Retinopathy

What are the baseline predictors of outcomes in people with DMO treated with ranibizumab?

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There have been a number of randomised controlled trials that have contributed to the body of evidence supporting the use of anti-vascular endothelial growth factor (VEGF) agents for the treatment of diabetic macular oedema (DMO), and both NICE and the Scottish Drugs Consortium have approved the use of ranibizumab in individuals with visual impairment due to centre-involved DMO. Whilst ranibizumab has been shown to be more effective than laser treatment at improving visual acuity, there are some individuals who do not respond or only partially respond to anti-VEGF agents and consequently still have a poor visual outcome.

The RISE and RIDE studies were parallel phase III, multicentre, double-masked, sham-controlled studies in which individuals were randomised 1:1:1 to intravitreal ranibizumab 0.3 mg, 0.5 mg and sham injection.

The paper by Sophie et al (summarised alongside) explores the baseline characteristics of the patients who were enrolled into the studies in order to assess whether there are any characteristics that can predict the outcome in both patients with and without ranibizumab treatment. Rescue laser treatment was allowed after 3 months, and this was used frequently in the sham group.

Assessment is confined to baseline characteristics and does not consider changes in characteristics such as HbA_{1c}, hypertension and hyperlipidaemia over the 2-year duration of the studies. The authors looked at functional outcomes, i.e. visual outcomes – a final best corrected visual acuity (BCVA) of 20/40 or better (equivalent to 6/12 in the UK – the standard for driving); and gain or loss of 15 or more letters – and an anatomical outcome – resolution of DMO and restoration of normal central retinal thickness (≤250 µm on ocular coherence tomography).

Although medical factors were explored, the main predictive factors seemed to relate to pathological features, and this was further confirmed by a separate *post hoc* analysis of the same patients in which improvement in visual acuity and reduction of DMO were independent of the baseline HbA_{1c} (Bansal et al, 2015). However, renal disease was associated with a reduced chance of achieving a final BCVA of 6/12 or better, a 4-fold higher chance of loss of 15 letters and a 5-fold increased chance of visual impairment affecting daily living tasks in the patients who did not receive ranibizumab. Patients with cardiovascular disease were less likely to achieve a final BCVA of 6/12 even with treatment.

When retinal features were considered, patients receiving treatment who had fluid under the macula (as well as intraretinal fluid) were almost three times more likely to gain a final BCVA of 6/12 and 15 letters improvement than those without submacular fluid. In the sham group, however, submacular fluid predicted a poor visual outcome. The presence of intraretinal cysts was also predictive of a poor outcome in the sham group and the likelihood of a poor outcome rose with the size of the cysts. Intraretinal cysts did not adversely predict outcome in the treated group. Submacular fluid and macrocystoid changes have traditionally been considered a bad sign, but clearly anti-VEGF treatment is superior to laser treatment in these cases.

Patients with a shorter duration of diabetes and of younger age had the best outcomes and individuals who had had previous pan-retinal photocoagulation did not get such good results. It is likely that this reflects both the extent of the damage to the retinal circulation and the comparative resilience of the macula in younger people.

The authors have produced an interesting and thought-provoking paper that should allow for a more informed prognosis when discussing treatment options with patients. ■

Bansal AS, Khurana RN, Wieland MR et al (2015) Influence of glycosylated hemoglobin on the efficacy of ranibizumab for diabetic macular edema: a post hoc analysis of the RIDE/RISE trials. *Ophthalmology* **122**: 1573–9

Ophthalmology

Baseline predictors for response to ranibizumab treatment

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 Following two identical placebo-controlled clinical trials (RIDE and RISE) that investigated the effectiveness of intravitreal ranibizumab injections in diabetic macular oedema (DMO), *post hoc* analyses were carried out to determine the baseline predictors of relevant outcome measures 2 years after treatment. These included best-corrected visual acuity (BCVA) and central foveal thickness (CFT).

2 In this analysis, 502 people were randomised to ranibizumab and 257 were randomised to placebo.

3 Among the ranibizumab-treated individuals, baseline predictors of BCVA ≥20/40 were the following: good BCVA, submacular fluid, no cardiovascular disease, no scatter photocoagulation and male gender.

4 Among the placebo-treated individuals, the baseline predictors of BCVA ≥20/40 were mild increase in CFT, presence of hard exudates in centre subfield and absence of renal disease.

5 Individuals with DMO and submacular fluid, intraretinal cysts, severe thickening or renal disease responded poorly when left untreated but responded well when administered monthly injections of ranibizumab.

6 The authors conclude that aggressive, sustained suppression of vascular endothelial growth factor can overcome poor prognostic features at baseline.

Sophie R, Lu N, Campochiaro PA (2015) Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. *Ophthalmology* **122**: 1395–401

J Diabetes Complications

Comparing quality of life after different DMO treatments

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 The aim of this study was to compare the changes in vision-related quality of life (VR-QoL) in people with diabetic macular oedema (DMO) undergoing intravitreal ranibizumab (IVR) injections and focal/grid laser.

2 Seventy people with DMO were randomised to undergo IVR injection (n=35) and laser (n=35). Clinical measures and the Turkish version of the 25-item Visual Function Questionnaire (VFQ-25) were used before the intervention and 6 months after.

3 The VFQ-25 measures VR-QoL and comprises 25 items wherein participants are expected to assess the level of difficulty of particular visual symptoms and day-to-day activities.

4 At baseline, the treatment groups had similar characteristics.

5 Distance and near visual acuities improved more in the IVR group than the laser group (P<0.01). Also, the reduction in central retinal thickness (CRT) in the IVR group was higher than that in the laser treatment group (P<0.01); another benefit of the IVR intervention.

6 In both groups, the VFQ-25 composite score tended to improve from baseline to 6 months. At 6 months, the changes in composite VFQ-25 score were significantly higher in IVR group than in laser group (P<0.05).

7 The authors inferred that IVR treatment can improve VR-QoL more than laser treatment in DMO, as well as improving visual acuity and CRT.

Turkoglu EB, Celık E, Aksoy N et al (2015) Changes in vision related quality of life in patients with diabetic macular edema: ranibizumab or laser treatment? *J Diabetes Complications* **29**: 540–3

JAMA Ophthalmol

High intra-ocular pressure: A complication of anti-VEGF injections?

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 There have been reports that anti-vascular endothelial growth factor (VEGF) may cause sustained elevation of intraocular pressure (IOP) and may increase the risk of glaucoma for people with retinal disease.

2 Therefore, the authors planned to determine the risk of sustained IOP elevation and the need for IOP-lowering treatments for people who have received intravitreous injections of ranibizumab.

3 An analysis was undertaken within a Diabetic Retinopathy Clinical Research Network randomised clinical trial. Of 582 eyes (of 486 participants) with centre-involved diabetic macular oedema (DMO) and no pre-existing open-angle glaucoma, roughly half of the individuals received sham injection plus focal/grid laser treatment, and half received ranibizumab and sometimes focal/grid laser treatment.

4 The probability of sustained IOP elevation or starting IOP-lowering therapy in 3 years of follow-up after repeated ranibizumab injections was 9.5% for the ranibizumab injection group and 3.4% in the sham injection group (hazard ratio, 2.9 [99% confidence interval, 1.0–7.9]; P=0.01).

5 In eyes with centre-involved DMO and no prior open-angle glaucoma, repeated intravitreous injections of ranibizumab may increase the risk of sustained IOP elevation or the need for IOP-lowering treatment. Clinicians should, therefore, be aware of this risk.

Bressler SB, Almukhtar T, Bhorade A et al (2015) Repeated intravitreous ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. *JAMA Ophthalmol* **133**: 589–97

Ophthalmology

Can ranibizumab reduce blindness?

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The authors planned to estimate whether visual impairment (VI) and blindness can be avoided with intravitreal ranibizumab (IVR) 0.3 mg among Hispanic and non-Hispanic whites with centre-involved diabetic macular oedema (DMO) and visual acuity (VA) of 20/32 or worse.

2 They implemented a population-based effectiveness model to simulate changes in VI with and without IVR treatment every 4 weeks.

3 They estimated the total number of people with centre-involved DMO in the US for whom IVR treatment would be considered.

4 From approximately 102 million non-Hispanic white and Hispanic individuals over the age of 45 years in 2010, 37 274 (95% simulation interval [SI], 7249–16 077) people fit the criteria set out by the authors for the model: diagnosed with centre-involved DMO with VA of 20/32 and eligible for IVR treatment.

5 For these 37 274 eligible individuals, VI in the better-seeing eye was predicted in 11 438 (95% SI, 7249–16 077) who did not receive IVR treatment over 2 years. Over 2 years, IVR 0.3 mg every 4 weeks could cause a reduction in the number of cases of VI by 45% (95% SI, 36–53%).

6 Legal blindness was predicted in 1686 (95% SI, 987–2479) individuals not receiving IVR treatment over 2 years. Over 2 years, treatment with IVR 0.3 mg every 4 weeks could reduce the number of cases of legal blindness by 75% (95% SI, 58–88%) among Hispanic and non-Hispanic white people in the US.

Varma R, Bressler NM, Doan QV et al (2015) Visual impairment and blindness avoided with ranibizumab in Hispanic and non-Hispanic whites with diabetic macular edema in the United States. *Ophthalmology* **122**: 982–9

"Ranibizumab could reduce the cases of visual impairment by 45% and cases of legal blindness by 75% in the US among Hispanics and non-Hispanic whites."