

cities in low- and middle income countries. We don't yet know how effective PRN treatment might be when retreatment is guided by visual acuity alone, as both visual acuity and retinal thickness were measured at each visit in these trials.

Although intermittent regimes reduce the number of injections, patients still have to be reviewed every 1–2 months, which leads to very busy clinics; this is also a significant burden for the patients and for their families.

Which diseases can be treated?

Age-related macular degeneration

Lucentis, Avastin and Eyelea are equally effective in exudative AMD. There appears to be little difference between monthly and PRN dosing. The average (mean) improvement in vision is about 1–2 lines, and about one-third of patients will improve by three or more lines. With a PRN regime, an average of seven injections will be required in the first year. Most of these trials excluded eyes with a vision of less than 6/96 (4/60), and treatment is unlikely to be effective in advanced exudative AMD with sub-macular scarring or a vision of 'counting fingers' or 'hand movement'. Unfortunately, exudative AMD often co-exists with atrophic ('dry') AMD, and the anti-VEGF drugs only treat the exudative component. With longer follow-up (over 2 years), atrophic AMD may cause a gradual loss of vision despite effective anti-VEGF treatment.

Diabetic macular oedema

Once again, there seems to be little difference between the different anti-VEGF drugs. All three are effective at

treating diabetic macular oedema, and the average improvement in vision is about 1.5 lines. Roughly 25% of patients will have their visual acuity improve by three or more lines and 50% by two or more lines. An average of seven injections will be required in the first year of treatment with a PRN regime.

Not all patients with diabetic macular oedema need to be treated with anti-VEGF. Laser treatment still has an important role: macular oedema which does not involve the fovea is best treated with laser. These patients will normally have good vision, and the laser will help to preserve it. Moreover, laser is usually effective with a single treatment, which is much easier for the patient than repeated monthly injections.

If new vessels are present, they should be given pan-retinal laser treatment first, before any macular oedema is treated using anti-VEGF. This is because anti-VEGF makes the new vessels regress very quickly. As the treated vessels become fibrotic, they contract, which can cause a retinal detachment.

Retinal vein occlusion

There is good evidence from clinical trials that all three anti-VEGF drugs will reduce the risk of loss of vision following central retinal vein occlusion. About 50% of patients will gain three or more lines, with a mean improvement of about two lines. There is also a reduced risk of rubeosis and secondary glaucoma with anti-VEGF treatment.

Lucentis has been shown to improve outcomes after branch retinal vein occlusion as well. However, as many of these patients will improve spontaneously, this evidence is not quite as strong.

In summary, anti-VEGF drugs are probably the most significant advance in ophthalmology in the last decade. They have enabled us to treat what were previously untreatable conditions. They are not a perfect solution, however.

- They do not cure the underlying problem, so repeated treatment is necessary and most patients will require a lifetime of regular monitoring.
- The drugs are expensive, and even high-income countries have struggled with the costs and logistics of delivering thousands of intraocular injections every year.
- Although anti-VEGF drugs are the most effective treatment for many retinal diseases, the visual improvement is modest, averaging about two lines of vision. Relatively few patients will regain normal vision.
- Patients who present late, with very advanced disease and a visual acuity of less than 3/60, may not benefit from treatment.
- Most PRN treatment regimes rely on OCT imaging, which is rarely available in low and middle income countries. We have little information on the use of anti-VEGF in this setting, and we cannot be sure that the good results achieved in Europe and North America will be replicated in Africa, India, or China.

Despite these reservations, anti-VEGF drugs are going to play an increasing role in the prevention of blindness worldwide. As the global population ages, and becomes more overweight, both AMD and diabetic retinopathy will become more common. The drugs will become cheaper, and we may find better ways of monitoring treatment so that expensive OCT is no longer essential.

Anti-VEGF treatment for acute ROP – *not yet recommended!*



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There are several reasons why anti-VEGF agents are not recommended for acute, severe retinopathy of prematurity (ROP).

- There has only been one randomised trial, which compared laser with Avastin (bevacizumab) for Type 1 ROP. It was only more effective in preventing early recurrence of severe disease in Zone 1 (posterior), but the recurrence rate in the laser arm was worse than would be expected based on other studies. More babies died in the anti-VEGF arm of the trial, but the

difference was not statistically significant.

- There are major concerns about the short- and long-term impact of anti-VEGF agents on the lung, kidneys and brain of a baby.
- Follow-up studies, using fluorescein angiography, indicate that normal retinal vascularisation may not take place after administration of bevacizumab, with extensive areas of non-perfusion months after treatment.
- There are an increasing number of case reports which show that, although Avastin can lead to regression of ROP in the short term, the ROP can recur months later. This means that an acute disease with a known natural history has the potential to become a chronic

disease with an unknown and unpredictable natural history.

- Some surgeons use Avastin for Stage 4a or 4b ROP prior to surgery. This can make the surgery easier, but there is still the risk of systemic complications.

The leaking capillaries present in eyes with retinopathy increase the risk of large molecules (e.g. anti-VEGF drugs injected into the eye) entering the systemic circulation, and so the systemic safety of these drugs is important, particularly in preterm infants. If anti-VEGF drugs seem to be the only option to preserve sight when extensive laser has failed, or the infant is too sick for laser, this treatment can be offered, but **only** after parents have been fully informed of the possible consequences.