Novel insights into ocular disease: Rafiq Hasan

Therapeutic approaches to geographic atrophy

Age-related macular degeneration (AMD) is a chronic and progressive degenerative disease of the macula, the central part of the retina, which culminates in blindness. In its more advanced form AMD can develop into neovascular disease characterised by new leaky vessel formation in the back of the eye, or geographic atrophy (GA) characterised by atrophic changes in the retina and consequent visual impairment. The worldwide prevalence of AMD among individuals aged 45 to 85 years is 8.7%, with a projected number of affected people of 196 million in 2020, increasing to 288 million in 2040[1].

The management of neovascular AMD has been transformed by the introduction of the anti-VEGF therapies in the mid-2000s, which demonstrated significant improvements in vision with regular intravitreal injections. This clinical benefit has been accompanied by significant commercial success for the marketers of the anti-VEGF agents with the total market estimated to be $8 billion in 2021.

The other form of late stage AMD characterised by atrophic changes in the retina, GA, is the leading cause of central vision loss in individuals over 50 years old in developed countries. Global prevalence of GA continues to increase, reflecting ageing population demographics. Current estimates suggest that five million people suffer with GA worldwide, with approximately 1.1 million residing in the US. Currently, no approved therapy is available for GA with a number of assets in the pipeline.

In recent years, the role of the complement cascade in the pathogenesis of GA has been elucidated, supported by both genetic and histological evidence. Complement is a key part of the innate immune system in protecting against external pathogens, however there is now strong evidence that dysregulation of this system drives inflammation, a key characteristic of GA. Consequently, the focus of therapeutic innovation has centred around agents that modulate or inhibit the complement cascade with the potential to slow progression of this debilitating condition. To date, clinical trial data from complement inhibitors has demonstrated modest efficacy with an approximate 20-30% reduction in GA lesion progression at 12 months following monthly intravitreal injections[2,3].

Complement Therapeutics (CTx), an early stage biotechnology company, is benefitting from new insights into the pathophysiology of complement-driven diseases. In particular, and initially focusing on complement-driven GA, the company has identified a novel strategy to ensure that complement dysregulation is addressed in a more comprehensive manner that has the potential to yield superior outcomes.

GA is characterised by complement dysregulation in both the neurosensory retina as well as the choroidal tissues supplying the retina with blood. Intravitreal therapies are likely to be addressing complement dysregulation in the neurosensory retina whilst penetration of Bruch's membrane would be required to impact complement overactivation in the choroid[4]. The therapeutic approach being developed by CTx, focusing on the activity of a highly potent complement regulator, has the potential to be active in both compartments and therefore deliver more comprehensive rebalancing of the complement cascade. Packaging this approach as an AAV gene therapy additionally addresses the challenge of frequent intravitreal injections. The evolution of anti-VEGF therapy in neovascular AMD provides valuable learnings regarding the acceptability of monthly injections and the pursuit of more durable agents in recent years. Consequently, the potential for a single administration gene therapy for the long-term management of GA is an attractive proposition.

In addition, highly novel and ground-breaking research conducted at CTx has revealed the important role of the Factor H-related (FHR) proteins in the pathogenesis of AMD. These proteins are similar in structure to Factor H, a key part of the complement cascade responsible for downregulating activity, however, FHR proteins function as inducers of the complement system. Consequently, elevated levels of FHR proteins have been implicated in causing GA and an effective therapeutic would remain active in such patients[5]. The strategy being pursued by CTx has the potential to also be effective in such circumstances and thereby address a broad range of patients with complement-driven GA.

In summary, the complement cascade has recently been validated as an appropriate target in the management of GA, a late form of dry AMD. A number of pipeline assets are in development and may yield the first approved therapy in the near future for this devastating and common eye condition. Complement Therapeutics is building upon a foundation of ground-breaking science to further drive innovation in this sector with the potential for a superior, single administration gene therapy addressing a broad cohort of people with GA.

References:

1. Wong, W. L. *et al.* Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *The Lancet Global Health* **2**, e106–e116 (2014).

2. Jaffe, G. J. *et al.* C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. *Ophthalmology* **128**, 576–586 (2021).

3. Liao, D. S. *et al.* Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. *Ophthalmology* **127**, 186–195 (2020).

4. Clark, S. J., McHarg, S., Tilakaratna, V., Brace, N. & Bishop, P. N. Bruch's membrane compartmentalizes complement regulation in the eye with implications for therapeutic design in age-related macular degeneration. *Frontiers in Immunology* **8**, 1778 (2017).

5. Cipriani, V. *et al.* Beyond factor H: The impact of genetic-risk variants for age-related macular degeneration on circulating factor-H-like 1 and factor-H-related protein concentrations. *The American Journal of Human Genetics* **108***, 1385–1400 (2021).*

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