Translated from ***Rev Prescrire*** **May 2015; 35 (379): 328-329**

aflibercept (Eylea°) and diabetic macular oedema

A first-choice VEGF inhibitor in case of marked visual loss

● **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 administered a maximum of once a month, *ranibizumab* 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 EDTRS 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 (**c**).

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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]

a- The investigators and trial coordinators (but not the patients and assessors) were aware of treatment allocation (ref 5).

b- The 0.3-mg and 0.5-mg unit doses of ranibizumab are both approved in the United States (ref 5), while only the 0.5-mg dose is approved in the EU (ref 1).

c- The French Pharmacoeconomic Committee considers that Eylea° « provides a minor improvement compared to existing treatments » in patients with diabetic macular oedema whose visual acuity is less than or equal to 5/10 (our translation) (ref 7).

Selected references from Prescrire's literature search.

In response to our request for information, Bayer Healthcare provided us with no documentation on its product.

1- Prescrire Editorial Staff "Ranibizumab and diabetic macular oedema. After laser therapy" *Prescrire Int* 2012; **21** (125): 66.
2- Prescrire Rédaction "Bévacizumab: pas mieux que le ranibizumab dans l'œdème maculaire chez les patients diabétiques" *Rev Prescrire* 2015; **35** (378): 262.
3- Prescrire Editorial Staff "Aflibercept and central retinal vein occlusion. No proven advantages but many uncertainties" *Prescrire Int* 2015; **24** (157): 40.
4- EMA - CHMP "Assessment report for Eylea. EMEA/H/C/002392/II/0009" 26 June 2014: 79 pages.
5- The Diabetic Retinopathy Clinical Research Network "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema" *N Engl J Med* February 2015; www.nejm.org: 11 pages + appendix & protocol: 163 pages.
6- European Commission "SPC-Eylea" 24 February 2015: 27 pages.
7- HAS - Commission de la transparence "Avis-Eylea" 18 March 2015: 28 pages.

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