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LETTER TO THE EDITOR

The safety of bevacizumab and ranibizumab in clinical studies

Mauro De Rosa · Andrea Messori

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Abstract In comparing the safety of ranibizumab versus bevacizumab in age-related macular degeneration, the meta-analyses published thus far have given conflicting results, particularly about the risk of venous thrombotic events and ocular inflammation. From the comparison of the design and the findings of these meta-analysis, we tried to identify the potential explanations to account for these discrepancies. We separately evaluated the incidence of ocular inflammation with the two agents between randomized studies and non-randomized studies. While no increase in risk was found in randomized studies, non-randomized studies showed an increase in risk for bevacizumab versus ranibizumab. One interpretation of these findings is that bevacizumab itself does not represent any increase in risk of ocular inflammation and/or cardiovascular events under the rigorous conditions of a randomized study, but this agent can be at the origin of an increase in risk when administered in the "real world"; this setting could in fact leave space for less strictly controlled preparation of aliquots for intravitreal injection.

M. De Rosa (✉)
SIFACT, Società Italiana di Farmacia Clinica e Terapia (Italian Society of Clinical Pharmacy and Therapeutics), via Farini 81, 20100 Milan, Italy
e-mail: md3439@me.com

A. Messori
HTA Unit, ESTAV Toscana Centro, Regional Health Service, 50100 Florence, Italy

After the decision of the Italian Competition Authority to impose a fine on Novartis and Roche [1], the controversy about the risk–benefit and cost–benefit of Lucentis (ranibizumab) and off-label Avastin (bevacizumab) as treatments for age-related macular degeneration has attracted an enormous attention from the Italian media; this controversy has also been discussed within the Italian scientific community [2].

The debate in Italy has been stimulated by the simultaneous publication of the meta-analysis by Zhang and co-workers [3] and of another meta-analysis conducted by an Italian Cochrane Group [4], which was exclusively focused on systemic safety with no evaluation of ocular adverse effects. These two meta-analyses gave in fact opposite results (increased risk of ocular inflammation and, to a lesser extent, of venous thrombotic events according to the former; no difference in systemic safety between the two agents according to the latter), and so attempts to explain this discrepancy can be worthwhile. Another point that has been debated in Italy is the stability of galenic preparations of bevacizumab in syringes for intravitreal use; expiration times ranging from 2 days to 2 months have in fact be attributed to these syringes [5].

Within this conflicting context, one very simple interpretation of these two opposite results is that the Cochrane meta-analysis included only randomized studies, while the Zhang analysis included both randomized and non-randomized studies. In fact, if randomized and non-randomized studies are analyzed

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separately in the Zhang study, in the group of randomized studies there is no statistical difference between the two drugs; in contrast, there is a statistically significant difference in the group of non-randomized studies showing an increased risk for the two endpoints. This increase in risk is sufficiently large to influence the overall analysis of both randomized and non-randomized studies that consequently reaches the limit of statistical significance.

According to this interpretation, bevacizumab itself does not represent any increase in risk of ocular inflammation and/or cardiovascular events under the rigorous conditions of a randomized study, but this agent can be at the origin of an increase in risk when administered in the "real world" because this setting could leave space for less strictly controlled preparation of aliquots for intravitreal injection. Hence, careful attention should be given to the preparation practices.

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