CASE REPORT

# Delayed onset panuveitis following intravitreal aflibercept injection

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## SUMMARY

Aflibercept has been listed on the Australian Pharmaceutical Benefit Scheme for the past year for neovascular age-related macular degeneration. Since that time there have not been any reports of delayed onset panuveitis. We present two cases of anterior and posterior uveitis that have occurred 4 weeks or more after first intravitreal injection of aflibercept. Both patients had received other vascular endothelial growth factor inhibitors prior to aflibercept administration without signs of inflammation and both cases had sterile endophthalmitis. On resolution of the inflammation the patients were recommenced on ranibizumab without further incident.

## BACKGROUND

Angiogenesis associated with choroidal neovascularisation in wet age-related macular degeneration can be prevented by inhibiting vascular endothelial growth factor (VEGF). Aflibercept is an anti-VEGF trap medication that inhibits angiogenic activity by binding to VEGF receptors in blood vessels.

There is little literature about immune-mediated reactions postaflibercept injection following the addition of the drug onto the Australian Prescription Benefit Scheme in 2012. In addition, there is no current data on delayed immune-mediated reactions postintravitreal aflibercept injections. We present two cases of delayed onset, culture-negative endophthalmitis occurring 4–5 weeks postintravitreal injection of aflibercept.

## CASE PRESENTATION

### Case 1

A 68-year-old woman was treated in a tertiary hospital clinic since 2009 for a left subfoveal choroidal neovascular membrane secondary to age-related macular degeneration and bilateral primary open-angle glaucoma. She had 3 bevacizumab injections and 17 ranibizumab injections in the left eye with no adverse event to March 2013. Her best correct visual acuity was stable at right 6/7.6 and left 6/12. She was phakic with mild nuclear sclerotic cataracts. Her cup-to-disc ratio was stable at 0.7 bilaterally with no new changes in her optical coherence tomography (OCT) nerve fibre layer. She was using latanoprost 0.005% one drop nocte in each eye and intraocular pressures were less than 20 mm Hg. In January 2013 her clinical examination and OCT suggested a slight increase in the subretinal fluid and a slight decrease in visual acuity to 6/15, and the decision was made to change therapy from ranibizumab to aflibercept. At her February appointment she had a left aflibercept injection. The eye was cleaned with povidone iodine 5% and anaesthetised with a subconjunctival lignocaine 2%. Aflibercept 2 mg in 0.05 mL (Bayer and Bayer) was injected with a 30 G needle in the superotemporal quadrant. Patient 1 was advised to use one drop chloramphenicol four times a day for 5 days postinjection in the left eye.

She returned to the clinic 6 weeks later with a 1-week history of decreased vision in the left eye associated with stabbing pain and generalised irritation. On examination her visual acuity was unchanged in the right eye and was 6/9.5 best corrected in the left eye. The eye was moderately injected with 360° limbal injection. Anterior chamber (AC) showed 3+ cells with a nuclear cataract. There were 2+ vitreous cells reducing the view of the fundus. She was not systemically unwell, had no recent medication alterations but for the influenza vaccination 2 weeks prior to presentation. She was started on one drop of 1 mg/mL fluorometholone four times a day. The following day her vision had worsened to 6/48 in the left eye but she felt symptomatically better. The AC and anterior vitreous had fewer cells; however, the mid and posterior vitreous showed clumped cells. Over the next 3 weeks her uveitis and vitritis worsened but without pain, until best corrected visual acuity was hand movements vision in the left eye. At this stage a trace hypopyon was present. Her latanoprost 0.005% was ceased. She underwent a vitreous tap which showed no bacterial or fungal growth and no evidence of adenovirus, herpes simplex or herpes zoster viruses. Intravitreal vancomycin 0.1 mL of 1 mg/0.1 mL and cefazolin 0.1 mL of 2.25 mg/0.1 mL were administered post-tap. She also had a normal systemic vasculitis screen including extractable nuclear antigen, dsDNA, syphilis, ACE, anti-nuclear antibody, anti-neutrophilic cytoplasmic antibodies, C-reactive protein, human leukocyte antigen B27, rheumatoid factor and flow cytometry. The following day she had left eye pain, worsened uveitis and vitritis and the hypopyon had increased in size to 0.5 mm. Over the next week she had photopsia and new onset of a left relative afferent pupil defect and slow to improve uveitis and vitritis. She underwent left vitrectomy 4 weeks after presenting with uveitis and vitritis. The vitrectomy specimen again showed no mycology or bacterial growth, no acid fast bacilli, viral PCR was negative for herpes simplex and herpes zoster viruses and flow cytology was non-diagnostic. In addition, she had a normal full blood count and urea/electrolyte/creatinine tests. She slowly

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improved postvitrectomy while on four times a day prednefrin forte and chloramphenicol. Her intraocular pressures increased to above 30 and she was recommenced on latanoprost 0.005%. Her most recent review showed no signs of intraocular inflammation, intraocular pressures were below 20 mm Hg, best correct visual acuity was right 6/9.5 and left 6/19 and she has been recommenced on intravitreal ranibizumab without inflammatory response.

### Case 2

An 88-year-old man was treated in a private ophthalmology clinic for bilateral exudative age-related macular degeneration. He had a disciform macular scar present in the right eye and severe pseudoexfoliative glaucoma. He was treated with ranibizumab in the left eye every 4–6 weeks, nocte left eye latanoprost 0.005%, twice daily left eye timolol 0.5%, twice daily left eye brinzolamide 1%. His best corrected visual acuity was stable with hand movements at ½ m on the right, and 6/19+2 on the left. The disc was almost completely cupped on the right and 0.95 on the left. The left eye had undergone a successful left vitrectomy lensectomy in 2012 for cataract with phacodonesis related to pseudoexfoliation syndrome. A Verisyse Aphakic IOL was inserted (AMO, Australia). He had been on regular monthly intravitreal injections of ranibizumab, and in February 2013 clinical examination and OCT showed increased subretinal fluid. A decision was made to change to aflibercept in March 2013. The eye was cleaned with povidone iodine 5% and anaesthetised with topical amethocaine 1%. Aflibercept 2 mg in 0.05 mL (Bayer and Bayer) was injected with a 30 G needle. He was advised to use one drop chloramphenicol four times a day for 5 days postinjection in the left eye. He returned to the clinic 5 weeks post his first aflibercept injection. He had noticed rapid onset of decreased vision over 1 day and on examination had hand movements acuity in only the lower temporal field. Intraocular pressures were right 9 and left 5 mm Hg. There were 3+ AC cells, there were 3+ vitreous cells (vitrectomised) and no clear view of the fundus. There was no pain or injection noted on examination. He was started on prednefrin forte four times a day left eye. Within 24 h his vision improved subjectively but was still recorded to hand movements at 1 m. There were 3+ AC cells but minor vitreous haze and no macular haemorrhage or retinal tears. He continued to take prednefrin forte four times a day and his regular glaucoma medications. Within a week there was improvement in visual acuity to almost baseline of 6/24–2. AC and vitreous cells had completely cleared. There were no tears in the retina and the macula was dry. He was changed to 1 mg/mL fluorometholone 0.1% twice daily and was back to best corrected visual acuity 6/19 within 4 weeks. At his next appointment he was given intravitreal ranibizumab with no subsequent recurrence of inflammation.

## DISCUSSION

Aflibercept was approved for use for neovascular age-related macular degeneration in Australia in December 2012. There have been no reports of delayed anterior or posterior inflammation postinjection. In our cases the patient presented with inflammation greater than 4 weeks after injection. Most studies that examine postintravitreal injection triggered inflammation discuss signs of inflammation within the first week postinjection.[1–4] Kiss *et al*[1] found no difference in levels of AC inflammatory activity between control and bevacizumab-injected eyes in 61 consecutive patients with neovascular age-related macular degeneration. However, this study, like many others, only reported on inflammation that followed in the first week postinjection point. Not following up with the patient for longer may have resulted in missing patients with delayed onset inflammation or diagnosing the inflammation due to a different cause.

Anterior and posterior chamber inflammation postinjection has been documented for intravitreal bevacizumab and ranibizumab injections.[5] The initial data from the MARINA study showed a rate of serious uveitis of 1.3% when combining both ranibizumab injection groups.[5] The initial ANCHOR study had a similar rate of serious uveitis across both ranibizumab injection groups.[6] Phase III data from both studies continue to suggest that serious uveitis occurs in 2.1% and 2.9% of treated eyes.[7] ANCHOR also reported rates of less severe intraocular inflammation that included iritis, iridocyclitis, vitritis, uveitis, AC inflammation occurring in between 10.2% and 15.0% of treated eyes in the anti-VEGF injection groups.[6] The study did not specify when the inflammation occurred in relation to receiving the intravitreal injection.

There have been previous concerns about bevacizumab-induced intraocular inflammation.[8] However, in a large study of 16 166 patients postbevacizumab injection, only 0.27% had inflammation. The inflammation settled with topical antibiotics and steroid alone suggesting the inflammation was not due to infective endophthalmitis.[4] Newer studies such as CATT and BRAVO suggest the serious uveitis rate for ranibizumab and bevacizumab is 0.3–0.5%.[9] There has been a case study report of ranibizumab potentially triggered sterile endophthalmitis similar to case 1; however, this happened within 48 h of injection and visual acuity was regained with topical steroid treatment only.[10]

There have been no previous reports of late onset panuveitis with ranibizumab or bevacizumab.

It has been hypothesised that repeated intravitreal injections may trigger an inflammatory response due to immune-mediated response to the medication. In the case of ranibizumab it is hypothesised that this is due to its recombinant humanised monoclonal antibody.[11] It was thought that bevacizumab was more likely to trigger immune reactions as it is a full antibody.[11] However, little difference has been shown between the agents. Our cases occurred in patients who had undergone many uneventful anti-VEGF injections with ranibizumab or ranibizumab and bevacizumab before developing an inflammatory response post the first injection with aflibercept.

To date the authors can only find one paper, very recently published, about early postaflibercept sterile inflammation. The Therapeutic Surveillance Subcommittee of the American Society of Retinal Specialists (ASRS) has reported on similar cases to our patients.[12] They monitored US retinal specialists from February 2012 to end of March 2012, and found 15 cases of early postaflibercept inflammation that were presumed sterile. In the ASRS paper the treating ophthalmologist decided when to conduct vitreous tap. There were no guidelines about when to treat or with which medication. Therefore, not all cases underwent vitreous tap. Those that did were likely biased to cases where the treating doctor suspected infectious endophthalmitis and negative results may represent culture-negative infectious endophthalmitis. More importantly, the cases reported were all in patients where inflammation occurred *within3 days of injection*.[12] Furthermore, 11 of the 15 cases that were reported came from one practice and may be associated with issues with that practice and injection techniques.[12]

Patient 1 had the influenza vaccination 2 weeks prior to presentation. There are a few reports suggesting that influenza vaccination can trigger an anterior or panuveitis.[13 14] The case reports suggest systemic issues as well as intraocular inflammation such as vasculitis and polyarthropathy which patient 1 did not report.[13 14] Another brief case from 1994 reports about a

patient with unilateral anterior and posterior uveitis but the patient developed her symptoms within 48 h and had a fever and other blood results suggestive of systemic immune reactions neither of which were present in patient 1.[15]

We have presented a novel potential side effect of aflibercept with two cases of late onset anterior and posterior inflammation postaflibercept intravitreal injection. This is the first report of a case series of delayed panuveitis postaflibercept injection. Clinicians should be aware of this possibility and encourage age-related macular degeneration patients being treated with anti-VEGF to report late onset changes in symptoms. The potential side effects are of great importance, particularly in individuals, such as case 2, with no useful vision in the other eye who have been stable on ranibizumab for a prolonged duration. The benefit of less frequent injections needs to be balanced against the risk of visual loss from an inflammatory reaction.

## Learning points

- Clinicians need to be aware of late onset sterile uveitis and vitritis after aflibercept injection.
- Patients should be encouraged to report any change in vision or new symptoms as early as possible postaflibercept injection.
- While late presenting inflammation was able to be controlled, patients with single eye only vision who are stable on other anti-VEGF inhibitors need special consideration.
- The risk of late onset panuveitis with aflibercept intravitreal injections needs to be weighed against the risk of infective and non-infective endophthalmitis with other anti-VEGF inhibitors which need to be injected more regularly and therefore affords more opportunity for endophthalmitis postinjection to occur.

**Contributors** The concept of the paper came from JE after seeing two cases in quick succession and then another patient presenting to SRL and JAG with a similar scenario. JAG was involved in the literature review and manuscript writing and content. JEC, SRL and DS were involved in proof-reading and suggesting additional studies for inclusion in the discussion. All cases had multidoctor involvement. Case 1 saw each of the authors for their care. Case 2 saw SRL and JEC in a private consulting setting.

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**Patient consent** Obtained.

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