Introduction

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The treatment of chorioretinal vascular conditions has improved significant with the advent of anti-vascular endothelial growth factor inhibitors (VEGF). Diseases such as age related macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity are all being treated by delivering intravitreal therapy to knock down VEGF.[1–4] As ophthalmologists, we are now fortunate to have many anti-VEGF options to choose from which include off label therapy with bevacizumab, and on label therapy with ranibizumab, aflibercept, and pegaptanib. In addition, we have learned how to best track the need for retreatment by clinical exam and optical coherence tomography findings and are able to effectively treat patients on an as needed basis.

The vast majority of specialists treated with bevacizumab even without the presence of a multicentered randomized clinical trial in each disease category to show its efficacy and safety. Recent studies have found it to be equally efficacious and safe in comparison to ranibizumab atleast for the treatment of exudative AMD.[5] This has been confirmed in other multicentered randomized trials for exudative AMD and other trials are now underway to compare these drugs for the other disease categories mentioned.

When considering initiating therapy for patients, the decision is typically based not solely on the physician or practice, but also on the patient. More than ever, we are involving patients in the discussion of drug selection evaluating their side effects, costs to the patient, convenience, and potency. While the drugs at face value appear to be quite similar, slight nuances exist and it's been found that in particular clinical pictures, one drug may work better than the others. For example, in the treatment of fibrovascular pigment epithelial detachment (PED) from exudative AMD, aflibercept appears to be more potent in resolving the underlying PED based on recent studies.[6] The CATT trial highlighted the higher propensity seen of geographic atrophy in those treated with monthly ranibizumab, than those treated in the other arms of the studies.[7 8] Finally, there have been recent studies which have highlighted systemic VEGF suppression with the use of intraocular bevacizumab which was not seen in the use of intraocular ranibizumab. One additional factor that contributes to selection of a drug for a patient is cost. A single dose of ranibizumab costs 40 times as much as a single dose of bevacizumab or aflibercept.[9] This cost differential has important economic implications when extrapolated to the more than 250,000 patients who are treated for neovascular AMD annually in the United States.[10]

The purpose of this supplement was to highlight some interesting findings from pilot studies and literature reviews that might help the clinician and patient better differentiate between these drugs. In the first article by Sharma and colleagues, the authors compared the pathology detection rates of various spectral domain OCT devices to a time domain OCT device.[11] The study is of particular interest given that the majority of comparative effectiveness trials between different anti-VEGF agents have only used time domain OCT in their primary endpoints while the majority of specialists have migrated to spectral domain OCT. The study found that the increased resolution and image quality of SDOCT devices over TDOCT allows for finer discrimination of retinal structures. The increased speed of SDOCT allows for dense coverage of the macula resulting in the ability to see smaller areas of pigment epithelial detachments and subretinal fluid and thus might improve visual outcomes.

In the second article, Dr. Robert Avery evaluates the safety issues surrounding the use of anti-VEGF drugs.[12] There is an awareness within the community that VEGF agents delivered to the vitreous do have systemic and fellow eye biological activity. This was first highlighted in a report by the same author which found unilateral treatment with bevacizumab resulted in bilateral improvement in diabetic retinopathy. His report and reviews the most recent results on safety from the comparative effectiveness trials and summarizes the compelling data to consider on the systemic safety of these drugs.

In the third article, Malik *et al* evaluated the safety profiles of anti-VEGF on human retinal pigment epithelium cells in culture.[13] Administering these doses on the cell cultures of the RPE is significant, since past literature has highlighted the important interactions between the choriocapillaries, choroidal neovascularization, and RPE. Most recently, in the CATT trial, Ranibizumab was determined to cause a greater amount of geographic atrophy (or loss of RPE cells) than Bevacizumab at 2 years.[8] Thus the article is timely since the evaluation of RPE effects are necessary to consider in light of the drug chosen for treatment.

In the fourth article by Dr. Phil Ferrone, patients treated with other anti-VEGF inhibitors were transitioned to Aflibercept in a retrospective fashion.[14] In the fifth article by Singh *et al*, the anti-VEGF inhibitor aflibercept was used to transition patients to standardized dosing by the drug label with q8 week dosing.[15] Aflibercept has several theoretical advantages over other VEGF blockers: (1) it has a much higher binding affinity for VEGF (~0.5 pM dissociation constant for $VEGF_{165}$ and $VEGF_{121}$) than either bevacizumab or ranibizumab;[16] (2) it binds related growth factors such as placental growth factor 1 and 2 (PLGF1 and PLGF2) and VEGF-B, which may be advantageous in certain disease situations, including retinal neovascularization;[17] and (3) the vitreous half life of aflibercept (18 days) is longer than ranibizumab (9 days), but slightly shorter than bevacizumab (21 days).[18] With the approval of any new anti-VEGF therapy, there are many subjects who have received previous anti-VEGF treatments and were switched to the new medication.[19–22] These trials are different because of their prospective nature and their anatomic evaluation of outcomes following treatment.

We have focused these articles strictly on the management of exudative AMD and hope that these articles provide stimulus for discussion in our field. In evaluations such as these, there are obvious limitations to the analyses such as the retrospective biases from chart reviews, smaller patient numbers, and lack of comparator arms to name a few. However, the studies have significant merit highlighting some of the many questions with clinicians grapple with on a day-to-day basis. Hopefully these studies elucidate some salient points that can be integrated into the practice of physicians.

Competing interests None.

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Provenance and peer review Commissioned; externally peer reviewed.

OPEN ACCESS

To cite Singh RP. *Br J Ophthalmol* 2014;**98**:i1–i2.

Br J Ophthalmol 2014;**98**:i1–i2.
doi:10.1136/bjophthalmol-2014-305502

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