Overall, VEGF inhibitors administered by intravitreal injection have a similar harm-benefit balance. However, a publicly funded trial has shown that aflibercept is more effective than ranibizumab and bevacizumab in patients with marked loss of visual acuity.

Diabetic retinopathy is sometimes associated with focal or diffuse macular oedema, leading to severe loss of visual acuity (1). Few treatments are effective (1). Laser photocoagulation alone rarely improves visual acuity. When combined with laser therapy, intravitreal injections of ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor, markedly improves visual acuity in about 15% of patients at 12 months (1). However, ranibizumab can have serious ocular and systemic adverse effects, particularly cardiovascular disorders. Intravitreal bevacizumab provides no noteworthy advantages (2).

**Aflibercept** (Eylea®, Bayer Pharma), another VEGF inhibitor, is authorised for intravitreal administration in this setting (3,4). How does it compare to ranibizumab?

Two trials versus laser therapy and one versus a VEGF inhibitor. The data analysed by the European Medicines Agency are mainly based on two randomised trials, each of which lasted 12 months. These studies compared laser therapy with intravitreal injections of aflibercept 2 mg and sham injections in a total of 872 diabetic patients with focal macular oedema (4). At 12 months, there was significantly greater improvement in visual acuity with aflibercept than with laser therapy (4).

A US publicly funded randomised trial including 660 patients compared injections of aflibercept 2 mg and bevacizumab 0.3 mg or bevacizumab 1.25 mg (a,b) (5). At one year, the average improvement in visual acuity was generally similar in the three groups, with a gain of about a dozen letters on the ETDRS scale (Early Treatment Diabetic Retinopathy Study scale, ranging from 10 to 90 letters). In the subgroup of 305 patients with marked visual impairment at baseline (acuity less than 20/40 on the Snellen scale), the gain in ETDRS letters was greater with aflibercept than with ranibizumab (19 versus 14 letters, p=0.003) or bevacizumab (12 letters, p=0.001) (5). This analysis was planned in the protocol, and the patients were stratified accordingly.

**Ocular and systemic adverse effects.** In both trials versus laser therapy, all patients received subconjunctival anaesthesia whether they were randomised to aflibercept or sham injections. Severe adverse events were more frequent with laser therapy (4.2%) than with aflibercept (1.7%) (4).

The following ocular adverse effects were more frequent with aflibercept than with laser therapy: conjunctival haemorrhage (28% versus 17%), eye pain (9% versus 6%), ocular hypertension (2% versus 0%), vitreous floaters (6% versus 3%), and punctate keratitis (3% versus 1%) (4).

Six deaths occurred in the aflibercept group versus two in the laser group. Three deaths were due to cardiac events, and the role of aflibercept could not be ruled out in two cases (4). There was also an increase in arterial thromboembolic events among patients treated with aflibercept (3.3% versus 2.8% (6). Other adverse events occurring more frequently with aflibercept included heart failure (2.6% versus 0.3%), peripheral oedema (4.5% versus 2.8%), pneumonia (2.6% versus 1.4%) and anaemia (4.8% versus 2.4%) (4).

In the trial versus other VEGF inhibitors, the mortality rate (about 2%) and the frequency of serious adverse events (affecting about one-quarter of patients) were similar in the three groups (5). There was one case of endophthalmitis in the aflibercept group, one in the ranibizumab group, and none in the bevacizumab group (5).

**Risk of overdose.** The vials of Eylea® are overfilled, creating a risk of overdose (3).

**In practice.** Aflibercept has similar efficacy to other VEGF inhibitors administered by intravitreal injection. Its adverse effect profile is also similar. However, a publicly funded trial showed that aflibercept was more effective than its competitors in patients with marked visual loss, making it the drug of choice in this setting (6).

**Aflibercept solution for intravitreal injection**

**Eylea®**

- **4 mg** of aflibercept in 0.1 ml

**VEGF Inhibitor**

- New indication: “(….) visual impairment due to diabetic macular oedema (…)”.

[EU centralised authorisation]