EDITORIAL

A clearer view of evidence in treating macular degeneration: off-label policies and independent research

Giulio Formoso, Anna Maria Marata, Nicola Magrini, Lisa Bero

Cochrane Database of Systematic Reviews 2014;(9):ED000090 **https://doi.org/10.1002/14651858.ED000090**

Publication date: 15 September 2014

In February 2014 the Italian Antitrust Authority (IAA) fined Roche and Novartis a combined total of EUR 182.5 million for "cartelizing the sales of two major ophthalmic drugs".[1][2] An appeal is pending. The IAA issued a decision finding that the two companies "colluded to exclude the cheap drug Avastin" (bevacizumab, a Roche drug) used off-label in age-related macular degeneration (AMD) and "channel demand towards the much more expensive drug Lucentis" (ranibizumab, commercialised by Novartis in the EU). Roche owns the mother firm of both drugs (Genentech), and so it has a commercial interest in ranibizumab too, receiving royalties from Novartis.

Both drugs are monoclonal antibodies that inhibit vascular endothelial growth factor (VEGF). Bevacizumab was first approved in 2004 in the United States as a treatment for colorectal cancer. Soon after, bevacizumab gained popularity as an off-label treatment of the pathological neoformation of blood vessels in AMD using intravitreal injections with doses 400 to 500 times lower than in oncology. Although there were no randomised controlled trials (RCTs) testing the efficacy of the drug for that indication, there was also a lack of effective treatments at that time.[3] Ranibizumab is structurally related to bevacizumab and was specifically conceived for intravitreal use. Its registration for the treatment of AMD (in 2006 in the United States and in 2007 in the EU) was supported by two RCTs, comparing the drug with sham injections and with laser therapy, respectively.[3] The drug was priced at about USD 2000 per injection, which is about the same cost of 40 injections of bevacizumab.

This sharp difference in price led to the design of two head-to-head RCTs, supported by the US National Institutes of Health and the UK National Health Service programme.[4][5] They were soon followed by seven other independent RCTs in six other countries.[6] These trials showed that bevacizumab and ranibizumab were similarly effective (in terms of visual acuity). Although not powered to show differences in adverse events, the studies did not suggest a different safety profile between the two drugs. The CATT trial (mean age: 79 years) was the exception: borderline higher rates of hospitalisations for any cause occurred in the bevacizumab group. Surprisingly, these results were in patients taking the drug 'as needed' rather than by monthly administration, where exposure would have been higher.[4]

Guidelines consider bevacizumab as a possible therapeutic option in AMD, provided that patients are informed of its off-label status and that they give their consent.[7][8] The World Health Organization (WHO) also included the off-label use of bevacizumab in AMD in its Essential Medicines List in April 2013.[9]

In most EU countries reimbursement for intravitreal bevacizumab has been difficult due to off-label legislation; in Italy, off-label uses were only allowed for drugs included in a specific list and until recently were forbidden when a registered product was available. The Italian Medicines Agency (AIFA) initially added bevacizumab to the off-label list but deleted it for use in AMD when ranibizumab was registered. Bevacizumab was then excluded from the list for all other off-label uses in 2012, following the introduction of warnings in its summary of product characteristics, despite the same safety information (defined as 'product-class-related adverse reactions') being included in the summary of product characteristics for ranibizumab.[10][11] Following the IAA decision, a law permitting off-label use of drugs when comparative safety and effectiveness are adequately demonstrated was approved in Italy in June 2014,[12] and bevacizumab was re-listed as a therapeutic option for AMD. In July 2014, the French National Assembly passed a law opening up the possibilty of using bevacizumab in AMD.[13] These decisions are consistent with recommendations in guidelines,[7][8] and with the WHO's inclusion of the drug in its Essential Medicines List, which includes drugs of demonstrated public health importance showing a favourable benefit-risk profile, even if the specific indications have not been approved by regulatory authorities.[9]

In the absence of any commercially sponsored studies comparing the effectiveness and safety of the two drugs, independently conducted research was crucial. This question is relevant for public health, considering the relatively high prevalence of AMD, a pathology that affects more than 3% of people over 65,[14] and the affordability of treatments. In the US, for example, switching to bevacizumab could result in savings of up to $18 billion over 10 years.[15] In Italy, doubts about the safety of bevacizumab led the Emilia-Romagna region, a third payer and one of the plaintiffs in the Antitrust proceeding, to commission an independently conducted systematic review to be published by Cochrane.[6] This review, involving a multidisciplinary and multinational

team of ophthalmologists, epidemiologists, statisticians and pharmacists, working closely with the Cochrane Eyes and Vision Group, found low- or moderate-quality evidence of no difference between the two drugs. Specifically, using random-effects models, the estimated risk ratio (RR) of bevacizumab compared with ranibizumab was 1.10 for death (95% confidence interval (CI) 0.78 to 1.57) and 1.08 for all serious systemic adverse events (SSAEs; 95% CI 0.90 to 1.31). Among secondary outcomes, bevacizumab showed a higher risk of gastrointestinal disorders (RR 1.82; 95% CI 1.04 to 3.19, corresponding to a slight absolute increase of 1.3%) but not of gastrointestinal perforation. No differences were found for either myocardial infarction (RR 0.84; 95% CI 0.42 to 1.66) or stroke (RR 0.83; 95% CI 0.42 to 1.66).

This story highlights the crucial role of independent research in producing relevant evidence for decision-makers on the safety and effectiveness of affordable health interventions. The evidence base would be further strengthened by head-to-head randomised comparisons between alternative treatments, and by observational data from large databases capturing clinically relevant events. The overall assessment of available evidence is key: the Cochrane Review by Moja and colleagues is a good example of a timely and rapidly conducted systematic review to support regulatory bodies in their decision-making. This strategy could help to underpin more efficient allocation of resources for universal access to cost-effective treatments.

Author Information

Giulio Formoso[1], Anna Maria Marata[1], Nicola Magrini[1,2], Lisa Bero[3]

[1]Drug Evaluation Area, Regional Agency for Health and Social Care, Bologna, Italy. [2]Essential Medicines List Secretariat, Essential Medicines and Health Products Department, World Health Organization, Geneva, Switzerland. [3]Medicines Use and Health Outcomes, Faculty of Pharmacy and Charles Perkins Centre, University of Sydney, Australia

Declarations of interest

The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request). GF works for the Emilia-Romagna (ER) Region, in the Drug Evaluation Area of the Health and Social Care Agency and in the secretariat of the regional Drug and Therapeutics Committee. AMM works for the Emilia-Romagna Region, as temporary head of the Drug Evaluation Area of the Health and Social Care Agency and head of the regional Drug and Therapeutics Committee. NM works for the Emilia-Romagna Region, as head of the Drug Evaluation Area of the Health and Social Care Agency; he is also temporarily working in the WHO Essential Medicines and Health Products Department. LB was chair of the WHO Essential Medicines List at the time that bevacizumab was listed. The Emilia-Romagna Region was one of the plaintiffs of the IAA proceeding and has funded the Cochrane Review. Although it is opportune to acknowledge these circumstances, they have not influenced the reporting of facts (which have not been commented) related to the IAA sentence, nor the reporting of the results of the Cochrane Review. Comments on the latter were focused on the relevance of independent research to support regulatory bodies and health care decision-making, and not on recommending any therapeutic choice for age-related macular degeneration. The Emilia-Romagna Region had no role in developing the Cochrane Review or this related editorial. The authors declare no other conflicts.

Provenance and peer review

This editorial was commissioned and was not externally peer reviewed.

References

1. Italian Competition Authority. Pharmaceuticals and antitrust: the Italian Competition Authority fines Roche and Novartis over Eur 180 million for cartelizing the sales of two major ophthalmic drugs, Avastin and Lucentis. www.agcm.it/en/newsroom/press-releases/2106-i760-pharmaceuticals-and-antitrust-the-italian-competition-authority-fines-roche-and-novartis-over-eur-180-million-for-cartelizing-the-sales-of-two-major-ophthalmic-drugs-avastin-and-lucentis.html (accessed 10 September 2014).

2. Italian Competition Authority. Proceedings of the Italian Competition Authority against Roche and Novartis. www.agcm.it/stampa/news/6799-farmaci-antitrust-sanziona-roche-e-novartis-per-un-cartello-che-ha-condizionato-le-vendite-dei-principali-prodotti-destinati-alla-cura-della-vista-avastin-e-lucentis-oltre-180-milioni-di-euro-di-multa.html [in Italian] (accessed 10 September 2014).

3. Epstein P. Trials that matter: two faces of progress in the treatment of age-related macular degeneration. *Annals of Internal Medicine* 2007;146:532–534. doi.org/10.7326/0003-4819-146-7-200704030-00011

4. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *New England Journal of Medicine* 2011;364(20):1897–908. doi.org/10.1056/NEJMoa1102673

5. IVAN study investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119(7):1399–411. doi.org/10.1016/j.ophtha.2012.04.015

6. Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular agerelated macular degeneration. *Cochrane Database of Systematic Reviews* 2014;(9):CD011230. doi.org/10.1002/14651858.CD011230.pub2

7. Royal College of Ophthalmologists. Age-related macular degeneration: guidelines for management. September 2013. www.rcophth.ac.uk/core/core_picker/download.asp?id=1851 (accessed 10 September 2014).

8. American Academy of Ophthalmology. Age-related macular degeneration summary benchmark – 2013. one.aao.org/summary-benchmark-detail/agerelated-macular-degeneration-summary-benchmark- (accessed 10 September 2014).

9. World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee, 2013. WHO technical report 985. apps.who.int/iris/bitstream/10665/112729/1/WHO_TRS_985_eng.pdf (accessed 10 September 2014)

 | https://doi.org/10.1002/14651858.ED000090
www.cochranelibrary.com

10. Roche. Summary of product characteristics: Avastin. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf (accessed 10 September 2014)

11. Novartis. Summary of product characteristics: Lucentis. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf (accessed 10 September 2014)

12. www.agenziafarmaco.gov.it/it/content/avastin-nella-lista-dei-farmaci-di-uso-consolidato-la-degenerazione-maculare-senile-0 (accessed 10 September 2014)

13. Ask M. Drug companies oppose moves to reimburse off-label medicine. Wall Street Journal, July 25 2014. online.wsj.com/articles/drug-companies-oppose-moves-to-reimburse-off-label-medicine-1406287000 (accessed 10 September 2014)

14. Augood CA, Vingerling JR, de Jong PTVM, Chakravarthy U, Seland J, Soubrane G, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). *Archives of Ophthalmology* 2006;124:529–35. doi.org/10.1001/archopht.124.4.529

15. Hutton D, Newman-Casey PA, Tavag M, Zacks D, Stein J. Switching to less expensive blindness drug could save Medicare Part B $18 billion over a ten-year period. *Health Affairs* 2014;33:931–9 doi.org/10.1377/hlthaff.2013.0832

 | **https://doi.org/10.1002/14651858.ED000090**
www.cochranelibrary.com