



Brolucizumab-related intraocular inflammation in Japanese patients with age-related macular degeneration: a short-term multicenter study

Ichiro Maruko¹ · Annabelle A. Okada² · Tomohiro Iida¹ · Taiji Hasegawa · Takahiko Izumi · Moeko Kawai · Ruka Maruko · Makiko Nakayama · Akiko Yamamoto · Hideki Koizumi · Tamaki Tamashiro · Nobuhiro Terao · Sorako Wakugawa · Ryusaburo Mori · Hajime Onoe · Koji Tanaka · Yu Wakatsuki · Kanako Itagaki · Akihito Kasai · Masashi Ogasawara · Tetsuju Sekiryu · Hiroaki Shintake · Yukinori Sugano · for the Japan AMD Research Consortium

Received: 13 January 2021 / Revised: 20 February 2021 / Accepted: 26 February 2021 / Published online: 15 March 2021
© The Author(s) 2021

Key messages

What is known

- Brolucizumab-related intraocular inflammation occurred more frequently in Japanese patients with age-related macular degeneration, compared to other patients in phase 3 global clinical trials.

New information

- Between 9 and 10% of both treatment-naïve and switched Japanese patients in our study developed intraocular inflammation after brolucizumab administration.
- Of patients with intraocular inflammation, 75% developed it at a mean of 23.2 ± 9.3 (range 10–36) days after the first brolucizumab injection.
- Rates of intraocular inflammation were not higher in women.
- Inflammation resolved within 2 months.

Dear Editor,

We report short-term data on the development of intraocular inflammation (IOI) after intravitreal brolucizumab injection for exudative age-related macular degeneration (AMD) in Japanese patients in this letter.

Brolucizumab (Novartis Pharma AG, Basel, Switzerland), a new anti-vascular endothelial growth factor (VEGF) agent for the treatment of exudative AMD, differs from previous anti-VEGF agents by its smaller molecular weight allowing administration at high concentrations and presumably improved tissue penetration. In the HAWK and HARRIER studies, brolucizumab was reportedly non-inferior to aflibercept in terms of visual outcomes and more effective in reducing intraretinal and subretinal fluid [1]. Early US reports regarding the adverse effect of IOI [2] prompted a Novartis-appointed Safety Review Committee (SRC) to re-evaluate data from the clinical trials [3]. At the 2020 Annual Meeting of the American Academy of Ophthalmology, Heier et al. [4] described SRC findings suggesting that female gender and Japanese ethnicity were risk factors.

✉ Ichiro Maruko
imaruko@twmu.ac.jp

¹ Department of Ophthalmology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

² Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, Japan

Table 1 Characteristics of 127 eyes of 127 patients treated with intravitreal brolocizumab injection for exudative age-related macular degeneration

		<i>n</i> (%)
Gender	Male	109 (85.8%)
	Female	18 (14.2%)
Treatment-naive		43 (33.9%)
Switched		84 (66.1%)
IOI		12/127 (9.4%)
IOI with retinal vasculitis		4/127 (3.1%)
IOI with retinal vasculitis <i>and</i> retinal vascular occlusion		2/127 (1.6%)

Treatment-naive = eyes without any prior treatment

Switched = eyes previously treated with other anti-VEGF agents

VEGF = vascular endothelial growth factor

IOI = intraocular inflammation

Brolocizumab was approved in Japan in May 2020 and used to treat 149 eyes of 149 patients over the 6-month period May–November 2020 by the Japan AMD Research Consortium. Clinical data for 127 eyes of 127 consecutive patients who had at least 1 follow-up visit after the first brolocizumab injection were retrospectively analyzed. Forty-three patients were treatment-naive (36 men, 7 women) and 84 patients were switched from other anti-VEGF agents (73 men, 11 women).

Mean follow-up after the first brolocizumab injection was 12.4 ± 4.7 (range 4–24) weeks. Of 127 eyes, 12 (9.4%) developed IOI consisting of anterior chamber cells and/or vitreous cells, with retinal vasculitis documented in 4 eyes (3.1%) and retinal vascular occlusion in 2 eyes (1.6%) (Table 1). The IOI was noted after the first injection in 9 eyes at a mean of 23.2 ± 9.3 (range 10–36) days post-injection; in the remaining 3 eyes, it occurred after the second or third injections. Rates of IOI were similar for treatment-naive cases (9.3%) and switched

cases (9.5%), and were not higher in women (Table 2). IOI was treated with topical corticosteroids (0.1% betamethasone eyedrops) in all eyes and additional sub-Tenon's injection of triamcinolone acetonide (20 mg) in the 4 eyes with retinal vasculitis. No patient received systemic corticosteroids. Active inflammation resolved within 2 months in all patients. Although the retinal vascular occlusion observed in 2 eyes was located outside the vascular arcades, visual acuity decreased markedly from 74 to 35 Early Treatment of Diabetic Retinopathy Study letters then improved to 65 letters in 1 month for one eye, and decreased from 59 to 50 letters then improved to 65 letters in 1 month for the other eye.

Overall, the SRC found IOI in 4.6% of patients, retinal vasculitis in 3.3%, and retinal vascular occlusion in 2.1%. However, among 101 Japanese patients enrolled in the HAWK study, the rates were 2- to 3-fold higher; IOI in 12.9%, retinal vasculitis in 9.9%, and retinal vascular occlusion in 4.95% [5]. In addition, Heier et al. reported that female gender was associated with higher risk for IOI [4]. Previous case reports of IOI associated with brolocizumab were also predominantly in women [6]. The reasons for higher rates of inflammatory adverse effects in Japanese or women have yet to be delineated.

Because Japanese patients may be at higher risk, we believe it is important to report our early experience with brolocizumab over our first 6 months of use. We found IOI rates to be between 9 and 10%, still high but slightly lower than reported by the SRC for Japanese trial patients. The majority (75%) occurred after the first injection, and one-third developed retinal vasculitis or retinal vascular occlusion.

Acknowledgements Japan AMD Research Consortium: Taiji Hasegawa, MD, PhD, Tomohiro Iida, MD, PhD, Takahiko Izumi, MD, Moeko Kawai, MD, Ichiro Maruko, MD, PhD, and Ruka Maruko, MD, PhD (Department of Ophthalmology, Tokyo Women's Medical University, Japan); Makiko Nakayama, MD, PhD, Annabelle A. Okada, MD, PhD, and Akiko Yamamoto, MD, PhD (Department of Ophthalmology, Kyorin

Table 2 Characteristics by patient gender of treatment-naive and switched eyes that developed intraocular inflammation after intravitreal brolocizumab injection

	Total patients (<i>n</i> =43)	Men (<i>n</i> =36)	Women (<i>n</i> =7)
Treatment-naive			
IOI	4/43 (9.3%)	3/36 (8.3%)	1/7 (14.3%)
IOI with retinal vasculitis	1/43 (2.3%)	1/36 (2.8%)	0/7 (0%)
IOI with retinal vasculitis <i>and</i> retinal vascular occlusion	0/43 (0%)	0/36 (0%)	0/7 (0%)
Switched			
IOI	8/84 (9.5%)	7/73 (9.6%)	1/11 (9.1%)
IOI with retinal vasculitis	3/84 (3.6%)	3/73 (4.1%)	0/11 (0%)
IOI with retinal vasculitis <i>and</i> retinal vascular occlusion	2/84 (2.4%)	2/73 (2.7%)	0/11 (0%)

Treatment-naive = eyes without any prior treatment

Switched = eyes previously treated with other anti-VEGF agents

VEGF = vascular endothelial growth factor

IOI = intraocular inflammation

University School of Medicine, Japan). Hideki Koizumi, MD, PhD, Tamaki Tamashiro, MD, Nobuhiro Terao, MD, PhD, Sorako Wakugawa, MD (Department of Ophthalmology, Graduate School of Medicine, University of the Ryukyus, Japan); Ryusaburo Mori, MD, PhD, Hajime Onoe, MD, Koji Tanaka, MD, PhD, Yu Wakatsuki, MD, PhD (Department of Ophthalmology, Nihon University School of Medicine, Japan). Kanako Itagaki, MD, Akihito Kasai, MD, Masashi Ogasawara, MD, Tetsuju Sekiryu, MD, PhD, Hiroaki Shintake, MD, and Yukinori Sugano, MD, PhD (Department of Ophthalmology, Fukushima Medical University, Japan).

Declarations

Ethics approval This was a retrospective study, and the procedures used conformed to the tenets of the Declaration of Helsinki. The Institutional Review Boards of Kyorin University, Fukushima Medical University, Nihon University, Tokyo Women's Medical University, and University of the Ryukyus approved the procedures used. Informed consent was obtained from all individual participants included in the study.

Conflict of interest Dr Maruko reported grants from JSPS KAKENHI (Grant Number JP20K09781); personal fees from Alcon, Bayer, Canon, Nidek, Novartis, Santen, Senju, and Topcon outside the submitted work.

Dr Okada reported consulting fees from Astellas, Bayer, Biocon Biologics, Daiichi Sankyo, HOYA, Kowa, and Novartis; personal support from Abbvie, Alcon, Bayer, Mitsubishi Tanabe, Novartis, Pfizer, Santen, and Senju outside the submitted work.

Dr Iida reported consulting fees from Bayer and Chugai; personal fees from AMO, Alcon, Bayer, Canon, HOYA, JFC, Kowa, Nikon, Nidek, Novartis, Otsuka, Pfizer, Santen, Senju, and Topcon outside the submitted work.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a

credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Dugel PU, Singh SR, Koh A et al (2020) HAWK and HARRIER: 96-week outcomes from the phase 3 trials of brodalumab for neovascular age-related macular degeneration. *Ophthalmology*. <https://doi.org/10.1016/j.ophtha.2020.06.028>
2. Novartis AG (2020) Novartis provides update on use and safety of Beovu (brodalumab). Available at: <https://www.brodalumab.info/>. Accessed 10 December 2020
3. Monés J, Srivastava SK, Jaffe GJ et al (2020) Risk of inflammation, retinal vasculitis and retinal occlusion-related events with brodalumab: post-hoc review of HAWK and HARRIER. *Ophthalmology* S0161-6420(20):31075–31077. <https://doi.org/10.1016/j.ophtha.2020.11.011>
4. Heier JS, Rosenbaum JT, Barakat MR et al. (2020) Assessing characteristics of patients with or without intraocular inflammation (IOI) in the brodalumab treatment arms from the HAWK and Harrier, phase 3 studies. Presented at the Annual Meeting of the American Academy of Ophthalmology (virtual) November 14-17
5. Iida T, Takahashi K, KinfeMichael G, Ogura Y (2020) Sub-population analysis of Japanese patients from brodalumab HAWK study. Presented at the 74th Annual Congress of Japan Clinical Ophthalmology (virtual) October 15-18
6. Bauman CR, Spaide RF, Vajzovic L et al (2020) Retinal vasculitis and intraocular inflammation after intravitreal injection of brodalumab. *Ophthalmology* 127(10):1345–1359. <https://doi.org/10.1016/j.ophtha.2020.04.017>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.