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Aim: To compare the treatment effect of brolucizumab, a novel anti-vascular endothelial growth factor therapeutic, with a putative placebo in patients with wet age-related macular degeneration.

Materials and Methods: Clinical treatment-effect data from patients receiving brolucizumab 6 mg in the HAWK and HARRIER studies were compared with modelled placebo data using a previously developed and validated indirect response, non-linear, mixed effects model describing the natural visual acuity decline in wet age-related macular degeneration. The placebo model incorporated patient-level data from the sham injection arms of the MARINA and PIER studies, corrected for baseline best corrected visual acuity and age difference between these studies and the HAWK and HARRIER studies.

Results: Compared with a modelled placebo, brolucizumab treatment was associated with an overall best corrected visual acuity gain of approximately 22 Early Treatment Diabetic Retinopathy Study letters at Week 48 and 28 letters at Week 96.

Conclusions: As anti-vascular endothelial growth factor therapy is now a standard of care for wet age-related macular degeneration, it is not feasible to conduct placebo-controlled trials for new wet age-related macular degeneration treatments. By allowing comparison with the natural decline in visual acuity without treatment, this analysis conveys the clinical importance of brolucizumab for the treatment of wet age-related macular degeneration.

Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss globally, with a prevalence of 8.7% [1,2]. Although accounting for ~10% of AMD cases, wet AMD (wAMD; also known as neovascular AMD) was responsible for ~90% of AMD-associated vision loss before the advent of therapy in the 1980s [3,4]. Initial thermal laser treatment was only effective in preventing wAMD-associated vision loss in a small number of cases, however, and often resulted in retinal scarring and recurrent neovascularisation [5,6]. From the late 1990s, photodynamic therapy was shown to slow progression of vision loss, although the majority of patients did not experience improvements in best corrected visual acuity (BCVA) [7].

The introduction of anti-vascular endothelial growth factor (VEGF) therapy in wAMD substantially improved patient outcomes. Pivotal trials showed that intravitreal anti-VEGF therapy significantly improves BCVA, with >16 Early Treatment Diabetic Retinopathy Study (ETDRS) letters difference versus placebo after a year of treatment [8,9]. Following the approval of anti-VEGF therapies, such as ranibizumab, in the mid-2000s the rate of incident blindness and vision loss associated with wAMD reduced substantially [10]. Another anti-VEGF molecule, aflibercept, was subsequently approved for wAMD treatment in 2011 in the US and 2012 in the EU. With anti-VEGF therapy having become the gold standard for wAMD treatment, approval was based on demonstrating non-inferiority to ranibizumab in pivotal studies [11].

On October 7th 2019, a new generation anti-VEGF molecule, brolucizumab, was approved by the FDA, and has also been submitted for marketing authorization to the EMA and licencing bodies in several other countries and regions. Brolucizumab has a high affinity for VEGF and will be the first humanized single-chain antibody fragment for ophthalmic use [12]. Its low molecular weight and size allows for more drug per dose and the potential for rapid and more effective tissue penetration compared with other anti-VEGF molecules [12–14]. Clinically, the efficacy of brolucizumab in wAMD was confirmed in the Phase III HAWK and HARRIER studies, which demonstrated non-inferiority of brolucizumab to aflibercept in BCVA while showing superior anatomical results; this was achieved with >50% of patients on a 12-weekly regimen directly after loading [15].

As anti-VEGF therapy is now a standard of care in wAMD, a non-inferiority approach is necessary when evaluating new treatments and placebo-controlled studies are not considered feasible for ethical reasons. However, due to the lack of a placebo-controlled trial, the clinical value of this new anti-VEGF therapy relative to the natural disease course of wAMD may be underappreciated in the ophthalmology community. Therefore in this study, we have used a previously developed model of natural disease progression in wAMD to compare treatment effect data for brolucizumab with a putative placebo.

Materials and Methods

Clinical data

In the Phase III HAWK and HARRIER trials, eligible patients were aged ≥50 years and had untreated, active choroidal neovascular lesions secondary to AMD affecting the central subfield of the study eye as assessed by fluorescein angiography [15]. A BCVA between 78 and 23 letters, inclusive, in the study eye at screening and baseline using ETDRS testing were prerequisit for study inclusion, respectively. Patients received a brolucizumab injection at Weeks 0, 4, and 8 (loading phase) and thereafter every 12 weeks (q12w) but were interval adjusted to every 8 weeks (q8w) if disease activity was present [15]. In this study, patient-level data on the treatment effect of brolucizumab 6 mg on BCVA from both HAWK and HARRIER through to Week 96 [15,16] were compared with modelled data from untreated wAMD patients.

Modelled data

An empirical Bayesian indirect response, non-linear, mixed effects model of natural disease progression in wAMD and treatment effect in anti-VEGF treatment-naïve patients was previously developed using data from the ranibizumab Phase III ANCHOR, MARINA, PIER, and EXCITE studies [8,9,17–19]. Patient-level data from 298 patients from the sham arms of the MARINA [9] and PIER [18] studies were used to describe the natural decrease in BCVA with placebo. In this model, BCVA score was treated as non-stationary at baseline and decreased to steady state (k_{in}/k_{out}) at the BCVA deterioration rate constant (k_{out}) without treatment [17]. BCVA at baseline influenced the rate of BCVA change over time and patient age influenced this rate through its correlation with baseline BCVA. No other covariates were identified that affected the BCVA time profile in sham treated patients [17]. The model was validated by comparing real outcomes with modelled outcomes using data from the HARBOR trial [20], which was not used for model development [17].

The putative placebo arm was simulated using the specific covariates of baseline BCVA and age of patients from the brolucizumab 6 mg arms of the HAWK and HARRIER studies. The posterior distributions of the population parameters were used to sample the same number of subjects as the treated arms for both studies. Simulations were performed using RStan software version 2.17.3 (Stan Development Team, www.mc-stan.org).

Results

In the brolucizumab 6 mg arms in the HAWK (N=360) and HARRIER (N=370) studies, mean age at baseline was 76.7 and 74.8 years, respectively [15]. Mean baseline BCVA was 60.8 (HAWK) and 61.5 (HARRIER) ETDRS letters, and approximately 75% of study eyes had BCVA ≤70 letters [15].

In our study, brolucizumab treatment was associated with a BCVA gain of ~22 ETDRS letters at Week 48 and ~28 letters at Week 96 versus simulated sham injection for both the HAWK and HARRIER studies (Figure 1 and Table 1).

Discussion

Pivotal trials validated anti-VEGF-A therapy for wAMD with monthly treatment, showing greatly improved patient outcomes. However, the need for frequent clinic and injection visits coupled with the anticipated increased prevalence of patients with wAMD may lead to a clinical scenario that is difficult to sustain. The HAWK and HARRIER studies successfully evaluated an alternative treatment option, and demonstrated robust BCVA gains with brolucizumab dosed with a q12w or q8w regimen. As these trials had a non-inferiority design, it is difficult to assess the impact of this new therapeutic relative to natural disease progression in wAMD.

In this comparison with a putative placebo group, brolucizumab 6 mg consistently showed BCVA gains, with approximately 28 ETDRS letters difference after 96 weeks of treatment for both the HAWK and HARRIER trials. This corresponds to the difference between mild–moderate visual impairment with near-normal reading ability and severe visual impairment with the requirement for high-power magnifiers and restricted field of vision [21]. In the absence of treatment, the same model describes a gradual decrease in BCVA across the patient population (although individual drops can be sudden) to a steady state of 11 ETDRS letters [17] (the International Council of Ophthalmology defines near-blindness as ≤10 ETDRS letters [21]). These data speak to the value of anti-VEGF therapy in wAMD.

It is not possible to directly compare treatment effect data for brolucizumab in the HAWK and HARRIER studies with placebo data from the MARINA and PIER studies due to differences in patient populations. Baseline BCVA in the sham arms of the MARINA and PIER studies was 6–7 ETDRS letters lower than in HAWK and HARRIER and patients were 2–3 years older [9,15,18]. Baseline BCVA, and to a lesser extent age, was shown to impact BCVA change over time under both treatment and placebo conditions. During model development it was determined that gender did not affect BCVA over time. Furthermore the status of choroidal neovascularization (CNV) type and baseline BCVA were confounded, and including CNV type into model did not improve it. Based on these aspects, differences in BCVA and age between studies were corrected for in the model used [17]. Furthermore, this model has been shown to hold true over the complete range of BCVA scores [17].

The model provides a unique opportunity to demonstrate BCVA score behaviour under natural disease progression. Its accuracy in describing natural disease progression and treatment effect in anti-VEGF treatment-naïve patients has been shown through external validation using data from the HARBOR study. In that study, modelled data was shown to correlate well with actual data for ranibizumab, including prediction of a 2 mg ranibizumab dose that was not used for model development [17,20]. An earlier version of the model, using 1-year data from the same studies, supported a label update approval by the EMA for individualised visual acuity-guided treatment with 0.5 mg ranibizumab [22].

Limitations of the study include the relatively low number of placebo patients informing the model, totalling 298 patients from two studies [17]. In addition, unknown covariates that were not identified during model development, and therefore not used in simulations to adjust for differences in the HAWK and HARRIER populations, could influence the BCVA time profile in untreated patients.

Given the success of anti-VEGF therapies in wAMD, it is easy to forget the debilitating effects of this disease, where vision loss is almost guaranteed without treatment. In this study, brolucizumab provided vision gains of ~22 letters at Week 48 and ~28 letters at Week 96 versus natural (untreated) visual acuity decline in cohorts with mean baseline BCVA below 71 ETDRS letters. Furthermore, in HAWK and HARRIER, gains with brolucizumab treatment were achieved with >50% of patients on a 12-weekly retreatment regimen, commenced immediately after loading. Our analysis enables better understanding of the clinical value of this new-generation intravitreal anti-VEGF treatment for wAMD. Future research will focus on understanding the utility of this new molecule in other anti-VEGF responsive indications.

Conflicts of Interest

Andreas Clemens and Etienne Pigeolet are employed by and hold shares in Novartis Pharma AG. Zufar Mulyukov is an employee of Novartis Pharma AG and Valeria Colafrancesco is an employee of Novartis Farmaceutica SA. David Gaucher is a board member for Novartis and Thea, and has received financial support for congress attendance from Bayer, FCI, and Allergan. Miltiadis Tsilimbaris has received research grants and financial support for congress attendance from Novartis, Bayer, Johnson & Johnson, and Allergan. Pilar Calvo is a board member and has received lecture fees from Novartis, and financial support for congress attendance from Novartis, Thea, Bayer, and Allergan. Novartis has provided travel and study grants to Freiburg University Hospital, where Hansjürgen Agostini and Felicitas Bucher are employed.

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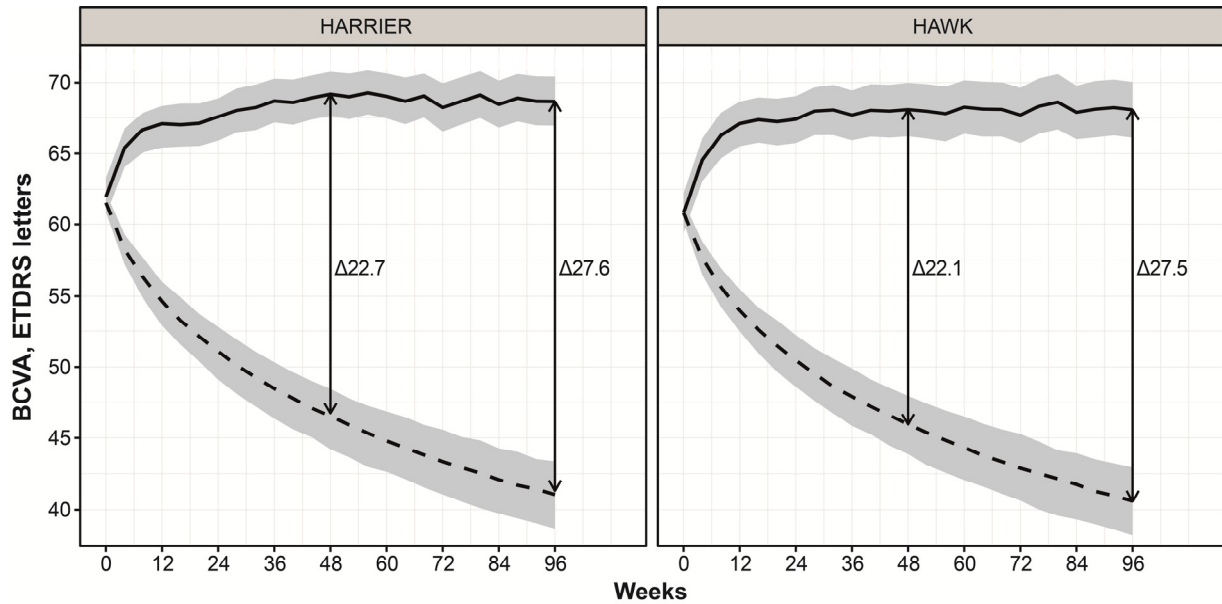
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Table 1. Mean observed BCVA. BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error

Study	Week	n	Mean observed BCVA, ETDRS letters (SE)		
			Brolucizumab (6 mg)	Simulated sham	Delta
HARRIER	48	352	69.2 (0.8)	46.5 (1.1)	22.7 (1.4)
HAWK	48	326	68.1 (1.0)	45.9 (1.1)	22.1 (1.5)
HARRIER	96	342	68.7 (0.9)	41.1 (1.3)	27.6 (1.5)
HAWK	96	304	68.1 (1.0)	40.6 (1.2)	27.5 (1.6)

Figure 1. Mean BCVA in the HARRIER (n=352 at 48 weeks and n=342 at 96 weeks) and HAWK (n=326 at 48 weeks and n=304 at 96 weeks) studies versus putative placebo. In HAWK and HARRIER, patients received brolucizumab 3 mg/6 mg at Weeks 0, 4, and 8 (loading phase) and thereafter every 12 weeks but were interval adjusted to every 8 weeks if disease activity was present. Solid lines show brolucizumab 6 mg treatment effect, dashed lines show modelled natural disease progression. Shaded areas show 95% confidence intervals. BCVA = best corrected visual acuity