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Single-Chain Antibody Fragment VEGF Inhibitor RTH258 for Neovascular Age-Related Macular Degeneration

A Randomized Controlled Study

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Purpose: To assess the safety and efficacy of different doses of RTH258 applied as single intravitreal administration compared with ranibizumab 0.5 mg in patients with neovascular age-related macular degeneration (AMD).

Design: Six-month, phase 1/2, prospective, multicenter, double-masked, randomized, ascending single-dose, active-controlled, parallel-group study.

Participants: A total of 194 treatment-naive patients, aged ≥50 years, with primary subfoveal choroidal neovascularization secondary to AMD.

Methods: Patients received a single intravitreal injection of RTH258 0.5 mg (n = 11), 3.0 mg (n = 31), 4.5 mg (n = 47), or 6.0 mg (n = 44), or ranibizumab 0.5 mg (n = 61).

Main Outcome Measures: The primary efficacy end point was the change from baseline to month 1 in central subfield thickness (CSFT) measured by spectral-domain optical coherence tomography. The secondary efficacy end point was the duration of treatment effect measured as time from the initial injection to receipt of post-baseline therapy (PBT) guided by protocol-defined criteria. Adverse events (AEs) were recorded throughout the study.

Results: RTH258 demonstrated noninferiority compared with ranibizumab in mean change in CSFT from baseline to month 1 for the 4.5- and 6.0-mg dose groups (margin: 40 μm, 1-sided alpha 0.05). The difference in CSFT change at month 1 comparison with ranibizumab was 22.86 μm (90% confidence interval [CI], −9.28 to 54.99) and 19.40 μm (95% CI, −9.00 to 47.80) for RTH258 4.5 and 6 mg, respectively. The median time to PBT after baseline therapy was 60 and 75 days for patients in the RTH258 4.5- and 6.0-mg groups, respectively, compared with 45 days for ranibizumab. Changes in best-corrected visual acuity with RTH258 were comparable to those observed with ranibizumab. The most frequent AEs reported for the RTH258 groups were conjunctival hemorrhage, eye pain, and conjunctival hyperemia; the majority of these events were mild in intensity.

Conclusions: This first-in-human study of RTH258 demonstrated noninferiority in the change in CSFT at 1 month for the 4.5- and 6.0-mg doses compared with ranibizumab and an increase of 30 days in the median time to PBT for the 6.0-mg dose. There were no unexpected safety concerns, and the results support the continued development of RTH258 for the treatment of neovascular AMD. *Ophthalmology 2016;123:1080-1089 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Macular diseases, notably age-related macular degeneration (AMD), are leading causes of irreversible blindness and visual impairment. The 2010 global population statistical data indicate that 1 in 15 blind people and 1 in 32 visually impaired people had macular disease.[1] In addition, the rate of blindness due to macular diseases increased by 36% from 1990 to 2010.[1]

Anti−vascular endothelial growth factor (VEGF) therapies and novel imaging techniques, including spectral-domain optical coherence tomography (SD OCT), have contributed to remarkable improvements in early diagnosis, monitoring, and functional outcomes for patients with neovascular AMD[2] leading to decreasing or at least stable prevalence of blindness and visual impairment associated

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with macular disease in developed regions.[1,3,4] Current anti-VEGF therapies delivered via intravitreal injection include ranibizumab and aflibercept, as well as off-label bevacizumab,[5] and national and international guidelines recommend these anti-VEGF agents as first-line therapy for the treatment of neovascular AMD.[5,6] Research is ongoing regarding other molecular targets in the AMD disease pathway, including platelet-derived growth factor, mammalian target of rapamycin, several complement components, and combination therapies to improve the treatment of wet and dry AMD.[7]

Although anti-VEGF therapies have resulted in improved patient outcomes, there are limitations associated with these treatments. Anti-VEGF therapies require frequent clinical assessment to monitor patient response to treatment and, in some cases, monthly or bimonthly intravitreal injections.[2,7] The burden associated with frequent clinic visits or intravitreal injections for patients, caregivers, and physicians is significant and may lead to suboptimal outcomes because of adherence problems and underdosing.[2] LUMINOUS, an ongoing 5-year prospective, multinational, observational study designed to evaluate the outcomes of treatment with ranibizumab 0.5 mg in routine clinical practice, showed that patients with newly diagnosed neovascular AMD have an average of 7.5 visits and 4.7 injections in the first year of therapy, resulting in a gain of 4.4 letters. Over 2 years, the average number of visits was 13.6 with 8.7 injections and a gain of 2 letters.[8] Thus, there is a logistical disconnect between the realities of community practice and the strict monthly-visit regimen of well-known clinical trial schedules.[9–12] The AURA (A retrospective noninterventional study to assess the effectiveness of existing Anti-vascUlar endothelial growth factor [anti-VEGF] treatment Regimens in patients with wet Age-related macular degeneration) study, a retrospective analysis of 2227 real-world ranibizumab-treated patients with wet AMD who were followed for 2 years, reported a good initial response to therapy, with improved visual acuity over the first 120 days.[13] However, the average gains in visual acuity were not maintained over the 2-year follow-up.[13] Intravitreal injections declined from a mean of 5.0 injections in the first year to 2.2 injections in the second year. There was also a decline in the number of visits to the treating ophthalmologist over the same time period.[13] Alternative treatments or long-acting drug delivery systems would be required to offset the compromise between treatment burden and visual outcomes by increasing the drug efficacy and durability of treatment response.[7,14]

RTH258 (formerly ESBA1008) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A. It is the smallest anti-VEGF inhibitor tested in humans with a molecular weight of only 26 kDa compared with 48 kDa for ranibizumab or 115 kDa for aflibercept.[15] Because of its high stability and solubility, it is possible to concentrate RTH258 up to 120 mg/ml, allowing the administration of 6 mg in a single 50-μl intravitreal injection.[15] This enables the delivery of a much higher molar dose in the same volume as the current VEGF inhibitors in clinical use,[15,16] potentially supporting an early initiation and a prolonged duration of treatment effect. Furthermore, animal studies have shown that the small size of RTH258 leads to a fast systemic clearance and a 4-fold lower systemic exposure[15,16] compared with anti-VEGF agents like ranibizumab and bevacizumab, potentially reducing the risk of systemic side effects. The smaller size also may allow for better ocular tissue penetration.[16] The tolerability of high doses of RTH258 in animals, the high affinity to VEGF, and the lower molecular weight suggest that RTH258 may be an effective ocular anti-VEGF therapy in humans, with extended duration of efficacy.

The objective of this first-in-human study was to assess the safety, tolerability, and effect of treatment on ocular outcomes after a single intravitreal administration of 1 of 4 dose levels of RTH258 compared with ranibizumab 0.5 mg in patients with neovascular AMD.

Methods

Study Design

This phase 1/2, 6-month, prospective, multicenter, double-masked, randomized, ascending single-dose, active-controlled, parallel-group study compared the safety and efficacy of a single intravitreal injection of RTH258 (ascending doses) or ranibizumab as therapy for treatment-naive patients with neovascular AMD. The study protocol was approved by all institutional review boards and complied with the ethical standards defined by the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participating in the study (ClinicalTrials.gov identifier, NCT01304693).

The study was conducted in 2 phases: (1) a dose escalation phase of RTH258 to the maximum feasible dose (MFD) for intravitreal injection (MFD = 6.0 mg RTH258) and (2) an MFD expansion phase. In the dose escalation phase, patients were randomized 5:2 to receive RTH258 (0.5, 3.0, or 4.5 mg) or ranibizumab 0.5 mg. Each dose level cohort was reviewed by a safety committee before the next ascending dose level cohort was treated and evaluated. Details regarding the safety review decision points for the ascending doses and the stopping criteria for the study are reported in the Appendix (available at www.aaojournal.org). Within each dose level cohort, the first 4 patients enrolled and treated with a single dose were sequentially assessed with a waiting period of ≥24 hours between patients to allow sufficient time for safety review for each patient before approving injection of the next patient. After the first 4 patients in a given dosing cohort received treatment and were reviewed for safety, the remaining patients in the cohort were treated in parallel.

The MFD expansion phase of the study consisted of 2 parts. In the first part, patients were randomized 1:1 to RTH258 4.5 mg or ranibizumab 0.5 mg. In the second part, patients were enrolled and randomized 5:30:35:9 to RTH258 0.5-, 3.0-, or 6.0-mg doses, or ranibizumab 0.5 mg. The randomization schedule was determined in part by additional data requirements for separate pharmacokinetic/pharmacodynamic studies related to RTH258.

All randomized patients were evaluated for safety and efficacy over 13 study visits, including screening, day of treatment, and 11 post-treatment follow-up visits (day 1, weeks 1 and 2, and months 1, 1.5, 2, 2.5, 3, 4, 5, and 6). Eligible patients were randomized using an interactive web response system to receive a single intravitreal injection of their assigned study drug in the study eye on day 0. Details regarding the randomization process are provided in the Appendix (available at www.aaojournal.org). The dose,