·Letter to the Editor·

When important steps for a reliable Meta-analysis are missing: the bevacizumab versus ranibizumab case

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Dear Sir,

We have read with attention and interest the systematic review on the effectiveness and safety of bevacizumab and ranibizumab in the treatment of age-related macular degeneration (AMD) written by Zhang *et al*[1] and published on number of April 2014 of *International Journal of Ophthalmology*. The authors, who collected data from 4 randomized clinical trials (RCTs) and 11 observational studies, for a total number of more than 4000 patients, concluded that treatment effectiveness was similar, but ranibizumab was better tolerated than bevacizumab. For the outcome ocular inflammation the authors found a relative risk (RR) of 0.45 with 95% confidence interval (CI) of 0.23 to 0.89, and for venous thrombosis a RR of 0.27 (95% CI 0.08 to 0.89), in favour of ranibizumab over bevacizumab.

Here we report some methodological limitations that might have hampered the analysis.

OLD SEARCH

The search was limited to October 2012, which means excluding key randomized clinical trials such as multicenter anti- vascular endothelial growth factor (VEGF) trial in Austria (MANTA)[2] and French evaluation group avastin versus lucentis (GEFAL)[3], and including only the one-year follow-up of the inhibition of VEGF in a age related choroidal neovascularization study (IVAN)[4], a multicenter study conducted in the UK with a follow-up of two years.

FIXED- VERSUS RANDOM-EFFECTS

This systematic review combined the results from RCTs with those from observational studies. While some authors recommend excluding observational studies from meta-analyses, others advise to include them only when valid reasons exist (for example, lack of RCTs, power issues or inadequate length of follow-up of RCTs to observe the effect). In any case, the two groups of studies should generally be analysed in two separate meta-analyses[5]. However, if the decision is to combine RCTs and observational studies, then an appropriate and conservative analytical approach should be used, namely a random-effects analysis, which produces confidence intervals wider than a fixed-effect analysis, as a consequence of the high level of heterogeneity given by lumping together the two types of studies. In the case of the outcomes death from any cause and ocular inflammation, the authors used a fixed-effect analysis, although they combined together observational studies with RCTs.

REANALYZING DATA FOR OCULAR INFLAMMATION AND VENOUS THROMBOSIS

Re-analyzing the data for the outcome eye inflammation using a random-effects analysis produces a RR of 0.60 (95% CI 0.18 to 2.07), which is no longer statistically significant and clinically inconclusive. In addition, a sensitivity and influence analysis shows that the final results are strongly influenced by the Sharma *et al*'s study[6], an observational study which included a patient population without AMD, failed to adjust for potential confounders, and might have suffered from sponsorship bias. The exclusion of this study yields a RR of 0.91 (95% CI 0.37 to 2.25), again statistically not significant and clinically inconclusive. For these reasons, it is conservatively to assume the reduction in risk of ocular inflammation in favour of ranibizumab found by the authors of the systematic review is at least unreliable.

Regarding the outcome venous thrombosis, the result is due to the combination of two randomized clinical trials, comparison of age-related macular degeneration treatments trials (CATT)[7] and IVAN[8], the latter included with incomplete data because the search was not updated. Reviewing the risk of venous thrombosis using the updated data of IVAN[4], a RR of 0.43 (0.16 to 1.07) is obtained, once more statistically not significant and clinically inconclusive.

In conclusion, we believe that the results of this systematic review are misleading. We are concerned that policy makers, doctors and patients, without acknowledging all these methodological limitations, may take decisions on the basis of this review.

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