REAL-WORLD INJECTION INTERVALS IN WET AMD

Aided by a large database, researchers explore treatment patterns with anti-VEGF agents.

BY MATHEW W. MACCUMBER, MD, PHD

The burden of monthly anti-VEGF injections—the gold standard treatment regimen—is considerable for patients with wet age-related macular degeneration (AMD). Anti-VEGF injections cost Medicare $2.7 billion annually, accounting for more than 12% of the Medicare Part B budget.[1] US ophthalmologists perform 2.5 million injections annually, with the busiest retina specialists performing as many as 50 per day.[1] Patients and caregivers bear the additional costs of time for appointments, lost productivity, and discomfort.

To reduce this burden of care, many physicians have adopted treat-and-extend (TAE) or as-needed (prn) treatment protocols. In the past decade, published studies have demonstrated that these variable dosing schedules can be as effective as monthly treatment while reducing treatment burden.[2-5] In the 2019 ASRS Preferences and Trends survey, 86.8% of respondents said that TAE is their preferred treatment regimen for wet AMD, and 5.5% reported that they rely on a prn regimen.[6]

IRIS REGISTRY DATA

My colleagues and I began working with Verana Health, the AAO's data curation and analytics partner, and study sponsor Novartis, to examine data on injection intervals from the AAO's IRIS Registry. The IRIS Registry is the largest specialty clinical database in medicine, with more than 300 million patient visits reported by more than 15,000 ophthalmologists and eligible clinicians as of April 2020.

The volume of data contained in the IRIS Registry and its comprehensive nature (a majority of US ophthalmic practices participate) provides an opportunity to better understand real-world treatment patterns. Verana Health uses IRIS Registry data to allow ophthalmologists to benchmark their individual clinical care patterns to a cohort of their peers. I have previously published an IRIS Registry study evaluating the effects of anti-VEGF therapy on IOP.[7] Others have used data from the IRIS Registry to assess characteristics and complications of IOL implantation after cataract surgery, factors influencing time to blindness in patients with diabetic retinopathy, and strabismus reoperation rates.[8]

STUDY DESIGN

To limit confounding factors, we reviewed data only of patients with treatment-naïve wet AMD. We assessed patients with anti-VEGF injections received from the index date (first injection) through 1 and 2 years of follow-up.[9] The follow-up periods were selected for the purpose of examining treatment patterns, such as injection interval at the end of years 1 and 2.

Patients were required to be in the IRIS Registry database for a baseline period of at least 6 months before the index date and not to have had any anti-VEGF therapy or diagnosis of other conditions that would be treated with anti-VEGF therapy (eg, retinal vein occlusion or diabetic macular edema) during that baseline period. This allowed a defined starting point and reasonable confidence that we were studying injection patterns for treatment-naïve, newly diagnosed eyes.

We looked at all injection intervals over the study period and the final injection interval (ie, time between the final

AT A GLANCE

- IRIS Registry data, curated by Verana Health, contains real-world data about treatment frequency for patients with wet AMD.
- Nearly 40% of patients treated with anti-VEGF therapy required treatment less than every 8 weeks during the first 2 years of treatment.
- During the second year of anti-VEGF therapy, patients with wet AMD were most likely to be dosed every 6 to 7 weeks or 12 weeks or longer.

and penultimate injections) at the end of years 1 and 2. The final injection interval provided us with an estimate of how long the injections had been extended by the end of each year, compared to the more frequent pattern of injections or loading doses that we would expect to see at the beginning of year 1. In the final injection interval data set, we confined our analyses to eyes that had been treated with the same drug at the beginning and end of the reference period (1 or 2 years).

Records for 56,672 eyes (54,392 patients) met the criteria for analysis. Among them, 33,601 eyes (32,354 patients) had at least 2.5 years of follow-up. The mean age of the patients was approximately 81 years, and nearly 65% were women. Approximate mean VA at baseline was 20/80. About one-quarter of the eyes had worse than 20/200 VA at baseline.

We also compared injection intervals for all anti-VEGF therapies to the intervals for eyes treated with aflibercept (Eylea, Regeneron; n = 13,467 eyes at 1.5 years and 7,654 at 2.5 years) and ranibizumab (Lucentis, Genentech; n = 9,128 eyes at 1.5 years and 5,990 at 2.5 years), which are the only commonly used drugs approved by the US FDA for the treatment of wet AMD that have a history of treatment long enough for this study.

OVERALL INJECTION INTERVAL PATTERNS

Looking at all eyes and all injections, we found that the mean number of injections per eye was approximately 5 per year among patients who received treatment within a given year (Figure 1). There was little apparent difference between years 1 and 2 among treated patients or among the two FDA-approved anti-VEGF agents studied. This represents fewer injections annually than we would have expected to occur with adherence to TAE injection protocols, and it is consistent with what has been reported by other researchers using claims databases.[10]

The data set likely includes patients who were lost to follow-up for a period of time or who saw multiple providers, and thus what appears to be a long interval may actually be a discontinuation. This may explain the large number of injections at intervals of 12 weeks or longer during year 1 (Figure 2). Obeid et al reported a similar rate of loss to follow-up or discontinuation in wet AMD patients.[11] Additionally, we know from the PrONTO study that about 20% of AMD patients can stop treatment after three injections when assessed at 1 year. The even higher percentage of injection intervals of at least 12 weeks in year 2 (Figure 2) likely reflects not only loss to follow-up and successful extension to 12 weeks, but also those patients whose disease required only a few treatments.

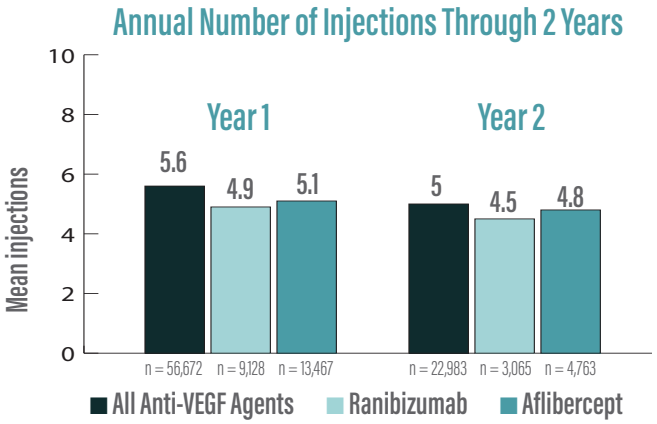

Figure 1. The average number of anti-VEGF injections through the first 2 years is illustrated here.

The most common interval (32%) for all injections in year 1 was 4 to 5 weeks. By year 2, the most common intervals for all injections were 6 to 7 weeks and 12 weeks or more (Figure 2).

DRUG-SPECIFIC RESULTS AT END-OF-YEAR

When we evaluated eyes treated with a single drug, nearly 40% needed injections more frequently than every 8 weeks by the end of the first year (Figure 3). At 2 years, the pattern was similar among eyes that continued to receive treatment, with minimal change in injection intervals.

By the end of the study periods, eyes treated with an

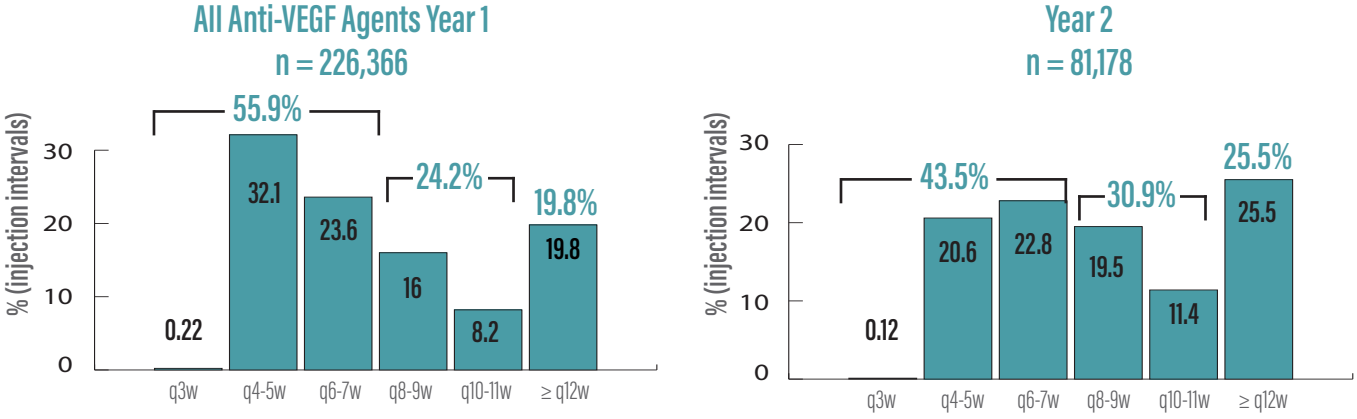

Figure 2. The most common injection interval in year 1 was 4-5 weeks. At year 2, injection intervals of 6-7 weeks and 12+ weeks were most common. The high percentage of patients who went at least 12 weeks without an injection in year 1 may be attributed to patients whose initial diagnosis was changed.

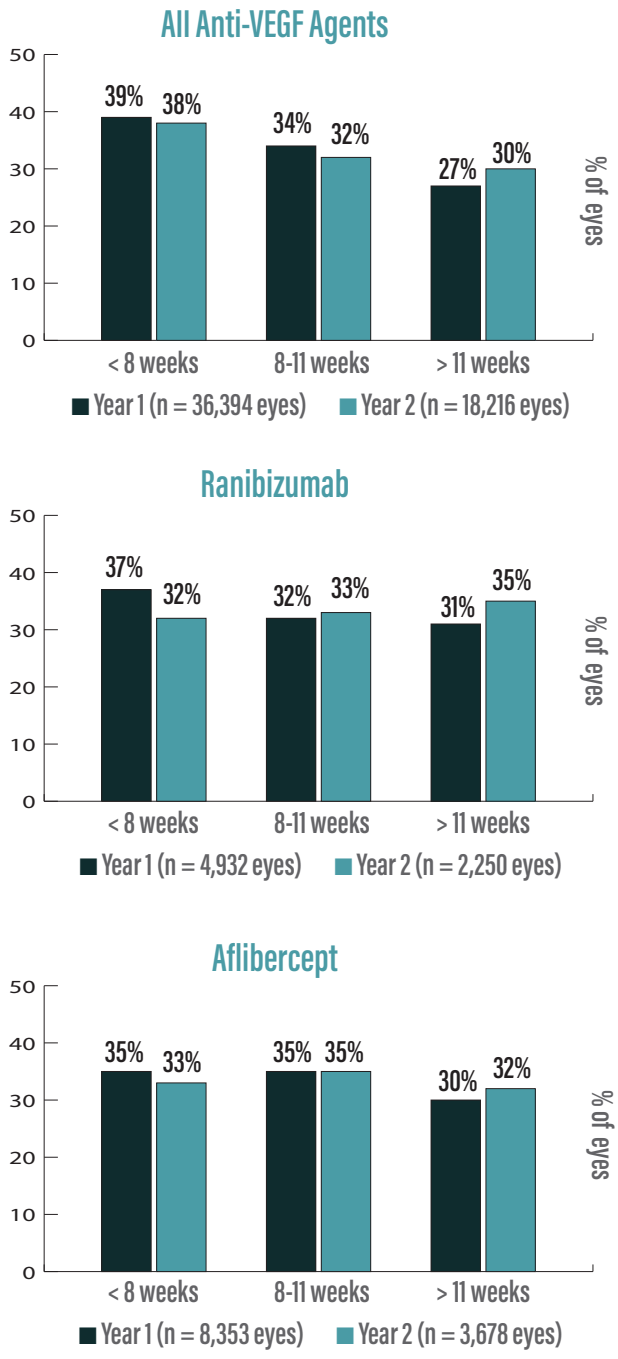

Figure 3. By the end of year 1, nearly 40% of eyes undergoing anti-VEGF therapy with any anti-VEGF agent needed injections less than every 8 weeks. Little change in injection interval was observed at the end of year 2.

FDA-approved anti-VEGF agent were more likely to require a treatment interval of at least 8 weeks compared with total eyes treated with any anti-VEGF agent (Figure 3). Note, however, that this is a descriptive study and no formal statistical analyses adjusting for differences between treatment groups were conducted.

These results confirm what we already suspected: We are getting better at extending the interval. However, injection intervals are still frequent enough to be a significant burden to patients and physicians. An extension of even a few more weeks between injections could save billions of dollars for the health care system and make effective care less burdensome.

We will continue to analyze IRIS Registry data as new drugs and devices enter the landscape. The anti-VEGF agent brolucizumab (Beovu, Novartis) has been approved for administration every 8 to 12 weeks after three monthly loading doses, and it may allow longer treatment intervals if used on a TAE regimen. We will know more in a few years; the drug was approved in 2019. Additionally, new agents that may complement anti-VEGF therapy and sustained-release devices will warrant future research to determine the extent to which they are able to reduce treatment burden.

Future studies using IRIS Registry data to evaluate clinical outcomes of AMD treatment are planned. In particular, it will be important to evaluate the impact on visual acuity or macular fluid on OCT. These outcome variables are more complex to analyze because of inconsistencies in the way they are reported by doctors in EHR systems, but correlating outcomes with injection intervals would certainly be a valuable next step.

KNOWING MORE ABOUT REAL-WORLD BEHAVIOR

Data from the IRIS Registry have provided important insights into ophthalmologists' real-world treatment patterns for wet AMD. Despite stated preferences for TAE regimens, the data show that actual injection intervals can be longer or shorter than expected. Ongoing analysis of this large trove of data can supplement what we learn from clinical trials to better understand treatment patterns and the efficacy of treatment as applied in real-world patient care. ■

1. Patel S. Medicare spending on anti-vascular endothelial growth factor medications. *Ophthalmol Ret*. 2018;2(8):785-791.
2. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897-1908.
3. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO study. *Am J Ophthalmol*. 2009;148(1):43-58.
4. Rufai SR, Almuhtaseb H, Paul RM, et al. A systematic review to assess the 'treat-and-extend' dosing regimen for neovascular age-related macular degeneration using ranibizumab. *Eye (Lond)*. 2017;31(9):1337-1344.
5. Vardarinos A, Gupta N, Janjua R, et al. 24-month clinical outcomes of a treat-and-extend regimen with ranibizumab for wet age-related macular degeneration in a real-life setting. *BMC Ophthalmol*. 2017;17(1):58.
6. American Society of Retina Specialists, Stone TW. ASRS 2019 Preferences and Trends Membership Survey. Chicago, IL; 2019.
7. Atchison EA, Wood KM, Mattox CG, et al. The real-world effect of intravitreous anti-vascular endothelial growth factor drugs on intraocular pressure: an analysis using the IRIS Registry. *Ophthalmology*. 2018;125(5):676-682.
8. Research. Verana Health. www.veranahealth.com/research. Accessed January 22, 2020.
9. MacCumber M, Yu, JS, Sagkriotis A, et al. Injection intervals in treatment-naïve neovascular AMD patients who received anti-VEGF agents: an analysis of the IRIS Registry. Paper Presented at: American Academy of Ophthalmology Annual Meeting October 12-15, 2019; San Francisco. 2019: PO471.
10. Holekamp NM, Liu Y, Yeh WS, et al. Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. *Am J Ophthalmol*. 2014;157(4):825-833.
11. Obeid A, Gao X, Ali FS, et al. Loss to follow-up among patients with neovascular age-related macular degeneration who received intravitreal anti-vascular endothelial growth factor injections. *JAMA Ophthalmol*. 2018;136(11):1251-1259.

MATHEW W. MACCUMBER, MD, PHD
- Professor and Associate Chairman for Research, Department of Ophthalmology, Rush University Medical Center, Chicago
- Private Practice, Illinois Retina Associates, Chicago
- Past Chair, AAO Council and AAO Board of Trustees
- mmaccumber@illinoisretina.com
- Financial disclosure: Consultant (Genentech, Novartis Pharma AG, Regeneron)