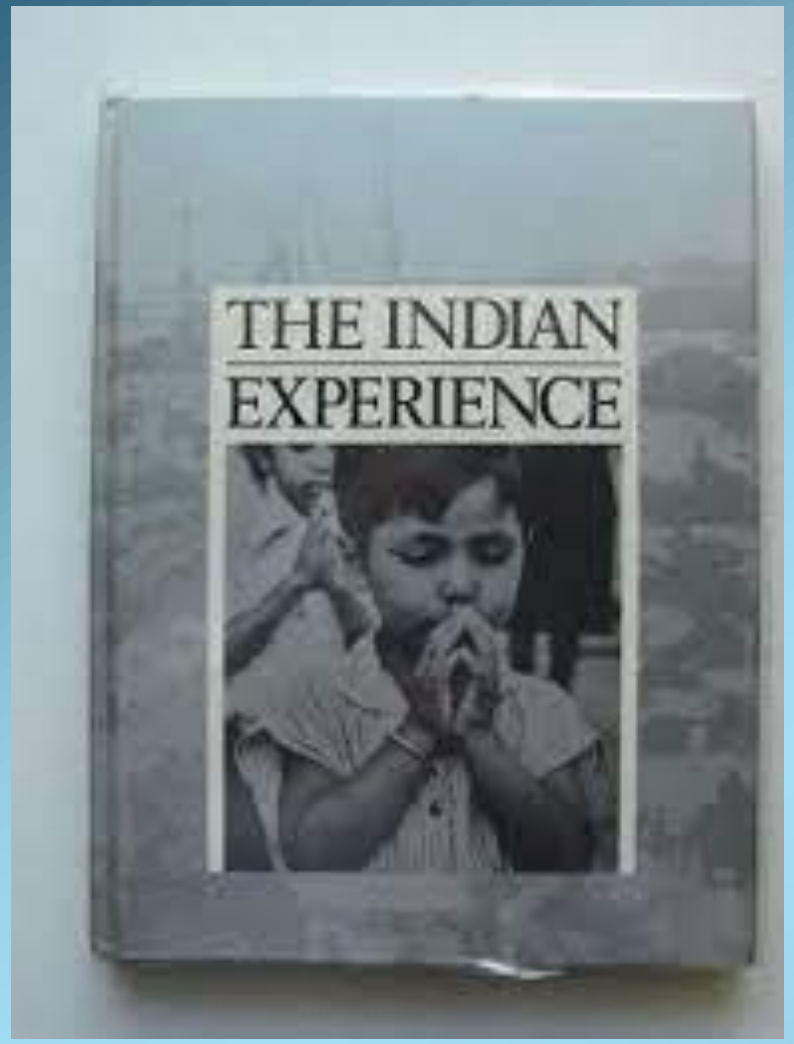


Patient and Physician Experience with Ophthalmic Biosimilars from India

Dr Ashish Sharma MD
Lotus Eye Hospital and Institute, Coimbatore, TN, India

Our Contribution

1. Sharma, A., Parachuri, N., Kumar, N. *et al.* Fear of safety compromise with biosimilar anti-VEGF—perception or truth. *Eye* (2022).

2. Sharma, A., Kumar, N., Parachuri, N. *et al.* Retina: a unique subspecialty in the biosimilar landscape. *Eye* (2022).

3. Sharma A, Kuppermann BD. Biosimilars for Retinal Diseases: Understanding the Phase 3 Clinical Trial Design. *Ophthalmology*. 2022;129(1):65-66.

4. Sharma A, Kumar N, Parachuri N, Bandello F, Kuppermann BD, Loewenstein A. Biosimilars for Retinal Diseases: An Update. Am J Ophthalmol. 2020 Dec 9;224:36-42.

5. Sharma A, Kumar N, Parachuri N. Biosimilar Ranibizumab (SB11) vs Reference Ranibizumab: Diving deeper for safety and efficacy. JAMA Ophthalmology. Published online April 29, 2021. doi:10.1001/jamaophthalmol.2021.1037.

6. Sharma A, Hafeez Faridi M, Kumar N, Parachuri N, Sharma R, Kuppermann BD ,Bandello F, Loewenstein A, Regillo CD. . Immunogenicity and efficacy after switching from original Ranibizumab to a Ranibizumab biosimilar: real-world data. *Eye (Lond)*. 2020;34(6):1008-1009.

7. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Understanding biosimilars and its regulatory aspects across the globe: an ophthalmology perspective. *Br J Ophthalmol*. 2020;104(1):2-7. doi:10.1136/bjophthalmol-2019-314443

8. Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: "Is there a big change on the horizon?". Clin Ophthalmol. 2018;12:2137-2143. Published 2018 Oct 24. doi:10.2147/OPTH.S180393

9. Sharma A, Kumar N, Kuppermann BD, Francesco B, Lowenstein A. Ophthalmic biosimilars: Lessons from India. Indian J Ophthalmol 2019; 67:1384-5. Available from: http://www.ijo.in/text.asp?2019/67/8/1384/263143

10. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Biologics, biosilimars, and biobetters: different terms or different drugs? Eye (Lond). 2019 Jul;33(7):1032-1034. doi: 10.1038/s41433-019-0391-5.

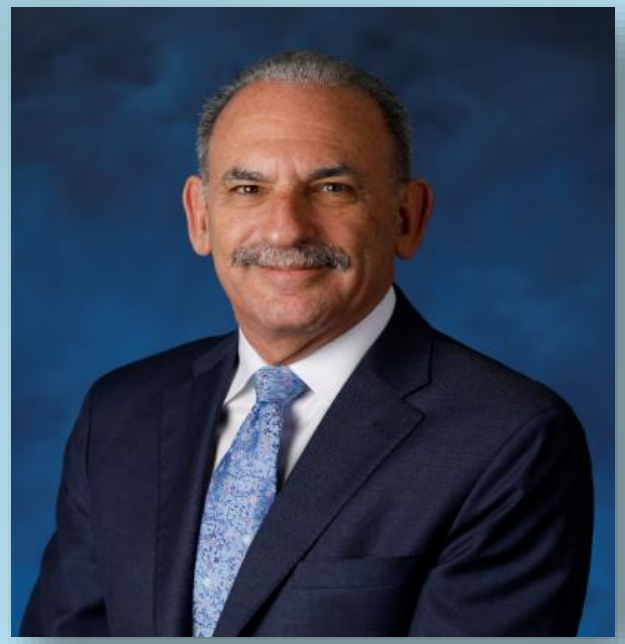
11. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Biotherapeutics and immunogenicity: ophthalmic perspective. Eye (Lond). 2019 Sep;33(9):1359-1361. doi: 10.1038/s41433-019-0434-y.

12. Sharma A, Kumar N, Bandello F, Loewenstein A, Kuppermann BD. Need of education on biosimilars amongst ophthalmologists: combating the nocebo effect. Eye (Lond). 2020 Jun;34(6):1006-1007.

13. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Ophthalmic biosimilars and biologics-role of endotoxins. Eye (Lond). 2020 Apr;34(4):614-615.

Dr Nilesh Kumar (DNB)

Dr Nikulaa parachuri (DNB)



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USA

Dr Anat Loewenstein
ISRAEL

Dr Francesco Bandello
ITALY

Dr Carl D Regillo
USA

Financial Disclosure

Consultant and Speaker

-Novartis India
-Allergan Global
-Bayer India
-Intas India
-Lupin India
-Reliance India

Founder

-MII Ret Cam Inc.

Communicating with your patients

- Need of Multiple Injections to be established
- Cost effectiveness of Biosimilars without any compromise to be established

Concern/ Hesitation Of patients

Is it as good as the reference drug

Will it work the same way as its cheaper

Is it as safe as reference drug as its cheaper

Switching patient

Example from other specialties

Evidence from our own study

Immunogenicity and efficacy after switching from original Ranibizumab to a Ranibizumab biosimilar: real-world data

Ashish Sharma, M. Hafeez Faridi, ... Carl D. Regillo + Show authors

Eye **34**, 1008–1009 (2020) | Cite this article

564 Accesses | **9** Citations | Metrics

Feedback after Switch

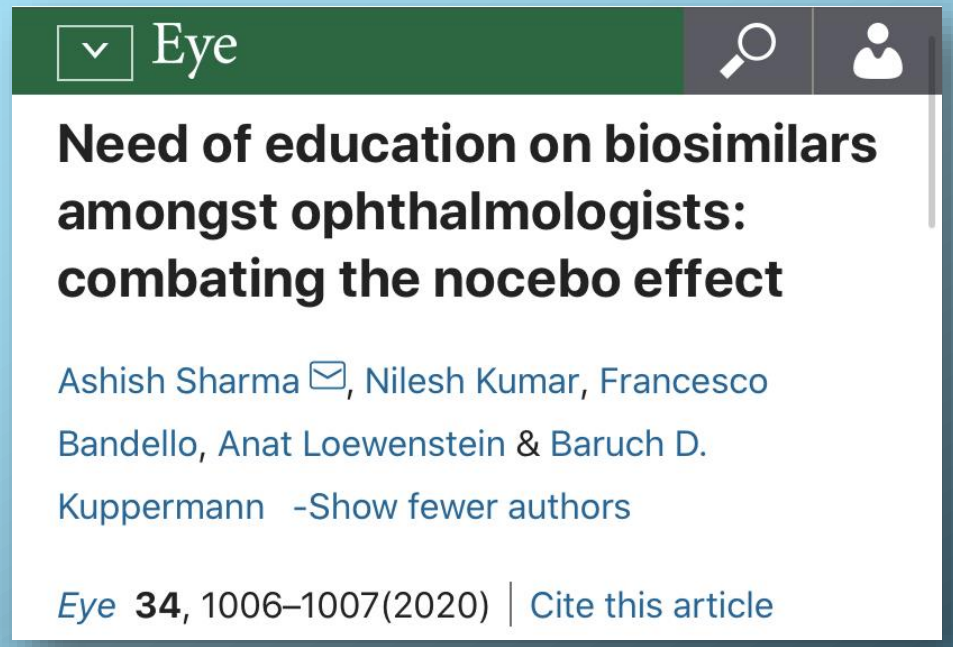
Never Negative

None of our patients asked to switch back to reference

Successful educational initiatives

India

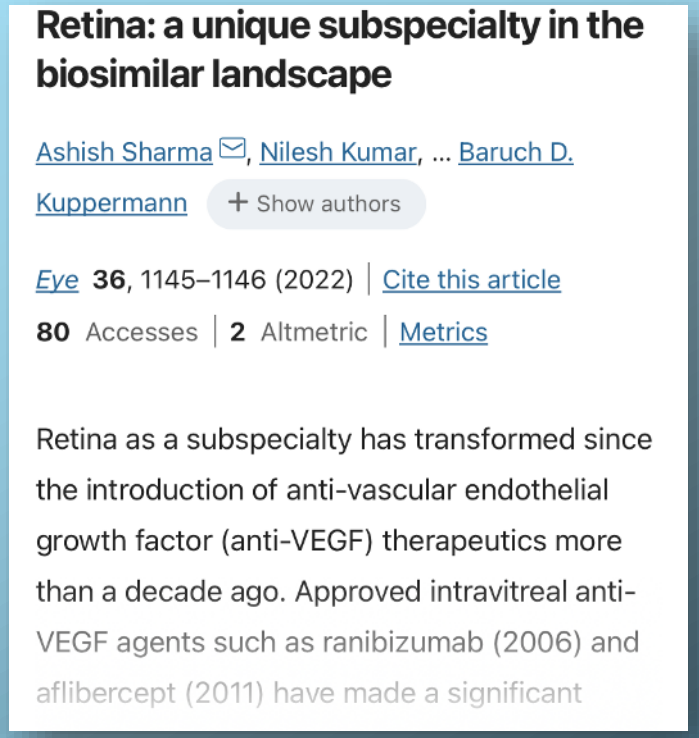
Physicians Education is of paramount Importance (Compared to Patients)



Challenges Retina Subspecialty

Presence of off label bevacizumab

India Centric pricing of reference molecule



Retina: a unique subspecialty in the biosimilar landscape

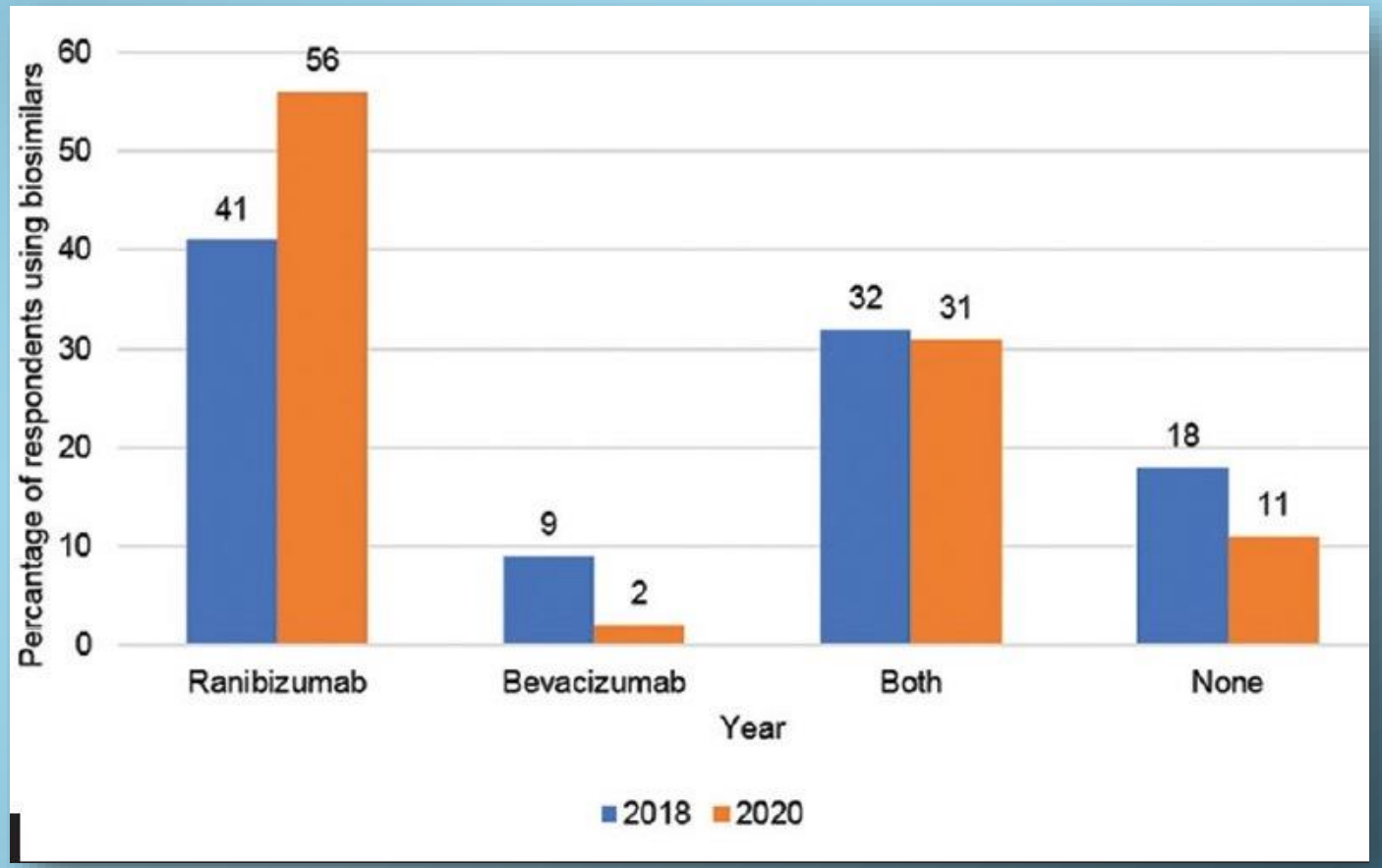
Ashish Sharma, Nilesh Kumar, ... Baruch D. Kuppermann + Show authors

Eye **36**, 1145–1146 (2022) | Cite this article

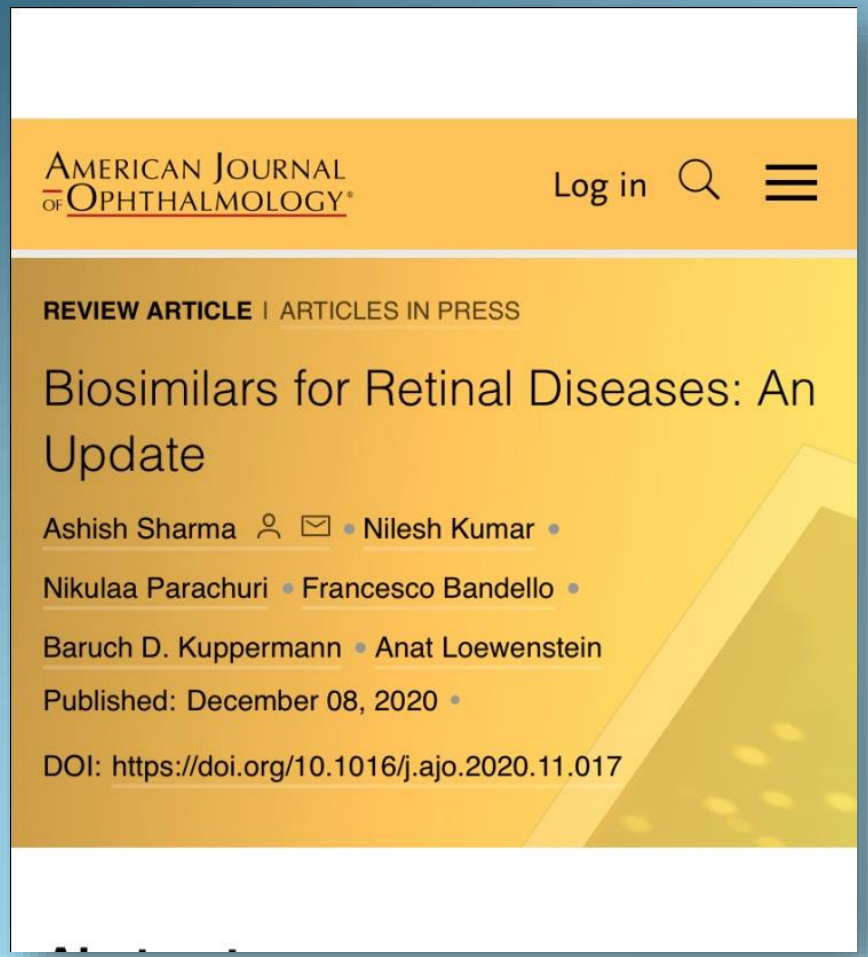
80 Accesses | **2** Altmetric | Metrics

Retina as a subspecialty has transformed since the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapeutics more than a decade ago. Approved intravitreal anti-VEGF agents such as ranibizumab (2006) and aflibercept (2011) have made a significant

India Usage of First Ranibizumab Biosimilar



Sheth JU, Stewart MW, Khatri M, et al. Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey. *Indian J Ophthalmol*. 2021;69(2):352-356.



2 more Biosimilar Ranibizumab Approved

Ranizurel (Reliance Life Sciences, Mumbai)

Rani eyes (Lupin Ltd, Mumbai)

All the indications

nAMD

RVO

DME/DR

ROP

American Journal of Ophthalmology Case Reports
Volume 25, March 2022, 101358

Ranizurel safety evaluation in real-world -(RaSER) study

Ashish Sharma [a], Jayshree Arunaprakash [b], Atheeshwar Das [c], Ashraya Nayaka [d], Nilesh Kumar [a, e], Nikulaa Parachuri [a, f], Baruch D. Kuppermann [g]

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[e] Madhavi Netralaya Ara, Bihar, India
[f] Sankara Eye Hospital, Coimbatore, TN, India
[g] Gavin Herbert Eye Institute, University of California Irvine, Irvine, CA, USA

Received 7 May 2021, Revised 23 July 2021, Accepted 22 January 2022, Available online 2 February 2022, Version of Record 5 February 2022.

Real World data

Ranizurel (Reliance Life Sciences, Mumbai)

No safety and Efficacy Concern

Minor Difference
(Highlighted by the Innovator Company)

MAbs. 2017 Nov/Dec;9(8):1337-1348. doi: 10.1080/19420862.2017.1366395. Epub 2017 Aug 28.

Identification of multiple serine to asparagine sequence variation sites in an intended copy product of LUCENTIS® by mass spectrometry.

Griaud F[1], Winter A[1], Denefeld B[1], Lang M[1], Hensinger H[1], Straube F[1], Sackewitz M[1], Berg M[1].

Author information

1 a Analytical Development and Characterization NBEs, Biopharmaceutical Product and Process Development, Biologics Technical Development and Manufacturing, Novartis Pharma AG , Basel , Basel-Stadt, Switzerland.

Results Go to:

Potency assays

Relative potency was determined for 2 RAZUMAB batches. The potency assay analyzing binding to VEGF showed 96% and 97% relative binding activity versus the LUCENTIS® reference standard. The cell-based functional potency assay revealed 99% and 100% relative potency in comparison with the LUCENTIS® reference standard, respectively (Table 1).

Griaud F, Winter A, Denefeld B, et al. Identification of multiple serine to asparagine sequence variation sites in an intended copy product of LUCENTIS® by mass spectrometry. *MAbs*. 2017;9(8):1337-1348.

The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

COMMENT

Fear of safety compromise with biosimilar anti-VEGF—perception or truth

Ashish Sharma[1✉], Nikulaa Parachuri[2], Nilesh Kumar[3], Francesco Bandello[4] and Baruch D. Kuppermann[5]

Eye; https://doi.org/10.1038/s41433-022-02117-z

The first biosimilar of ranibizumab (Byooviz, Biogen, USA) has received approval from the United States- Food and Drug Administration (US-FDA) and European Medicines Agency (EMA) recently [1, 2]. And the International Retina Biosimilar Study Group (Inter BIOS Group) has conducted a survey (Bio-USER- unpublished data) which has revealed that many retinal physicians from Europe and the US have concerns regarding the safety of biosimilars. Safety is predominantly related to drug-induced intraocular inflammation (IOI) apart from nonocular safety parameters. Anti-vascular endothelial growth factors (Anti-VEGF) are biologics under the category of monoclonal antibodies. Biologics are exogenous proteins and thus, inherently have the potential to cause immunogenicity [3].

In this manuscript, we will try to compare the safety of ranibizumab biosimilar and innovator ranibizumab (Lucentis, Genentech, USA) by analyzing parameters used to assess safety in the landmark phase 3 trial that has led to the approval of these molecules [4–6]. All the biosimilar ranibizumab molecules are compared against the innovator (reference- Lucentis) molecule during the phase 3 trial. For better understanding, we will use the brand name in this manuscript.

Lucentis was approved based on the results of the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) trials [4, 5]. The MARINA trial was designed as a phase 3, randomized, multicentre, double-masked, sham-controlled study enrolling 716 patients with minimally classic lesions or occult with no classic lesions. Patients were randomized 1:1:1 to either sham ($n = 238$), ranibizumab 0.3 mg ($n = 238$), or ranibizumab 0.5 mg ($n = 240$). The ANCHOR trial, also a phase 3 randomized, multicentre, double-masked study, was designed as an active treatment-controlled study. All of the patients in the study ($n = 423$) had predominantly classic lesions. Randomization was 1:1:1 with 143 patients assigned to PDT, 140 patients to treatment with ranibizumab 0.3 mg, and 140 patients to ranibizumab 0.5 mg.

Biosimilars require only one equivalence trial compared to two superiority or non-inferiority trial for innovator molecules. SB11 (Byooviz) long-term safety data were published in the recent past [6]. It was a randomized, double-masked, parallel-group, phase III equivalence study. Patients were randomized 1:1 to either SB11 ($n = 351$), or Lucentis 0.5 mg ($n = 354$).

Here is the comparison of various safety parameters between the approved innovator and biosimilar ranibizumab.

INTRAOCULAR INFLAMMATION

The ANCHOR trial demonstrated inflammation in 17.1% of cases. Most of the cases had trace cells (8%) followed by 1 + (2.2%), 3 + (1.5%) and 2 + (0.7%) during the cumulative 12 months period. The MARINA trial demonstrated inflammation in 20.9% of cases. Most of the cases had trace cells (14.6%) followed by 1 + (3.3%), 4 + (1.3%), 2 + (0.8%), and 3 + (0.8%) during the cumulative 24 months period. The above-described rate of inflammation was noticed with the commonly used dose of 0.5 mg of ranibizumab. The phase 3 trial results of SB11 demonstrated inflammation in 0.9 % of cases {(iridocyclitis (0.3%), uveitis (0.3%) and vitritis (0.3%))}.

OTHER OCULAR ADVERSE EVENTS

ANCHOR and MARINA studies showed endophthalmitis rates of 1.4% and 1.3% respectively. Whereas in the SB11 trial it was 0.6%. None of the cases in the ANCHOR study showed vitreous hemorrhage, retinal tear, or lens damage whereas the MARINA trial showed vitreous hemorrhage, retinal tear, and lens damage in 0.4% of each. The SB11 trial showed retinal hemorrhage at 0.3%, and retinal pigment epithelium tear in 0.3% of cases.

NON OCULAR ADVERSE EVENTS

There was no myocardial infarction or stroke event in the SB11 trial. The ANCHOR trial revealed myocardial infarction in 2.1% and stroke in 0.7% of cases. The MARINA trial showed myocardial infarction in 1.3% and stroke in 2.5% of cases. The ANCHOR and MARINA trials showed hypertension in 6.4 and 16.3% of cases whereas the SB11 trial showed hypertension in 0.9% of cases. Deaths were 0.6% during 12 months (52 weeks) of the SB11 trial whereas it was 1.4% and 2.6 % in the ANCHOR and MARINA trials respectively.

As per the above-described safety data of the ANCHOR (12 months), MARINA (24 months), and SB11 phase 3 trials (52 weeks), except for retinal hemorrhage and retinal pigment epithelial tears, numerically the ANCHOR and MARINA trials had more adverse events. However, this comparison may not be

[1]Lotus Eye Hospital and Institute, Avinashi Road, Coimbatore, TN, India. [2]Sankara Eye Hospital, Coimbatore, TN, India. [3]Madhavi Netralaya, Ara, Bihar, India. [4]University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy. [5]Gavin Herbert Eye Institute, University of California, Irvine, Irvine, CA, USA. ✉email: drashish79@hotmail.com

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Published online: 26 May 2022

LOTUS
EMPOWERING EYES ILLUMINATING LIVES

Lower than the Innovator

INTRAOCULAR INFLAMMATION
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Sharma A, Kumar N, Kuppermann BD, Francesco B, Lowenstein A. Ophthalmic biosimilars: Lessons from India [published correction appears in Indian J Ophthalmol. 2020 Oct;68(10):2331]. *Indian J Ophthalmol*. 2019;67(8):1384-1385. doi:10.4103/ijo.IJO_430_19

Takeways from india

- Every anti-VEGF (Lucentis, aflibercept, Ranibizumab biosimilar of India) had inflammation at some point of time in few cases

  Start Slow

- Biosimilars are as efficacious and safe as originator

  No Efficacy and safety Compromise

- Negative perception has been associated with biosimilars and sometimes created by innovators by highlighting minor differences in the initial stages

  Believe in regulatory authority for approval and their process

- India lack compounding pharmacies for bevacizumab hence biosimilar ranibizumab has been adopted as cost effective option

  Bevacizumab might be a major determinant in the success of biosimilar anti-VEGF in the US

Many Lives are becoming better with Biosimilars in India

Thank you