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The views expressed are those of the author.

Update on Medical Retina

I took over as the Focus Editor about four years ago and it is time now for me to move on. I am going to take this opportunity to write a final article on medical retina as this has changed dramatically in the past 10 years; I will focus on the developments in the past three years.

Age-related macular degeneration (AMD)

Lucentis vs Avastin

Lucentis is still the treatment of choice in the UK. In both CATT and IVAN studies, Avastin was demonstrated to have similar ocular efficacy (non-inferior in CATT, inconclusive in IVAN) but there is some uncertainty on the systemic safety profile. In IVAN, patients treated with Avastin had a reduction of systemic VEGF level but patients treated with Lucentis had no significant changes. The debate will go on.

Fixed dosing vs PRN i.e. 'as required' (discontinuous)

In the CATT study, a 'zero-tolerance' re-treatment policy, mainly based on time domain OCT changes, was employed. In the study, using a tight re-treatment criteria, PRN treatment with Lucentis showed a non-inferior outcome compared with monthly Lucentis treatment. However, this was based on a monthly visit and treatment if there was any doubt. The outcome was statistically non-inferior but it was numerically worse for vision (8.5 letters gain on monthly vs 6.8 letters on PRN) and PRN treatment was also worse in all the anatomical secondary endpoints. Furthermore, in order to achieve these results, the mean number of injections was 6.9 compared to 11.7 in the monthly group. When the reading centre read the OCT, they would have treated more patients, so it might be possible to get true equal gain but another two injections might be needed.

In IVAN, the discontinuous group had much closer results to the monthly group. The discontinuous group was treated with three loading doses at monthly intervals, followed by monthly monitoring. If there were recurrences, another three injections at monthly intervals were given. This might be the optimum regimen with Lucentis, as it would reduce OCT monitoring visits.

Eylea two monthly vs Lucentis monthly

Eylea (VEGF trap-eye) was approved by the FDA in November 2011. It is expected to be licensed in Europe in 2012. The VIEW study compared monthly Lucentis, monthly low dosage of VEGF trap-eye, monthly Eylea and two-monthly Eylea after a loading dose of three injections. All four arms showed almost identical results. Although monthly Eylea got 9.3 letter gain in the study, let us just focus on the visual gain for the monthly Lucentis versus two-monthly Eylea which were 8.7 letter and 8.4 letter respectively. That is a very close non-inferiority outcome, not CATT (8.5 vs 6.8) type non-inferiority.

So when Eylea becomes available in the UK, we will be able to carry out two-monthly treatments to get the same result as monthly Lucentis and with only seven to eight treatment visits instead of 12 to 13 visits. Moreover, no interim visit between the two-monthly treatment visit will be required.

The price of Eylea in Europe is unconfirmed but in the US it is $100 cheaper per vial (at the time of writing) than Lucentis. We hope the price will be even lower in Europe, compared with Lucentis but will not know until it is approved by the MHRA.

In year two of the VIEW study, the difference between Lucentis and Eylea was less. In the second year, the treatment regimen was changed to a capped PRN. Patients were treated at least once every three months, but could be treated more frequently and monitored monthly. In both groups, the vision was reduced by 0.8 letters during the second year and the number of injections was 4.7 and 4.2 for Lucentis and Eylea respectively. The study finished at 96 weeks though – not fully two years – so if they had continued to give two-monthly Eylea injections, it would need five injections. This goes back to the discussion of whether monthly visits are needed. Furthermore, it is not known whether giving Lucentis every two months would give a similar (non-inferior) result even at year 1.

Treat and Extend
Treat and Extend is based on the principle of extending the treatment interval as well as the visit interval, based on the treatment response. In brief, you treat every four weeks until the retina is completely dry on SD-OCT. Then this is extended to a visit after six weeks. If the retina is dry, on OCT, the patient would be treated, and the next visit would be extended to eight weeks. If the retina is not dry, the patient would be treated and the next visit reduced to four weeks. I would only extend to a maximum of 16 weeks based on personal experience in the first two years of treatment. So, the patient is treated at every visit, but the OCT guides the treatment visit interval. It has yet to be shown to be effective in a large scale randomised controlled trial comparing monthly injection or PRN regimen, although many retinal specialists like it. It works well in units when appointments can be easily adjusted, but in practice it can be difficult. It does slow down the clinic, but at least some patients would only need to visit once every four months.

NeoVista VIDION (Epi-RAD)
Based on visual acuity outcomes, the CABERNET study evaluating epimacular brachytherapy for the treatment of wet AMD did not achieve its primary endpoint at two years.

The phase three, multicentre, prospective, randomised CABERNET study included 457 treatment-naïve patients who were divided into two arms. Patients in the treatment arm (n=302) underwent strontium-90 beta radiation with epimacular brachytherapy (NeoVista) and two mandatory Lucentis treatments. Patients in the control arm (n=155) received Lucentis following a modified PIER protocol, which included three initial monthly injections followed by injections once every three months. Patients were seen on a monthly basis, and rescue therapy was permitted, at the investigators' discretion.

The primary endpoint of CABERNET was visual acuity, specifically, the percentage of patients losing fewer than 15 letters of vision. In patients treated with epimacular brachytherapy, six injections were required at the two-year mark for a mean 2.5 letter loss. Patients treated with Lucentis required 11 injections and achieved a mean 4.4 letter gain. So in the Lucentis group, five more injections were required for a difference of 6.9 letters, but also without a vitrectomy. This result is unlikely to gain FDA approval as it is considered as a surgical appliance, however, it has already received the CE mark. Based on these results, it is difficult to justify using it on treatment-naïve patients. It might have a role in patients who require a high number of Lucentis injections.

Diabetic macular oedema (DMO)
Lucentis was licensed for DMO but so far has not been approved by NICE. The main reason is no doubt on cost, but unlike AMD patients, in clinical trial, DMO patients did not lose much vision with sham or laser treatment, and the gain with Lucentis was only modest. The role of the laser remains unclear. It might reduce the number of injections slightly but with a mild loss of vision.

Micropulse laser might be the way to go for non-foveal involving DMO or early foveal involving DMO with central OCT thickness less than 300 microns (based on time-domain OCT). For anything else, an injectable might be needed.

Ilvein was licensed for DMO in the UK. It is a steroid which can provide treatment benefit for up to three years but it is not yet approved by NICE. In the FAME study, in the chronic DMO group (oedema for more than three years), the visual gain was most significant. The main problem is cataract and pressure rise. Most patients would need cataract surgery and over 70% of patients have experienced pressure rise, but fortunately only 5% require glaucoma surgery.

Ozurdex is not licensed for DMO, as the phase III data is not yet published or presented at the time of writing although the study was completed. More data will become available very soon.

The role of lasers, steroids and anti-VEGF in DMO either on their own or in combination, will no doubt become clearer in the future.

Retinal vein occlusion (RVO)
Lucentis and Ozurdex are licensed for macular oedema secondary to RVO. However, only Ozurdex is approved by NICE. It is unclear whether Lucentis is better than Ozurdex or vice versa, due to differences in trial design. There are several head-to-head studies in progress and more will be known soon.

Ozurdex was initially studied as a treatment to be used every six months, but there is increasing evidence that it might not last as long as that. It is probably more likely to last for four to five months. Despite the NICE guidance, which has not restricted the timing of the re-treatment of Ozurdex, some PCTs in England do not allow patients to be re-treated until six months has lapsed. This seems illogical, and patients might not get the maximum benefit of the treatment.

Vitreomacular adhesion (VMA)
Microplasmin was shown to be able to release VMA in 26.4% as compared to 10.2% in the placebo-treated group at 28 days after a single injection in two phase III clinical trials. It has received favourable opinion by the FDA expert panel but it is not yet approved.

Patients without epiretinal membranes were more likely to have resolution of VMA (37.4% compared to 14.3% of placebo patients). In patients with a full thickness macular hole, 40.6% of patients saw closure at 28 days with one injection compared to 10.6% of the placebo group. The need for surgical intervention was significantly less in the microplasmin group (17.6% compared to 26.7% placebo).

Conclusion
More drugs, more injections, more choices! Ten years ago, we had the laser. It was easy then. Just treat or not treat. Now, we have to figure out which treatment, how often to give the treatment, when to add another treatment, and when to stop.

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