Rapid Expansion of Intravitreal Drug Injection Procedures, 2000 to 2008

A Population-Based Analysis

Robert J. Campbell, MD, MSc; Susan E. Bronskill, PhD; Chaim M. Bell, MD, PhD; J. Michael Paterson, MSc; Marlo Whitehead, MSc; Sudeep S. Gill, MD, MSc

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 up-take 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.


Author Affiliations: Department of Ophthalmology, Hotel Dieu Hospital (Dr Campbell) and Department of Ophthalmology (Dr Campbell and Ms Whitehead) and Division of Geriatric Medicine (Dr Gill), Queen’s University, and Division of Geriatric Medicine, St Mary’s of the Lake Hospital (Dr Gill), Kingston, the Institute for Clinical Evaluative Sciences (Drs Campbell, Bronskill, Bell, and Gill, Mr Paterson, and Ms Whitehead), Departments of Health Policy, Management, and Evaluation (Drs Bronskill and Bell and Paterson) and Medicine (Dr Bell), University of Toronto, and Department of Medicine and Keenan Research Centre, Li Ka Shing Knowledge Institute of St Michael’s Hospital (Dr Bell), Toronto, and Department of Family Medicine, McMaster University, Hamilton (Mr Paterson), Ontario, Canada.

The development of vascular endothelial growth factor (VEGF) inhibitors has revolutionized the treatment of age-related macular degeneration (AMD), the leading cause of blindness in Western nations. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD trial have demonstrated that the VEGF inhibitor ranibizumab not only slows vision loss but also improves visual acuity in many patients with neovascular AMD.

During the progress of these pivotal trials, case series suggested that bevacizumab, a closely related VEGF inhibitor, might also dramatically improve outcomes for patients with AMD. Because of the significantly lower cost and immediate availability of bevacizumab, it became the treatment of choice in many centers. However, off-label intravitreal injection of this drug has generated controversy worldwide.

Access to new VEGF inhibitor therapies may be limited by a number of factors, including regulatory approval, cost, and the necessity of administering these drugs via serial intravitreal injections under the care of an ophthalmologist. At a population level, the widespread uptake of drug therapies requiring direct physician administration has the potential to significantly affect the practice of many ophthalmologists, yet quantitative data describing the evolution of intravitreal injection procedure rates over time are lacking. To address this, we conducted a retrospective population-based study to evaluate developments in patterns of care for AMD.

METHODS

We studied monthly fee claims for intravitreal injections submitted to the Ontario Health Insurance Plan for intravitreal injection procedures (E9489 and E9491) from January 1, 2000, to March 30, 2008. We linked procedures to the physicians who performed them using a unique identifier for each physician. We excluded procedures submitted by nonphysician providers (e.g., nurse practitioners and physician assistants) and claims with incomplete provider identifiers. We also excluded procedures for patients younger than 65 years of age at the time of injection, as they are not eligible for the Ontario Health Insurance Plan.

We obtained monthly fee claims data from the Ontario Health Insurance Plan and linked the claims to the physicians who performed them using a unique identifier for each physician. We excluded procedures submitted by nonphysician providers (e.g., nurse practitioners and physician assistants) and claims with incomplete provider identifiers. We also excluded procedures for patients younger than 65 years of age at the time of injection, as they are not eligible for the Ontario Health Insurance Plan.

We estimated monthly injection rates by calculating the number of injections for each month and dividing by the average monthly population of Ontario. We calculated the average monthly population of Ontario by dividing the total population of Ontario in each month by the number of months in the study period. We calculated the average monthly population of Ontario by dividing the total population of Ontario in each month by the number of months in the study period.
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. 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 described 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. 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-
follow its regulatory approval for colorectal cancer in September 2005 and preceding regulatory approval of ranibizumab in June 2007. While the first VEGF inhibitor approved for AMD, pegaptanib sodium, received regulatory approval in Canada in May 2005, this drug is less effective than other anti-VEGF medications and is not commonly used. We confirmed that very few prescriptions for pegaptanib were dispensed in Ontario during our study period (data not shown). Moreover, although there has been renewed interest in intravitreal injection of triamcinolone acetonide for retinal diseases, the relative contribution of this drug to the trends we document is also likely small. Finally, the injection of intravitreal antibiotics is a relatively rare procedure and the rate of postoperative endophthalmitis in Ontario was stable over the study period. As a result, these drugs have also contributed minimally to the rapid increase in intravitreal injection rates.

The magnitude of off-label bevacizumab use suggested by our findings has important implications. Recently, off-label intravitreal bevacizumab injections have been 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. However, reassuringly, this outbreak was linked to an outbreak of severe intraocular inflammation and has prompted warnings from the US Food and Drug Administration and Health Canada. Although the focus of our investigation was intravitreal injection rates, our data provide an opportunity to begin to evaluate the potential costs associated with the use of VEGF inhibitors at a population level (Table). This cost analysis does not incorporate the comparative effectiveness and safety of ranibizumab and off-label bevacizumab, which remain the subjects of intense debate. As a result, the National Eye Institute is currently undertaking the Comparison of Age-Related Macular Degeneration Treatments Trials to provide comparative data on these 2 related VEGF inhibitors.

Our findings highlight the concentration of intravitreal injection procedures in the hands of relatively few ophthalmologists. New procedures often diffuse over time from a small group of early adopters to a broader section of physicians. However, the specialized skills required to diagnose and manage AMD, combined with limited access to necessary diagnostic testing equipment, may restrict such diffusion in this case. The remarkable number of injection procedures required with current administration regimens, together with the limited supply of ophthalmologists and retina subspecialists, has the potential to limit equitable access to intravitreal injections in some regions 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.
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Correspondence: Robert J. Campbell, MD, MSc, Department of Ophthalmology, Queen’s University and Hotel Dieu Hospital, 166 Brock St, Kingston, ON K7L 5G2, Canada (rob.campbell@queensu.ca).

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REFERENCES