BMJ 2017;359:j5016 doi: 10.1136/bmj.j5016 (Published 2017 October 30)

FEATURE

INVESTIGATION

Are the odds shifting against pharma in the fight for cheaper treatment for macular degeneration?

Doctors plan to prescribe bevacizumab despite legal threats from drug companies, and against GMC and NICE guidance. Responses to the policy and new legal rulings hint at a turning point in a long-running battle in which £0.5bn potential NHS savings are at stake, reports **Deborah Cohen**

Deborah Cohen *associate editor, The BMJ*

The tide may be turning in the story of bevacizumab (Avastin) as a treatment for wet age-related macular degeneration (AMD). In response to *The BMJ*'s revelation that doctors in the north east of England face legal action over their new policy to offer patients that option,[1] commissioning leaders have thrown their weight behind them—and the doctors' regulator seems to be softening its stance against such moves.

What is at stake, say the doctors involved in the latest battle, is the principle that the choice between clinically effective and safe drugs should be one for clinicians and patients, not drug companies. They estimate that prescribing bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), could save the NHS millions of pounds in their 12 clinical commissioning group (CCG) areas (see commentary).[2] Across England, those savings could total over £500m (€570m; $660m) if it is used for all relevant eye conditions.

In addition, the latest chapter in this story calls into question the influence of the government on guidance from the National Institute for Health and Care Excellence (NICE).

Potential savings

Two anti-VEGF drugs are approved to treat wet AMD on the NHS: ranibizumab (Lucentis), marketed by Novartis in Europe, and aflibercept (Eylea) produced by Bayer. Roche markets bevacizumab for use in various cancers—not all of which uses have evidence of clinically meaningful benefit—but has never licensed it for use in the eye despite the fact that meta-analysis of several publicly funded clinical trials found that bevacizumab is as safe and effective as ranibizumab for wet AMD.[3]

Bevacizumab is also far cheaper. In 2015 a group of ophthalmologists found, through freedom of information requests, that NHS eye units had given more than 50 000 injections of anti-VEGFs—including 1410 of bevacizumab—costing the NHS an estimated £45m in a single month. Some of the injections were for other indications such as diabetic macular oedema, for which there is some evidence that bevacizumab is also effective.[4 5] They calculated that if bevacizumab was used for all injections instead of ranibizumab or aflibercept, the estimated cost would be £729 500 a year, saving the NHS an estimated £539m a year.[6]

The new policy from the North East and North Cumbria CCG Forum aims to realise some of these savings by offering patients a choice. Clinicians will tell patients newly diagnosed with wet AMD that bevacizumab is the preferred choice but that they are free to choose one of the NICE approved treatments—ranibizumab and aflibercept—in line with English law.

This is in line with private practice, in which bevacizumab is routinely used, according to Andrew Lotery, professor of ophthalmology at Southampton University. "Many insurance companies don't pay for chronic conditions such as age-related macular degeneration," he says. "Patients have to pay themselves and so opt for bevacizumab, which is far cheaper than the licensed drugs."

The CCGs are backed by their representative organisation NHS Clinical Commissioners. Its chief executive, Julie Wood, tells *The BMJ*: "We support our members in doing all they can within the law to deliver the greatest value for the commissioning pound while getting the best outcomes for patients. Using bevacizumab off-label to treat wet AMD is an opportunity for them to do just that."

Off-label prescribing

However, doctors prescribing bevacizumab for wet AMD will be doing so off-label and therefore going against the GMC's guidance on prescribing and managing medicines, which discourages use of off-label products when there is a licensed alternative.

Ophthalmologists say that the GMC guidance has deterred them from prescribing bevacizumab despite the evidence of its efficacy and safety and the financial strain on the NHS. The

dcohen@bmj.com

Royal College of Ophthalmologists cannot take a position that flies in the face of the doctors' regulator, says Lotery, who chairs the college's scientific committee and was an investigator on the UK publicly funded IVAN trial that compared bevacizumab with ranibizumab for wet AMD. "It's purely the regulatory framework that is stopping bevacizumab's widespread use in the NHS," he says.

Back in 2015, *The BMJ* questioned the interpretation of European law that led to the GMC's stance.[7] The advice seemed at odds with clinical practice in other European countries.

In the Netherlands, as well as being used for wet AMD, bevacizumab had become standard treatment for diabetic macular oedema—the most common eye condition treated with anti-VEGFs—on the basis of cost.[8] The Guernsey eye service also used only bevacizumab in 2015, which Lotery provided.[9] The GMC has confirmed that doctors practising there are registered with them. No fitness to practise case has ever been brought because a doctor was using bevacizumab for ocular conditions rather than a drug licensed for that purpose.

Despite this, Niall Dickson, then chief executive of the GMC, told *The BMJ* at the time that doctors in the UK couldn't use intravitreal bevacizumab for legal reasons. "The main problem is the law," he said, adding later that it was unequivocal and pointing to a 2012 European Commission case against the Polish government to support the GMC's view.

The court found against Poland because they were importing unlicensed drugs for economic reasons when licensed ones were available. "The European Court has in effect ruled out the adoption of blanket policies that permit the off-label/unlicensed prescribing of medicines on the grounds of cost," said Dickson.[7]

The BMJ queried the relevance of this case and asked the GMC for a copy of the legal opinion that resulted in the guidance, but the regulator refused. A spokesperson said it attracted "legal professional privilege" and the public interest was best maintained by not releasing it.

Public health consultant Greg Fell pointed out at the time: "Without this, it is impossible to judge the validity of the GMC's line."

And the validity of the GMC's line is in question. If it is shown to be wrong, it has potentially cost the NHS hundreds of millions—if not billions—of pounds and distorted clinical priorities.

Shifting legal position

At the end of last month, an official adviser to the European Court of Justice (ECJ) gave his opinion on a case referred by Roche and Novartis, who were seeking to overturn a 2014 ruling by Italy's competition authority.

This led to the companies being fined €180m for allegedly colluding to prevent the use of bevacizumab by exaggerating the risks of using it to treat wet AMD and portraying ranibizumab as safer. Italy's health ministry had also announced that it would seek damages of €1.2bn in 2014.

A spokesperson for Roche told *The BMJ* that it doesn't comment on ongoing legal action. In a statement, Novartis said: "Some information produced by the CCGs about the policy appears misleading and could persuade clinicians and pharmacists to act in accordance with the policy, even if such practice might be in breach of their respective professional obligations."

Henrik Saugmandsgaard Øe, an ECJ advocate general, took the view that off-label drugs can be considered in place of licensed drugs for various reasons, including their price.[10] If the advocate general's opinion is upheld by the ECJ—and it usually is—it will be "potentially helpful in tackling some of the legal challenges" to the north east CCGs, Wood says.

Faced with this news, the GMC is less strident than two years ago on commissioning policies, saying that it is "sympathetic to the frustrations of doctors and organisations seeking to use resources effectively."

"We understand there may be current legal cases that could clarify the legal position on commissioning and prescribing decisions around certain unlicensed drugs, and are keeping a close watch on how this might develop," assistant director of standards and ethics Mary Agnew tells *The BMJ*.

"We hope that some sort of licensing solution for drugs such as Avastin may be forthcoming, or alternatively that the situation is clarified in the courts to give doctors more assurance about when they can prescribe this drug safely and within the law.

"We will of course consider and act on any cases which have implications for our guidance."

The BMJ approached the UK Medicines and Health Care Products Regulatory Agency for comment, but its spokesperson said "it would be premature for it to comment before a final decision has been reached."

A spokesperson for Bayer told *The BMJ* that bevacizumab needs to be "compounded into syringes creating a different and unlicensed medicine."

Using "unlicensed medicines" instead of a licensed NICE approved option "runs the risk of setting a precedent that undermines the regulatory framework and NHS constitution."

"Bayer feels it has to act to challenge the decision taken by these CCGs," the spokesperson said, which includes the possibility of legal proceedings. "We are determined to work with the appropriate authorities to ensure a resolution that is lawful and protects the interests and wellbeing of patients."

The CCGs, however, are questioning whether intravitreal use of bevacizumab, which needs to be split into vials, is indeed unlicensed. In 2015, the European Medicines Agency dismissed the notion that bevacizumab was an unlicensed product when used in this way. It stated that the use was "off-label." The US Food and Drug Administration agreed.[9]

NICE guidance

The ECJ ruling could also affect the recommendations in NICE's draft guideline for the treatment of macular degeneration.[11]

When NICE was instructed by the Department of Health in 2014 to produce the guideline, it knew it was controversial. Sources have told *The BMJ* that the institute was prepared to fight its corner; it was willing to recommend the most cost effective drug based on the evidence, irrespective of the licensing situation.

This would have given doctors a firm rationale for their decision making if they opted to use bevacizumab over a licensed drug because of cost effectiveness and, as a result, ended up in court or in front of the GMC.

But NICE backtracked. *The BMJ* has learnt that, behind the scenes, senior governmental health officials have suggested that NHS decision makers need to be mindful of the needs of the drug industry, particularly in light of Brexit.

While the draft NICE guidelines state that bevacizumab provides the best value for money for treating macular degeneration, it cautions that GMC guidance should be considered if prescribing outside a licensed indication. Cost should not be taken into

account. It adds that bevacizumab can be prescribed for AMD only if a "person has a specific need and no other licensed product meets that need."

When *The BMJ* asked NICE about the inclusion of this clause in light of the advocate general's opinion it batted the decision over to the GMC. "Our guidance, in respect of the off-label/unlicensed use of medicines, reflects the rules imposed by the GMC. As such we will continue to reference the GMC in our guidance," a spokesperson said.

In the private sector, however, an individual's need may include cost. In the NHS, the cost need is transferred onto someone else—a person potentially losing out on a treatment because the money has been spent on a more expensive drug.

The NHS desperately needs the £0.5bn that the unravelling of these various legal knots—and therefore the prescribing of bevacizumab for wet AMD—could save, not least in eye services themselves, says Lotery. His eye unit at University Hospital Southampton is experiencing "extreme pressure" because of lack of capacity—as are other hospital eye services across the country, he says.

"Savings made by using bevacizumab should be reinvested into the hospital eye service to build capacity to deliver sight saving treatment for age-related macular degeneration."

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Cohen D. Are the odds shifting against pharma in the fight for cheaper macular degeneration treatment?*BMJ* 2017;359:j5016
2 Hambleton D. NHS patients should have a choice of drug for wet age-related macular degeneration, despite pressure from pharma. *BMJ* 2017;359:j5013.
3 Moja L, Lucenteforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2014;1:CD011230.pmid:25220133.
4 Wells JA, Glassman AR, Ayala AR, et al. Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193-203. doi:10.1056/NEJMoa1414264 pmid:25692915.
5 Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol* 2017;28:636-43. doi:10.1097/ICU.0000000000000424 pmid:28837425.
6 Shalaby AK, Lewis K, Bush K, Meredith PR, Di Simplicio S, Lockwood AJ. Licence to save: a UK survey of anti-VEGF use for the eye in 2015. *Eye (Lond)* 2016;30:1404-6. doi:10.1038/eye.2016.154 pmid:27518544.
7 Cohen D. Why have UK doctors been deterred from prescribing Avastin?*BMJ* 2015;350:h1654. doi:10.1136/bmj.h1654 pmid:25834024.
8 Schauwvlieghe AM, Dijkman G, Hooymans JM, et al. Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with diabetic macular edema: a randomized clinical trial (the BRDME study). *BMC Ophthalmol* 2015;15:71. doi:10.1186/s12886-015-0043-x pmid:26149170.
9 Lotery A, MacEwen C. What is stopping the NHS from using bevacizumab for macular degeneration and other retinal disorders?*BMJ* 2014;349:g6887. doi:10.1136/bmj.g6887 pmid:25406142.
10 Case C-179/16: F. Hoffmann-La Roche Ltd and Others v Autorità Garante della Concorrenza e del Mercato (AGCM). Opinion of advocate general 21 Sep 2017. http://curia.europa.eu/juris/document/document.jsf?text=&docid=194802&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=878976
11 NICE. Macular degeneration. https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658