Effect of Regulatory Requirement for Patient-Specific Prescriptions for Off-label Medications on the Use of Intravitreal Bevacizumab

Steven Holfinger, MD; Alexander G. Miller; Llewelyn J. Rao, MD; Douglas Y. Rowland, PhD; Joan H. Hornik, AB; David G. Miller, MD

IMPORTANCE Requirements regulating pharmaceutical prescriptions can affect physicians' choice of therapy in a clinical setting.

OBJECTIVE To evaluate the change in bevacizumab use after the regulatory requirement for patient-specific prescriptions (PSPs) for off-label medications in Ohio.

DESIGN, SETTING, AND PARTICIPANTS This study retrospectively reviewed the aggregate data from the billing records of patients receiving 1.25-mg injections of bevacizumab, 0.3- or 0.5-mg injections of ranibizumab, or 2.0-mg injections of aflibercept for age-related macular degeneration or diabetic macular edema in a 9-member retinal specialty private practice. The review assessed 4488 intravitreal injections in the 3-month period before (May 1 to July 30, 2012) and 5253 injections in the 3-month period after (May 1 to July 30, 2013) the Ohio Board of Pharmacy’s requirement of PSPs for bevacizumab. Relative proportions of the drugs used for intravitreal injections were calculated and frequencies were compared. A Likert scale survey was conducted among the 9 physicians to identify reasons for their change in prescription of bevacizumab. The survey inquired about (1) the burden of PSPs, (2) concern about differences in efficacy, and (3) concern about differences in safety.

MAIN OUTCOMES AND MEASURES Difference in drug use before and after the PSP requirement for bevacizumab and the physicians’ reasons for change in their drug use.

RESULTS Bevacizumab use decreased from 2752 of 4488 pre-PSP injections (61.3%) to 1503 of 5253 post-PSP injections (28.6%), a change of −32.7% (95% CI, −34.6% to −30.8%; P < .001). Use of 0.5-mg ranibizumab injections increased from 1122 of 4488 pre-PSP injections (25.0%) to 1838 of 5253 post-PSP injections (35.0%), a change of 10.0% (95% CI, 8.2% to 11.8%; P < .001). Use of 0.3-mg ranibizumab injections increased from 0 of 4488 (before US Food and Drug Administration approval) to 429 of 5253 post-PSP injections (8.2%), a change of 8.2% (95% CI, 7.4% to 8.9%; P < .001). Use of aflibercept injections increased from 614 of 4488 pre-PSP injections (13.7%) to 1483 of 5253 post-PSP injections (28.2%), a change of 14.6% (95% CI, 13.0%-16.1%; P < .001). In the survey of the 9 physicians concerning their reasons for decreased use of bevacizumab, 7 (78%) strongly agreed and 1 (11%) agreed that the burden of PSPs changed their choice of drug used for injection.

CONCLUSIONS AND RELEVANCE Use of bevacizumab was reduced by 32.7% 1 year after the regulatory requirement for PSPs for compounded (repackaged) medications. This change seemed to have more association with the requirement for PSPs than with a known change in efficacy or safety concerns. Although this study was based on a single US practice, regulation of repackaged medication for safety concerns should also consider the evaluation of treatment burden, cost, and adherence.
Intravitreal anti-vascular endothelial growth factor therapies have become an important treatment option for patients with neovascular and other ocular vascular diseases. Off-label use of intravitreal bevacizumab (Avastin) for the treatment of neovascular age-related macular degeneration began in May 2005, and its off-label use has expanded to include treatment of diabetic macular edema (DME), venous occlusive diseases, neovascular glaucoma, chorioidal neovascularization unrelated to macular degeneration, proliferative diabetic retinopathy, and others. Intravitreal ranibizumab (Lucentis) was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of neovascular age-related macular degeneration, and subsequently gained FDA approval for treatment of retinal vein occlusion in 2010 and DME in 2012. Aflibercept (Eylea) also gained FDA approval for treatment of neovascular age-related macular degeneration in 2011 and subsequently for DME in 2014.

A substantial cost differential exists among repackaged bevacizumab, ranibizumab, and aflibercept. These differences prompted studies into cost-effectiveness. In 2014, Stein et al concluded that bevacizumab is of significantly greater value than ranibizumab in the treatment of neovascular age-related macular degeneration. In addition, these medications have similar efficacy and safety profiles except for a large-related macular degeneration. In addition, these medications have similar efficacy and safety profiles except for a large-related macular degeneration.

An outbreak of fungal meningitis caused by 3 lots of preservative-free methylprednisolone acetate compounded at New England Compounding Center in September 2012 prompted the FDA to tighten regulations on compounding pharmacies. This regulation was enacted on a state-specific level by enforcing a 1997 Ohio law to require patient-specific prescriptions (PSPs). Subsequently, the Drug Quality and Security Act of 2013 was enacted, with the result that the FDA now requires PSPs nationwide for compounded medications. Consequently, physicians who prescribe repackaged bevacizumab have new burdens to conform to regulations or risk monetary and legal ramifications. Thus, PSPs have become a barrier to the use of bevacizumab. This study aims to quantify the effects of stricter regulation of compounding pharmacies on the use of bevacizumab in a retinal practice while acknowledging that confounding factors associated with time and other occurrences, known and unknown, might have affected the change in prescription pattern independently of the change in regulations.

Methods

We used aggregate billing records to analyze retrospectively the use of 1.25-mg injections of bevacizumab, 0.5- and 0.3-mg injections of ranibizumab, and 2.0-mg injections of aflibercept within a 9-member single retinal specialty practice during the 3-month periods before (May 1 to July 30, 2012) and after (May 1 to July 30, 2013) the requirement of PSPs for bevacizumab by the Ohio Board of Pharmacy. The 0.3-mg dose of ranibizumab for treatment of DME was approved in August 2012.) The Retina Associates of Cleveland Research Administration determined that because no identifying patient information could be obtained from the billing records, institutional review board approval was not required.

Data were collected and analyzed from August 26 to November 29, 2013. The relative proportions (95% CIs) were calculated using the modified Wald method. We used the ${\chi}^2$ test of proportions to compare frequencies in different years. $P < .05$ was taken as being statistically significant.

Using a Likert scale approach with responses varying from strongly disagree (1) to strongly agree (5), we surveyed the 9 physicians in the practice regarding 3 possible reasons for the change in bevacizumab use. We assigned values of 1 to 5 for the different possible responses. The categories surveyed included the requirement of PSPs, concerns regarding efficacy differences between the medications, and concerns regarding safety differences between the medications.

Results

The change in drug use is shown in the Figure. The relative number of bevacizumab injections decreased from 2752 of 4488 (61.3% of pre-PSP injections) to 1503 of 5253 (28.6% of post-PSP injections), a change of −32.7% (95% CI, −34.6% to −30.8%; $P < .001$). The relative number of 0.5-mg ranibizumab injections increased from 1122 of 4488 (25.0% of pre-PSP injections) to 1838 of 5253 (35.0% of post-PSP injections), a change of 10.0% (95% CI, 8.2%–11.8%; $P < .001$). The relative number of 0.3-mg ranibizumab injections for DME increased from 0 of 4488 (before FDA approval) to 429 of 5253 (8.2% of post-PSP injections), a change of 8.2% (95% CI, 7.4%–8.9%; $P < .001$). The relative number of aflibercept injections increased from 614 of 4488 (13.7% of pre-PSP injections) to 1483 of 5253 (28.2% of post-PSP injections), a change of 14.6% (95% CI, 13.0%–16.1%; $P < .001$).

The Likert survey results of the physicians’ responses regarding decreased bevacizumab use are shown in Table 2. Eight of the 9 physicians (89%) agreed (7 [78%] strongly agreed and 1 [11%] agreed) that the burden of PSPs was the reason. The results indicate that the decrease in bevacizumab use seemed to have more association with PSP requirements than with a known change in efficacy or safety concerns in this practice of 9 retinal specialists.
Discussion

In Ohio, a state where PSPs for off-label medications became mandatory, physicians shifted away from the use of off-label bevacizumab and toward the use of on-label ranibizumab and aflibercept in a single retinal specialty practice. The physicians were surveyed to identify their motivation for switching medications. Nearly all of them agreed that PSPs, rather than efficacy or safety, induced them to change the drug they administered. Patient-specific prescription requirements appeared to have contributed to a large shift away from repackaged bevacizumab toward on-label use of ranibizumab and aflibercept.

The financial effect on this practice alone was notable. The mean cost per injection between the 2 study periods increased from $808 to $1365, which was associated with a decrease in the use of bevacizumab from 61.3% to 28.6% for all intravitreal injections. During the course of a year, these data represent a mean increase in total costs of $393,455 per physician.

The PSP requirements were limited in the number of states affected during this study, but that situation has changed. Congress passed and the President signed into law the Drug Quality and Security Act of 2013. Federal law supersedes state laws, and this law now directs the FDA to regulate off-label compounding pharmacies. The FDA now requires PSPs nationwide for compounded medications. However, repackaging bevacizumab without PSPs is allowed by certified outsourcing facilities regulated by the FDA. Another restriction being considered is the FDA's proposed beyond-use dates for traditional compounders and outsourcing facilities (docket No. FDA 2014-D-1525 [Geoff Emerson, MD, PhD, American Society of Retina Specialists Federal Affairs Committee, email communication, April 16, 2015]). This proposal would also impede the use of bevacizumab.

Although the intention of requiring PSPs of compounded medications is to improve patient safety and regulate potentially dangerous medications, a burdensome effect on the practice of medicine results. This burden ultimately leads to an increase in costs by driving a shift in medication selection to more expensive but convenient alternatives, namely, the on-label medications. These medications may not be any more effective, but when patients, families, and physicians are faced with additional visits or unused PSPs, a logical shift toward the on-label medications occurs. Regulation of off-label compounded medication for safety concerns should also include some evaluation of the treatment burden, cost, and adherence.

Although this study appears to support the conclusion that the burden from PSPs for off-label medications causes a change in the use of pharmaceuticals, the study is limited in several ways. This small study includes only a single retinal practice in a single state. In addition, confounding factors associated with time and other occurrences, known and unknown, might have affected the change in prescription pattern independently of the change in regulations. Further analysis using multiple practices within states that require PSPs would be of interest, especially compared with practice environments in other states where PSPs were not required during the same period.

Conclusions

In this study, bevacizumab use was reduced by 32.7% 1 year after the regulatory requirement for PSPs for compounded (repackaged) medications. This change seems to be more

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allowable Rate, $</th>
</tr>
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<tbody>
<tr>
<td>Bevacizumab</td>
<td>60.00 60.00</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>1212.90 1194.03</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>2012.50 1990.05</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>1961.00 1961.00</td>
</tr>
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</table>

Abbreviation: CMS, Centers for Medicare & Medicaid Services.

Table 2. Physicians’ Responses to Survey

<table>
<thead>
<tr>
<th>Response</th>
<th>Reason for Change in Drug Use, No. (%) of Physicians (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly agree</td>
<td>PSP Burden Efficacy Safety</td>
</tr>
<tr>
<td>Strongly agree</td>
<td>7 (78) 0 0</td>
</tr>
<tr>
<td>Agree</td>
<td>1 (11) 2 (22) 0</td>
</tr>
<tr>
<td>Neutral</td>
<td>0 0 2 (22)</td>
</tr>
<tr>
<td>Disagree</td>
<td>1 (11) 5 (56) 1 (11)</td>
</tr>
<tr>
<td>Strongly disagree</td>
<td>0 2 (22) 6 (67)</td>
</tr>
</tbody>
</table>

Abbreviation: PSP, patient-specific prescription.
associated with the requirement for PSPs than with a known change in drug efficacy or safety concerns. Although this study was based on a single US retinal specialist practice, regulation of repackaged medication for safety concerns should also consider evaluation of treatment burden, cost, and adherence.

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Study concept and design: Holfinger, A. G. Miller, D. G. Miller.
Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: Holfinger, A. G. Miller, Rao, Hornik, D. G. Miller.

Statistical analysis: Holfinger, Rowland.

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Study supervision: D. G. Miller.

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REFERENCES