ABSTRACT

Anti-vascular endothelial growth factor (anti-VEGF) drugs – ranibizumab, aflibercept, and off-label bevacizumab – are vital to the treatment of common retinal diseases, including exudative age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema (ME) associated with retinal vein occlusion (RVO). Given the high prevalence of AMD and retinal vascular diseases, anti-VEGF agents represent a large cost burden to the United States (US) healthcare system. Although ranibizumab and aflibercept are 30-fold more expensive per injection than bevacizumab, the two more costly medications are commonly used in the US, even though all three have been shown to be effective and safe for treatment of these retinal diseases. We investigated the availability and content of professional ophthalmic guidelines on cost consideration in the selection of anti-VEGF agents. We found that current professional guidelines were limited in availability and lacked specific guidance on cost-based anti-VEGF drug selection. This represents a missed opportunity to encourage the practice of value-based medicine.

KEYWORDS: ophthalmology, pharmacoeconomics, off-label drugs, value-based medicine

INTRODUCTION

Age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinal vein occlusion (RVO) are leading causes of visual loss in the United States [US]. Anti-vascular endothelial growth factor (anti-VEGF) drugs such as bevacizumab, ranibizumab, and aflibercept have become the mainstay of treatment in patients with these retinal diseases. The two medications approved by the Federal Drug Administration – ranibizumab and aflibercept – are significantly more expensive than bevacizumab, which is used off-label for ophthalmic disease; Medicare reimbursements are $50, $1,903, and $1,850 for bevacizumab, ranibizumab, and aflibercept, respectively. Although multiple studies have deemed the three agents to be effective and safe for treatment of AMD, DR, and ME secondary to RVO, ranibizumab and aflibercept are commonly used in the US. Ranibizumab accounted for the second highest Medicare Part B drug expenditure ($1,278 million) in 2012, constituting one-sixth of the drug budget. Specific medical society-sanctioned guidelines that weigh anti-VEGF cost-utility analysis could help ophthalmologists practice value-based medicine. In light of the rising cost burden of anti-VEGF therapy, we investigated published guidelines for drug selection.

MATERIALS AND METHODS

We searched publications from the American Academy of Ophthalmology (AAO), the American Society of Retina Specialists (ASRS), the New England Ophthalmology Society, the American Medical Association, the American Society for Bioethics and Humanities, the American Society of Law, Medicine, and Ethics, and the public-domain section of each state ophthalmological society website (if existent) under the terms, “medication cost selection,” “medication cost guideline,” “Lucentis,” “ranibizumab,” “Avastin,” “bevacizumab,” “Eylea,” and “aflibercept.” Using the same terms, we also searched PubMed, Web of Science, Google Scholar, the Cochrane Library, and the National Guidelines Clearinghouse between 2009 and 2015. Inclusion criterion included a published direct statement on cost consideration in ophthalmic anti-VEGF selection. We excluded non-English articles and articles that targeted non-U.S. audiences.

RESULTS

Two ophthalmology societies published statements on cost consideration in the selection of anti-VEGF agents. The AAO recommended that ophthalmologists observe cost efficacy without compromising care. The ASRS advocated against a price-based guideline that mandates a trial of bevacizumab before the use of ranibizumab and/or aflibercept, rationalizing physician medical judgment should not have cost guideline constraints. Forty-two state ophthalmological societies had websites: only one, the Florida Society of Ophthalmology, published a report on the price differences between bevacizumab and ranibizumab, stating “...we should use the best medicine we can use for our patients regardless of cost.”

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We found limited guidance from professional societies on how to account for cost in selecting ophthalmic anti-VEGF agents. This poses a unique challenge for ophthalmologists. Given that ophthalmic anti-VEGF medications are comparable in efficacy and adverse event risk for most retinal neovascular disease, one would choose bevacizumab in a cost-conscious healthcare environment. However, data from Medicare Part B drug expenditure suggests this is not the case for a sizable number of ophthalmologists. Approximately one-third of patients receiving intravitreal anti-VEGF in 2010 were administered ranibizumab while roughly two-thirds of patients received bevacizumab.

The reasons for these anti-VEGF therapy practice patterns remain to be determined. One may be the potential drawbacks associated with bevacizumab, which is not FDA-approved for ophthalmic use. The lack of regulation has enabled the circulation of foreign counterfeit bevacizumab in US medical practices. Additionally, systemic bevacizumab must be converted into ophthalmic form through a compounding process performed by local pharmacies; contamination introduced during the compounding of bevacizumab for ophthalmic use also increases the risk of post-injection endophthalmitis. Bevacizumab from compounding pharmacies may contain drug concentrations lower than those used in clinical trials supporting bevacizumab efficacy. These bevacizumab-specific concerns may deter physicians from choosing bevacizumab despite its proven clinical efficacy and financial advantage for patients and raise the potential for malpractice lawsuits.

In addition, only two randomized controlled trials (RCTs) directly compare bevacizumab to one or both of the FDA-approved agents. Indirect validation in the setting of few direct comparison RCTs may not bear enough weight against bevacizumab-specific concerns to affect ophthalmologists to choose bevacizumab despite its cost value. Newer studies – such as those from the Diabetic Retinopathy Clinical Research Network outlining the role of aflibercept in DME and ranibizumab in proliferative diabetic retinopathy – may also guide the use of more expensive anti-VEGF agents over bevacizumab.

A limitation of the present study is that it was based on publically available information only; the members of the medical societies examined herein may have had access to additional information.

Ultimately, by supporting ophthalmologists wrestling with cost versus safety, medical society-sanctioned guidelines could help promote value-based medicine by encouraging more widespread use of cost-effective anti-VEGF therapy.

References


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