Rapid Expansion of Intravitreal Drug Injection Procedures, 2000 to 2008

A Population-Based Analysis

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Objective: To evaluate patterns of care for age-related macular degeneration following the introduction of vascular endothelial growth factor inhibitors.

Methods: Using a population-based retrospective design, we studied monthly fee claims for intravitreal injections submitted to the Ontario Health Insurance Plan between January 1, 2000, and March 30, 2008, and linked procedures to the physicians who performed them. This database records physician services provided as part of universal health care insurance coverage in Ontario, Canada. This program covers all residents of Ontario, which had an average population of 12.1 million during the study period.

Results: Following regulatory approval of bevacizumab for colorectal cancer in 2005, off-label use of this drug for the treatment of retinal disease, particularly age-related macular degeneration, became increasingly common. The rate of intravitreal injections in Ontario rapidly grew 8-fold, and this growth preceded the availability of ranibizumab by more than a year. Moreover, in 2007, more than 50% of intravitreal injections in Ontario were performed by 3% of ophthalmologists.

Conclusions: The development of vascular endothelial growth factor inhibitors has revolutionized the treatment of age-related macular degeneration. To our knowledge, this study is the first to quantify the dramatic uptake of these treatments at a population level. Our findings also suggest that off-label injection of bevacizumab was highly prevalent in Ontario. Serial intravitreal injections requiring direct physician administration and the concentration of injection procedures in the hands of a small number of ophthalmologists have the potential to affect services for other vision-threatening conditions.


Methods

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Insurance Plan between January 1, 2000, and March 30, 2008. This database records physician services provided as part of universal health care insurance coverage in Ontario, Canada. This program covers all residents of Ontario, which had an average population of 12.1 million during the study period. Billing outside the program is not permitted; hence, data can be considered population-based. The Ontario Health Insurance Plan database has excellent reliability for procedure performance.5 Unique, encrypted identifiers and associated specialty codes were used to link injections to the ophthalmologists who administered them. We calculated each surgeon’s annual intravitreal injection volume based on the number of claims submitted for each year.

We anticipated that intravitreal injections would become more frequent after the VEGF inhibitor bevacizumab received regulatory approval in Canada in September 2005. Although bevacizumab was licensed for use in colorectal cancer, off-label intravitreal use of this drug for AMD was first described4 in July 2005 and quickly became popular because of bevacizumab’s immediate availability and low cost as compared with the VEGF inhibitor ranibizumab, which did not receive regulatory approval in Canada until June 2007.1,4 The study protocol was approved by the research ethics boards at Queen’s University, Kingston, and Sunnybrook Health Sciences Centre, Toronto, both of which are in Ontario, Canada.

RESULTS

Following the regulatory approval of bevacizumab in September 2005, the rate of intravitreal injections in Ontario rapidly grew 8-fold to its peak level in November 2007 (growth from 3.5 to 25.9 injections per 100,000 Ontarians per month) (Figure 1). This striking upswing in injections preceded the availability of ranibizumab in Ontario by almost a year.

In contrast, the number of ophthalmologists performing injections rose more modestly from 39 (10% of all ophthalmologists) in September 2005 to 64 (15% of all ophthalmologists) in November 2007. Among ophthalmologists performing intravitreal injections, the median monthly number of injections grew from 7.0 in 2005 to 30.5 in the first quarter of 2008, while the 90th percentile grew from 35 to 105 injections per month during the same period (Figure 2).

In 2007, more than 50% of intravitreal injections were performed by just 3% of Ontario’s ophthalmologists (Figure 3), and the monthly number of injections performed by this group of intensive service providers grew from 162 to 1436 between September 2005 and November 2007.

COMMENT

The development of VEGF inhibitors has ushered in an exciting era in the treatment of AMD. To our knowledge, this study is the first to quantify the dramatic uptake of these treatments at a population level. Strengths of our study include the large numbers of surgeons and procedures evaluated in our population-based data. We were unable to confirm which drug was administered with each injection because off-label drug use was not directly quantifiable. Nevertheless, our findings strongly suggest that off-label use of bevacizumab accounts for the vast majority of injection procedures in the period fol-
Canada. However, reassuringly, this outbreak was linked to an outbreak of severe intraocular inflammation. This Canadian-centered outbreak has attracted international attention and has prompted warnings from the US Food and Drug Administration and Health Canada, and may also negatively affect access to services for other vision-threatening eye conditions. Although this may be mitigated somewhat by decreased use of alternative treatments such as photodynamic therapy, the broader indications for VEGF inhibitors and the need for serial injections will nevertheless result in significant net increases in demand for retina services. Hence, further research is needed to quantify these effects and guide physician human resource projections and planning. Moreover, efforts will be needed to search for alternative approaches to posterior-segment drug delivery.

In summary, we have quantified a recent dramatic surge in intravitreal injection procedure rates. This rapid uptake preceded the availability of ranibizumab, strongly suggesting that off-label intravitreal injection of bevacizumab has been highly prevalent. Although this substitution provides great cost savings, establishing the efficacy and safety of bevacizumab will have to await outcomes of ongoing clinical trials.

<table>
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<tr>
<th>Location</th>
<th>Ranibizumab total cost</th>
<th>Bevacizumab total cost</th>
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<td>1 658 180 000</td>
<td>25 510 000</td>
<td>1 632 670 000</td>
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</table>

*Based on peak injection rate in Ontario (November 2007) and an assumption that 90% of injections deliver vascular endothelial growth factor inhibitors. Estimated drug costs per injection are $1950 for ranibizumab and $30 for bevacizumab. Extrapolated data for Canada and the United States are based on observations from Ontario.*
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Author Contributions: Dr Campbell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES