WORLD VIEW

The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide

A E Fung, P J Rosenfeld, E Reichel

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See end of article for authors' affiliations

Correspondence to: A E Fung, Pacific Eye Associates, 2100 Webster Street, Suite 214, San Francisco, CA 94115, USA; annefungmd@yahoo.com

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Aim: Off-label intravitreal injections of bevacizumab (Avastin) have been given for the treatment of neovascular and exudative ocular diseases since May 2005. Since then, the use of intravitreal bevacizumab has spread worldwide, but the drug-related adverse events associated with its use have been reported only in a few retrospective reviews. The International Intravitreal Bevacizumab Safety Survey was initiated to gather timely information regarding adverse events from doctors around the world via the internet.

Methods: An internet-based survey was designed to identify adverse events associated with intravitreal bevacizumab treatment. The survey web address was disseminated to the international vitreoretinal community via email. Rates of adverse events were calculated from participant responses.

Results: 70 centres from 12 countries reported on 7113 injections given to 5228 patients. Doctor-reported adverse events included corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation or uveitis, cataract progression, acute vision loss, central retinal artery occlusion, subretinal haemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischaemic attack, cerebrovascular accident and death. None of the adverse event rates exceeded 0.21%.

Conclusion: Intravitreal bevacizumab is being used globally for ocular diseases. Self-reporting of adverse events after intravitreal bevacizumab injections did not show an increased rate of potential drug-related ocular or systemic events. These short-term results suggest that intravitreal bevacizumab seems to be safe.

Off-label intravitreal injections of bevacizumab (Avastin, Genentech, Roche, Basle, Switzerland) were given primarily for the treatment of neovascular age-related macular degeneration (AMD) beginning in May 2005. In July 2005, the use of intravitreal bevacizumab for the treatment of ocular diseases was introduced to the international retina community.[1 2] Since then, the clinical use and research on intravitreal bevacizumab for neovascular and exudative ocular diseases has spread worldwide.[3–12]

As of June 2006, drug-related adverse events associated with intravitreal bevacizumab have been reported in only three retrospective reviews including 50, 79 and 279 patients.[3 12 13] Before these reports, the most concerning drug-related adverse events, after high-dose systemic intravenous bevacizumab treatment combined with 5-fluorouracil every 2 weeks for cancer treatment, were hypertension and a doubling of the thromboembolic risk, including myocardial infarction and cerebrovascular accidents (CVAs). Meta-analysis of the cancer trial data found an increase in the rates of cerebrovascular arterial events (1.9% *v* 0.5%) and cardiovascular arterial events (2.1% *v* 1.0%) in patients receiving chemotherapy and Avastin versus chemotherapy alone.[14] In one small series of patients with neovascular AMD treated with intravenous bevacizumab, mild hypertension was the only systemic adverse event identified.[15] Several studies have not shown any evidence of ocular toxicity after the use of bevacizumab at or beyond the therapeutic levels expected with the standard dose of intravitreal bevacizumab used in the routine care of patients.[4–6 16 17] The assays used to test bevacizumab toxicity included an in vitro ocular cell culture system and in vivo electrophysiological testing on both rabbit and human eyes after an intravitreal injection of bevacizumab.

To gather timely information on the adverse events related to the use of intravitreal bevacizumab from doctors around the world via the internet, we initiated the International Intravitreal Bevacizumab Survey.

METHODS

Approval for the International Intravitreal Bevacizumab (Avastin) Safety Survey was obtained from the institutional review board or ethics committee of the California Pacific Medical Center, San Francisco, California, USA. Possible adverse events associated with intravitreal bevacizumab treatment for ocular diseases were identified and a web-based survey was conducted. The website address with a request for participation in the survey was initially sent via email to clinical sites using bevacizumab, but the information was subsequently disseminated via email throughout the international vitreoretinal community.

The questionnaire first requested identifying information from the site to allow verification of data and then requested information on the number of patients treated, the number of bevacizumab injections given and the number of specific adverse events identified at that centre since intravitreal bevacizumab was first used. A third page was then generated by the website software to request specific details on the severity and outcomes of each adverse event reported (figs 1–3). To protect this sensitive information, site identifiers were separated from the data after verifying the data and screening for redundant submissions.

Abbreviations: AMD, age-related macular degeneration; CVA, cerebrovascular accident; DVT, deep venous thrombosis; TIA, transient ischaemic attack

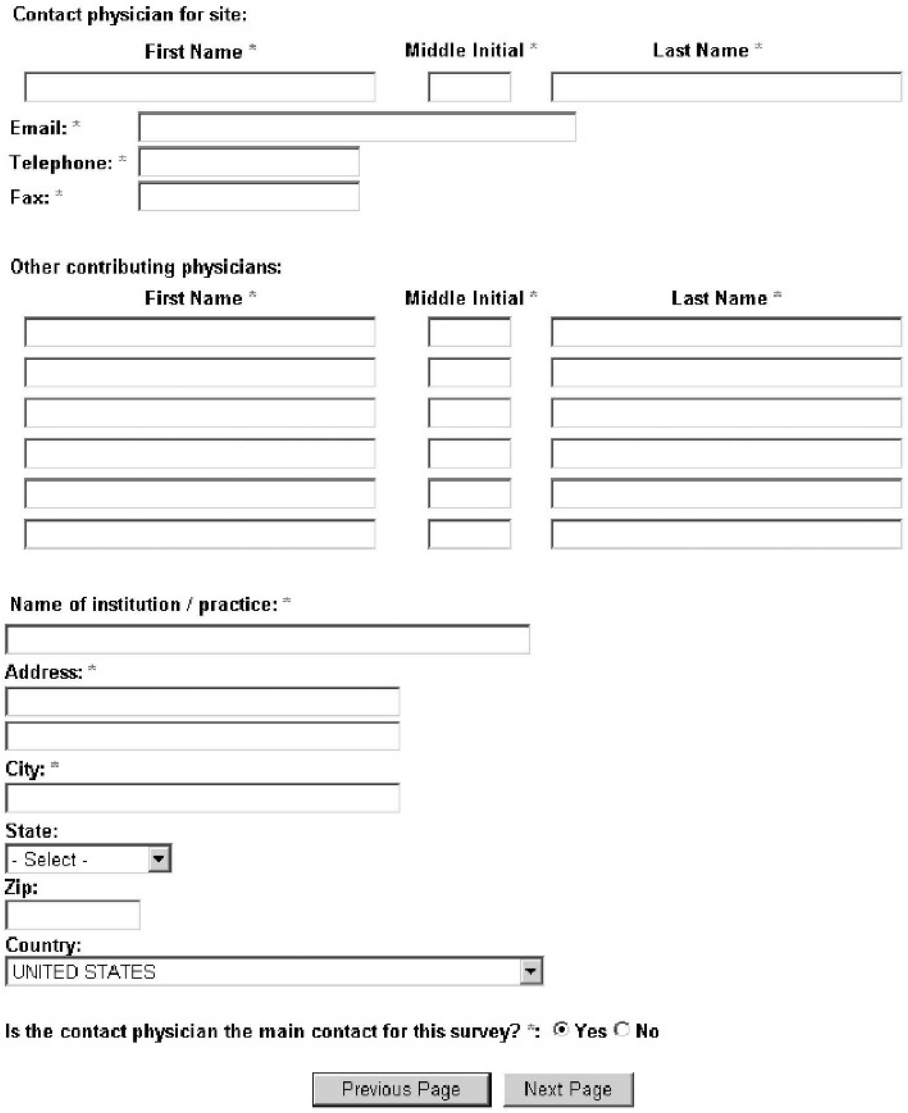


Figure 1 Page 1 of the International Intravitreal Bevacizumab Safety Survey requesting centre demographic information.

To create the form, host the site and securely store the data, an internet company specialising in this technology was employed (FormRouter, Cary, North Carolina, USA). FormRouter engineers programmed the website and securely stored the data. The FormRouter staff did not have access to the database once information was entered by the participating doctors. Client software was used by AEF to intermittently download the information into a database. After screening for redundant submissions, data were compiled, identifying information removed, and adverse event incidence rates were calculated. Initial identifying information was sufficiently detailed to prevent bogus submissions.

RESULTS

From November 2005 to April 2006, 70 centres representing 12 countries on 4 continents responded to our request for participation. The total number of injections reported was 7113 in 5228 patients. Centres reported on a mean of 75 patients, median 40 (range 1–506) patients, and a mean of 102 injections, median 50 (range 1–691) injections. Participating centres reported a range of follow-up from 1 to 7 (median 3.0, mean 2.8) months. A mean follow-up of 3.5 months per patient was calculated when the number of patients per centre was considered. Table 1 shows the rates of specific adverse events.

Adverse events were divided into two groups—procedure-related and possible drug-related. The possible drug-related adverse events were divided further into ocular and systemic events.

Potential procedure-related adverse events included corneal abrasion (n = 11 (0.15%)), lens injury (n = 1 (0.01%)), endophthalmitis (n = 1 (0.01%)) and retinal detachment (n = 3 (0.04%)), mild surface discomfort (n = 10 (0.14%)) and subconjunctival haemorrhage (n = 2 (0.03%)). The lens injury occurred when the lens capsule was damaged by the needle during the injection. A pars plana lensectomy with sulcus-fixated intraocular lens was required to repair the resulting cataract. The only case of endophthalmitis developed 5 days after treatment and required pars plana vitrectomy. Three retinal detachments were reported for an incidence of 0.04%. Two patients developed large subconjunctival haemorrhages after treatment. These adverse events related to the injection procedure are in the expected range for intravitreal injections.[18]

Ocular adverse events possibly related to bevacizumab included episodes of inflammation (n = 10 (0.14%)), cataract

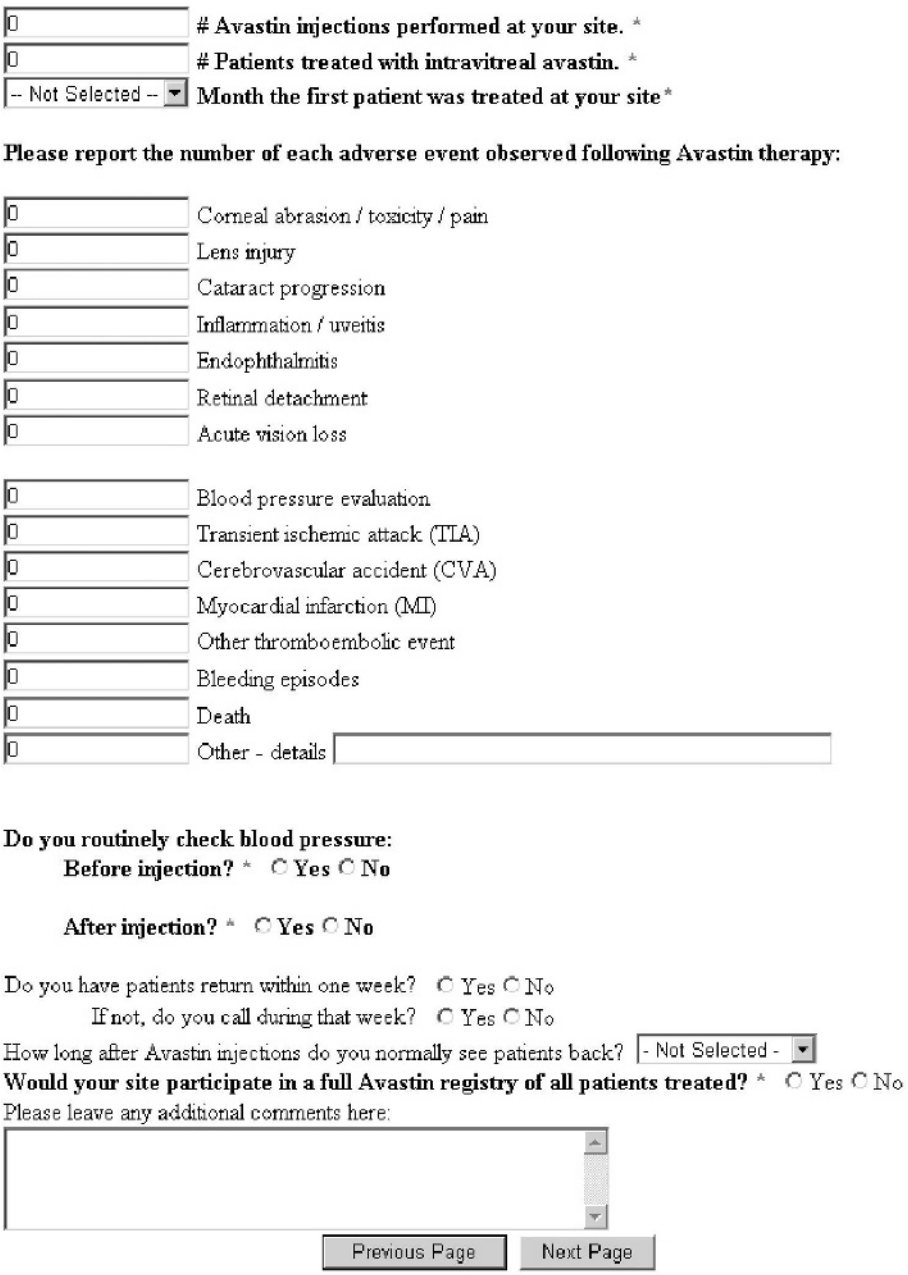


Figure 2 Page 2 requesting numbers of patients treated, injections and adverse events observed with treatment.

progression (n = 1 (0.01%)), acute vision loss (n = 5 (0.07%)), central retinal artery occlusion (n = 1 (0.01%)), new or progressive subretinal haemorrhages (n = 4 (0.06%)) and tears of the retinal pigment epithelium (n = 4 (0.06%)). The cases of inflammation were graded mild to moderate, occurred between 2 and 7 days after the treatments, and lasted no longer than 1 week. None of the cases featured hypopyon nor progressed to endophthalmitis. The case of cataract progression occurred in a patient with a pre-existing mature cataract.

Five episodes of acute vision loss were reported. Two patients experienced decreased vision owing to subretinal bleeding 2 days after treatment. Another case occurred 3 weeks after treatment despite improvement on optical coherence tomography without evidence of ischaemia on fluorescein angiography. A fourth case occurred for unknown reasons and the fifth case was diagnosed as progression of pre-existing geographical atrophy.

One central retinal artery occlusion was reported within 1 week of injection. Four tears of the retinal pigment epithelium were documented, three of which occurred within 1 month of treatment. Four cases of subretinal haemorrhage were documented.

Systemic adverse events possibly related to bevacizumab included mild blood pressure increase (n = 15 (0.21%)), transient ischaemic attack (TIA; n = 1 (0.01%)), CVAs (n = 5 (0.07%)) and deep venous thrombosis (DVT) (n = 1 (0.01%)). Episodes of raised systolic blood pressure did not exceed 200 mm Hg and were reported as mild. The TIA occurred 1 day after treatment in a patient with uncontrolled hyperlipidaemia. After the TIA resolved, the patient continued to receive at least one additional injection without another event. Four cases of CVA occurred between 1 and 10 days after treatment. Most cases required hospitalisation but did not result in disability. One death occurred as a consequence of a CVA, but this patient was at high risk owing

Table 1 Rates of specific adverse events

Potential treatment-related AEs	
Corneal abrasion	11 (0.15)
Lens injury	1 (0.01)
Endophthalmitis	1 (0.01)
Retinal detachment	3 (0.04)
Other	
Mild discomfort	10 (0.14)
Itching	1 (0.01)
Transient raised IOP	1 (0.01)
Subconjunctival haeme	2 (0.03)
Potential drug-related ocular AEs	
Inflammation/uveitis	10 (0.14)
Cataract progression	1 (0.01)
Acute vision loss	5 (0.07)
CRAO	1 (0.01)
Other	
Increased/new SRH	4 (0.06)
RPE tears	4 (0.06)
Potential drug-related systemic AEs	
Blood pressure increase	15 (0.21)
Deep venous thrombosis	1 (0.01)
Transient ischaemic attack	1 (0.01)
Cerebrovascular accident	5 (0.07)
Myocardial infarction	0 (0)
Death	2 (0.03)

AEs, adverse events; CRAO, central retinal artery occlusion; IOP, intraocular pressure; RPE, retinal pigment epithelium; SRH, subretinal haemorrhage.
Values are n (%).

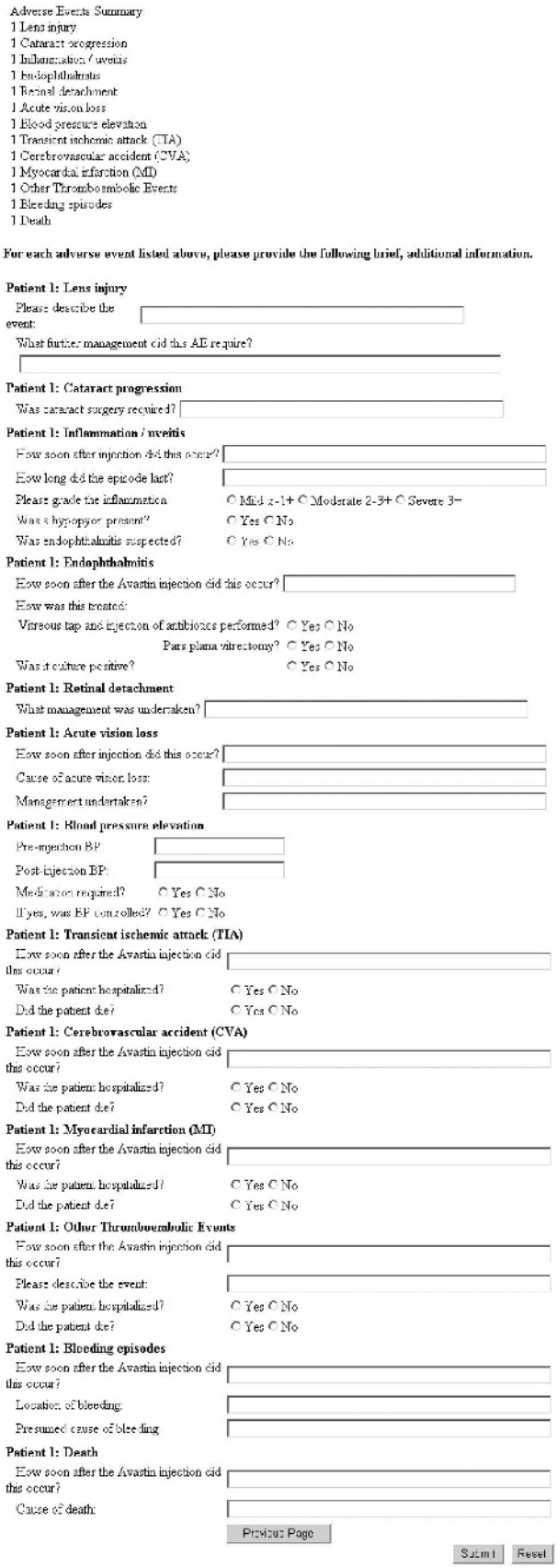
to pre-existing atrial fibrillation with mural thrombosis. The patient had refused coumadin treatment and insisted on receiving intravitreal bevacizumab despite the potential risks. The fifth CVA was evolving on the day of injection, but the patient ignored the symptoms at the time of injection and fortunately had no major subsequent impairment. One recurrent DVT was reported in a patient with a history of DVT. No cases of myocardial infarction were reported.

Two deaths (0.03%) were reported. The first patient died 3 weeks after injection as a result of pneumonia. He was hospitalised with pneumonia and subsequently died, with the cause of death listed as cardiopulmonary arrest. The second patient had a CVA that was previously described.

Data were rapidly transferred without incident from the internet company managing the site into an Access database. Only three redundant submissions were discovered. These were found to be a result of redundant doctor entries, not software malfunction. Redundant submissions were manually screened by verification of identifiers, such as the name of the submitting doctor, before entering the information into the final database. Most of the data were collected within the first month of the email request. Sixty one centres reported 6090 injections on 4576 patients during the first month of data collection. The rate of response is unknown as the email was originally sent to a defined number of centres, but was then subsequently disseminated via email and list servers to an unknown number of recipients.

DISCUSSION

The International Intravitreal Bevacizumab Safety Survey, a survey of retina doctors using off-label intravitreal bevacizumab, found no short-term evidence of an increase in potential drug-related systemic adverse events beyond the incidence rates expected for an elderly population. The adverse events that were identified were expected and mostly related to the injection procedure. Corneal abrasion was probably related to the anaesthetic or antiseptic preparation before the intravitreal injections. Even the rates of the expected injection-related adverse events were lower than those reported in a 1-year study on patients with AMD treated with pegaptanib.[19] In addition, cases of intraocular


Adverse Events Summary
1 Lens injury
1 Cataract progression
1 Inflammation / uveitis
1 Endophthalmitis
1 Retinal detachment
1 Acute vision loss
1 Blood pressure elevation
1 Transient ischemic attack (TIA)
1 Cerebrovascular accident (CVA)
1 Myocardial infarction (MI)
1 Other Thromboembolic Events
1 Bleeding episodes
1 Death

For each adverse event listed above, please provide the following brief, additional information.

Patient 1: Lens injury
Please describe the event:
What further management did this AE require?

Patient 1: Cataract progression
Was cataract surgery required?

Patient 1: Inflammation / uveitis
How soon after injection did this occur?
How long did the episode last?
Please grade the inflammation: ○ Mild 1-1+ ○ Moderate 2-3+ ○ Severe 3-
Was a hypopyon present? ○ Yes ○ No
Was endophthalmitis suspected? ○ Yes ○ No

Patient 1: Endophthalmitis
How soon after the Avastin injection did this occur?
How was this treated:
Vitreous tap and injection of antibiotics performed? ○ Yes ○ No
Pars plana vitrectomy? ○ Yes ○ No
Was it culture positive? ○ Yes ○ No

Patient 1: Retinal detachment
What management was undertaken?

Patient 1: Acute vision loss
How soon after injection did this occur?
Cause of acute vision loss:
Management undertaken?

Patient 1: Blood pressure elevation
Pre-injection BP:
Post-injection BP:
Medication required? ○ Yes ○ No
If yes, was BP controlled? ○ Yes ○ No

Patient 1: Transient ischemic attack (TIA)
How soon after the Avastin injection did this occur?
Was the patient hospitalized? ○ Yes ○ No
Did the patient die? ○ Yes ○ No

Patient 1: Cerebrovascular accident (CVA)
How soon after the Avastin injection did this occur?
Was the patient hospitalized? ○ Yes ○ No
Did the patient die? ○ Yes ○ No

Patient 1: Myocardial infarction (MI)
How soon after the Avastin injection did this occur?
Was the patient hospitalized? ○ Yes ○ No
Did the patient die? ○ Yes ○ No

Patient 1: Other Thromboembolic Events
How soon after the Avastin injection did this occur?
Please describe the event:
Was the patient hospitalized? ○ Yes ○ No
Did the patient die? ○ Yes ○ No

Patient 1: Bleeding episodes
How soon after the Avastin injection did this occur?
Location of bleeding:
Presumed cause of bleeding:

Patient 1: Death
How soon after the Avastin injection did this occur?
Cause of death:

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Figure 3 Page 3 requesting follow-up details on each adverse event reported.

inflammation after intravitreal bevacizumab were low—lower than those reported after treatment with intravitreal injections of ranibizumab in early phase I/II studies.[20] These results suggest that intravitreal bevacizumab treatment seems safe over the short term.

Although the annualised rates cannot be estimated, these data for short-term follow-up are encouraging. In this survey, the reported rates of systemic adverse events were 0.01% for TIAs, 0.07% for CVAs, 0% for myocardial infarctions and 0.03% for deaths. Unfortunately, specific incidence rates of systemic thromboembolic events for an elderly population remain unknown despite attempts to estimate them. Gragoudas *et al*[19] published a 10% incidence of hypertensive disorders, 2–3% incidence of haemorrhagic adverse events and 6% incidence of thromboembolic events after 1 year of using pegaptanib sodium. A Health, United States publication by the National Center for Health Statistics, Hyattsville, Maryland, USA, and the Center for Disease Control and Prevention, Atlanta, Georgia, USA, in 2005 only stated death rates for all age groups through 2002—the all-ages death rate from heart disease was 0.24% and that from stroke 0.056%. Specific data about the incidence of heart disease or stroke events were not published, only death rates from these events.[21]

We acknowledge the limitations of this study, including self-reporting of adverse events, which may cause under-reporting owing to concern for medico-legal liability or the human tendency not to publicly acknowledge adverse events in clinical practice. Furthermore, all responses were voluntary, did not require a systematic chart review and represented varying periods of follow-up. But given these limitations, the survey has provided a report of real-world complications after intraocular bevacizumab treatment. Although this safety survey did not demand the rigours of a clinical research protocol, perhaps the adverse event rates are illustrative of real-world observations and experiences. Ideally, ophthalmologists would have complete knowledge of all systemic diseases for which patients are treated through communication with medical colleagues. In reality, doctors' access to a patient's medical history is limited to that which a patient is able to report. Given these shortcomings, this real-world collection of adverse events data presents a safety-profile snapshot that does not show an alarming short-term signal regarding ocular or systemic adverse events after the use of intravitreal bevacizumab. It should be acknowledged that this survey represents a short-term follow-up between 2 and 4 months, and is not intended to expose potential systemic effects that could be associated with monthly chronic dosing of intravitreal bevacizumab.

A search of Pubmed did not disclose any previous studies of a doctor-organised, internet-based system for reporting adverse events related to the use of a drug. However, email and internet technologies have been used to assist the medical community in gathering timely global data about medical errors and patient-reported symptoms in a drug trial. The internet was used to examine medical errors in 54 neonatal intensive care units in a geographical area.[22] Health professionals were asked to contribute voluntarily and anonymously via a secure website, which led to the discovery of a broad range of medical errors. Another study achieved almost 80% patient participation via the internet to collect self-reports by patients of toxicity-related symptoms during a chemotherapy drug trial.[23] Our collaboration with FormRouter, a form management process company, which customarily assists business clients with secure transfer of client inquiries and financial information, allowed a scientific question to be answered quickly and efficiently by using pre-existing technology. Furthermore, participating doctors and their staff were able to navigate the website without difficulty; no requests for clarification of how to use the internet questionnaire were received. This study shows the ability of the internet to rapidly, easily and securely acquire information on disease processes and novel treatment strategies, including worldwide experiences with different drugs.

In summary, the self-reporting of adverse events via the internet after intravitreal bevacizumab injections did not show an increased rate of potential drug-related ocular or systemic events beyond that expected in an elderly population. These short-term results suggest that intravitreal bevacizumab seems to be safe.

Authors' affiliations

A E Fung, Pacific Eye Associates, San Francisco, California, USA
P J Rosenfeld, Department of Ophthalmology, Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami, Miami, Florida, USA
E Reichel, Department of Ophthalmology, New England Eye Center, Tufts University Medical Center, Boston, Massachusetts, USA

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Competing interests: AEF and ER have participated in Genentech-sponsored scientific advisory boards, for which they received honoraria and reimbursement for travel expenses. PJR has received clinical research support from Genentech and reimbursement of travel expenses and honoraria from Genentech for participation in scientific advisory boards.

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