ASRS American Society of Retina Specialists

April 2, 2018

Joseph B. Sobel, MD, MPH, MBA
Vice President & Chief Medical Officer
Senior Products
1 Cameron Hill Circle
Chattanooga, TN 37402

Dear Dr. Sobel:

On behalf of the American Society of Retina Specialists (ASRS), we write to express our concern regarding Blue Cross and Blue Shield of Tennessee's new required policy aimed at restricting the use of aflibercept (Eylea). While lower-cost Avastin (bevacizumab) can be effective for some patients and is often used by retina specialists, we believe that physician choice is essential to treating retinal diseases. We ask that your revise the aflibercept policy to:

- Be based on sound clinical and scientific evidence for diabetic macular edema and age-related macular degeneration;
- Remove the Spectral-Domain Optical Coherence Tomography (OCT) guidance;
- Prevent patients who have qualified for Eylea to repeat step therapy when annual medication renewals occur; and
- Reflect that safety issues may affect intravitreal therapy choices.

ASRS is the largest retina organization in the world, representing over 3,500 board certified ophthalmologists who have completed fellowship training in the medical and surgical treatment of retinal diseases. The mission of the ASRS is to provide a collegial open forum for education, to advance the understanding and treatment of vitreoretinal diseases, and to enhance the ability of its members to provide the highest quality of patient care.

Avastin, when used off-label, is among the three most utilized anti-vascular endothelial growth factor (anti-VEGF) agents to treat eye diseases that cause fluid to leak into or under the retina, such as neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema, diabetic retinopathy, and macular edema following a retinal vein occlusion. However, only ranibizumab (Lucentis) and Eylea have specific FDA approval for these eye conditions.

These three anti-VEGF agents are not interchangeable in their efficacy and safety. Therefore, clinicians should determine which agent is the appropriate drug for a specific disease presentation in the setting of an individual patient's comorbidities and risks. Recent clinical data have focused on the potential benefits of each of these three agents when care is directed by a retina specialist and targeted to the specific anatomic and visual response of that patient.

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Diabetic Macular Edema

The randomized Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study, funded by the National Eye Institute, compared Eylea, Lucentis and Avastin.[1] In this study, Avastin had a statistically significant inferior effect on reducing diabetic macular edema in all subgroups of patients studied when compared to Lucentis or Eylea. In addition, within the subgroup of patients who started with a visual acuity of 20/50 or worse, a statistically significant inferior visual outcome was found in Avastin-treated patients when compared to patients treated with Lucentis and Eylea at 2 years. Avastin therefore, may not be medically appropriate in patients with diabetic macular edema with a visual acuity of 20/50 or worse based on the results of DRCR.net Protocol T.

As required by BCBS policy, prior to starting with Eylea, the physician would have to show that the patient had a poor response based on criteria in the new insurance policy, or demonstrate an allergic or immunologic reaction to both Avastin and Lucentis. This added delay in care of switching medications is particularly harmful when data from VISTA/VIVID trials for Eylea[2] and RISE/RIDE trials for Lucentis[3] are considered, because they showed that persistent chronic edema from delayed treatment can lead to irreversible vision loss. We strongly urge BCBS to change its policy to reflect that starting with Avastin is clearly inappropriate in some patients.

Age-Related Macular Degeneration

Just as Avastin was shown to be inferior to Lucentis and Eylea in anatomic reduction of macular edema due to diabetes by the DRCR.net Protocol T trial, the NIH funded CATT trial for AMD showed Avastin to be statistically inferior to Lucentis in inducing complete resolution of retinal edema, the main measure of disease activity.[4] Although this study did not evaluate Eylea, the VIEW studies compared Eylea to Lucentis, and found Eylea to be superior to Lucentis in inducing complete resolution of retinal edema.[5] There is extensive patient-to-patient variation in the responsiveness of edema to anti-VEGF therapy, with

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[1] The New England Journal of Medicine, The Diabetic Retinopathy Clinical Research Network, "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema," (also known as Protocol T, Year 1), March 26, 2015. http://www.nejm.org/doi/full/10.1056/NEJMoa1414264#t=article

[2] Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID Studies [published online September 17, 2016]. Ophthalmology 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032.

[3] Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema, results from 2 phase III randomized trials: RISE and RIDE [published online February 11, 2012]. Ophthalmology. 2012;119(4):789-801. doi:10.1016/j.ophtha.2011.12.039.

[4] Comparison of Age-related Macular Degeneration Treatment Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012 Jul;119(7):1388-98.

[5] Schmidt-Erfurth U, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014 Jan;121(1):193-201.

some patients requiring at least monthly injections to dry the retina, and others requiring only one or two within a year. Given this variability, physicians should have the ability to tailor the treatment to the individual patient and the patient's response to therapy. To restrict access to the most powerful drying agent will inhibit our ability to fully treat the disease activity in the most severe cases. Persistent edema has been correlated with poorer visual outcomes in a variety of studies, including a post hoc analysis of the VIEW studies looking at patients with persistent retinal fluid following the initial 3 monthly anti-VEGF injections. These patients with persistent fluid were less common following Eylea treatment than Lucentis treatment, and in this population, the visual acuity gain from baseline to week 52 was greater with monthly Eylea compared with monthly Lucentis ($p < 0.01$). The analysis suggests that a more difficult-to-treat, persistent fluid, wet AMD patient population, may benefit more from monthly Eylea compared to monthly Lucentis.[6]

OCT Requirement

As briefly outlined above, multiple trials have shown that persistent fluid for six months can lead to visual acuity loss that is not recovered, even after switching therapies and eliminating the diabetic macular edema. The CATT trial for AMD demonstrated prn treatment could rival monthly treatment in visual outcomes, but retreatment was mandated for any retinal edema, despite the central thickness on OCT. Other prn trials had not achieved similar visual outcomes with less stringent treatment criteria. Therefore, we believe that for example, a patient with 345 micron thickness after three treatments with Avastin (considered a successful treatment by the outlined policy) is still not adequately treated. The stated OCT requirements are too restrictive. Instead, if step therapy cannot be eliminated altogether based on the above evidence based medicine, we recommend that if the patient does not respond to Lucentis or Avastin or has any persistent fluid after the first three treatments, Eylea should be approved according to physician discretion, and without having to meet such specific OCT criteria.

Renewal Criteria

As per the proposed policy, to be renewed, an individual must continue to meet initial approval criteria. We fear that a strict interpretation of this criteria as worded might create a vicious cycle of repeated trials of Avastin to demonstrate inadequate response. This interpretation could lead to the following scenario: A patient fails to respond to a course of Avastin and receives an injection of Eylea, which improves the vision and retinal thickness significantly from the previous course of Avastin therapy. If the improvement is such that the initial approval criteria are not met, then Eylea will not be approved for use, and the patient must return for another course of the failed Avastin therapy. In other words, Eylea just proved to be a superior treatment for this individual, and now the patient must go back to the inferior treatment. We believe the policy should be modified to state "individual continues to meet medical necessity criteria." This would assure that patients who respond better to Eylea would have continued access to the superior treatment without unnecessary and visually harmful interruptions.

[6] Jaffe GJ, Kaiser PK, Thompson D, et al. Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid. Ophthalmology, 2016; 123(9): 1856 – 1864.

Safety

Systemic safety of these agents in at-risk populations is controversial and has not been well tested, especially in regard to Avastin, which lacks registration trials. Avastin not only lacks specific FDA approval for use in the eye, it must be used in a repackaged form. Our society recently learned of class action lawsuits directed against doctors who use and pharmacies that repackage Avastin because of silicone droplets present in the syringes used for Avastin. Therefore, this aflibercept step therapy policy may subject Blue Cross Blue Shield to increased litigation if the insurance company is dictating therapy, rather than allowing a decision to be made by the physician and patient.

In addition, the large doses of anti-VEGF agents used in cancer treatment carry an increased risk of thromboembolic events. Fortunately, the lower doses used for the eye seem safe in the general population. However, these agents get into the bloodstream at very different concentrations, and there are only limited data about their safety in patients with recent stroke or heart attack, as these patients were excluded from the registration trials.[7] The systemic exposure of Avastin after intravitreal injection has been reported to be up to 70 fold higher than that of Lucentis in pharmacokinetic studies, and caution has been recommended about its use in at-risk populations.[8] To be required to use Avastin in patients with recent stroke or heart attack could potentially increase the risk of systemic complications and your risk of liability.

Summary

The concept of tiered therapy, when each of the three anti-VEGF agents has been found to have unique anatomic responses, negates the importance of individualized patient care whereby the retina specialist selects the most effective drug for each unique patient. Ultimately, the retina specialist utilizes clinical judgment to select the best drug to use for treatment. This ability to individualize treatment and select the most efficacious agent for each patient is the key to the major improvements gained in recovering and maintaining visual acuity and retinal function in patients with blinding diseases of the retina.

In short, ASRS does not endorse step therapy and we strongly urge Blue Cross Blue Shield to allow retina specialist to make wise and judicious choices based on the patient's unique risk factors, clinical appearance, availability of compounded drugs, and economic requirements. We would like to arrange a conference call with our physician experts to further discuss the requests outlined in this letter. We look forward to a response from you. Please do not hesitate to contact Monica Horton at monica.horton@asrs.org if you have any questions. Thank you for your consideration.

Sincerely,

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[7] Avery RL, et al. What is the evidence for systemic effects of intravitreal anti-VEGF agents, and should we be concerned? *Br J Ophthalmol*. 2014 Jun;98 Suppl 1:i7-i10.

[8] Avery RL, et al., Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular age-related macular degeneration. British Journal of Ophthalmology. 2014 Dec;98(12):1636-41.

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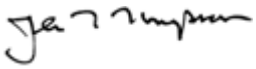

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cc: Jill Blim
ASRS Executive Vice President