JAMA Ophthalmology | Brief Report

Evaluating Effects of Switching Anti–Vascular Endothelial Growth Factor Drugs for Age-Related Macular Degeneration and Diabetic Macular Edema

Frederick L. Ferris III, MD; Maureen G. Maguire, PhD; Adam R. Glassman, MS; Gui-shuang Ying, PhD; Daniel F. Martin, MD

IMPORTANCE When a patient with neovascular age-related macular degeneration or diabetic macular edema does not respond to an initial anti–vascular endothelial growth factor agent, usually after several injections, ophthalmologists may switch to another anti–vascular endothelial growth factor agent. Authors of case series have suggested beneficial effects from switching. However, to our knowledge, there are no studies with an appropriate control group to evaluate how such patients would do without switching agents.

OBJECTIVE To assess outcomes in patients who have a poor initial response but continue treatment without switching agents.

DESIGN, SETTING, AND PARTICIPANTS We obtained data from 2 multicenter clinical trials, the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Diabetic Retinopathy Clinical Research Network (DRCR.net). Based on typical clinical reasons for switching agents, we developed "switching rules" at both 3 and 6 months after initiation of treatment. Using these switching rules, we identified a 3-month and a 6-month cohort of "treatment failures" from both CATT and DRCR.net studies.

INTERVENTIONS Although the cohorts from each study met criteria for switching, they were treated with the initial agent throughout the study (bevacizumab or ranibizumab in CATT and ranibizumab in DRCR.net).

MAIN OUTCOMES AND MEASURES Primary outcomes were change in visual acuity and change in central retinal thickness on optical coherence tomography from the 3- or 6-month visit at which switching rules were met.

RESULTS The 126 patients from CATT and the 59 patients from DRCR.net who were selected for the switching analysis were similar in age, sex and race/ethnicity to the overall study populations. Among the participants who met the criteria for switching, the CATT participants were a mean (SD) of 79.7 (7.8) years of age, 65.9% women, and 97.6% white, while the DRCR.net participants were a mean (SD) of 65.5 (9.3) years of age, 44.1% women, and 76.3% white In all 4 cohorts, there was a 3- to 5-letter improvement in mean visual acuity over the 3 months after the switching rules were met, although all patients continued on their originally assigned treatment. Mean central retinal thickness also improved by 40 to 70 μM.

CONCLUSIONS AND RELEVANCE These results demonstrate the importance of having a comparison group to evaluate the effect of switching anti–vascular endothelial growth factor agents for treatment of neovascular age-related macular degeneration or diabetic macular edema. Without a comparison group, it is impossible to know whether any improvement observed after switching was related to the new treatment or was related to regression to the mean and time effects as observed in the 4 cohorts presented here. Randomization to switching or not switching drugs would provide a basis for valid conclusions about the effects of switching.

JAMA Ophthalmol. 2017;135(2):145-149. doi:10.1001/jamaophthalmol.2016.4820
Published online December 22, 2016.

Author Affiliations: National Eye Institute, National Institutes of Health, Bethesda, Maryland (Ferris); Department of Ophthalmology, University of Pennsylvania, Philadelphia (Maguire, Ying); Jaeb Center for Health Research, Tampa, Florida (Glassman); Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio (Martin).

Corresponding Author: Adam R. Glassman, MS, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (drcrstat2@jaeb.org).

Intravitreous anti–vascular endothelial growth factor (VEGF) agents (bevacizumab, ranibizumab, and aflibercept) are effective for the treatment of neovascular age-related macular degeneration and diabetic macular edema. However, there are large variations in the treatment responses across patients, and some patients do not respond well to treatment. The decision regarding which anti-VEGF agent to initiate treatment is based on several factors including efficacy and cost. When a patient does not respond to the initial anti-VEGF agent, usually after several monthly injections, ophthalmologists may switch to another anti-VEGF agent. In the last several years, a spate of articles have been published extolling the beneficial effects of switching anti-VEGF agents for intravitreous treatment of neovascular age-related macular degeneration[1,2] and diabetic macular edema.[3,4] In general, the treating ophthalmologists in these studies changed treatment when they thought the original treatment was ineffective, although there are no consistent switching rules across studies. A serious problem with all of these case series reports is that they do not include a randomized control group. As such, it is impossible to compare the effect of switching with the effect of continuing the original treatment. The assumption is that if treatment with 1 anti-VEGF agent failed to achieve the desired success over a period of 3 or more months, further treatment with that same anti-VEGF agent is futile. Data from both the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Diabetic Retinopathy Clinical Research Network

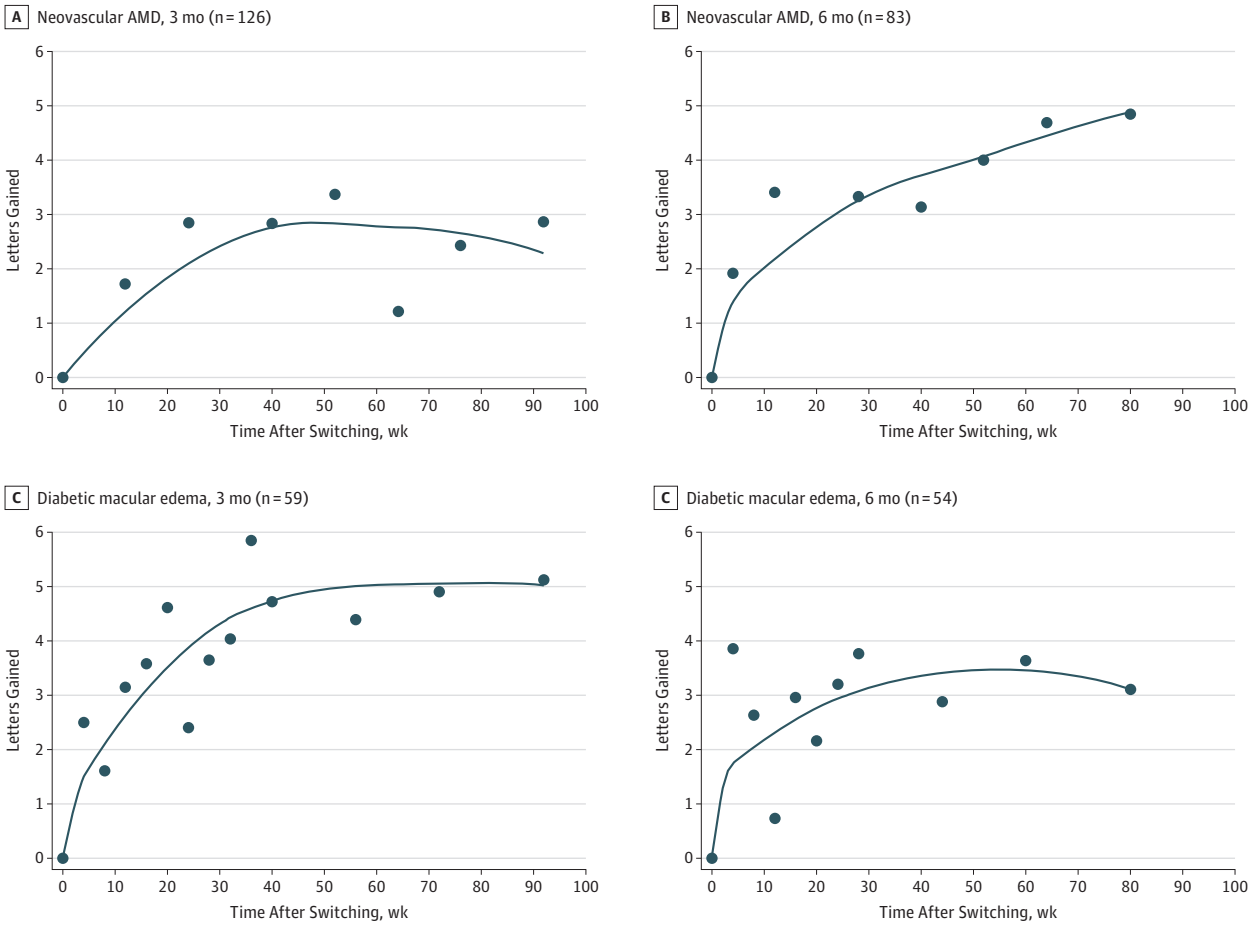
Key Points

Question In studies of effects of switching anti–vascular endothelial growth factor agents after poor initial response, can it be assumed that there will be no future improvement if there is no switching?

Findings In eyes meeting criteria for switching but maintained on the original agent, improvements in visual acuity and retinal thickness were observed.

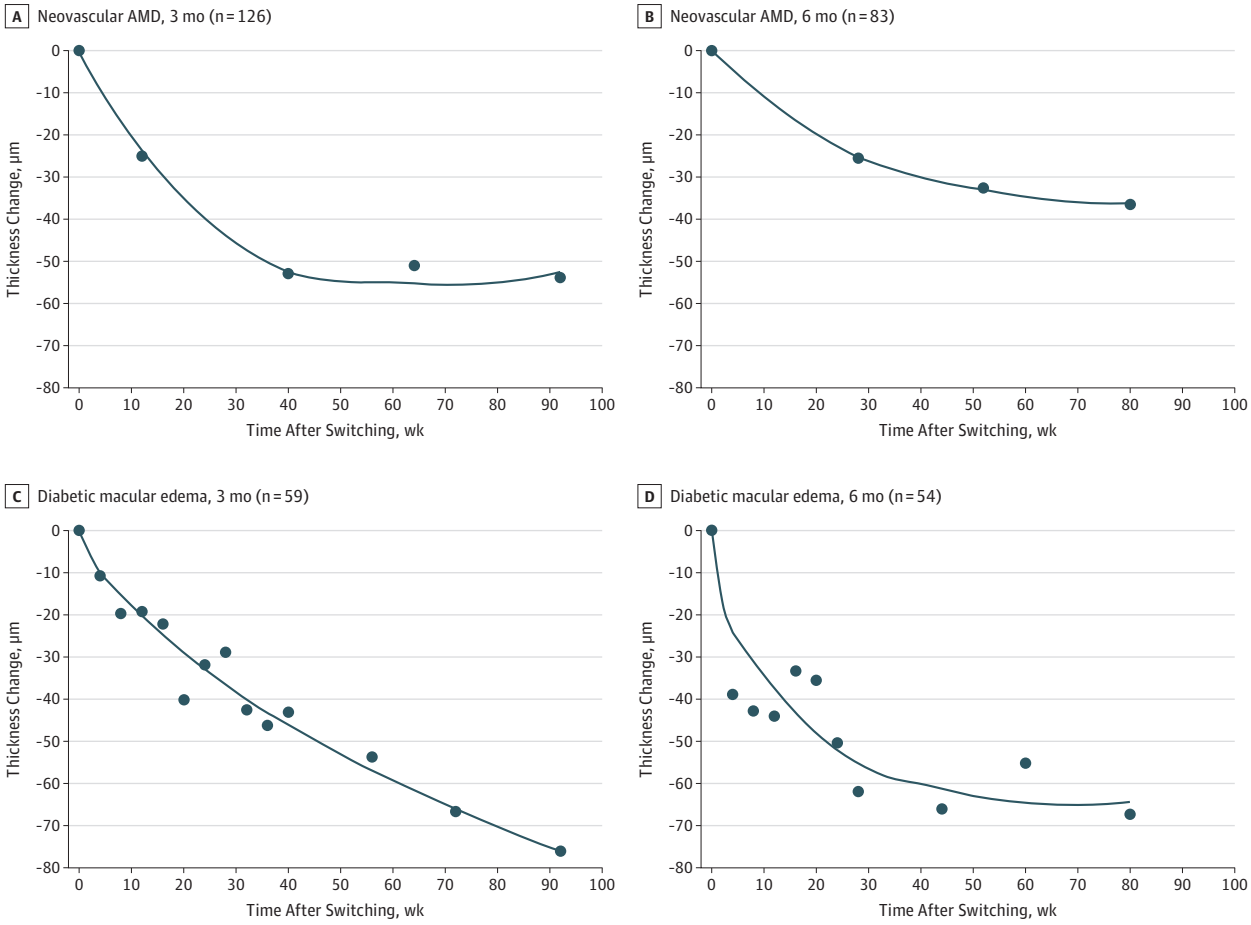
Meaning A control group maintained on the original agent should be included in studies of switching agents to make valid conclusions.

Figure 1. Mean Visual Acuity Change After Switching



Scatterplots with the locally weighted scatterplot smoothing line for mean change in visual acuity from the time point when switching rules were met at 3 months and 6 months in the Comparison of Age-Related Macular Degeneration Treatments Trials and Diabetic Retinopathy Clinical Research Network studies. AMD indicates age-related macular degeneration.

Figure 2. Mean Change in Central Retinal Thickness After Switching



Scatterplots with the locally weighted scatterplot smoothing line for mean change in central retinal thickness from the time point when switching rules were met at 3 months and 6 months in the Comparison of Age-Related Macular Degeneration Treatments Trials and Diabetic Retinopathy Clinical Research Network studies. AMD indicates age-related macular degeneration.

(DRCR.net) were used to investigate the degree to which early failure is a predictor of eventual outcome.[5,6]

Methods

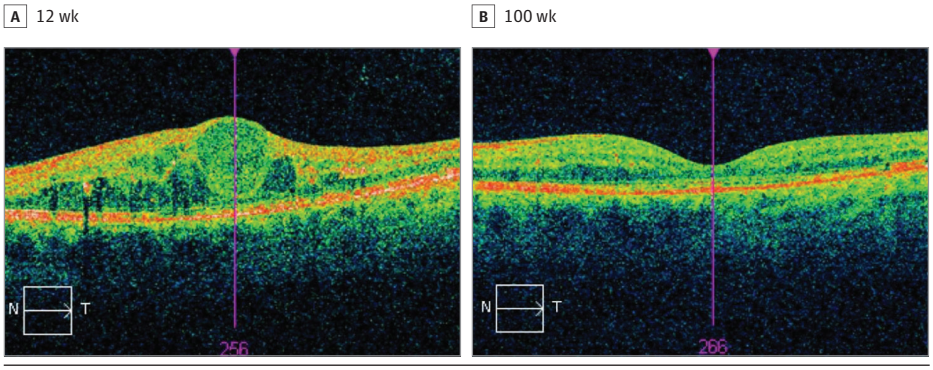
We investigated the clinical course of eyes that met typical criteria for switching treatment but did not have a change in treatment. Because CATT and DRCR.net participants continued receiving the same anti-VEGF agent throughout the studies, analyzing changes in visual acuity and retinal thickness in a cohort of eyes that met switching rules would provide some assessment of the likely clinical course in such eyes if the treatment remained unchanged. Based on typical clinical reasons for switching agents, we developed switching rules for both 3 months and 6 months after initiation of treatment. To meet the criteria for switching at 3 months or 6 months, an eye was required to meet all of the following criteria: persistent central retinal thickness on optical coherence tomography; visual acuity (VA) 20/40 or worse; 1-line gain or less in VA from baseline; and treatment with all planned injections at 3 months or at least 5 of 6 injections at 6 months.

Using these switching rules, we identified a 3-month and a 6-month cohort of "treatment failures" from both CATT and DRCR.net studies.[5,6] The protocols for both of these studies were approved by the institutional review board associated with each participating center, and all participants provided written informed consent. In CATT, 126 of the 1185 patients (11%) qualified for switching at 3 months and 83 patients (7%) did so at 6 months. In DRCR.net, 59 of the 361 patients (16%) qualified for switching at 3 months and 54 patients (15%) did so at 6 months.

Results

The mean changes in VA in each of these 4 cohorts during the year and a half following the time when the switching criteria were met are presented in **Figure 1**. In these 4 cohorts, there was a 3- to 5-letter improvement in mean VA

Figure 3. Selected Example of Dramatic Change in Central Retinal Thickness After Not Switching Agents



Example Diabetic Retinopathy Clinical Research Network eye, showing dramatic decrease in retinal thickening between 3 months and 2 years without switching anti-vascular endothelial growth factor agents at 3 months.

during the 3 months after the switching rules were met, although all study participants continued their originally assigned treatment (bevacizumab or ranibizumab in CATT and ranibizumab in DRCR.net). This improvement in VA is greater than that reported in numerous case series, where typically the VA change ranged from no change to 5-letter improvement after switching treatment, exemplified by the previously cited studies.[1-4]

We also evaluated the mean change in central retinal thickness from the point of switching for the 4 cohorts (**Figure 2**). The measurement of central retinal thickness was at the retinal center point in CATT and was for the central subfield in DRCR.net. As with VA, there was improvement with continued treatment over time, with a mean 40- to 70-μM reduction in central retinal thickness from the time the switching rules were met. Again, these results are similar to previously reported results after switching to another anti-VEGF agent.

The positive effect of switching anti-VEGF agents may be illustrated by the selected presentation of dramatic cases. As seen in **Figure 3**, dramatic decreases in retinal thickness between 3 months and 1 year also may be achieved without switching anti-VEGF agents.

Discussion

These results demonstrate why it is important to have a comparison group to evaluate the effect of switching anti-VEGF agents for treatment of neovascular age-related macular degeneration or diabetic macular edema. Switching agents after a longer period of poor response or outside of the protocols for follow-up and treatment evaluation of multicenter clinical trials may have results different than those observed in these 4 cohorts. However, without a comparison group, it is impossible to know whether any improvement observed after switching is related to the new treatment or is related to regression to the mean or to time effects, as observed in the cohorts presented here. Randomization to switching or not switching drugs would provide a basis for valid conclusions about the effects of switching.

Limitations

The main limitation of this study is that it is presented for demonstration purposes only. We have no data on rates of change in patients who switch treatments. However, we purposely chose 2 different diseases to demonstrate the need for a comparison group when assessing the effect of switching treatments.

Conclusions

These results demonstrate the importance of having a comparison group to evaluate the effect of switching anti-VEGF agents for treatment of neovascular AMD or diabetic macular edema. Without a comparison group, it is impossible to know whether any improvement observed after switching was related to the new treatment or was related to regression to the mean and time effects as observed in the 4 cohorts presented here.

ARTICLE INFORMATION

Accepted for Publication: October 18, 2016.

Published Online: December 22, 2016. doi:10.1001/jamaophthalmol.2016.4820

Author Contributions: Mr Glassman and Dr Maguire had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ferris, Maguire, Glassman, Martin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ferris, Glassman, Martin.
Critical revision of the manuscript for important intellectual content: Ferris, Maguire, Ying, Martin.
Statistical analysis: Maguire, Glassman, Ying.
Obtained funding: Maguire, Martin.
Administrative, technical, or material support: Ferris.
Supervision: Ferris, Maguire.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Maguire reports grants and fees from the National Institutes of Health and Genentech/La Roche. Mr. Glassman reports grants from the National Institutes of Health, Genentech/Roche, and Regeneron. Dr Ying reports grants and payments from the National Institutes of Health; Janssen Research and Development, LLC; and Chengdu Kanghong Biotech Co, Ltd. Dr Martin reports a grant from the National Institutes of Health. No other disclosures were reported.

Funding/Support: Comparison of Age-Related Macular Degeneration Treatments Trials was supported by cooperative agreements EY017823, EY017825, EY017826, EY017828, EY023689, and R21EY023689 from the National Eye Institute, National Institutes of Health, and the US

Department of Health and Human Services. Diabetic Retinopathy Clinical Research Network was supported by cooperative agreements EY14231, EY23207, and EY18817 from the National Eye Institute and the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, and the US Department of Health and Human Services.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Ciulla TA, Hussain RM, Ciulla LM, Sink B, Harris A. Ranibizumab for diabetic macular edema refractory to multiple prior treatments. *Retina*. 2016;36(7):1292-1297.

2. Heussen FM, Shao Q, Ouyang Y, Joussen AM, Müller B. Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(6):909-915.

3. Lim LS, Ng WY, Mathur R, et al. Conversion to aflibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab. *Clin Ophthalmol*. 2015;9:1715-1718.

4. Moisseiev E, Katz G, Moisseiev J, et al. Switching treatment for neovascular age-related macular degeneration from bevacizumab to ranibizumab: who is likely to benefit from the switch? *Retina*. 2015;35(7):1323-1330.

5. Elman MJ, Aiello LP, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064-1077.e35.

6. Ying GS, Maguire MG, Daniel E, et al; Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group. Association of baseline characteristics and early vision response with 2-year outcomes in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology*. 2015;122(12):2523-31.e1.