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Short Communication

Switching from ranibizumab (0.5 mg) to brolucizumab (6 mg) in the management of wet age-related macular degeneration, real-life one year data

Libor Hejsek[1,2,*], Martina Rubesova[3], Lenka Havlickova[3]

[1]Eye clinic, Charles University, Faculty of Medicine in Hradec Kralove, Czech Republic

[2]Department of Ophthalmology, University Hospital in Hradec Kralove, Czech Republic

[3]Cornea Lexum Prague, Czech Republic

*Author for correspondence: Email: libor.hejsek@gmail.com

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Introduction

Age-related macular degeneration (AMD) is a common and potentially devastating eye disease affecting millions of people worldwide. Among the two major subtypes of AMD, the wet form poses a significant threat to vision due to the development of choroidal neovascularization and subsequent retinal damage. Anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the treatment landscape for wet AMD, particularly with the advent of ranibizumab, a widely used monoclonal antibody targeting VEGF-A [1].

The incidence of wet AMD has been steadily increasing with the ageing population, leading to a growing public health concern. Early diagnosis and prompt initiation of effective treatment are critical to preserving vision and preventing disease progression. The introduction of anti-VEGF agents, particularly ranibizumab, has significantly improved visual outcomes for many patients, leading to a reduction in severe visual loss and stabilizing or even improvement in visual acuity.

Despite the significant benefits observed with ranibizumab therapy, the treatment burden, including frequent injections and monitoring visits, is a challenge for patients and healthcare providers [2,3].

Long-term administration of anti-VEGF agents such as ranibizumab requires frequent intravitreal injections and regular monitoring visits, often leading to treatment fatigue, non-adherence, and increased healthcare resource utilization. In addition, potential complications such as endophthalmitis and retinal detachment associated with frequent injections underscore the importance of exploring alternative therapeutic options.

In recent years, brolucizumab, a newer anti-VEGF agent with a smaller molecular size and an extended dosing interval, has emerged as a potential alternative for the treatment of wet AMD management. The need for optimized therapeutic approaches in wet AMD has prompted investigations into the safety, efficacy, and feasibility of switching from ranibizumab to brolucizumab. The advantages of brolucizumab are thought to be due to its unique structure as a single-chain antibody fragment, characterized by a lower molecular weight, potentially allowing better penetration into tissues and higher concentrations. Two major clinical trials have recently shown that brolucizumab is not inferior to the comparator aflibercept in terms of visual outcomes. The extended dosing interval may reduce the treatment burden and potentially improve patient compliance and treatment outcomes. Additional post-trial analyses showed generally positive effects on ocular anatomy. However, it is important to note that both the clinical trials and post-marketing reports have identified safety concerns. These include instances of intraocular inflammation (IOI) and retinal vasculitis, with or without occlusion [4,5].

The aim of this article is to review the real-world data on inadequate ranibizumab therapy and the potential benefits and considerations of switching to brolucizumab.

Materials & Methods

This is a retrospective 12 month study of real-world based patient data. Patients who met these indication criteria were included in the follow-up of the study: active wet form of AMD (any type), age ≥ 50 years, initial visual acuity in the range of 20/40 – 20/200 (ETDRS optotype), the extent of the lesion is a maximum of 8 disc areas (DA), the extent of possible submacular bleeding is a maximum of 25% of the lesion. These patients were treated with primary ranibizumab therapy .

Before the first injection, patients underwent a comprehensive ophthalmic examination with artificial mydriasis, as well as a photo of the fundus (fundus camera Zeiss Clarus 500) and Optical coherence tomography (OCT, Zeiss Angioplex) of the macula. Patients were treated (ranibizumab) in the treat and extend intention (starting with the loading phase of 3 monthly doses), during each visit were the best corrected visual acuity (BCVA with number of letters read on ETDRS optotype) and OCT scans (macular cube measuring central retinal thickness – CRT, and high definition cross) were performed.

The indications for switching from ranibizumab (0.05 ml / 0.5 mg) to brolucizumab (0.05 ml / 6 mg) were: persistent or progressive activity (according to the OCT findings) and the associated inability to extend the intervals between applications of ranibizumab. The transition from ranibizumab to brolucizumab therapy always started with the new loading phase and continued according to the recommended on-label dosage (of brolucizumab).

Patients continued to be monitored biomicroscopically, using BCVA and OCT, this time focusing on potential manifestations of intraocular inflammation in the anterior and posterior segment of the eye. The development / progression of OCT findings (presence of any type of fluid: intraretinal, subretinal, sub - RPE) as well as the size of the lesion over time were evaluated according to the Zeiss Forum program.

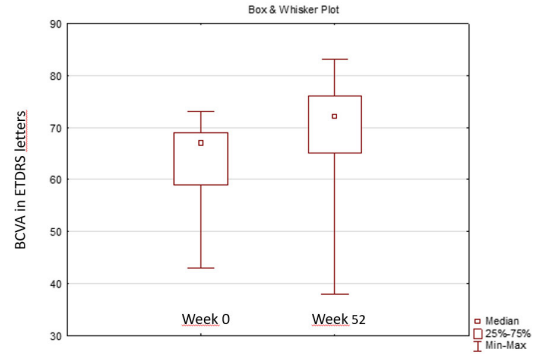
Eyes with a decrease in BCVA of 3 lines, BCVA worse than 20/200, eyes with the development of fibrosis / or atrophy of macula, were excluded from the study. Statistical analysis was performed using the non-parametric Wilcoxon test.

Results

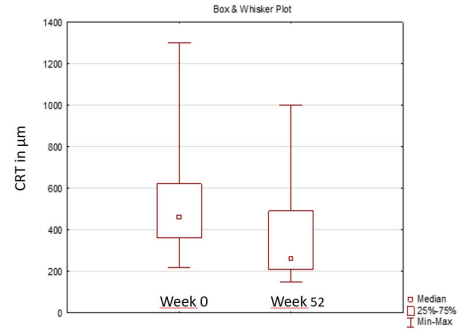
From the beginning, 59 patients were studied, but 3 of them (3 eyes) were excluded due to non-infectious intraocular inflammation, and other 5 eyes were discontinued because of a decrease in BCVA below 20/200 (fibrosis or atrophy development in the macula).

All criteria after 1–year follow up (after switch) were met in 53 eyes (2 of patients had bilateral disease). The group of patients consisted of 32 women and 19 men aged 62-89 years (median 76). At the time of the switch from ranibizumab to brolucizumab, the average number of previous injections was 10 (4 to 32 doses), median of visual acuity was 67 letters, and CRT 460 μm. In all patients treated with ranibizumab, it was not possible to perform an extension longer than 6 weeks due to the active finding of fluid according to OCT (failure of the treat and extent dosing regimen).

One year after switching to brolucizumab, 12 eyes (23%) were able to continue treatment at 12-week intervals due to the minimal amount of inactive fluid of absence of fluid. The remaining 41 eyes (77%) showed some degree of persistent (changeful) fluid and required continuation of regular injections at 8-week intervals. The average number of injections (brolucizumab) was 7.5 in the study year. After one year of switching therapy to brolucizumab, the median visual acuity was 72 (gain, +5.0 ETDRS letters), and the CRT was 260 (decrease, -200 μm), both statistically significantly improved (both p<0,001) (**Graph 1,2**). Slightly better results were seen already after 6 months from the switch, but without statistical significance.



Graph 1.



Graph 2.

The whole group of patients can be divided into four major groups according to the OCT findings:

(A) patients who had no fluid or other signs of activity (17 eyes, 32%).

(B) patients with reduced (but persistent or fluctuating) activity (26 eyes, 48% of the total group of 53 eyes),

(C) patients with approximately the same activity (2 eyes, 4%), and

(D) patients with progression (8 eyes, 16%)

Manifestations of non-infectious intraocular inflammation were found in 3 eyes out of 61 (5 %), it was vitritis without signs of vasculitis in all cases. The inflammatory reaction in the anterior chamber was minimal. All inflammatory manifestations occurred

within the first 3 months of initiation of brolucizumab therapy. Treatment with this drug was discontinued in these eyes. However, these patients continued to be followed. Despite the potentially serious complications, these eyes remained anatomically stable with resolved activity on OCT (after the inflammation subsided).

Discussion

The management of wet age-related macular degeneration (AMD) has been significantly transformed with the advent of anti-vascular endothelial growth factor (anti-VEGF) therapies. Ranibizumab, a widely used anti-VEGF agent, has shown notable efficacy in stabilizing or improving visual outcomes for patients with this debilitating condition. However, a substantial proportion of patients still experience limited anatomical and functional responses, leading to the exploration of alternative treatment options such as transitioning from ranibizumab to a different anti-VEGF drug [6].

The clinically favorable response to ranibizumab may be shorter than we would need. It may even be less than the minimal recommended dosing interval [7].

While ranibizumab has significantly contributed to improved patient outcomes, a substantial proportion of patients continue to experience limited therapeutic effects, necessitating the evaluation of newer treatment options.

Switching from ranibizumab to brolucizumab represents a potential strategy to address the challenges of suboptimal response and treatment burden. In our study, we treated low degree of response to ranibizumab (0.5 mg) therapy in patients with wet AMD by switching to brolucizumab 6 mg. Results at 1 year showed complete anatomic success in 32% of patients, at least moderate effect in 48% and brolucizumab treatment failure in 20% (patients progressing / or with the same activity as before the change).

Structural improvement was associated with an increase in ETDRS letter gain (+5.0) BCVA gain, and CRT decrease (-200 μm) are similar to HAWK a HARRIER study, but statistical significance is confirmed only after a year of follow-up (the restitution of the finding requires a longer time). The larger proportion of eyes also required a more frequent 8-week interval (77 %) compared to the HAWK and HARRIER registry studies. We only achieved a q12w interval in 23% of eyes.

Registration studies have probability that an eye could be maintained on an q12w interval after loading was 45.4% for the brolucizumab 6 mg (HAWK), respectively, and 38.6% for the brolucizumab 6 mg group in HARRIER. [4]

These results underscore the heterogeneity of treatment response and highlight the need for individualized approaches in the management of wet AMD. And the results of the registration studies are also only on treatment-naïve eyes. Comparing our study results with the literature on the transition from ranibizumab to brolucizumab, we find parallel trends in terms of anatomical and functional improvements. Previous studies have reported anatomical improvements in a comparable percentage of patients, with the extended dosing interval of brolucizumab potentially offering enhanced patient convenience and adherence.

Conclusion

The results can be concluded that after changing therapy from ranibizumab (0.5 mg) to brolucizumab 6 mg (in patients who did not respond to the initial treatment), a positive effect can be achieved: complete disappearance of anatomical activity in 32% and stabilization/reduction of activity in 48%. However, in 20% of eyes the activity progressed further or there was an inadequate response to the change in therapy.

At the same time, there is a risk of complications (non-infectious intraocular inflammation), which was 5% in our study.

Anatomical improvement is also associated with slightly better visual function after one year of the subsequent therapy. We see the benefit of switching from ranibizumab to brolucizumab in the good anatomical efficacy of primarily non-responsive findings. However, there is still remains a group of resistant findings that progress without responding to this therapy, and the search for a therapy with an optimal response is still needed.

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