EDITORIAL

Off-Label Use as a Standard of Care

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IN THE OCTOBER ISSUE OF THE *JOURNAL*, BROWN AND ASsociates[1] reported that 3 intravitreal vascular endothelial growth factor inhibitors—ranibizumab, aflibercept, and bevacizumab—were cost effective for the treatment of neovascular age-related macular degeneration. In addition, they found that bevacizumab was several-fold more cost effective than ranibizumab and aflibercept.[1] While neither of us are pharmacoepidemiologists, the methods used by this experienced group of researchers appear to be valid. One might question whether the use of a national average cost for physician time as well as for pharmacotherapy can be generalized to all patients in the United States; however, given the manifold difference in pharmaceutical cost, it is unlikely to dramatically change the conclusions.

Nonetheless, we suggest some considerations about the use of these data in setting public health policy. Two of these treatments, ranibizumab and aflibercept, are approved, marketed products. The story of the adoption of bevacizumab, approved by the U.S. Food and Drug Administration (FDA) for systemic use to treat cancer, for this off-label use was recently reviewed, including perspectives vis à vis development decisions made by the manufacturer.[2]

The 2 approved products were initially available in a vial that needed to be drawn into a syringe and dosed to the correct volume by the physician at the moments preceding an injection. Both products are now available as prefilled syringes. Storey and associates[3] reported that in a large, multicenter, retrospective study, the use of prefilled syringes during intravitreal injection of ranibizumab was associated with a reduced rate of culture-positive endophthalmitis, including from oral flora. In patients with endophthalmitis related to prefilled syringe injection, final visual acuity outcomes were better than those who had infections related to conventional vascular endothelial growth factor inhibitor preparations.[3]

For intravitreal injection of the third product, bevacizumab, vials are aliquoted in a sterile fashion by the pharmacy into syringes and a sterile cap is placed on the end of the syringe. Similar to factory prefilled products, the filled syringe then needs to be uncapped, a fine-gauge needle placed, the excess volume of drug pushed out, and then administered to the patient.

Compounding pharmacies and off-label use of medication by physicians are both allowed in the United States. However, the FDA noted that "…Although compounded drugs can fill an important role for patients and the FDA recognizes the need to preserve access to these products, they may also present a greater risk to patients because, among other things, they are not required to undergo the agency's premarket review for safety, effectiveness and quality." The risks associated with compounded drugs that must be sterile are particularly relevant in the ophthalmic space.[4] A Pew report notes several case reports of adverse events, including loss of vision with formulations of triamcinolone, moxifloxacin, and bevacizumab.[4,5] In addition, the highly publicized outbreaks of endophthalmitis caused by poor compounding of bevacizumab left an indelible impression on all retina providers.[6,7] However, Bavinger and associates[8] showed that in the absence of outbreaks, sterile loading of syringes by compounding of bevacizumab resulted in a reduced risk of endophthalmitis when compared with office loading of conventional vials of ranibizumab and aflibercept (odds ratio = 1.29). Similarly, Baudin and associates[9] showed that factory-prepared syringes of ranibizumab were less associated with postinjection endophthalmitis compared with office prepared ranibizumab (incident rate ratio = 1.40) and aflibercept (incident rate ratio = 1.46). In a recent editorial, the logical suggestion was made that a move toward sterile loading of syringes may be indicated to obviate the increased risk of infection associated with office loading.[10] While sterile loading appears to be safer in general, pharmacy compounding of off-label medications is not identical to factory preparation of prefilled syringes. The relatively large number of local pharmacies and personnel involved in compounding when compared with factory filling of syringes introduces increased variables, no matter how stringent the practices. Therefore, the theoretical possibility of an episode of tainted product is higher when compounding off-label medications. To mitigate this risk, we advocate using a centralized facility to help reduce the risks when multiple local pharmacies and personnel are involved in compounding.

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There are additional considerations to off-label use. First, the product and the physician time may not be reimbursed by payers under certain clinical circumstances, though the same could be argued regarding marketed products. Second, the off-label use is at risk of continued availability of the product. For example, bevacizumab had been indicated for both colorectal cancer and breast cancer at one point, but the data did not support the second indication, and thus the indication was removed. If for some reason it is no longer available—eg, long-term efficacy and safety data in the oncology indication change its risk–benefit ratio, other products are available with better therapeutics, the manufacturer chooses to no longer market the product, or environmental factors unrelated to the product—then it will no longer be available for the ophthalmic indication. We have seen decreased availability of products for ophthalmology (eg, chloramphenicol,[11] ecothiophate iodide, and a glaucoma microstent[12]) as well as in systemic medicine (eg, terfenadine, rofecoxib[13] and, most recently, hydroxychloroquine for patients with lupus[14]).

Intracameral moxifloxacin is widely used as an off-label and frequently compounded agent to prevent endophthalmitis in cataract surgery.[15] Recent reports of adverse events with intracameral moxifloxacin may put this use at risk.[16] We see similar risks for the continued availability of off-label, compounded bevacizumab for the treatment of neovascular age-related macular degeneration.

In summary, Brown and associates[1] present a valuable financial analysis but, in our opinion, are not able to quantify the potential future risks associated with off-label, compounded use of bevacizumab. The use of intravitreal treatments for neovascular age-related macular degeneration is likely to change with the expiration of a patent for one of the marketed products and the potential availability of a biosimilar of this product, the development of novel agents, and several drug delivery systems and an ophthalmic bevacizumab in clinical development. The community should therefore consider a revisitation of this analysis as new alternatives become available for patient and physician. We favor ready access to vascular endothelial growth factor inhibitors by all patients in society. We hope that competition eventually achieves the affordable quality-adjusted life year that Brown and associates[1] calculated for the off-label medication also for marketed options that will not require local drug compounding.

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