Concern about endophthalmitis risk, IOP spikes following anti-VEGF injections

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in Fort Lauderdale

With the growing use of intravitreal injections to treat exudative age-related macular degeneration, retinal specialists are collecting and analysing data to more fully characterise the risks. The information is particularly important for establishing the safety profile of bevacizumab (Avastin, Genentech), which has come into widespread off-label use without being studied first in large clinical trials.

At the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), two groups of American researchers reported on the immediate effect of intravitreal injections on IOP. Other investigators examined rates of endophthalmitis and other complications in large series of eyes treated with intravitreal bevacizumab (Avastin).

Researchers from Mexico undertook a retrospective study to characterise ocular and systemic complications in patients being treated with intravitreal bevacizumab injections. Over a period of 14 months, a total of 1,910 injections of bevacizumab 2.5 mg/0.1 ml were delivered. The safety profile was favourable and consistent with that reported in the controlled studies of the approved anti-VEGF treatments, reported Maximiliano Gordon MD, vitreoretinal service, Asociacion para Evitar la Ceguera en Mexico Hospital, Mexico.

Trabecular retinal detachment occurred after four injections (0.2 per cent) in patients with proliferative diabetic retinopathy, and there were single cases of rhegmatogenous retinal detachment and vitreous haemorrhage (0.03 per cent for both). Three cases of endophthalmitis occurred (0.15 per cent). There were no systemic adverse events attributable to the injections.

“These findings reinforce the importance of adhering to a strict aseptic protocol for intravitreal injection to reduce the risk of endophthalmitis, and we also believe they support a recommendation to avoid treatment in eyes with diabetic retinopathy and extensive neovascular proliferation. It is likely that in those eyes, anti-VEGF treatment causes contraction of the neovascular proliferation leading to retinal detachment,” said Dr Gordon.

Ophthalmologists from the University of Mannheim reported their safety experience with intravitreal bevacizumab with a focus on risks of infectious and non-infectious endophthalmitis following the injection. Their series included 684 eyes. The dose of bevacizumab was 1.5 mg/0.1 ml and 334 eyes received a second treatment after a minimum interval of four weeks for a total of 1,218 consecutive injections.

The indication for treatment in all cases was exudative AMD. Endophthalmitis developed in a single eye three days after a second injection. The patient presented with ocular pain, NLP vision, and dense infiltrate in the vitreous. Pars plana vitrectomy was performed and microbiological culture of a vitreous sample was negative. Full vision recovery to 20/100 was achieved. Visual acuity prior to bevacizumab injection was 20/200.

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“The rate of endophthalmitis in this series was about one in 1,000 injections, but we have now performed about 2,000 injections of intravitreal bevacizumab without any more cases of endophthalmitis occurring,” noted Ulrich Spandau, MD, department of ophthalmology, University of Mannheim, Germany.

“We are careful to adhere to a sterile technique and all patients are treated in the OR rather than in an in-office procedure. There is no reason to believe that the rate of endophthalmitis will be higher with bevacizumab injections compared with other anti-VEGF agents. However, the medicolegal implications if that complication occurs are different with bevacizumab because it is being used off-label,” said Dr Spandau.

Two patients in the series developed systemic reactions after intravitreal bevacizumab. One patient was a 67-year-old woman who presented to the department of dermatology with generalised erythema on the first day post-treatment. She was diagnosed with a medication-induced dermatitis and recovered fully within a few days.

In addition, a 72-year-old woman developed asthenia, nausea, and hypertension on the day after the intravitreal injection. The internist who evaluated her attributed the findings to the bevacizumab treatment, noting they are similar to those documented in patients treated with intraocular bevacizumab treatment for colorectal cancer. Her symptoms also disappeared within a few days without intervention.

Significant IOP spikes

Researchers from the East Florida Eye Institute, Stuart, Florida, reported findings from an analysis designed to determine the magnitude and duration of IOP increases after intravitreal anti-VEGF injections as well as the risks in patients with glaucoma. Based on their findings showing the development of significant IOP spikes, along with their clinical experience involving glaucoma patients who suffered permanent optic nerve damage after sustaining high IOP spikes, they believe caution is warranted.

They previously reported findings from a small study showing intravitreal injection of pegaptanib sodium 0.3mg/0.09ml (Macugen, Pfizer) resulted in a transient but marked increase in IOP. Data were also analysed from an even smaller group of patients treated with bevacizumab 1.25mg/0.05ml, which showed it also resulted in an early but lower IOP spike.

The researchers presented data from an expanded cohort comprised of 169 injections administered to 57 patients, including 75 injections of pegaptanib sodium, 69 injections of bevacizumab, and 25 injections of ranibizumab 0.5mg/0.05ml (Lucentis, Genentech).

In all patients, IOP measurements were obtained within one minute after the injection and then every five to 10 minutes until IOP returned to a safe level. In addition, vision was evaluated immediately after injection, and anterior chamber paracentesis was performed immediately in any eye where IOP rose above 55 mmHg.

All patients in the series were Caucasian, with an average age of 78 years. Among the 57 patients there were 14 with chronic open angle glaucoma, three with normal tension glaucoma, and five glaucoma suspects.

The IOP data were analysed for each medication separately. Across all three medication groups, mean IOP ranged from 12.6 to 14.1 mmHg at baseline, and it spiked significantly after injection. However, the mean IOP achieved after injection of pegaptanib sodium (41.6 mmHg) was significantly higher than the mean measured in the bevacizumab (36.8 mmHg) and ranibizumab (37.2 mmHg) groups.

After all three treatments, mean IOP fell progressively over time. However, at 21 to 30 minutes post-injection, IOP was still elevated from baseline in all groups, and the value in the pegaptanib sodium (22.9 mmHg) and bevacizumab (21.9 mmHg) groups was significantly higher compared with eyes treated with ranibizumab (16.6 mmHg). When patients returned for follow-up visits after approximately one to two weeks, mean IOP in all three medication groups was at or below the baseline level.

The vision testing showed four (5.3 per cent) of 75 injections of pegaptanib sodium resulted in transient no light perception (NLP) vision immediately following the injection. There were no cases of NLP vision in the other treatment groups. Mean IOP occurring immediately after the injection in cases developing NLP exceeded 55 mmHg compared with 39.4 mmHg in eyes retaining light perception vision. Vision returned to baseline levels as IOP decreased minutes after the injection.

“The prescribing information for both ranibizumab and pegaptanib sodium mention the occurrence of post-injection increases in IOP occurring within 30 and 60 minutes, respectively, while a paper published in the American Journal of Ophthalmology in 2006 reported detecting no IOP spikes after intravitreal pegaptanib injection. However, the first IOP measurement in that study was taken at 30 minutes post-treatment,” said Allison Toler OD.

“We felt it was important to obtain more specific information about this reaction, particularly because our practice includes a large glaucoma population. Considering that the anti-VEGF treatments may be repeated every four to six weeks, we were concerned about the impact the post-injection IOP spikes might have on the optic nerve in those patients,” she told EuroTimes.

The researchers believe the greater increase in IOP after pegaptanib sodium injection is a volume-mediated phenomenon. Based on that idea and because progression of glaucoma has been observed in two patients with advanced glaucoma who have been receiving intravitreal injections for their AMD every four weeks, patients who have significantly damaged optic nerves and visual field loss who have had an IOP spike post-intravitreal injection are offered treatment with a lower volume of bevacizumab, said Ronald Frenkel, MD, FACS, FBIICS, voluntary associate professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, East Florida Eye Institute Eye Research Foundation.

“There is no dose-response curve available for bevacizumab, and it is possible that a dose lower than the typically used 1.25mg dose is effective. In fact, we and others have unpublished data indicating possible efficacy of lower doses, and we also presented a study at this meeting showing a contralateral eye effect after intravitreal injection of bevacizumab in selected patients,” he noted.

“By administering a lower volume, we are hoping to achieve a therapeutic effect while diminishing the IOP spike, and we have IOP data that supports this approach,” Dr Frenkel said.
He also noted that post-injection “target” IOP values are being set for patients receiving an anti-VEGF injection. Those values are individualised according to the state of the optic nerve, and patients are not sent home until the IOP declines to the target level. In addition, the potential risk of transient NLP is included in the informed consent.

“Patients who develop transient NLP after an IOP spike are having an ischemic optic neuropathy. If they are told this event may occur, they are more understanding when it happens,” he said.

At the Mayo Clinic, Rochester, Minnesota, retinal specialists have been routinely measuring and recording IOP data in patients receiving intravitreal treatment with an anti-VEGF agent or triamcinolone acetonide (Kenalog). They reported results from analyses of 212 injections in 161 patients, including 76 bevacizumab injections (125mg/0.05 ml), 42 triamcinolone injections (4mg/0.1ml), and 94 pegaptanib injections (0.3mg/0.09ml). IOP measurements were taken prior to injection, usually with Goldmann applanation tonometry, and then post-injection with a TonoPen XL beginning after five minutes and at various time points thereafter for up to 50 minutes until IOP decreased below 30 mmHg.

In an analysis of mean IOP at all time points, there were no significant differences between treatments. The data were also analysed to determine the proportions of eyes in each group in which IOP remained below 35 mmHg, rose above 10 mmHg, or rose above 10 mmHg. Those analyses also showed no significant differences between treatment groups.

Considering all treatments and all time points, IOP was below 35 mmHg in more than 90 per cent of all eyes and rose by 10 mmHg or less in about two-thirds of eyes.

Three eyes receiving triamcinolone had a persistent elevation of IOP above 35 mmHg and received treatment with a topical IOP-lowering medication. No such treatment was needed in any of the eyes treated with bevacizumab or pegaptanib, and no eyes required a paracentesis.

Spare the paracentesis

“The fact that paracentesis was unnecessary in any eyes in our series is our most important take-home message. Some retinal specialists are routinely performing paracentesis before or after intravitreal injection. Our experience indicates it is not needed and we believe that practice should be avoided because it adds to the risk of intravitreal injection,” said Sophie Bakri MD, assistant professor of ophthalmology, Mayo Clinic.

Approximately one-fourth of injections were given to glaucomatous eyes. Eyes with glaucoma were significantly less likely than eyes with no history of glaucoma to have an IOP below 35 mmHg at 10 minutes. However, the difference did not persist at later measurement times even though IOP elevations tended to persist longer in the glaucomatous eyes.

“The difference in IOP profiles between the glaucoma patients and non-glaucoma patients is explained by the fact that the trabecular meshwork drainage system is not working as well in glaucomatous eyes,” Dr Bakri told EuroTimes.

“We are especially careful in monitoring glaucoma patients after an intravitreal injection. Immediately post-treatment we examine the eye to make sure the optic nerve is perfused and check the vision. If NLP vision occurs, we would perform anterior chamber paracentesis immediately, but that has not been necessary so far.”

Dr Bakri and colleagues concluded that their data highlight the inter-individual variability in IOP responses after intravitreal injection. They postulate that several factors may play a role, including differences in actual volume of drug delivered due to inaccuracy in dosing exactly the intended amount, inter-individual differences in scleral rigidity, and reflux post-injection.

“We use a 31-gauge needle for bevacizumab injection and a 27-gauge needle for the triamcinolone and pegaptanib sodium treatments. Although the volume injected is greater with triamcinolone and pegaptanib sodium, it is likely that the larger bore needles used for those treatments allows for greater reflux,” Dr Bakri said.

She also observed that due to concern that reflux might be associated with an increased risk of intraocular infection, their practice initially was to place a cotton-tipped applicator over the injection site immediately after the needle was withdrawn in order to minimise reflux.

“Now we don’t mind seeing reflux because we know it helps to equilibrate the IOP after the injection. To minimise infection risk we instil five per cent povidone-iodine drops on the ocular surface after the needle is withdrawn, in addition to the meticulous prep of the ocular surface, lids and lashes done before the procedure,” Dr Bakri said.

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