



6-13-2012

## Comparing Treatments for Age-related Macular Degeneration: Safety, Effectiveness and Cost

Maureen G. Maguire

Follow this and additional works at: [https://repository.upenn.edu/ldi\\_issuebriefs](https://repository.upenn.edu/ldi_issuebriefs)

 Part of the [Health Services Research Commons](#)

---

Maguire, Maureen G.. Comparing Treatments for Age-related Macular Degeneration: Safety, Effectiveness and Cost. LDI Issue Briefs. 2012; 17 (8). <http://ldi.upenn.edu/policy/issue-briefs/2012/06/13/comparing-treatments-for-age-related-macular-degeneration-safety-effectiveness-and-cost>

This paper is posted at ScholarlyCommons. [https://repository.upenn.edu/ldi\\_issuebriefs/102](https://repository.upenn.edu/ldi_issuebriefs/102)  
For more information, please contact [repository@pobox.upenn.edu](mailto:repository@pobox.upenn.edu).

---

# Comparing Treatments for Age-related Macular Degeneration: Safety, Effectiveness and Cost

## Abstract

Comparative effectiveness research (CER) has received widespread attention and federal funding because of its potential to inform and improve treatment decisions. Since 2005, patients and their ophthalmologists have faced a dilemma in treating age-related macular degeneration (AMD)—the leading cause of blindness in the United States. Two closely related drugs have produced dramatic improvements in vision; one has been rigorously tested for use in AMD patients, while the other has been rigorously tested for use in cancer patients, but is now widely used to treat AMD. One drug costs 40 times as much as the other. This Issue Brief summarizes a CER study comparing these drugs head-to-head, and provides the most definitive evidence to date about the safety and effectiveness of the two alternatives.

## Keywords

evidence development & decision science, comparative effectiveness research/PCORI

## Disciplines

Health Services Research

## License



This work is licensed under a [Creative Commons Attribution-NonCommercial 4.0 International License](https://creativecommons.org/licenses/by-nc/4.0/).

**Maureen G. Maguire, PhD***LDI Senior Fellow,**Carolyn F. Jones**Professor of Ophthalmology**University of Pennsylvania*

## ***Comparing Treatments for Age-Related Macular Degeneration: Safety, Effectiveness and Cost***

Editor's note: Comparative effectiveness research (CER) has received widespread attention and federal funding because of its potential to inform and improve treatment decisions. Since 2005, patients and their ophthalmologists have faced a dilemma in treating age-related macular degeneration (AMD)—the leading cause of blindness in the United States. Two closely related drugs have produced dramatic improvements in vision; one has been rigorously tested for use in AMD patients, while the other has been rigorously tested for use in cancer patients, but is now widely used to treat AMD. One drug costs 40 times as much as the other. This Issue Brief summarizes a CER study comparing these drugs head-to-head, and provides the most definitive evidence to date about the safety and effectiveness of the two alternatives.

### ***Age-related macular degeneration (AMD) treatment breakthrough leads to clinical dilemma***

About 200,000 cases of severe (so-called “wet”) AMD are diagnosed each year in the U.S., primarily in people 60 and older. Before 2005, most of these patients faced a progressive loss of central vision and legal blindness. But in 2005, clinical trials showed that monthly intraocular injections of a new drug, ranibizumab (Lucentis, Genentech) could slow the rate of vision loss and improve visual acuity for people with wet AMD. Lucentis works by inhibiting abnormal growth and leakage of blood vessels behind the retina.

- While awaiting approval for Lucentis from the Food and Drug Administration (FDA), ophthalmologists began using bevacizumab (Avastin, Genentech), a closely related drug already on the market. Avastin had been approved by the FDA as an intravenous cancer therapy in 2004. Lucentis and Avastin share anti-vascular growth properties.
- This off-label use of Avastin spread widely, despite the absence of high quality data supporting its use. Avastin quickly became the most commonly used drug for treating wet AMD. Even after the FDA approved Lucentis in 2006, ophthalmologists continued to use Avastin. The reason was primarily financial: a single dose of Lucentis costs about \$2,000 compared to a single dose of Avastin, which costs about \$50 after being repackaged from the much larger intravenous dosages used in cancer treatment. Ophthalmologists also adopted an as-needed regimen for both drugs, a departure from the monthly regimen of Lucentis tested in clinical trials.

- 
- The manufacturer of both drugs, Genentech, actively discouraged the use of Avastin for AMD, saying that Lucentis had been developed and tested specifically for intraocular use, and warning that the safety and efficacy of repackaged Avastin was unknown. The need for a head-to-head trial comparing Avastin and Lucentis became obvious. In 2006, the National Eye Institute funded the Comparison of AMD Treatments Trials (CATT).

---

### ***Randomized clinical trial compares Avastin and Lucentis, and tests different dosing schedules***

The CATT study was designed to answer two questions about AMD treatment: Is Avastin as safe and effective as Lucentis? Does “as needed” dosing of either drug compromise long-term visual outcomes, compared to fixed monthly dosing? Patients were randomly assigned to one of four groups: monthly Avastin, monthly Lucentis, as-needed Avastin, and as-needed Lucentis. In the as-needed groups, after the first mandatory injection, injections were given when an ophthalmologist saw signs of active disease, such as fluid leakage, at a monthly evaluation.

- The investigators assessed changes in visual acuity after one year, as measured by letters on a standardized eye chart. They also measured anatomic changes in the retina (thickness and fluid), serious adverse events, and total drug costs in each group.
- After one year, the patients assigned to monthly treatments were reassigned randomly, to continue with monthly treatments or switch to as-needed treatment. This design enabled the investigators to assess the longer-term outcomes of the original treatment groups and to understand the impact of switching from monthly to as-needed treatment.
- From February 2008 to December 2009, the CATT study enrolled 1,208 patients at 44 clinical centers in the U.S. The patients were at least 50 years old, had previously untreated wet AMD, and visual acuity between 20/25 and 20/320.

---

### ***At one year, Avastin and Lucentis led to similar improvements in vision***

A total of 1,105 patients completed the one-year follow up. Almost all patients were over 60, with a median age of over 80. At one year, Avastin and Lucentis had equivalent effects on visual acuity when administered according to the same schedule.

- On average, patients gained 6-7 letters on the eye chart in all four study groups. Most of the improvement occurred during the first six months. Monthly injections of Avastin and Lucentis produced the same visual improvement. Lucentis given as needed was equivalent to Avastin given as needed and Lucentis given monthly. The comparison of monthly Avastin with as-needed Avastin was inconclusive.
  - Both drugs resulted in substantial reductions in central retinal thickness, but monthly Lucentis produced a greater decrease than the other groups. Although these differences in anatomy had no impact on vision at one year, the long-term implications are not known.
  - No significant differences in ophthalmic adverse events were noted between the two drugs. The study detected no differences in relatively rare events such as death, heart attacks, and stroke, which had been a concern when Avastin was used intravenously for cancer treatment.
-

- 
- However, when the dosing-regimen groups were combined, patients in the Avastin groups had higher rates of adverse events (24%), primarily hospitalizations, than the Lucentis groups (19%). The hospitalizations were not for conditions identified with Avastin in cancer trials involving patients who received intravenous doses 500 times those used in intraocular injections. Further, the as-needed groups, which had fewer doses of the drug, had higher rates of adverse events than the monthly groups.
  - The as-needed groups averaged 6.9 injections of Lucentis and 7.7 injections of Avastin. The average drug cost per patient was \$385 for the Avastin as-needed group, \$595 for the Avastin monthly group, \$13,800 for the Lucentis as-needed group, and \$23,400 in the Lucentis monthly group.

---

### ***At two years, both Avastin and Lucentis produced dramatic improvements in vision***

At two years, the CATT study confirmed that Avastin and Lucentis had similar and substantial effects on visual acuity when the dosing regimen was the same. At two years, two-thirds of patients had driving vision (20/40 vision or better).

- Most of the change in visual acuity occurred during the first year, with very little change during the second. The anatomic differences observed in the first year persisted in the second year.
- As-needed dosing resulted in 10 fewer eye injections over the two-year period than monthly dosing. However, as-needed dosing of either drug produced slightly less gain in visual acuity, whether instituted at enrollment or after one year of monthly treatment. This slight difference amounted to an average of 2.4 letters (half a line) gained on the eye chart.
- The number of eye complications, deaths, strokes and heart attacks were similar for all groups. The rates of serious adverse events remained higher in the combined Avastin groups (40%) than the Lucentis groups (32%). The greatest difference was in gastrointestinal disorders, which has been an area of concern in previous studies of intravenous Avastin. But even when all events known to be associated with Avastin were excluded, most of the imbalance remained.
- The two-year drug cost per patient ranged from \$705 in the Avastin as-needed group, \$1,170 in the monthly Avastin group, \$25,200 in the Lucentis as-needed group and \$44,800 in monthly Lucentis group.

---

### ***POLICY IMPLICATIONS***

These results confirm the dramatic and lasting improvement in vision that both Avastin and Lucentis provide for AMD patients. In that context, this comparative effectiveness study provides patients and clinicians with evidence upon which to base their treatment decisions.

- In 2010, Lucentis accounted for nearly 10% of the entire Medicare Part B drug budget, its single largest expenditure at \$1.1 billion. Medicare beneficiaries face a \$400 copayment for each dose of Lucentis, compared to an \$11 copayment for Avastin. As treatment for AMD continues indefinitely, the financial impact will also continue. The choice of drug and dosing regimen must balance the comparable effects on vision, the possibility of true differences in adverse events, and the 40-fold difference in cost per dose between Avastin and Lucentis.
- Patients and clinicians now have better data upon which to base decisions about dosing regimens. Patients can weigh the risks and benefits of monthly versus as-needed treatments, and decide whether the small gain in vision is worth 10 extra injections over two years.

---

*Continued on back.*

## POLICY IMPLICATIONS

Continued

- The higher rate of adverse events in Avastin groups, without a typical dose-response relationship and in organ systems not targeted by the drug, remains unexplained. It may be that the difference was the result of chance, unobserved differences in the groups at baseline, or truly higher risk. Results from ongoing trials worldwide may provide additional insight into the risk of Avastin relative to Lucentis.
- This study exemplifies how CER can identify clinical inefficiencies and promote cost-effective care. Further, it highlights the importance of public funding of such studies in cases when a drug manufacturer has an economic disincentive to investigate the use of an existing drug for new purposes.

*This Issue Brief is based on the following articles: Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group Writing Committee: D.F. Martin, M.G. Maguire, S.L. Fine, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology, in press, available online May 1, 2012, <http://dx.doi.org/10.1016/j.ophtha.2012.03.053>; CATT Research Group Writing Committee: D.F. Martin, M.G. Maguire, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine, May 19, 2011, vol. 364, pp. 1897-1908; D. F. Martin, M.G. Maguire, S.L. Fine. Identifying and eliminating roadblocks to comparative-effectiveness research. New England Journal of Medicine, July 8, 2010, vol. 363, pp. 105-107.*

*Published by the Leonard Davis Institute of Health Economics, University of Pennsylvania, 3641 Locust Walk, Philadelphia, PA 19104.*

*Janet Weiner, MPH, Associate Director for Health Policy, Editor*

*David A. Asch, MD, MBA, Executive Director*

Visit us on the web at <http://ldi.upenn.edu>

*Issue Briefs synthesize the results of research by LDI's Senior Fellows, a consortium of Penn scholars studying medical, economic, and social and ethical issues that influence how health care is organized, financed, managed, and delivered in the United States and internationally. The LDI is a cooperative venture among Penn schools including Medicine, Nursing, Dental Medicine, Communication, Law, and Wharton, and the Children's Hospital of Philadelphia. For additional information on this or other Issue Briefs, contact Janet Weiner (e-mail: [weinerja@mail.med.upenn.edu](mailto:weinerja@mail.med.upenn.edu); 215-573-9374).*

© 2012 Leonard Davis Institute

Published by the  
Leonard Davis Institute  
of Health Economics  
University of Pennsylvania

## Issue Brief



3641 Locust Walk  
Philadelphia, PA 19104-6218  
215.898.5611  
fax 215.898.0229  
ADDRESS CORRECTION REQUESTED

Nonprofit Organization  
U.S. Postage  
PAID  
Permit No. 2563  
Philadelphia, PA 19104