THE ROYAL COLLEGE OF OPHTHALMOLOGISTS

Focus

Winter
2009

An occasional update commissioned by the College. The views expressed are those of the author.

Medical Retina Update

Age-related macular degeneration (AMD), diabetic macular oedema (DMO) and retinal vein occlusion (RVO) account for over 70% of severe visual loss in the developed world. In the past few years, several major studies have further advanced our knowledge in combating these conditions.

Age-related macular degeneration

Lucentis has dramatically changed the life of millions who suffered from wet AMD. Pivotal studies (Anchor and Marina) have shown that at 12 months, on average there is an 8 letter gain in vision on the ETDRS chart after monthly injection of Lucentis. However, monthly injections are costly and carry a significant burden to the patient and the health care system.

Pronto study was a small but important case series. It introduced the concept of the separation of the loading phase and the maintenance phase. In the loading phase, injections are given monthly until the retina is "dry", and typically 3 injections are required. This is followed by monthly monitoring, and the patient is retreated only if there is recurrence, with criteria such as increased retinal thickness in optical coherent topography (OCT), presence of new haemorrhage or visual loss. In this study, an 8 letter gain was achieved. However, the patients in the Pronto study were not treatment naïve, unlike those in the pivotal studies. Despite that, it has become the "standard treatment" in most countries, including Britain. Sustain study is a large scale Pronto, involving over 500 patients. Unlike the pivotal studies, there is no sham treatment group. At 12 months, the average gain in vision was 3.6 letters with average of 5.6 injections. Fewer injections can achieve slightly worse visual outcome.

The Pier study was carried out at the same period as the pivotal studies. A loading phase of 3 injections at monthly intervals was followed by injections given as 3 monthly intervals. At 12 months, no letter gain was achieved but it was much better than the sham treatment group of 16 letter loss. A head to head study comparing monthly injection with the "Pier" treatment schedule (Excite) was reported. Monthly injected patients had on average an 8.3 letter gain (similar to the pivotal studies) as compared to a 3.8 letter gain in the 3 loading doses then quarterly treated patients, which is better than PIER.

So what about combination?

The theoretical benefit of combining photodynamic therapy (PDT) with Lucentis is clear, as they act differently, so it is likely to have synergy effect. The Mont Blanc study compared standard PDT with Lucentis to Lucentis alone, using the "Pronto" type protocol. The Lucentis monotherapy group had a 4.4 letter gain with 5.1 injections while the combination group had a 2.5 letter gain with 4.8 injections and 1.7 PDT treatments. We are still waiting for the Denali study which has a reduced fluence arm, to see whether that would give a better result. Otherwise, combination is not superior to monotherapy and it is not recommended routinely.

What do I think about the results?

Individualisation of treatment has become the buzzword in medicine. However, whether that can be achieved in practice is often in doubt. We have 2 large scale studies (Sustain and Mont Blanc monotherapy arm), using individualisation by monthly monitoring. In these 2 studies, we achieved approximately a 4 letter gain with 5.5 injections. So far, no treatment regimen has better results than monthly injection with 8 letter gain. It remains to be seen whether tighter retreatment criteria and more injections can achieve better result than the "Pronto" regimen. In patients who cannot attend on a monthly basis, using the Excite regimen (loading then quarterly) may be a reasonable but controversial option. In clinical trials, there is approximately a 4 letter gain with 6 injections, which is very similar to the Pronto regimen. Further research is needed to determine which patients should go on to which regimen and we should not forget that about 20% of patients do not need any more treatment after the loading doses.

Diabetic macular oedema

Diabetic retinopathy clinical research network (DRCR.net) has becoming a major research powerhouse. Its objective is to develop and operate a collaborative network to facilitate multicentre clinical research, and is funded by the National Eye Institute, Industry and Charity Foundation. So far, all the centres are based in the US, but they have just started to accept international sites.

I will summarise a few published studies from the DRCR.net related to DMO.

- Comparing traditional ETDRS laser treatment to the more commonly used mild macular grid laser, it was found that both are effective in terms of vision but the traditional method has significantly greater reduction of retinal thickness as measured by OCT.
- Comparing intravitreal triamcinolone (ivTA) to laser for DMO, laser has better results beyond 6 months. Further more, the final result was the same whether the patient was treatment naïve or had previous laser, as well as regardless of baseline retinal thickness. Combination of ivTA and laser was not studied.
- A short study on Avastin with or without laser for DMO found the dosage of 1.25mg or 2.5mg makes very little difference. However, in the short term, Avastin was found to be effective but combination does not add much value. That is not totally unexpected as laser might take a lot longer to work.

Further information can be found in *www.drcr.net*

Outwith the DRCR.net, Lucentis has been studied in the READ-2 study for 6 months, it compared Lucentis (4 injections), combination of laser and 2 injections of Lucentis and laser alone. The results were 7.6, 3.8 and -1.1 letter gains respectively. Monthly Lucentis as studied in the Resolve Study, patient gains about 10.3 letters as compared to -1.4 letters in sham treated group at 12 months. Macugen was also effective in DMO with 6 weekly injections achieving a 4.7 letter gain at week 36 as compared to -0.4 letters in the sham group.

All these results are encouraging, but none of these studies had included patients with ischaemic DMO. A significant proportion of our patients suffer from ischaemic DMO and it remains the most difficult to treat. These agents have to be studied in ischaemic DMO.

Finally, not all of us would be keen to inject monthly in patients with focal macular oedema. In these patients, laser remains the main treatment option. My group has published a randomised controlled trial comparing micropulse laser to mild macular grid laser. It was found both were equally effective in terms of vision and OCT thickness reduction, but micropulse laser is 8x less likely to have visible scaring. Micropulse laser delivers laser energy in pulses allowing cooling between pulses. This enables high level of energy to the retinal pigment epithelium with less collateral damage in the retina.

Retinal vein occlusion

Osurdex: Osurdex is the first FDA approved treatment for macular oedema caused by retinal vein occlusion. It has not received EMEA approval yet, but in theory, it is available in the UK at least in the private sector. It is an intravitreal implant containing 0.7 mg dexamethasone in the solid polymer drug delivery system, similar to a vircyl suture, which dissolves completely. It can be injected into the vitreous using a 22 gauge needle. The FDA's decision was based on data from 2 multicenter, double-blind, randomized parallel studies (n = 1626). In each individual study and in pooled analysis, dexamethasone was significantly faster than placebo in achieving a 3-line (15 letter) or greater improvement in best-corrected visual acuity ($P < .01$), an effect that was maintained for about 1 to 3 months. For 20% to 30% of patients, the onset of a 3-line improvement in best-corrected visual acuity occurred within the first 2 months of implantation.

Adverse events most commonly reported during the first 6 months of dexamethasone therapy included increased intraocular pressure (25% vs 1% for placebo) and conjunctival haemorrhage (7% vs 5%). Increased intraocular pressure peaked at day 60 and returned to baseline levels within 6 months; during the initial treatment period, only 0.7% of patients required laser or surgical procedures to manage this condition. Further details can be found in *www.allergan.com/assets/pdf/ozurdex_pi.pdf*

Lucentis in BRAVO and CRUISE: BRAVO is a multicenter study of 397 patients using monthly Lucentis in patients with macular oedema secondary to branch-RVO. CRUISE is a similar multicenter study of 392 patients using monthly Lucentis in patients with macular oedema secondary to central-RVO.

Data from the BRAVO study showed at month six, patients who received 0.3 mg of Lucentis had a mean gain of 16.6 letters and patients who received 0.5 mg of Lucentis had a mean gain of 18.3 letters (compared to 7.3 letters in patients receiving sham injections). In the CRUISE study, at month six, patients who received 0.3 mg of Lucentis had a mean gain of 12.7 letters and patients who received 0.5 mg of Lucentis had a mean gain of 14.9 letters (compared to 0.8 letters for patients receiving sham injections). In both trials, a statistically significant mean gain in best correct visual acuity was observed as early as day seven for both doses of Lucentis compared with sham. Further details can be found in *www.gene.com/gene/news/press-releases/display.do?method=detail&id=12367*

Triamcinolone in SCORE: Intravitreal preservative free triamcinolone at 1mg and 4mg were compared with standard care for BRVO (i.e. laser) and CRVO (i.e. observation). In BRVO, laser and triamcinolone have very similar outcomes but laser has a significantly lower frequency of adverse events. Hence, the use of ivTA was not recommended. Nonetheless, combination was not studied.

In CRVO, triamcinolone is better than observation. Both 4 mg and 1mg were equally effective, and 1mg has significantly lower frequency of adverse events than 4mg. So the 1mg dose was recommended to be used in CRVO. However, the study preparation of 1mg is not commercially available. So we do not know whether giving 1mg of commercially available triamcinolone would get the same results. Also it is practically difficult to give 0.025ml. Furthermore, in the CRVO study, the mean change of vision was -12.1, -1.2, and -1.2 for usual care, 1 mg and 4 mg groups respectively. The sham group has much worse results than the sham patients in the CRUISE study, suggesting different patient population.

Conclusion

Anti-VEGF therapies, steroids, and laser appear to be effective in these blinding conditions. The best way of using them remains unclear.

Victor Chong,
Oxford Eye Hospital, University of Oxford, Oxford

References:

- Mitchell et al., BJO, 2009 May 20 Epub – AMD studies
- Figueira et al., BJO 2009 93: 1341-4 – Micropulse laser
- Nguyen et al., Ophthalmology 2009 116 2175-81 – READ-2
- Cunningham et al., Ophthalmology 2005 112: 1747-57 – Macugen for DME
- Scott et al., Arch Ophthal 2009 127:1115-28 – SCORE BRVO
- Ip et al., Arch Ophthal 2009 127:1101-14 – SCORE CRVO

Figure Legend: A) Wet age-related macular degeneration B) Diabetic macular oedema C) Central retinal vein occlusion D) Branch retinal vein occlusion