >100 μm decrease in CFT from baseline. After injection, the CFT improved in 148 (96.7%) eyes and worsened in 5 (3.3%) eyes. Tables 2 and 3 show the comparison of mean difference in CDVA and CFT from baseline to month 1 and 3 after biosimilar Ranibizumab administration.

The mean difference between pre- and post-injection IOP on day 1 was 1.58 ± 1.9 mmHg. Only five (3.3%) eyes had an IOP rise >5 mm Hg. The mean post-injection IOP on day 1 was 14.8 ± 2.75 mmHg, with none of the eyes recording IOP >20 mmHg. No evidence of inflammation in the anterior or posterior segment was noted during the follow-up period. None of the patients developed serious ocular adverse effects such as endophthalmitis, retinal/choroidal detachment, or optic atrophy. No systemic adverse events were reported during any of the follow-up visits.

Of 121 treatment naïve eyes, 57 eyes had DME, 55 eyes had CNVM, and 9 eyes had macular edema secondary to RVO. A total of three biosimilar Ranibizumab injections were received by 94 (77.7%) eyes, 2 injections by 9 (7.4%) eyes, and 1 injection by 18 (14.9%) eyes. Significant improvement in mean logMAR CDVA was observed from 0.60 ± 0.41 (Median 0.5) to 0.32 ± 0.32 (Median 0.2) in naïve DME eyes ($P < 0.001$), 0.64 ± 0.48 (Median 0.5) to 0.55 ± 0.54 (Median 0.3) in naïve CNVM eyes ($P < 0.001$), 0.49 ± 0.40 (Median 0.3) to 0.21 ± 0.15 (Median 0.2) in naïve RVO eyes ($P = 0.006$) at the end of 3 months [Fig. 3]. The mean CFT improved from 436.70 ± 174.33 μm to 275.04 ± 120.09 μm in naïve DME eyes ($P < 0.001$), 367.58 ± 222.85 μm to 269.58 ± 105.72 μm in naïve CNVM eyes ($P < 0.001$), 383.11 ± 202.36 μm to 231.44 ± 45.72 μm in naïve RVO eyes ($P = 0.074$) at 3 months follow-up [Fig. 4].

Discussion

Anti-VEGF agents benefit patients with retinal vascular and macular diseases as they are proven to improve vision and prevent further vision loss resulting in better outcomes, prognosis, and quality of life. Ranibizumab is a humanized, recombinant

monoclonal antibody fragment that binds to the receptor-binding site of active forms of VEGF-A, thereby preventing the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the endothelial cell surface, decreasing proliferation of endothelial cells, vascular leakage, and formation of new blood vessel.[27] The clinical studies such as READ, RESOLVE, RESTORE, ANCHOR, MARINA, HORIZON, BRAVO, CRUISE, and RABAMES have already revealed both efficacy and safety of biologic Ranibizumab in patients with DME, neovascular AMD, and RVO.[1-13]

The high cost of biologics has become a significant concern when it comes to healthcare costs in the management of retinal diseases. Biosimilars are molecules similar to existing innovator biologic reference products. However, they are large molecules derived from living cells, which could differ from the originator molecules and are not based on a fixed chemical formula. On the other hand, there is a possibility of biosimilar drugs being better than reference medicine due to the application of the latest technology by biosimilar companies compared to the technology used by innovator biologics. A biosimilar should prove comparable pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy to biologic reference drug to establish biosimilarity. Razumab® (Intas Pharmaceuticals Ltd., Ahmedabad, India) is the first and only approved biosimilar to Ranibizumab being used clinically at present.[20] In this study, we have assessed the short-term (3 months) clinical efficacy and safety of Razumab® in patients with chorioretinal vascular diseases.

The present study showed that the visual acuity improved significantly as early as 1 month after the administration of biosimilar Ranibizumab injection. The mean logMAR CDVA improved from baseline (0.62 ± 0.44) to month 1 (0.45 ± 0.42; $P < 0.001$) and maintained till 3 months (0.42 ± 0.44; $P < 0.001$). Visual acuity worsened in only 1 patient with CNVM (from 20/200 to counting fingers) due to the development of foveal scar.

The mean CFT showed significant reduction from baseline (405.68 ± 192.42 µm) to month 1 (286.08 ± 118.36 µm; $P < 0.001$) and month 3 (271 ± 104.24 µm; $P < 0.001$). The percentage (%) change in CFT was 29.5% at 1 month and 33.2% at 3 months. However, the CFT increased or worsened in 5 (3 DME and 2 CNVM) eyes after injection. The presence of vitreomacular traction with associated proliferative diabetic retinopathy and large CNV size could be one of the reasons for persistent edema, leading to non-responsiveness.

In 121 treatment naïve eyes, the mean CDVA improved significantly from baseline to month 3 in each sub-group (DME,

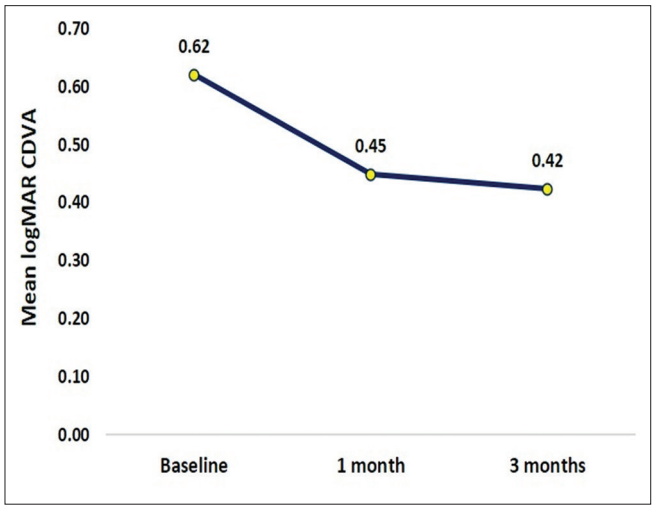

Figure 1: Pre-injection and post-injection mean corrected distance visual acuity (CDVA), Repeated measures analysis of variance $P < 0.001$, highly significant

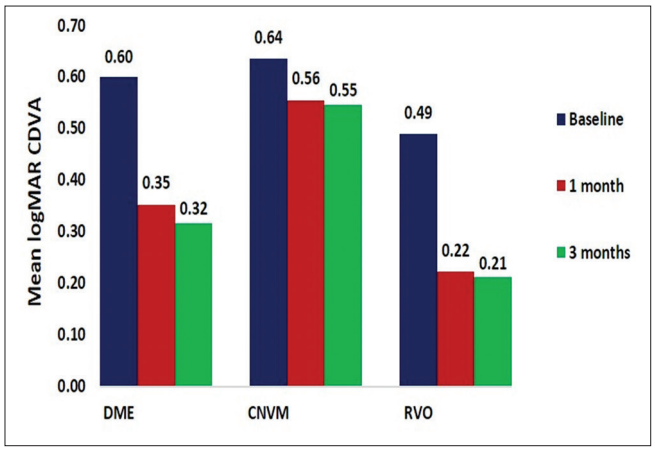

Figure 3: Pre-injection and post-injection mean corrected distance visual acuity (CDVA) in treatment naïve eyes in each sub-group

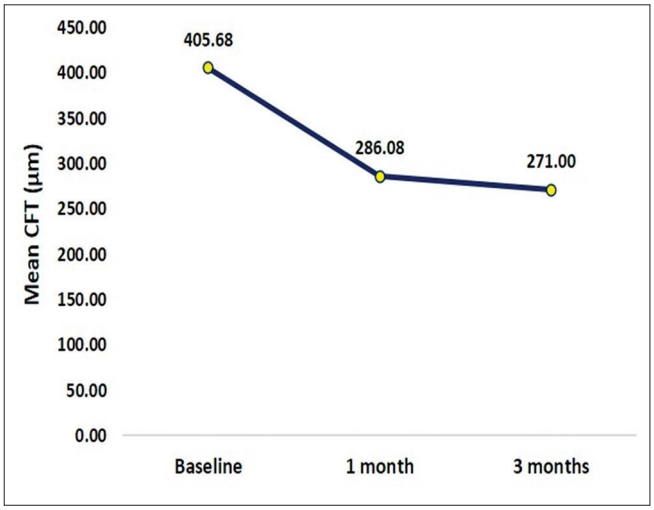

Figure 2: Pre-injection and post-injection mean central foveal thickness (CFT), Repeated measures analysis of variance $P < 0.001$, highly significant

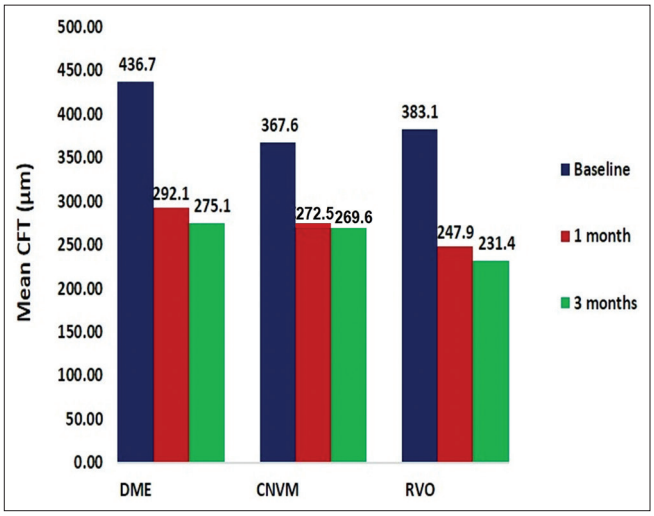

Figure 4: Pre-injection and post-injection mean central foveal thickness (CFT) in treatment naïve eyes in each sub-group

Table 1: Baseline characteristics of the study population

Characteristics	*n*
Number of eyes (patients)	153 (141)
Age, mean±SD (years)	67.01±14.13
Gender, *n* (%)	
Male	80 (56.7)
Female	61 (43.3)
Indication, *n* (%)	
DME	70 (45.8)
CNVM	70 (45.8)
RVO	13 (8.4)
Eye laterality, *n* (%)	
Right	80 (52.3)
Left	73 (47.7)
Treatment, *n* (%)	
Treatment naïve	121 (79.1)
Previously treated	32 (20.9)
Baseline CDVA, mean±SD (logMAR)	0.62±0.44
Baseline CFT, mean±SD (μm)	405.68±192.42
Baseline IOP, mean±SD (mmHg)	13.22±2.44

SD: Standard deviation, DME: Diabetic macular edema, CNVM: Choroidal neovascular membrane, RVO: Retinal vein occlusion, CDVA: Corrected distance visual acuity, CFT: Central foveal thickness, IOP: Intraocular pressure

Table 2: Comparison of mean difference in CDVA from baseline to month 1 and 3 after biosimilar Ranibizumab administration using post hoc analysis

	Mean difference in CDVA (logMAR)	Mean % change	Bonferroni *P*
Baseline - 1 month	0.17	27.7	<0.01*
Baseline - 3 months	0.20	31.8	<0.01*
1 month - 3 months	0.03	5.7	<0.01*

CDVA: Corrected distance visual acuity, *Highly significant with level of significance: *P*<0.01 at 95% confidence limit

Table 3: Comparison of mean difference in CFT from baseline to month 1 and 3 after biosimilar Ranibizumab administration using post hoc analysis

	Mean difference in CFT (μm)	Mean % change	Bonferroni *P*
Baseline - 1 month	119.59	29.5	<0.01*
Baseline - 3 months	134.68	33.2	<0.01*
1 month - 3 months	15.08	5.3	<0.01*

CFT: Central foveal thickness, *Highly significant with level of significance: *P*<0.01 at 95% confidence limit

CNVM, and RVO). The mean % change in CFT was 37% in naïve DME eyes, 26.7% in naïve CNVM eyes, and 39.6% in naïve RVO eyes at the end of 3 months. No evidence of toxicity or immunogenicity was noted after the intravitreal administration of biosimilar Ranibizumab. None of the eyes had an IOP >20 mmHg on day 1. Also, no systemic adverse events were reported upto 3 months follow-up.

The findings of this study are consistent with the data reported by Sharma *et al.* (RE-ENACT study), and Sameera *et al.*[19,21-26] The RE-ENACT (REal life assessmENt of safety And effeCTiveness of Razumab®) study conducted by the developers of the biosimilar drug (Intas Pharmaceuticals Ltd.) found significant improvements in visual acuity, central macular thickness, intra- and subretinal fluid with the use of the drug inpatients (n = 561) with wet AMD, DME, and RVO for a duration of 12 weeks.[21-23] The RE-ENACT 2 (n = 341) study evaluated the same variables for a longer-term (48 weeks) in patients with wet AMD, DME, RVO, and additionally in patients with myopic CNVM.[24-26] In the RE-ENACT study, all patients received three biosimilar Ranibizumab injections, but the RE-ENACT 2 study evaluated the patients who had been given one to five biosimilar Ranibizumab injections. Our study evaluated patients who had received one to three injections and observed a higher mean % change in CDVA (27.7%) and CFT (29.5%) at 1 month compared to RE-ENACT study (pooled analysis) which showed a change of less than 5% at 1 month.[21] However, at 3 months follow-up, the findings were almost similar between the studies. Regarding safety, both studies reported no serious adverse events.

Sameera *et al.* conducted a prospective study in Indian patients (n = 95) with wet AMD, DME, and RVO to evaluate the safety and efficacy of Razumab® for a duration of 1 month. They showed that biosimilar Ranibizumab treatment improved the visual acuity and central macular thickness with no ocular and systemic toxicity detected.[19]

Another retrospective study by Sharma *et al.* with a smaller sample size (n = 30) analysed the immunogenicity and efficacy after switching from biologic Ranibizumab to biosimilar Ranibizumab. No signs of immunogenicity and change in efficacy were noted at the end of 6 months. The reason for switching was due to financial constraints in all the cases.[18]

Because of their lower cost, biosimilars have the potential to reduce healthcare costs, thereby making it more accessible and affordable for a larger section of the patient population. Razumab® is available at 30-40% reduced cost compared to reference biologic Ranibizumab in India and its user base has multiplied in the last few years.[20] Biosimilars have a potential advantage in developing countries like India, where insurance companies do not reimburse for anti-VEGF agents, and compounding pharmacies are rare.[28] There is also a possibility of shift towards biosimilars in developed countries due to their low price. The insurance companies can have significant savings of 15-20% due to multiple injections, and the government can save on the health expenditure too.[20]

Ocular inflammation has been reported for specific batches of Razumab® initially, putting a question on its safety and quality control.[29] The issues were resolved by discontinuing the production for a while, revising the manufacturing process, and delivering the subsequent batches with careful monitoring.[20] Though rare instances of severe ocular inflammation have been reported with innovator biologic products also, stricter pharmacovigilance and immunogenicity testing assay before market approval should be enforced to counteract the nocebo effect around the biosimilar drugs.[28,30]

The limitations of the study include its retrospective design and short-term follow-up of 3 months, though the study provides definite evidence of clinical efficacy and safety of the biosimilar Ranibizumab for the treatment of retinal vascular diseases. Prospective, randomized controlled trials with longer follow-up are needed, which can provide more valuable information.

Conclusion

Our study demonstrates that the biosimilar Ranibizumab, Razumab®can be a safe and effective low-cost therapy in patients with chorioretinal vascular diseases such as DME, CNVM, and macular edema secondary to RVO. The data showed a rapid improvement in CDVA and CFT in most of the eyes with efficacy observed as early as 1 month and maintained till 3 months. The drug was well tolerated with no new safety issues over a period of 3 months.

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Conflicts of interest

There are no conflicts of interest.

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