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Ranibizumab or bevacizumab in AMD?

The Italian independent drug bulletin *Informazioni sui Farmaci*, a member of the International Society of Drug Bulletins (ISDB), published a review comparing *ranibizumab* versus *bevacizumab* for age-related macular degeneration (AMD). Its conclusion differs from that of *Prescrire's* review, published in issue 163. Giulio Formoso and Maria Font have offered on behalf of *Informazioni sui Farmaci* to present their evaluations. The position of *Informazioni sui Farmaci* is recapped below, and an English translation of the full article published in the Italian bulletin is available at english.prescrire.org. Giulio Formoso and Maria Font's letter is followed by a few points outlining *Prescrire's* position, already set out in detail in issue 163.

Dear *Prescrire* Editors,
We would like to inform you that we have published an article in the ISDB bulletin *Informazioni sui Farmaci* discussing the benefits and risks of *bevacizumab* and *ranibizumab* in age-related macular disease (AMD). In doing so, we have commented on your April 2015 review, trying to provide our readers with an overview of different evaluations (ours differs from yours) that can be made using the same evidence and, specifically, which drug should be used preferentially to treat this disease. Our article is also available online on an Italian internet forum where papers on drug policy are posted (<http://rivista.informazionisuifarmaci.it/avastin-contro-lucentis-ovvero-limpatto-clinico-della-sostenibilita-delle-terapie>).

We have translated our article to make it available for an open discussion (or a point/counterpoint discussion), which is always healthy. This may be of interest to our readers and to yours, and could stir up debate on access to effective drugs.

As for specific comments on your review, we agree with your view that, ideally, price should not prevent the use of effective and safe medicines, as also advocated by the WHO in its Essential Medicines List (EML). However, we are not sure that the price of *ranibizumab* could be easily reduced (as you say it should be) without actual competition from a much less expensive drug like *bevacizumab*. The safety and effectiveness of *bevacizumab* were evaluated favourably by the WHO itself, and this drug was included in the EML (but the much more expensive *ranibizumab* was not considered to offer any real advantages). We have pointed out that the high cost of *ranibizumab* has often prevented its use in clinical practice (for example, by treating only one eye or limiting its use to eyes with severe vision loss). This is a much

more serious unintended consequence than a very slight increase in gastrointestinal risk, since it may lead to blindness. Moreover, the 1.3% absolute increase in gastrointestinal events with *bevacizumab* is questionable, because this result is mainly drawn from the CATT study, in which the nature of the gastrointestinal events (whether nausea, vomiting or gastrointestinal haemorrhage) was not clear; these events occurred unexpectedly more often in patients receiving the drug "as needed" rather than in those treated on a regular basis. As for the risk of endophthalmitis, very limited data are available and mainly involve clustered cases that occurred due to failure to follow strict aseptic technique during preparation of the drug. Moreover, cases of endophthalmitis have also been described with *ranibizumab*.

Last but not least, we are concerned that the principle of avoiding the off-label use of drugs (even when such use is appropriate from a public health perspective) could be indirectly supported by denying that unlicensed drugs can be equally effective and as safe as licensed drugs. This issue could become increasingly relevant in the coming years. Of course, evidence rather than marketing authorisation should guide this kind of judgement (we concede that, in your review, you only look at evidence). In this specific case, as we maintain above, there is enough evidence to support the use of *bevacizumab*.

We look forward to your reply and send you our best regards,

Giulio Formoso and Maria Font



We gladly accept the debate proposed by Giulio Formoso and *Informazioni sui Farmaci*.

We are aware that our evaluation may cause unease, and this debate provides a good opportunity to recap both our position and how the pharmaceutical companies concerned have positioned these two drugs. Roche markets *bevacizumab* (Avastin[®]), but has not developed a commercial product containing an appropriate quantity of drug or with suitable packaging for single intravitreal injections. Novartis markets *ranibizumab* (Lucentis[®]) (1).

Roche has officially opposed the use of *bevacizumab* in age-related macular degeneration (AMD). And Novartis, with which Roche has been suspected of colluding, asked for and obtained an exorbitant price for *ranibizumab* (1,2).

This context is important but did not influence our evaluation of the use of *bevacizumab* in AMD; we analysed the data on efficacy, adverse effects and convenience of use, in accordance with our standard methodology. As in all our evaluations, we only considered the cost of treatment once we had determined the harm-benefit balance compared with that of the standard treatment.

Less favourable harm-benefit balance than ranibizumab

As *bevacizumab* and *ranibizumab* are closely related, their effects are likely to be similar. They differ in a few respects however: systemic absorption after intravitreal injection (greater with *bevacizumab*), elimination half-life, affinity for VEGF (vascular endothelial growth factor), number of binding sites, etc. The ►►

► clinical consequences of these differences, if any, are unknown (3).

Similar efficacy: improvement in visual acuity, but no evidence of efficacy in preventing complications. According to the clinical trials that were not industry-funded, *bevacizumab* and *ranibizumab* improve visual acuity to a similar degree: a gain of at least 15 letters on the ETDRS scale (i.e. 3 lines) in about 20% to 35% of patients (1,4).

Increased incidence of gastrointestinal disorders and endophthalmitis. The adverse effects of drugs are generally evaluated using data from clinical trials primarily designed to demonstrate their efficacy. In such trials, the evaluation of adverse effects is often less rigorous. Signals of adverse effects must therefore be taken into account too, even when the strength of evidence is low (5,6).

Comparative data on drugs belonging to the same class are rarely available, especially those generated independently of the pharmaceutical industry. The CATT trial is one of these rare trials. It was financed with US public funds and organised by the US public-sector research organisation, the National Institutes of Health. The trial is scheduled to last 5 years, and only the 1-year and 2-year interim results are currently available (1,7).

Other trials did not detect this signal, but they are not more convincing than the CATT trial. The meta-analyses of trials comparing *bevacizumab* versus *ranibizumab* did not detect heterogeneity among the results of the trials. They showed a difference in the frequency of serious gastrointestinal disorders, with a statistically significant excess in the *bevacizumab* group: about 3% versus 1.6% after 1 year, and about 4% versus 2% after 2 years (1,8). In the 2-year results published from the CATT trial, the serious adverse effects are not precisely described, but the gastrointestinal adverse effects reported include haemorrhage (9).

As Giulio Formoso points out, endophthalmitis is an infection with potentially severe consequences and a risk shared by all VEGF inhibitors administered by intravitreal injection (10). Because *bevacizumab* is not marketed in a formulation suitable for intravitreal injection, a number of manipulations are required that increase the risk of infection. This risk can be reduced by adhering to a

strictly defined protocol with quality controls. In France, the drug regulatory agency (ANSM) has taken steps to regulate the use of *bevacizumab* in AMD, including instructions on the preparation of ready-to-use syringes and their administration.

In summary, the higher incidence of serious gastrointestinal adverse effects and endophthalmitis with *bevacizumab* is a safety signal that carries particular weight in the harm-benefit balance, since the efficacy of these two drugs appears similar. This finding must be taken into account, for the sake of patients.

Cost to society versus cost to the unlucky patients

The price agreed for *ranibizumab* is excessively high. It appears to bear no relation to either research and production costs or to the therapeutic advance the drug represents.

It is understandable that health authorities are considering allowing *bevacizumab* to compete with *ranibizumab* so that they can renegotiate a lower price. The temptation to favour *bevacizumab* is also understandable when patients are denied access to *ranibizumab* due to its cost. In France, *ranibizumab* intravitreal injections are fully reimbursed by the national health insurance system (11). The problem posed by *ranibizumab*'s exorbitant price mainly relates to the utilisation of the funds available for universal healthcare provision, which are not adequately protected from pharmaceutical company greed.

However, health authorities and professionals who decide to use *bevacizumab* to gain bargaining power over the company that markets *ranibizumab* must accept that they do so at the expense of patients. According to the evaluation data, several patients will experience serious adverse effects they would not have had with *ranibizumab*. These unlucky few are the only ones who will pay the price of the power struggle created. Has compensation for these patients been included in the pharmacoeconomic equation?

How much money does society need to save for us to accept the individual human cost to the patients who will experience these serious adverse effects?

A few patients will pay the price for this increased risk of adverse effects, in their health and their lives. As the

victims of adverse drug reactions say themselves, they are the tacit price society accepts to pay when each new drug is approved (12).

A choice in the interest of patients

For the sake of both patients and healthcare systems, we too would have preferred to find that the cheapest drug has the best harm-benefit balance.

But the evidence available in early 2016 leads us to conclude that, at the patient level, *bevacizumab* has a less favourable harm-benefit balance than *ranibizumab*. At the societal level, depending on the treatment setting, the conditions of use and the health insurance system, some health authorities have deemed it acceptable to choose the cheapest drug. It would nevertheless be regrettable if the patients exposed were not informed, these adverse effects were not reported, and the existence of victims were concealed.

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Avastin® vs Lucentis®: how economic sustainability could influence clinical outcomes

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This article originates from a paper published in the Italian ISDB bulletin "Informazioni sui Farmaci" in July 2015 (available at <http://rivista.informazionisuifarmaci.it/avastin-contro-lucentis-ovvero-limpatto-clinico-della-sostenibilita-delle-terapie>)

The use of Avastin® (*bevacizumab*, Roche) and Lucentis® (*ranibizumab*, Novartis) in age-related macular degeneration (AMD) has been widely debated and such discussion has reverberated through mass media (1,2), scientific journals (3) and drug information bulletins (4,5) after a verdict by the Italian Antitrust Authority (6) imposed on Roche and Novartis a combined fine of 182.5 million euros for "cartelizing the sales of two major ophthalmic drugs...". This story is well known to many people in the healthcare sector, but a quick summary may help:

- Both drugs are monoclonal antibodies that inhibit vascular endothelial growth factor and are effective in AMD; independent randomised controlled trials (RCTs) showed that they are equally effective (7), but only *ranibizumab* has been granted marketing authorisation for the treatment of AMD;
- *Bevacizumab* has not been authorised for AMD because Roche did not ask for it; this drug was developed (and authorised) for indications in oncology – it has however been widely used for the off-label treatment of AMD, using doses 400-500 times lower than those employed in oncology (8);
- These two drugs are priced very differently: in Italy the cost of *bevacizumab* ranges from 15 to 80 euros per injection (split vial), whereas the price of one injection of *ranibizumab* is about 900 euros. Given the prevalence of AMD in elderly populations (9), this use has resulted in estimated savings of hundreds of millions of euros in Italy (10,11); similar estimates have been reported for other countries (3,12);
- The Italian Drug Agency (AIFA) had initially allowed off-label use of *bevacizumab* in AMD, but refused this use later when *ranibizumab* was authorised and when certain safety information was included in the summary of product characteristics (SPC) of *bevacizumab* (13), even though the same information (defined as "product-class-related adverse reactions") were also included in the SPC of *ranibizumab* (14);
- Against this background, the Italian Antitrust Authority (IAA) found out that the two firms had colluded to encourage the use of *ranibizumab* for their own interests (6): Roche benefited too since, in 2009, it purchased Genentech (the pharmaceutical company that developed both drugs) and earned royalties from Novartis proportional to the market success of *ranibizumab* (15);
- Following the IAA's decision, a law was passed in June 2014 allowing off-label uses of drugs when their efficacy and safety have been adequately demonstrated, and *bevacizumab* is now a permitted therapeutic option in AMD (16).

The Italian Society of Ophthalmology, one of the plaintiffs in the antitrust trial, estimated that when the use of *bevacizumab* in AMD was not permitted, more than 100 000 patients were denied access to treatment, because the Italian National Health System (NHS) could not afford to purchase *ranibizumab* for all the clinically appropriate cases (17). We cannot say whether these figures are plausible, but even if the true figures were 10 or 100 times lower, they should alarm NHS decision-makers who failed to provide effective treatment to so many patients, to cure a disease that leads to blindness.

In most European countries, legislation concerning off-label uses of drugs does not allow intravitreal use of *bevacizumab*. Following the antitrust trial in Italy, in July 2014 the French National Assembly passed a law enabling the use of *bevacizumab* in AMD (18). The Italian and French position is consistent with recommendations in clinical practice guidelines (19,20), and with the inclusion of *bevacizumab* in the World Health Organization (WHO) Essential Medicines List (EML) (21). *Ranibizumab* was not included in the EML because it was not considered safer and more effective than *bevacizumab* while being much more expensive (22). The same issues led to the exclusion of the other two drugs approved for AMD, *pegaptanib* and *aflibercept*.

Safety of intravitreal bevacizumab: the evidence base

A recent Cochrane systematic review, using data from 9 independent RCTs comparing *bevacizumab* and *ranibizumab* in AMD (including 3665 patients), showed that the safety of these drugs is similar apart from a 1.3% absolute increase in gastrointestinal (GI) events leading to hospitalisation with *bevacizumab* (23).

A closer look at the CATT study (24) (the largest of the studies identified in the Cochrane review, recruiting elderly patients with a mean age of 80) may help to assess the relevance of this outcome, since more than half of the GI events reported in the review came from this study: these events were unexpectedly more common in patients treated "as needed" than in those treated on a regular basis (monthly), and doubts may be raised over the plausibility of this result. In addition, GI events included nausea and vomiting, which are less relevant events than gastric haemorrhages, but their relative frequencies (how many of the total GI events were episodes of nausea, vomiting or haemorrhage) are unknown. As for the relevance of this result, the absolute difference in GI events is small even though the (much higher) relative difference (+ 82%) may appear alarming. Naturally, absolute differences provide a clearer idea of the impact in clinical practice, especially when the frequency of events is low.

In evaluating the relative safety of *bevacizumab* and *ranibizumab* and the appropriateness of their use, we have different opinions from those expressed in the review published in issue 378 of *la revue Prescrire* (which in our view remains a model for many independent drug bulletins). The *Prescrire* review selected 6 out of 9 RCTs included in the Cochrane review (excluding two unpublished trials and a tiny 2010 trial) (4). The two reviews came to similar conclusions, except for the slight difference in GI events leading to hospitalisation. *Prescrire* concludes that *ranibizumab* should be preferred because of its lower GI risk and the risk of contamination associated with the preparation of *bevacizumab* for intravitreal use. The huge price difference between these two drugs was not considered relevant for decision-making but, in *Prescrire's* view, "The question of *ranibizumab's* excessive price needs to be resolved by the public authorities" (25). ▶▶

When price could influence decision-making

The high cost of an effective therapy should not hinder access to it, and we absolutely agree with *Prescrire's* views in this regard. However, there is an alternative treatment to *ranibizumab* (as well as to *pegaptanib* or *afibercept*) in AMD, considering that the differences in safety between *bevacizumab* and *ranibizumab* are minor. As for the possible lack of sterility of *bevacizumab* prepared for intravitreal injection, cases of endophthalmitis associated with the use of *ranibizumab* (or *pegaptanib*) can also be found in the WHO adverse drug reactions monitoring database (26). Cases of endophthalmitis associated with *bevacizumab* use often involve clusters of patients treated on the same day in specific centres where rules for compounding sterile preparations had not been followed (27,28,29). Risks associated with pharmacy preparation are largely absent when these rules are followed and vials are prepared in hospital centres where their sterility can be ensured.

The main difference between *bevacizumab* and *ranibizumab* is their price which, in our opinion, should not be addressed optimistically thinking that "it should be made more reasonable" (4,30). This position appears simplistic, especially because it does not consider all the barriers to cutting the price of high revenue generating drugs. Competition among various therapeutic alternatives seems to have a much greater influence on drug prices than countries' bargaining ability. The price of *ranibizumab* is a case in point: it was reduced after off-label use of *bevacizumab* had been allowed. As a matter of fact, the agreements between Roche and Novartis uncovered by the IAA were intended to prevent free competition between the two drugs, in order to force use of the more expensive drug and keep its price high.

Why should drug prices influence treatment choice in AMD? Let's consider the pros and cons of these two drugs. On the *ranibizumab* side, even if we ignore the doubts discussed above, there may be 1.3% (on average) fewer GI events and (theoretically) a lower risk of unsterile preparations; on the *bevacizumab* side however, there may be the possibility of treating all patients who need treatment, preventing hundreds or maybe thousands of untreated cases due to the limits of the purchasing capacity of health systems. Since the best possible use of health care resources is of increasing concern, let's also consider a topical example. The Italian Ministry of Health asked Novartis and Roche for 1.2 billion euros as compensation for the excess cost of using *ranibizumab* instead of *bevacizumab* in AMD (11); how many more patients could be cured of hepatitis C in Italy if that money had been used to buy new antivirals instead of *ranibizumab*? In other words, the opportunity cost of using Lucentis® (what we could do if we made different use of these resources) is extremely high. Of course, these figures are quite relevant (especially in these times), considering the limits to healthcare funding and especially since this excess cost concerns just one drug, which has one quite relevant (and much cheaper) alternative. The WHO promotes the principle that effective and safe drugs should be accessible to everybody, regardless of their price, if no alternatives are available; but cheaper drugs are still preferred if no substantial differences exist to justify the use of more expensive drugs. In line with this principle, very expensive drugs with no equally safe and effective alternatives, such as new antivirals for hepatitis C, have been included in the 2015 version of the EML (31); *ranibizumab* has not, since an appropriate alternative is available and included in the list – *bevacizumab* (22). The EML Expert Committee specifically stated that "The Committee concluded that the available evidence shows *ranibizumab* and *bevacizumab* to have similar effectiveness and safety. In analyses of cost-effectiveness, *bevacizumab* is the

preferred option as *ranibizumab* is more expensive and offers no additional clinical benefits. The Expert Committee was concerned that the inclusion of *ranibizumab* for the treatment of these eye diseases might divert relevant resources from other interventions" (22). One of the reviewing experts commented more directly that "It seems difficult to justify as an essential medicine one that is ten times the cost and with similar effects of one currently on the list" (32).

In conclusion, our opinion is that universal access to safe and effective drugs is a basic principle which should be preserved. All possible means should be used to overcome the problem of limited resources, such as: legislative frameworks defending the right to good health; making adequate resources available for health care; strengthening the capacity of regulatory authorities to negotiate fair drug prices and to promote competition as a mechanism to select the best drugs while favouring their price control. The problem of healthcare sustainability should be addressed through a pragmatic and transparent approach, avoiding excessive optimism in the ability of regulatory authorities to secure dramatic price cuts for expensive drugs. As for AMD, the evidence base is quite robust, consisting of several independent studies that show the differences in safety to be uncertain and that, if any exist, they are of limited relevance compared with the very real risk of blindness faced by many patients who do not have access to available drugs. Avastin® represents one of the alternative treatments for this disease; it should be favoured to ensure that every AMD patient can be treated and so that the huge resulting savings can be diverted to effective treatments in other clinical settings, since funding is always limited, and will be even more so in the future.

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