Intravitreal VEGF inhibitors for diabetic macular oedema: Are they worth the cost?

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In 1985, the ETDRS (Early Treatment Diabetic Retinopathy Study) demonstrated that focal (direct/grid) laser photocoagulation reduces moderate vision loss caused by diabetic macular oedema (DMO) by 50% or more and described "clinically significant macular oedema" (ETDRS Research Group, 1985), which defined the parameters for treatment for the next 26 years.

In 2011, two large randomised controlled trials substantiated the safety and efficacy of anti-vascular endothelial growth factor (VEGF) drugs for diabetic retinopathy:

1. The RESTORE (Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema) study was an industry-sponsored, multicentre randomised controlled trial in 73 centres across 13 countries (Mitchell et al, 2011).
2. The DRCR.net (Diabetic Retinopathy Clinical Research Network) study, a randomised controlled trial funded by the US National Institutes of Health, was conducted at 52 clinical sites in the US (Elman et al, 2011).

In the RESTORE study, the proportions of participants gaining 10 letters in visual acuity in their treated eye after 12 months of treatment were 37% in those randomised to ranibizumab monotherapy, 43% in those randomised to ranibizumab plus laser photocoagulation and 15% in those randomised to laser photocoagulation alone ($P<0.001$). The proportions of participants who lost 10 letters of visual acuity in their treated eye after 12 months were 3%, 4% and 13%, respectively ($P<0.05$).

In the DRCR.net study, after 12 months of treatment a gain of 10 letters in visual acuity was reported in 47% of eyes treated with ranibizumab plus deferred laser photocoagulation, 51% of eyes treated with ranibizumab plus prompt laser photocoagulation and 28% of eyes treated with laser photocoagulation alone ($P<0.001$). After 12 months a loss of 10 letters in the treated eye was reported in 3%, 3% and 13% of eyes respectively, ($P\leq0.001$).

In 2011, NICE decided not to recommend ranibizumab for the treatment of DMO, largely owing to the high costs (approximately £1000 per injection at that time) associated with the drug. In early 2013, NICE overturned its ruling and recommended ranibizumab as an option for treating visual impairment due to diabetic macular oedema only if (NICE, 2013):

- The person has a central retinal thickness of 400 µm or more.
- And the manufacturer provides ranibizumab with the discount agreed as part of the patient access scheme (as revised in 2012).

Other possible VEGF inhibitors include aflibercept, which is currently being reviewed by NICE for DMO, and bevacizumab, which is a preparation that has yet to be tested sufficiently against DMO to be approved for use in this indication. In addition, there are other intravitreal VEGF inhibitors that have not yet obtained a European licence. Competition and time will reduce the cost.

The workload for intravitreal injections is increasing. In Gloucestershire, a county with a population of 600 000, we are needing to give over 7000 intravitreal injections per annum, the vast majority being for age-related macular degeneration. Approximately 700 of these were for diabetic macular oedema this year.

The economic arguments are complicated, pitting prioritisation of healthcare to prevent more visual loss from DMO against providing better facilities in other aspects of healthcare (e.g. renal dialysis or cardiac surgery).

Having watched people lose their vision over the years from centre-involving DMO and the potential that these drugs show, I believe that they are worth the cost. However, we also need further advances in this field, such as VEGF inhibitors that have a longer duration of action than 4 weeks, can be administered orally or in an eye drop preparation rather than requiring intravitreal injections, and are less expensive. ■

Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* **103**: 1796–806

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