TITLE: Modulation of Macrophages and Complement Dysfunction in Nonexudative Age-Related Macular Degeneration Utilizing a Sialic-acid Coated Nanoparticle

AUTHORS: Baruch Kuppermann, MD, PhD; David Callanan, MD; Tarek Hassan, MD; Michael Tolentino, MD; Christopher Scott, PhD; Mohamed Genead, MD; Anitha Krishnan, PhD

ABSTRACT BODY:
Purpose: Both the cellular and non-cellular components of the innate immune system are strongly implicated in the pathophysiology of age-related macular degeneration (AMD). Inhibition of the complement system has been shown to decrease the rate of progression of geographic atrophy in randomized clinical trials. We report a novel therapeutic strategy to address chronic inflammation in the retina by modifying the body's own self-recognition system on immune cells. The therapeutic molecule AVD-104 (Aviceda Therapeutics, Cambridge, MA) is an engineered dual function glycan (sialic-acid) nanoparticle that directly modulates the self-pattern recognition receptors on immune cells called **Siglecs** (**s**ialic-acid binding **i**mmuno**g**lobulin-like **lec**tin**s**), thereby dampening the inflammatory activity of macrophages and microglia. The significant anti-inflammatory effect of AVD-104 has been previously confirmed in in-vitro experiments. Additionally, AVD-104 has been shown to enhance the activity of complement factor H and down-regulate the alternative complement cascade and has been shown to be safe in 3 species, including non-human primates.

Methods: AVD-104 was intravitreally (IVT) injected in humanized Siglec transgenic mice to assess efficacy in both the bright light damage (BLD) model of retinal degeneration (n=15 eyes) and the laser-induced model of choroidal neovascularization (CNV, n=21 eyes). In the BLD model, animals were given an IVT injection of AVD-104 one day before intense light exposure and examined 7 days later. In the laser CNV model, animals were given an IVT injection of AVD-104, lasered on the same day, and examined 8 days later.

Results: There was greater dose dependent preservation of the outer nuclear layer ($p < 0.01$) and reduction in Tumor Necrosis Factor-α levels ($p < .0001$) in the BLD animals treated with AVD-104 than controls. In the laser CNV mice, there was greater dose dependent reduction in the size of the CNV lesion and reduced C5b-9 complement deposition (Membrane attack complex) in AVD-104 treated eyes than controls.

Conclusions: Intravitreal injections of AVD-104, a novel sialic-acid coated nanoparticle have shown a statistically significant beneficial effect in reducing inflammatory retinal damage in two different animal models. A Phase 2 Human Clinical Trial for patients with AMD is planned for Q1' 2023.