Systematic review of efficacy and meta-analysis of safety of ranibizumab biosimilars relative to reference ranibizumab anti-VEGF therapy for nAMD treatment

Amin Hatamnejad, Rohan Dadak, Samantha Orr, Charles Wykoff, Netan Choudhry

ABSTRACT

Topic This systematic review and meta-analysis provides a summary of the efficacy and safety of ranibizumab biosimilars relative to reference ranibizumab anti-vascular endothelial growth factor (VEGF) therapy for the treatment of neovascular age-related macular degeneration (nAMD).

Methods We conducted systematic searches from January 2003 to August 2022 on Ovid MEDLINE, EMBASE and the Cochrane Controlled Register of Trials. We included studies reporting changes in early treatment diabetic retinopathy study-measured best-corrected visual acuity (BCVA), number of patients who lost or gained more than 15 letters in BCVA from baseline, changes in retinal thickness and adverse events between treatment arms. The following studies were excluded: studies that did not report visual outcomes following biosimilar and reference ranibizumab intravitreal injections, study arms combining anti-VEGF agents with laser or steroid injections, sham injections as a control comparator, studies without English full texts and non-comparative, observational study design.

Results Five studies reported on four randomised controlled trials (RCTs) and 1544 eyes at baseline were included in this systematic review and meta-analysis. The studies in our systematic review found no significant differences between reference ranibizumab and ranibizumab biosimilar medications (FYB201, SB11, RanizuRel and Lupin's ranibizumab) for visual and anatomical outcomes. No significant differences were detected between biosimilar and reference ranibizumab for treatment emergent adverse events (risk ratio, RR 1.06, 95% CI (0.91 to 1.23), p=0.45, I²=52%) or IOP-related adverse events with significant heterogeneity (RR 2.59, 95% CI (0.11 to 62.25), p=0.56, I²=76%).

Conclusion This systematic review of four RCTs demonstrated no significant difference in visual outcomes, retinal thickness outcomes, as well as meta-analysis of adverse events between biosimilar and reference ranibizumab therapies for nAMD treatment.

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of blindness and vision loss among those aged 60 and older in industrialised countries. Approximately 80% of AMD patients have non-neovascular or atrophic AMD, but neovascular AMD (nAMD) accounts for the majority of severe central visual acuity (VA) loss. Choroidal neovascularisation in AMD leads to central vision loss if left untreated. Despite the fact that there is no cure, available treatment options for nAMD include laser surgery, photodynamic therapy and anti-vascular endothelial growth factor (VEGF) therapies. The standard of care for nAMD is repeated intravitreal anti-VEGF injections, first introduced in 2006. The commonly used anti-VEGF agents include ranibizumab (Lucentis, Genetech, South San Francisco, California, USA), aflibercept (Eylea,
Regeneron Pharmaceuticals, Tarrytown, New York, USA), brolucizumab (Beovu, Novartis Pharmaceuticals Corporation East Hanover, New Jersey, USA), off-label use of bevacizumab (Avastin, Genetech, South San Francisco, California, USA) and novel use of faricimab (Valbsmyz Genetech, South San Francisco, California, USA). These anti-VEGF biologics inhibit all isoforms of VEGF-A, thus preventing pathological vascular leakage, angiogenesis and nAMD progression. Faricimab, a novel bispecific antibody, is of additional interest in nAMD and can change with time and new technological developments, thus the guidelines may differ between some countries that is already on the market and in some circumstances to a reference drug 2. Following intravitreal injection, ranibizumab has a relatively short systemic half-life with reduced systemic exposure due rapid renal clearance. For patients and healthcare systems, anti-VEGF treatment for nAMD can be a substantial burden in terms of medication cost, time burdens and overall decrease in patient quality of life, as it is perceived as stressful and anxiety-provoking by patients. A biosimilar is a biologic that has similar physical, chemical and biological properties to a reference drug that is already on the market and in some circumstances has been demonstrated to reduce costs and even improve patient access to safe and effective biological medicines. Ranibizumab’s patents expired in 2020 in the USA and in 2022 in Europe, allowing ranibizumab biosimilars to be introduced into these markets. A total of 10 manufacturers are working on ranibizumab biosimilar medications and they are at various stages of approval and development with FYB201 under US Food and Drug Administration (US FDA) review, SB11 approved by US FDA in 2021, RanizuRel approved by Drugs Controller General of India (DGCI) in 2020 and Lupin’s ranibizumab in phase 3 trial. There are no fixed international guidelines for biosimilar approval, thus the guidelines may differ between some countries and can change with time and new technological developments. Therefore, the current systematic review and meta-analysis aims to address the variability in medication development stage and lack of unified approval guidelines, providing a comprehensive summary of the efficacy and safety of ranibizumab biosimilar medications that are approved by different agencies or are at different developmental stages relative to the reference ranibizumab anti-VEGF therapy for the treatment nAMD.

METHODS

Search strategy and eligibility criteria
This systematic review and meta-analysis adhered to the Declaration of Helsinki and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the ID number CRD42022326090. We conducted searches from January 2003 to August 2022 on Ovid MEDLINE, EMBASE and the Cochrane Controlled Register of Trials as illustrated in online Supplemental eTable 1. We included randomised controlled trials (RCTs) in which patients with nAMD were treated with intravitreal ranibizumab biosimilars or reference ranibizumab anti-VEGF agents. We included studies reporting changes in best-corrected visual acuity (BCVA) reported in early treatment diabetic retinopathy study (ETDRS) letters, number of patients who lost or gained more than 15 letters in BCVA compared with baseline, changes in retinal thickness and adverse events between treatment arms. The following studies were excluded: studies that did not report outcomes following biosimilar and reference ranibizumab intravitreal injections, study arms combining anti-VEGF agents with laser or steroid injections, sham injections as a control comparator, studies without English full texts and non-comparative, observational study designs.

Study selection and data collection
Title and abstract screening followed by full-text screening were conducted independently by two authors (AH and RD), with conflicts being resolved after discussion with a third author (NC). The study screening process for the included studies of this meta-analysis is illustrated in figure 1. We used Covidence (Veritas Health Innovation, Melbourne, Australia) for the screening and study selection stages. Additionally, we used Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) to collect all data, which included changes in BCVA from baseline as the primary outcome, changes in retinal thickness from baseline, changes in number of patients who lost or gained more than 15 letters in BCVA compared with baseline, and adverse events as secondary outcomes. Finally, if reported in the study, we collected the following baseline characteristics: country, publication year, biosimilar ranibizumab treatment agent, treatment regimen, number of eyes, number of right eyes, number of males, number of patients with phakic and aphantic/pseudophakic lens, mean age of participants, initial BCVA and retinal thickness. For change in retinal thickness, we included central subfield thickness (CST), central macular thickness (CMT) and foveal central subfield retinal thickness. We did not estimate values from figures and only included data explicitly reported in the text or received directly from the authors. We contacted authors via email requesting additional data for any missing outcomes such as the mean, SD and the number of patients that were included in our meta-analysis. A single follow-up email was sent 2 weeks later if no response was received. We included the most recent publications for RCTs that were part of a study series and we used previous papers in the series to supplement any data for outcomes not reported in the most recent paper.

Risk of bias and certainty of evidence assessment
Two independent authors (AH and RD) assessed the risk of bias and certainty of evidence with conflicts resolved through a third independent author (NC). In order to assess the risk of bias and certainty of evidence of the included studies, we used Cochrane’s Risk of Bias tool 2 (ROB2) 20 and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). 21

Regeneron Pharmaceuticals, Tarrytown, New York, USA, brolucizumab (Beovu, Novartis Pharmaceuticals Corporation East Hanover, New Jersey, USA), off-label use of bevacizumab (Avastin, Genetech, South San Francisco, California, USA) and novel use of faricimab (Valbsmyz Genetech, South San Francisco, California, USA). These anti-VEGF biologics inhibit all isoforms of VEGF-A, thus preventing pathological vascular leakage, angiogenesis and nAMD progression. Faricimab, a novel bispecific antibody, is of additional interest in nAMD and can change with time and new technological developments, thus the guidelines may differ between some countries that is already on the market and in some circumstances to a reference drug 2. Following intravitreal injection, ranibizumab has a relatively short systemic half-life with reduced systemic exposure due rapid renal clearance. For patients and healthcare systems, anti-VEGF treatment for nAMD can be a substantial burden in terms of medication cost, time burdens and overall decrease in patient quality of life, as it is perceived as stressful and anxiety-provoking by patients. A biosimilar is a biologic that has similar physical, chemical and biological properties to a reference drug that is already on the market and in some circumstances has been demonstrated to reduce costs and even improve patient access to safe and effective biological medicines. Ranibizumab’s patents expired in 2020 in the USA and in 2022 in Europe, allowing ranibizumab biosimilars to be introduced into these markets. A total of 10 manufacturers are working on ranibizumab biosimilar medications and they are at various stages of approval and development with FYB201 under US Food and Drug Administration (US FDA) review, SB11 approved by US FDA in 2021, RanizuRel approved by Drugs Controller General of India (DGCI) in 2020 and Lupin’s ranibizumab in phase 3 trial. There are no fixed international guidelines for biosimilar approval, thus the guidelines may differ between some countries and can change with time and new technological developments. Therefore, the current systematic review and meta-analysis aims to address the variability in medication development stage and lack of unified approval guidelines, providing a comprehensive summary of the efficacy and safety of ranibizumab biosimilar medications that are approved by different agencies or are at different developmental stages relative to the reference ranibizumab anti-VEGF therapy for the treatment nAMD.

METHODS

Search strategy and eligibility criteria
This systematic review and meta-analysis adhered to the Declaration of Helsinki and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the ID number CRD42022326090. We conducted searches from January 2003 to August 2022 on Ovid MEDLINE, EMBASE and the Cochrane Controlled Register of Trials as illustrated in online Supplemental eTable 1. We included randomised controlled trials (RCTs) in which patients with nAMD were treated with intravitreal ranibizumab biosimilars or reference ranibizumab anti-VEGF agents. We included studies reporting changes in best-corrected visual acuity (BCVA) reported in early treatment diabetic retinopathy study (ETDRS) letters, number of patients who lost or gained more than 15 letters in BCVA compared with baseline, changes in retinal thickness and adverse events between treatment arms. The following studies were excluded: studies that did not report outcomes following biosimilar and reference ranibizumab intravitreal injections, study arms combining anti-VEGF agents with laser or steroid injections, sham injections as a control comparator, studies without English full texts and non-comparative, observational study designs.

Study selection and data collection
Title and abstract screening followed by full-text screening were conducted independently by two authors (AH and RD), with conflicts being resolved after discussion with a third author (NC). The study screening process for the included studies of this meta-analysis is illustrated in figure 1. We used Covidence (Veritas Health Innovation, Melbourne, Australia) for the screening and study selection stages. Additionally, we used Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) to collect all data, which included changes in BCVA from baseline as the primary outcome, changes in retinal thickness from baseline, changes in number of patients who lost or gained more than 15 letters in BCVA compared with baseline, and adverse events as secondary outcomes. Finally, if reported in the study, we collected the following baseline characteristics: country, publication year, biosimilar ranibizumab treatment agent, treatment regimen, number of eyes, number of right eyes, number of males, number of patients with phakic and aphantic/pseudophakic lens, mean age of participants, initial BCVA and retinal thickness. For change in retinal thickness, we included central subfield thickness (CST), central macular thickness (CMT) and foveal central subfield retinal thickness. We did not estimate values from figures and only included data explicitly reported in the text or received directly from the authors. We contacted authors via email requesting additional data for any missing outcomes such as the mean, SD and the number of patients that were included in our meta-analysis. A single follow-up email was sent 2 weeks later if no response was received. We included the most recent publications for RCTs that were part of a study series and we used previous papers in the series to supplement any data for outcomes not reported in the most recent paper.

Risk of bias and certainty of evidence assessment
Two independent authors (AH and RD) assessed the risk of bias and certainty of evidence with conflicts resolved through a third independent author (NC). In order to assess the risk of bias and certainty of evidence of the included studies, we used Cochrane’s Risk of Bias tool 2 (ROB2) 20 and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). 21
Statistical analysis
We reported risk ratios (RRs) for dichotomous outcomes. We applied the inverse variance method to weighted mean differences and the Mantel-Haenszel method to RRs. Review Manager (RevMan V.5.4; The Nordic Cochrane Centre, Cochrane, Copenhagen, Denmark) was used to conduct this meta-analysis using a random effects model. We used a p value of 0.05 as the significance threshold for all analyses conducted and we assessed statistical heterogeneity using I² values, with 75% or higher identified as having significant heterogeneity.22

RESULTS
Study selection and characteristics
A total of 16712 studies underwent title and abstract screening and 30 studies underwent full text screening to assess eligibility. Five studies that reported on four RCTs with a total of 1544 eyes at baseline were included in this meta-analysis (figure 1).23–27 Two studies reported on results from the same RCT; therefore, the most recently published study24 on that trial was included in the meta-analysis and the previously published study25 was used to supplement any missing data. Ranibizumab biosimilars used in the included studies consisted of FYB201 (bioeq).23 SB11 (Samsung Bioepics and Biogen),24 25 RanizuRel (Intas Pharmaceutical)26 and Lupin’s ranibizumab (LUBT010, Lupin, Indian).27 The biosimilars are under Biologic License Application review by the US FDA, approved by US FDA in 2021, approved by DGCI in 2020 and in phase 3 trial, respectively.17

Of the included studies, age was reported as a range for one study, which included patients aged 50–94 years old23 while the other three studies reported mean age, which ranged from 67 to 74 years old.24 26 27 Proportion of males across included studies ranged from 43% to 70%. Lens status, number of right eyes, initial BCVA and initial retinal thickness were not consistently reported by the included studies. All reported study characteristics are displayed in table 1 and study outcomes are displayed in table 2.

Risk of bias and GRADE assessment
The risk of bias, using Cochrane’s ROB2 tool, is outlined in online supplemental eTable 2. There was a low risk of bias found in all four of the included studies for the randomisation process (100%) and deviation from intended interventions (100%). In addition, there was a low risk of bias for measurement of the outcome in three of the studies (75%), missing outcome data in two of the studies (50%) and industry sponsorship in one of the studies (25%). There were some concerns for risk of bias regarding conflicts of interest in all four studies (100%), industry sponsorship in three of the studies (75%) missing outcome data and selection of reported result in two of the studies (50%).

Summary of findings for the GRADE are outlined in online supplemental eTable 3. For the outcomes analysed in our meta-analysis, the certainty of evidence included was 78.5% low certainty and 21.2% very low certainty.

Systematic review: ranibizumab versus FYB201
The study by Holz et al was a prospective RCT of 477 eyes of patients with nAMD that were randomly divided into two groups and received monthly injections of (1) ranibizumab (239 eyes) or (2) FYB201 (238 eyes).23 The mean BCVA improved in both groups, with a mean change of
5.6 ETDRS letters for group I and 5.1 ETDRS letters for group II at week 8. Additionally, there were observed improvements in mean BCVA change from baseline of 7.1±10.42 ETDRS letters and 6.9±10.1 ETDRS letters at 6 months and 7.8±11.7 ETDRS letters at 12 months for group I and group II, respectively. The participants of the study saw an improvement in BCVA from the first dose of study medication throughout the study length in both groups. For retinal thickness measurements, there was a mean reduction from baseline 205.5±147.2 µm and 203.9±126.5 µm at 6 months, and 211.0±151.9 µm and 213.3±161.3 µm at 12 months for groups I and II, respectively. There were no obvious differences in either measure of retinal thickness decrease or change in BCVA between treatment groups.

**Systematic review: ranibizumab versus SB11**

The study by Bressler et al and Woo et al both reported on a prospective RCT of 705 eyes of patients with nAMD that were randomly divided into two groups and received monthly injections of (1) ranibizumab (354 eyes) or (2) SB11 (351 eyes). Mean change in BCVA from baseline to 2 months were 7.0±0.5 ETDRS letters and 6.2±0.5 ETDRS letters in groups I and II, respectively, with the adjusted treatment difference between groups was −0.8 letters (90% CI −1.8 to 0.2 letters). At 13-month time point change in BCVA was 10.4±11.5 ETDRS letters for group I and 9.7±11.4 ETDRS letters for group II. With regard to change in retinal thickness which was measured as CST, baseline at 1 month was −100.5 µm in group I and −108±5 µm in group II with the adjusted treatment difference between groups of −8 µm (95% CI −19 to 3 µm). At 13 months, change in retinal thickness was −128.4±116.1 µm for group I and −133.6±103.9 µm for group II. To conclude, final study results for change from baseline in BCVA and in CST showed that the reported improvements remained stable and appeared comparable between treatment groups at all time points up to week 52.

**Systematic review: ranibizumab versus RanizuRel**

The study by Apsangikar et al was a prospective RCT of 170 nAMD eyes who received monthly injections of (1) ranibizumab (53 eyes) or (2) RanizuRel (107 eyes). Overall, 100% of patients in group I and 98.11% of the patients in group II lost fewer than 15 letters in VA from baseline to 4 months. This trend continued at the 6-month time point, with less than 15 letters lost in 100% of patients in group I and 99.06% of patients in group II. The between-group difference in VA from baseline to 4 months (p=0.314) and 6 months (p=0.478) was statistically not significant between the two groups. At 6 months, the mean number of letter gain was 15.66 ETDRS letters and 12.11 ETDRS letters in groups I and II, respectively, with a non-significant difference between the two groups (p=0.07534). The mean change in CMT was −66.80 µm and −78.22 µm at 4 months and −64.42 µm −89.93 µm at 6 months in group I and II, respectively. The difference between the two groups was not statistically significant at 4 months (p=0.5502) and 6 months (p=0.2160).

**Systematic review: ranibizumab versus Lupin’s biosimilar ranibizumab**

The study by Singh et al was a prospective RCT of 202 eyes of patients with nAMD who received quarterly
injections of (1) ranibizumab (101 eyes) or (2) Lupin’s biosimilar ranibizumab (101 eyes). At 3 months 99% of patients in group I and 100% of the patients in group II lost fewer than 15 letters in VA from baseline. Additionally at 3 months, the estimated treatment difference between the two groups was well within the predefined equivalence margin of 8.5% for the proportion of patients who lost fewer than 15 letters. There was a consistent improvement in the mean BCVA score at 1 month, 2 months and 3 months as compared with the baseline score in both the treatment groups. The mean change in BCVA from baseline at 3 months was 7.6 ETDRS letters in group I and 8.9 ETDRS letters in group II.

**Meta-analysis: safety of ranibizumab biosimilars versus reference ranibizumab**

When examining adverse events, there was no significant difference in treatment emergent adverse events (TEAE) between ranibizumab biosimilar and reference ranibizumab groups in all four RCTs (RR 1.06, 95% CI (0.91 to 1.23), p=0.45, I²=52%, figure 2A). With respect to serious TEAEs, two RCTs reported no significant difference between ranibizumab biosimilar and reference ranibizumab groups (RR 1.25, 95% CI (0.76 to 2.04), p=0.38, I²=58%, figure 2B). In three RCTs, there was also no significant difference between ranibizumab biosimilar and reference ranibizumab groups in TEAEs related to the study drug (RR 1.19, 95% CI (0.70 to 2.02), p=0.53, I²=0%, figure 2C) and TEAEs leading to withdrawal of the study drug (RR 0.73, 95% CI (0.34 to 1.59), p=0.43, I²=0%, figure 2D).

Furthermore, in two RCTs, there was no significant difference between ranibizumab biosimilar and reference ranibizumab groups for serious adverse events (SAEs) (RR 1.24, 95% CI (0.74 to 2.06), p=0.42, I²=61%, figure 2E), conjunctival haemorrhage (RR 1.14, 95% CI (0.73 to 1.80), p=0.56, I²=0%, figure 2F), vitreous haemorrhage (RR 0.62, 95% CI (0.08 to 5.02), p=0.65, I²=0%, figure 2G), endophthalmitis (RR 0.76, 95% CI (0.08 to 7.22), p=0.81, I²=28%, figure 2H), retinal haemorrhage (RR 0.40, 95% CI (0.13 to 1.26), p=0.12, I²=0%, figure 2I) and retinal tear (RR 1.56, 95% CI (0.22 to 11.21), p=0.66, I²=32%, figure 2J). There was no significant change, with significant heterogeneity, in cataracts between ranibizumab biosimilar and reference ranibizumab groups (RR 2.59, 95% CI (0.11 to 62.25), p=0.56, I²=76%, figure 2K).

There was also no significant difference in IOP (intraocular pressure)-related adverse events, which included increases in IOP, ocular hypertension, glaucoma progression and initiation of IOP-lowering medication in two RCTs (RR 1.33, 95% CI (0.93 to 1.92), p=0.12, I²=0%, figure 2L). Intraocular inflammation (IOI) comparison was not conducted since it was not routinely reported in the included RCTs.

**DISCUSSION**

The current systematic review and meta-analysis assessed the safety of ranibizumab biosimilars relative to reference
ranibizumab anti-VEGF therapy for the treatment of nAMD. The reported studies in our review found no significant differences in visual and anatomical outcomes reference ranibizumab and the studied ranibizumab biosimilars (FYB201, SB11, RanizuRel and Lupin’s biosimilar ranibizumab) was identified. Furthermore, when analysing adverse events, our analyses revealed consistent results. Over the last decade, all of 26 FDA approved biosimilars have shown no discrepancies in the severity or frequency of adverse effects between biosimilars and reference medicines. Sharma et al conducted a comprehensive review of Razumab and concluded that its efficacy and safety have been consistently maintained across several prospective and retrospective studies totalling 1561 patients. Additional investigation is needed to determine whether different ranibizumab biosimilars are variable in their efficacy and safety as we were unable to conduct any subgroup analyses due to limited RCTs and limited sample sizes. Included RCTs had variations in reporting for several outcomes such as BCVA and retinal thickness at each time point as well as adverse events, which limited our conclusions.
400 patients. Singh et al followed patients for a total of 3 months which is a limitation of the RCT as it would not include patients who had postinjection inflammation after the 3-month follow-up time point in their safety analysis. In order to maximise our reporting capacity, some clinically related adverse events were aggregated, such as increases in IOP, ocular hypertension, glaucoma progression and initiation of IOP-lowering medication together. IOI analysis was not conducted since it was not routinely reported and cannot be compared across the included RCTs. The minimal data at each monthly time point inhibited us from conducting a meta-analysis for our primary outcomes and decreased our analytical power for adverse events as there was variability in RCTs reporting on these outcomes. The shortage of RCT studies in the literature limited the power of investigating different biosimilar medications or retinal pathologies. As we have outlined in our risk of bias assessment, factors such as industry sponsorship, missing outcomes and conflicts of interest may underpower our analysis any such similar analysis. Therefore, the findings of this systematic review and meta-analysis should be interpreted in the context of these limitations, and conclusions drawn at the group level may not necessarily translate to individual clinical significance. Overall, our systematic review involving four RCTs found comparable outcomes in the visual, anatomic measurements and our meta-analysis of safety outcomes did not yield significant outcomes when considering biosimilar and reference ranibizumab therapies for nAMD within the context of the stated limitations. These analyses provide clinical context for alternatives to ranibizumab for nAMD as they begin to be used commercially. Continued investigations of this topic with increased sample sizes are warranted to further characterise the safety and efficacy of anti-VEGF biosimilars.

Competing interests NC: consultant for Topcon, Optos, Bayer, Allergan, Hoffman

Author affiliations

1 Ophthalmology, McMaster University Michael G DeGroote School of Medicine, Hamilton, Ontario, Canada
2 Vitreous Retina Macula Specialists of Toronto, Etobicoke, Ontario, Canada
3 Octane Imaging Lab, Toronto, Ontario, Canada
4 Retina Consultants of Texas, Bellaire, Texas, USA
5 Blanton Eye Institute, Houston Methodist Hospital & Weill Cornell Medical College, Houston, Texas, USA
6 Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada
7 Cleveland Clinic Canada, Toronto, Ontario, Canada

Contributors All authors cited (AH, RD, SO, CW and NC) have sufficiently provided substantial contributions to the conception, design of the work, the acquisition, analysis, interpretation of data for the work. They have all been involved in drafting the work and revising it critically for important intellectual content. They all gave the final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NC acts as the guarantor for the work and conduct of the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclosure The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

REFERENCES


