Identifying systemic safety signals following intravitreal bevacizumab: systematic review of the literature and the Canadian Adverse Drug Reaction Database

Micieli JA, Micieli A, Smith AF

CRD summary
This review concluded that the systemic risk of intravitreal bevacizumab to patients treated for ocular disease was low, but that included studies may be limited because of their methodology and small sample size. These conclusions, which acknowledged the limitations of the included studies, appear appropriate.

Authors' objectives
To evaluate systemic adverse events associated with intravitreal bevacizumab in patients with ocular disease.

Searching
MEDLINE (including MEDLINE in Process and other non-indexed citations), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1996 (1999 for CENTRAL) to October 2009. 'Bevacizumab' was searched as a key word. The Canadian Adverse Drug Reaction Information System Database was searched from 1965 to October 2009 for reports of adverse events. References of relevant review articles and included studies were screened. Websites of the major ophthalmology journals were handsearched. The review was restricted to English language studies.

Study selection
Clinical studies that evaluated systemic adverse events following intravitreal injection of bevacizumab alone or in combination for any ocular condition were eligible for inclusion. Studies had to report on at least 100 eyes injected with the drug. Published case reports that described a suspected systemic event following bevacizumab were also eligible.

In included studies, bevacizumab (dose 1.0 to 2.5mg) was administered to treat age-related macular degeneration, diabetic retinopathy, retinal vascular occlusion, central retinal vascular occlusion, and diabetic macular oedema. Some studies excluded patients with myocardial infarction, stroke, pregnancy, diabetic macular oedema, uncontrolled hypertension, or a history of thromboembolism. Mean age of participants ranged from 44 to 82 years (where reported). The number of injections ranged from one to 15 per patient; the time between injections ranged from one to 86 weeks.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not report a formal assessment of study quality.

Data extraction
Data were extracted on the number of patients with each systemic adverse event.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The number and proportion of patients with each adverse event was summed across studies.

Results of the review
Twenty-two studies (12,902 eyes, 12,699 patients) were included in the review. These comprised one international safety survey, six retrospective studies that assessed the safety of intravitreal bevacizumab, seven prospective clinical studies, and eight retrospective clinical studies. Six case reports (seven patients) were also included. The duration of follow-up ranged from one to 25 months.
The most common side effect was increased blood pressure which was reported in 59 patients (0.46% of all patients). Other reported adverse events were cerebrovascular accidents (27 patients), myocardial infarction (24 patients), transient ischaemic attack (five patients), deep vein thrombosis (one patient), angina (18 patients), renal disorder (12 patients), gastrointestinal bleeding (11 patients), skin rash/redness (two patients) and menstrual irregularity (three patients). There were 23 deaths (0.18%).

Case reports reported a papulopustular rash, a third and sixth nerve palsy, transient global amnesia, early loss of pregnancy, and metrorrhagia.

The Canadian Adverse Drug Reaction Information System Database yielded one report of a possible systemic adverse event in a older man (79 years) who experienced a number of adverse events, but he was also taking multiple other drugs.

**Authors' conclusions**
The international safety survey, retrospective reviews, and small clinical trials suggest that the systemic risk of bevacizumab was low. However, these studies may be limited because of their methodology and small sample size. The systemic events temporally associated with intravitreal bevacizumab were mainly of cardiovascular and neurological origin and could be predicted from an exaggerated pharmacology, although a causal association could not be established at the time of study.

**CRD commentary**
The review addressed a defined question supported by appropriately broad inclusion criteria. An extensive literature search was conducted which included attempts to find unpublished data, but restriction of the review to English language studies raised the possibility of language bias. Details on the review process were not reported, so it was not possible to determine whether appropriate steps were taken to minimise bias and errors.

Study quality was not formally assessed, so the reliability of the included studies was unclear. However, given the study designs included, they were likely to have suffered from methodological weaknesses. A mainly narrative synthesis, with some summing across studies, appeared appropriate given the type of data available in the included studies.

The authors' cautious conclusions, which acknowledged the small sample size and methodological limitations of the included studies, seem appropriate.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that there is a need for more active surveillance beyond ongoing Phase II trials to study the long-term safety of drugs in larger populations and future studies should better evaluate the effects of bevacizumab on blood pressure.

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