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

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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.

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At a Glance

- The purpose of this study was to evaluate change in bevacizumab use in a single retina specialty practice after regulatory requirement changes.
- The change required patient-specific prescriptions for off-label medications in Ohio.
- The change was followed by a reduction in bevacizumab use (from 61.3% to 28.6%, for a difference of −32.7%; 95% CI, −34.6% to −30.8%; P < .001).
- In this single US practice, decrease in use had more association with regulatory requirements than with efficacy or safety concerns.
- Results in a larger, more diverse setting could differ from ours.

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.

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 retina 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
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 2013.23 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,19 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

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Table 1. CMS Allowable Rates for 2012 and 2013 for Bevacizumab, Ranibizumab, and Aflibercept

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allowable Rate, $</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>60.00</td>
<td>60.00</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3 mg</td>
<td>1212.90</td>
<td>1194.03</td>
<td></td>
</tr>
<tr>
<td>0.5 mg</td>
<td>2012.50</td>
<td>1990.05</td>
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</tr>
<tr>
<td>Aflibercept</td>
<td>1961.00</td>
<td>1961.00</td>
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</tbody>
</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>
<th>PSP Burden</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly agree</td>
<td>7 (78)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>1 (11)</td>
<td>2 (22)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>0</td>
<td>0</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Disagree</td>
<td>1 (11)</td>
<td>5 (56)</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>Strongly disagree</td>
<td>0</td>
<td>2 (22)</td>
<td>6 (67)</td>
<td></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.
Drafting of the manuscript: All authors.
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Statistical analysis: Holfinger, Rowland, Administrative, technical, or material support: A. G. Miller, Hornik.
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REFERENCES