THE **RETINA** PARTNERS

Encino Santa Monica Valencia Thousand Oaks Century City

(877) 3-RETINA

Case of the Month – February 2020

Presented by Christian Sanfilippo, MD

A 73 year old female presented with decreased central vision and distortion in the right eye. She had seen her optometrist earlier that day and was referred urgently on suspicion of new onset exudative age related macular degeneration. Visual acuities were measured as 20/40 in the right and 20/25 in the left eye. Her intraocular pressures were within normal limits. Other than mild cataract in both eyes, her anterior segment examination was unremarkable. Her funduscopic examination of the right eye was significant for drusen, RPE mottling, pigment epithelial detachment and subretinal fluid. Examination of the left retina showed drusen and RPE mottling, but no fluid or hemorrhage. OCT images at presentation are shown below.

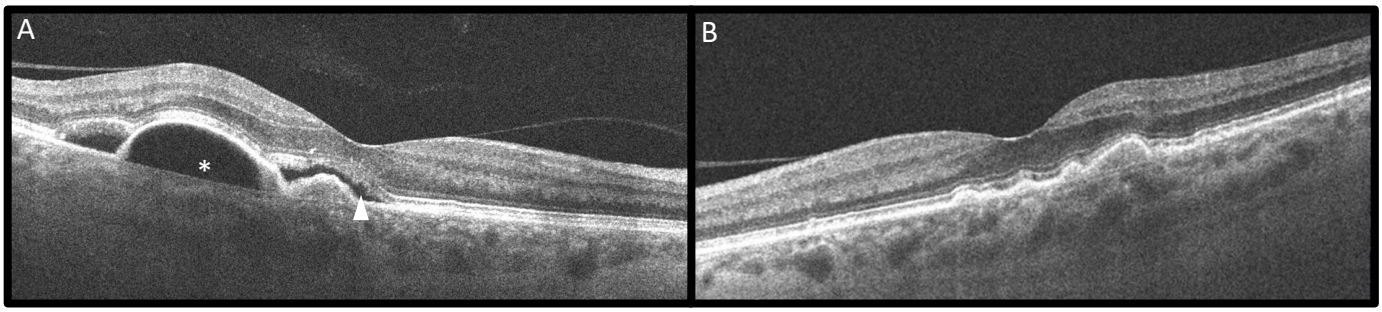

Figure 1: A. SD-OCT image of the right eye shows a pigment epithelial detachment (asterisk) with overlying subretinal fluid (arrowhead). B. SD-OCT image of the left eye shows multiple drusen, but without intraretinal or subretinal fluid.

Clinical Course:

The patient was diagnosed with exudative age related macular degeneration in the right eye and intermediate stage dry age related macular degeneration in the left eye. Intravitreal anti-VEGF therapy with bevacizumab (Avastin) was recommended for the right eye, as well as AREDSII supplementation given for the intermediate dry changes in the left eye. Follow up imaging of the right eye after 4 monthly Avastin injections is shown below.

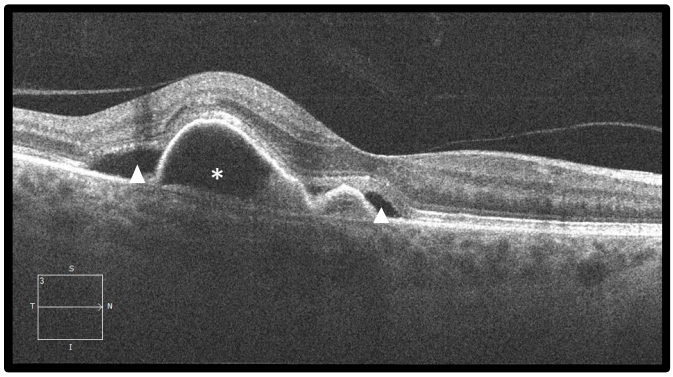

Figure 2: SD-OCT of the right eye following 4 monthly treatments with avastin shows persistent subretinal fluid (arrowheads), and slightly collapsed pigment epithelial detachment (asterisk).

The patient was continued on monthly anti-VEGF therapy but transitioned to a combination of branded medications including ranibizumab (Lucentis) and aflibercept (Eylea) given on a monthly basis. After nearly 6 years of monthly therapy, her visual acuity improved to 20/25 but she continued to show improved but mild persistent subretinal fluid. Shortly after Beovu was approved by the FDA for macular degeneration, she was challenged with this new medication.

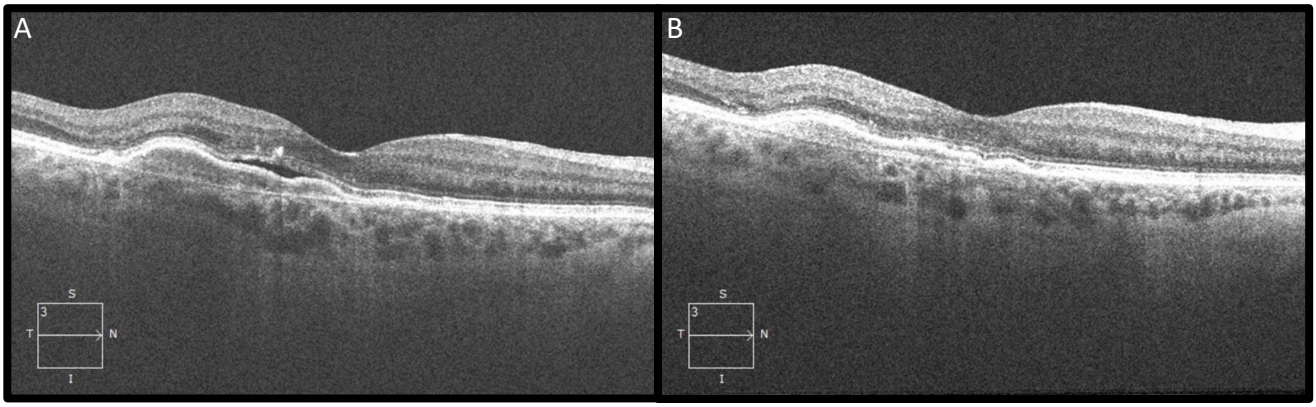

Figure 3: A. SD-OCT image of the right eye 4 weeks following aflibercept (Eylea) injection shows persistent shallow subretinal fluid overlying an irregular pigment epithelial detachment. The patient was treated with Beovu at this visit. **B.** SD-OCT image taken 4 weeks following the first Beovu injection shows complete resolution of subretinal fluid and flattening of the pigment epithelial detachment.

The patient was continued on brolucizumab treatment, according to a treat and extend protocol. She received her second Beovu injection and was instructed to follow up in 6 weeks. Her images are shown below.

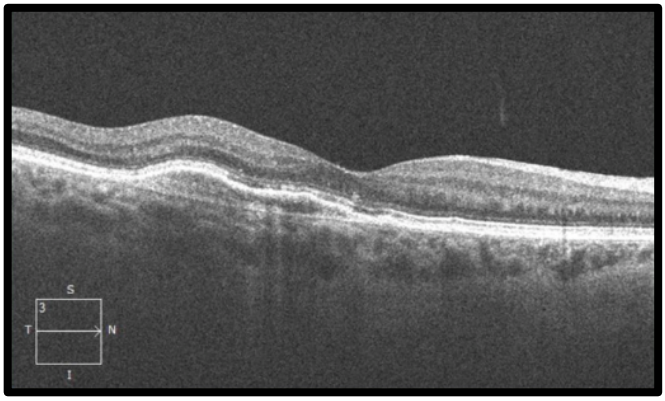

Figure 4: SD-OCT image of the right eye 6 weeks following second Beovu injection shows continued resolution of subretinal fluid at this longer interval.

Discussion:

Age related macular degeneration (AMD) is estimated to effect more than 8 million individuals in the United States, and this number is increasing. More than 1.75 million adults have the advanced form of the disease in the US, which includes both atrophic dry AMD and neovascular AMD (nAMD). The majority of these patients are effected by the neovascular form of the disease. Fortunately, we now have several treatment options for patients effected by neovascular AMD.

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy revolutionized the treatment of nAMD when it was first introduced in the early 2000's with pegaptanib (Macugen). Soon afterwards ranibizumab (Lucentis) was introduced. Up until this point, treatment was focused on slowing the visual decline of patients affected by nAMD. The introduction of Lucentis to the US market in 2006 represented the very first time a therapy for nAMD not only slowed visual decline, but could actually significantly improved visual acuity above baseline for a large proportion of patients. Around the same time, an anti-VEGF drug designed as a cancer

therapy called bevacizumab (Avastin), was noted to be effective and non-toxic when delivered into the intravitreal cavity. It took another 5 years before a third anti-VEGF therapy came to market. Aflibercept (Eylea) gained FDA approval in late 2011. In contrast to Lucentis, which was approved for every 4 week dosing, Eylea was approved to be used on an every 8 week dosing schedule, reflecting a possible longer duration of action for some patients (following 3 initial loading doses at 4 week intervals). While Macugen has largely phased out of the U.S. market due to inferior effectiveness compared to the other three agents, Avastin, Lucentis and Eylea all remain highly effective.

However, despite the considerable advances in therapy over the last 15 years, challenges still remain. Unfortunately, there is a small population of patients who never fully respond to maximum therapy – as defined by persistent subretinal or intraretinal fluid with monthly anti-VEGF therapy. Additionally, most patients would prefer to be able to increase the time between injection intervals as much as possible without sacrificing vision. These two goals predominantly drive new drug development.

Brolucizumab (Beovu) is the latest addition to the anti-VEGF arsenal, gaining FDA approval in late 2019. Beovu is a single chain antibody fragment, which is the smallest functional anti-body subunit which still maintains binding ability. Because of its small size, higher molar concentrations of drug can be delivered into the intravitreal cavity as compared to Lucentis, Avastin, or Eylea. In fact, its equivalent molar dose is approximately 10 times that of Eylea, and 20 times that of Lucentis and Avastin. Furthermore, its small size may provide superior retinal and choroidal penetration as compared to the other medications. Phase III clinical trials demonstrated non-inferiority in terms of visual acuity gains at 48 weeks compared to Eylea, and over 50% of patients on Beovu were able to be kept dry on an every 12 week dosing schedule.

Our early experience with Beovu thus far has been promising. Although all of the medications we have available work extremely well, occasionally, a patient will fail to completely respond to one or all of the drugs, or be unable to extend beyond the 4 week interval. This was the case for the patient presented above. Fortunately, she responded very well to Beovu. While further real-world experience is necessary to more completely understand which patients might benefit from Beovu over the other anti-VEGF therapies available, we welcome the addition of this new drug to our armamentarium.

Take Home Points

- Brolucizumab (Beovu) is a new anti-VEGF therapy approved for neovascular age related macular degeneration.
- Its small size and high molar concentration may theoretically translate into stronger and longer duration of effect.
- Our early experience is very promising, but further real-world experience and studies are necessary to determine which patients may benefit the most over other currently available drugs.

Thomas Hanscom Robert Engstrom Hajir Dadgostar Amir Guerami Christian Sanfilippo Stavros Moysidis