AMERICAN ACADEMY™
OF OPHTHALMOLOGY

UK Age-Related Macular Degeneration Electronic Medical Record System (AMD EMR) Users Group Report IV

Incidence of Blindness and Sight Impairment in Ranibizumab-Treated Patients

Robert L. Johnston, FRCOphth,[1,] Aaron Y. Lee, MD, MSCI,[2,3*] Miranda Buckle, MB BChir,[5] Richard Antcliff, MD, FRCOphth,[4] Clare Bailey, MD, FRCOphth,[5] Martin McKibbin, FRCOphth,[6] Usha Chakravarthy, MD, PhD,[7] Adnan Tufail, MD, FRCOphth,[3] on behalf of the UK AMD EMR Users Group*

Purpose: To study the incidence of blindness and sight impairment in treatment-naive patients receiving ranibizumab (Lucentis) for neovascular age-related macular degeneration (nAMD) in the United Kingdom (UK) National Health Service.

Design: Multicenter nAMD database study.

Participants: A total of 11 135 patients who collectively received 92 976 treatment episodes to 12 951 eyes.

Methods: Data were extracted from 14 UK centers using the same electronic medical record system (EMR). The EMR-mandated collection of a data set (defined before first data entry) including: age, Early Treatment Diabetic Retinopathy Study visual acuity letter score (VA) for both eyes at all visits, and injection episodes. Participating centers used overwhelmingly a pro re nata re-treatment posology at intended monthly follow-up visits following a loading phase of 3 monthly injections.

Main Outcome Measures: Incidence of blindness and sight impairment (VA in the better-seeing eye $<$38 letters [$\leq$20/200 Snellen, approximately], and $<$68 letters [$\leq$20/50 Snellen, approximately] at 2 consecutive visits, or 1 visit if no further follow-up data) in each year after initiating treatment.

Results: Information from $>$300 000 clinic visits (2.8 million data points) collected over 5 years was collated from 14 centers. Mean age at first treatment was 79.7 years (standard deviation = 9.19 years), with a female preponderance (63%). The mean (median) VA at baseline in the better-seeing eye was 67.2 (72.0) letters, 20/40− (20/40+) approximate Snellen conversion. The cumulative incidence of new blindness and sight impairment in patients with treated nAMD in at least 1 eye at years 1 to 4 after first injection were 5.1%, 8.6%, 12% and 15.6% for new blindness and 29.6%, 41.0%, 48.7%, and 53.7% for new sight impairment, but with significant reductions in the rates between year cohorts initiating treatment (blindness [$P = 4.72 \times 10^{-08}$], sight impaired [$P = 3.27 \times 10^{-06}$]).

Conclusions: To the best of our knowledge, this is the first multicenter real-world study on the incidence of blindness and sight impairment based on VA data in patients treated with ranibizumab for nAMD, and its results show low incidences of both blindness and sight impairment, which both declined during the study period. *Ophthalmology 2016;■:1−7 © 2016 by the American Academy of Ophthalmology*

Neovascular age-related macular degeneration (nAMD) is the leading cause of blindness in the United States, the United Kingdom (UK), and other developed countries, accounting for two-thirds of new cases of blindness in the elderly population and between 50% and 60% of new cases of blindness overall.[1−5]

The pivotal studies Anti−Vascular Endothelial Growth Factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[6] and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[7] demonstrated that ranibizumab (Lucentis) improves the mean visual acuity letter score (VA) at 2 years when given at monthly intervals in eyes with subfoveal nAMD.

Clinical trial data are, however, of limited use for providing a prognosis for patients, as the exclusion of second treated eyes means there is a paucity of evidence of the benefits that inhibitor of vascular endothelial growth factor

http://dx.doi.org/10.1016/j.ophtha.2016.07.037
ISSN 0161-6420/16

(anti-VEGF) treatments are delivering on a population level to reduce blindness and other degrees of visual impairment, which is determined by the patient's better-seeing eye.

When assessing the value of expensive new treatments, particularly in cash-limited health care economies, it is essential to quantify the clinical outcomes at the patient level rather than eye level and to understand the benefits on all VA states, not just the impact on blind and partial sight registration.

In the UK, the National Institute for Health and Care Excellence[8] approved the use of ranibizumab in August 2008, leading to almost exclusive usage of ranibizumab for nAMD in the UK National Health Service (NHS) for the following 5 years. In contrast to the pivotal studies, in routine clinical practice in the UK, ranibizumab therapy was administered almost universally as a loading phase of 3 injections given at monthly intervals followed by pro re nata treatment if active disease is detected at intended monthly assessment visits.[9]

A temporal and causative relationship has been noted between the widespread introduction of anti-VEGF drugs and a decrease in blindness registration caused by nAMD.[10–13] The incidence of blindness and partial sightedness in England and Wales has traditionally been estimated from the annual number of patients newly certified but the limitations of such data have been demonstrated repeatedly, with some studies showing that fewer than 50% of eligible patients are actually registered.[4,14–16]

The aim of this study was to use VA data, routinely and prospectively collected within electronic medical record systems (EMRs) at multiple sites across the UK, to analyze the real-world incidence of blindness and other degrees of visual impairment in patients receiving anti-VEGF injections for nAMD.

Methods

The methods involved in this study were thoroughly described in the first paper of the series[9] and are summarized briefly below:

Study Design

Anonymized data were remotely extracted from 14 centers using the same EMR (Medisoft Ophthalmology, Medisoft Limited, Leeds, UK) in April 2012. The lead clinician and Caldicott guardian (who oversees data protection) at each center gave written approval for the anonymized data extraction, and on this basis, formal ethics approval was not required. This study was conducted in accordance with the Declaration of Helsinki and the UK's Data Protection Act.

Settings

Fourteen NHS hospitals that deliver AMD treatment services in England and Northern Ireland submitted data to this study. Each site is the only NHS provider of nAMD care to their local population, and very few patients switch between providers or access care privately. All sites used ranibizumab almost exclusively during the study period to treat nAMD, from 2008, after approval from the National Institute for Health and Care Excellence, until data extraction in 2012. As only 163 patients received bevacizumab at any point in the follow-up, they were excluded. All sites used an overwhelmingly pro re nata re-treatment regimen at intended monthly follow-ups after a loading phase of 3 monthly injections.

Follow-up

For all patients, data were collected from the time of the first injection of ranibizumab in either eye to April 2, 2012. A number of patients were lost to follow-up, but it was not possible within the framework of this study to determine the cause of loss to follow-up. A previous article in this series explored the potential impact of patients lost to follow-up.[9]

Analysis

Analysis was restricted to treatment-naive NHS patients undergoing only ranibizumab monotherapy for nAMD. Patients who underwent combined therapies or who received bevacizumab in either eye at any time were excluded (n = 163 eyes). The mode of data entry into the EMR varied slightly between sites. At all sites, the collection of demographic data (age, gender, and ethnicity) was dependent on automatic download from the hospital's patient administration system to the EMR, and therefore the completeness of these variables was not under the control of the EMR. When the EMR was used optimally, assessment data from the preinjection, injection procedure, and follow-up were entered live directly into the EMR as an integral part of routine clinical care by all members of staff. Many sites ran entirely paperless clinics.

Although this study is retrospective, the data set was defined before the date of first data collection into the study. The EMR-mandated data fields were defined prospectively, in a manner similar to that of the electronic case-report forms used in clinical trials but with the data captured as a by-product of routine clinical care. Data collected at all sites included VA for both eyes (and the method of measurement) and treatment data, if treatment was required, with procedure details and mandatory reporting of the presence or absence of complications.

Data Sources and Measurements

In this report, the best-measured VA was mostly the best VA with habitual correction, if worn, and was measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score chart. Only a few sites measured a refracted best-corrected VA at baseline and at follow-up visits. When VA was recorded as counting fingers, hand movements, and light perception, these scores were replaced with ETDRS letter values of −15, −30, and −50, respectively.

Blindness, using the United States (US) criteria, was defined as VA in the better-seeing eye of 38 ETDRS letters or fewer and *sight impairment* as VA in the better-seeing eye of 68 letters or fewer at 2 or more consecutive visits or at 1 visit if no further data were recorded.[17] An even lower criterion of 25 letters was also evaluated.

Statistical Methods

Data were extracted from the EMR for both eyes of patients who had had at least 1 intravitreal injection of ranibizumab for nAMD. All statistics were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Results

Participants

The 14 sites entered their first treatment episodes into the EMRs during the following years: 2006 (2 sites), 2007 (5 sites), 2008 (4 sites), 2009