Impact of the Avastin case on prescribing medicines off-label

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In 2018, the High Court ruled that CCGs can prescribe bevacizumab (Avastin) off-label for wet age-related macular degeneration (wet AMD). This article discusses the background to the case and its wider implications for drug licensing and clinical practice.

A landmark UK High Court case in 2018 (Bayer Plc and Novartis Pharmaceuticals UK Ltd v Various Clinical Commissioning Groups) ruled against the manufacturers of two licensed products for the treatment of wet age-related macular degeneration (wet AMD). Bayer and Novartis challenged the lawfulness of the CCGs’ policy, which supported clinicians prescribing bevacizumab, an unlicensed but significantly cheaper alternative for wet AMD.1

This article explores the issues that this ruling highlights, as prescribers meet the challenges of prescribing safely and effectively within the financial constraints of the NHS, against the backdrop of medicines regulation and the commercial interests of the pharmaceutical industry.

Background

In wet AMD, abnormal blood vessels grow under the retina and macula, known as choroidal neovascularisation (see Figure 1). These changes have serious consequences for patients as vision loss can be rapid and severe.2 It has been estimated that around 39,800 people develop neovascular AMD in the UK each year.3

Up until the early 2000s, the only available treatment for wet AMD was laser therapy, which was limited by a lack of effectiveness and the risk of scarring with additional vision loss. More recently, anti-vascular endothelial growth factor (anti-VEGF) injections have completely transformed the treatment of macular degeneration. Nevertheless, the choice of anti-VEGF drug has been controversial. Two anti-VEGF drugs are licensed in the UK for AMD: ranibizumab (Lucentis) and aflibercept (Eylea).

Prior to 2007, when Lucentis gained a licence, AMD patients were treated with a different anti-VEGF drug, bevacizumab, and positive preliminary results were published in a number of small-scale studies.4,5 Roche pursued the development of a smaller anti-VEGF molecule, ranibizumab, which was thought to have a better chance of penetrating the retina for AMD treatment. This would have required significant investment given that the average cost of developing a medicine from bench to...
clinic is £1.15bn and typically takes 12 years.\textsuperscript{7}

Bevacizumab (Avastin) is only licensed in the UK for various carcinomas, and therefore use in the eye is often cited as being ‘off-label’. Nevertheless, the evidence base for the use of bevacizumab in AMD has grown in recent years. A randomised controlled trial to assess the clinical effectiveness and cost effectiveness of alternative treatments that inhibit VEGF in age-related choroidal neovascularisation (IVAN) was published in 2015. The study concluded that ranibizumab and bevacizumab have similar efficacy.\textsuperscript{8} Furthermore, in 2014 a Cochrane systematic review analysed nine studies including IVAN and non-industry sponsored randomised controlled trials (RCTs). The review concluded that, with regard to available data on systemic safety, there was no significant clinical or research evidence to support the preferential use of either Avastin or Lucentis in the treatment of neovascular AMD.\textsuperscript{9}

The continued use of bevacizumab for AMD is driven by cost, as Lucentis is considerably more expensive than Avastin. The Royal College of Ophthalmologists has stated that switching from Lucentis to Avastin for neovascular AMD could save NHS England alone at least £102 million per year.\textsuperscript{10}

Medicines regulation

The licensing processes are detailed in Section 10 of the Medicines Act 1968 and the Human Medicines Regulations 2012 (2012/1916) of UK legislation. Most of the current UK medicines legislation and pharmacy practice derives from European legislation in the form of Regulations and Directives.\textsuperscript{11} The licensing system comprises a centralised system, of which the European Medicines Agency (EMA) is a part, and a decentralised system based on national regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA). A product can be successfully authorised for marketing in all EU member states without any separate implementation of the national regulatory authorities in those states.

‘Unlicensed’ and ‘off-label’

The terms ‘unlicensed’ and ‘off-label’ are often used interchangeably and incorrectly in relation to the marketing and prescribing of medicinal products. To market a medicinal product in the UK requires a marketing authorisation, granted by the EMA or MHRA, for specified indications under certain conditions.

The Summary of Product Characteristics (SmPC) is the legal document approved as part of the marketing authorisation of each medicine. It lists indications, dose ranges, route of administration, age restrictions, contraindications and side-effects. Any use of a licensed medicine not in accordance with the SmPC is ‘off-label’ use. A common example includes a reduced dose of a medicine for neonates only licensed for use in adults. An unlicensed medicine is a medicine without a European or UK marketing authorisation and is not licensed to be marketed in the UK.

In the case of Avastin, it is a licensed UK medicine. The pharmaceutical form of the medicine was modified via dilution for ophthalmic use. Pharmaceutical modification of a licensed product can result in an unlicensed product. However, as pointed out by Aronson and Ferner in a recent review article in the British Journal of Clinical Pharmacology, how much pharmaceutical modification results in an unlicensed product is unclear.\textsuperscript{12} In addition, it should also be noted that licensing only relates to marketing and supply. The licensing restrictions do not discuss or relate to the act of prescribing by a registered medical practitioner. The practice and responsibility of prescribing sits within the therapeutic freedom of medical practitioners and prescribers.

In the case of Avastin, no licence may be required at all if it was compounded or modified ‘in house’ by a hospital’s own pharmacy and so is not ‘placed on the market’. When bevacizumab is used for the treatment of AMD, a hospital pharmacy can split a vial into small doses that can be administered intravitreally with a 14-day shelf life. In the IVAN trial, the bevacizumab product used was sourced from a compounding pharmacy that aliquoted and dispensed the drug, adhering to protocols for tests of potency and sterility approved by the MHRA.\textsuperscript{13}

In cases originating in Germany (2013) and Italy (2018), the Court of Justice of the European Union (CJEU) has accepted the description of bevacizumab for ophthalmic use as ‘off-label’ and has stated that the compounding process does not give rise to a new medicine.\textsuperscript{14,15} The important point made in each of those cases is that the medicine is not altered in its composition when used for ophthalmic use.

UK case outcome

In 2018, the drug companies Novartis and Bayer brought legal proceedings against 12 CCGs in the UK because they supported clinicians in the prescribing of bevacizumab, which is not licensed for the treatment of wet AMD, as opposed to ranibizumab and
A judicial review was forced by Novartis following a previous and similar case in 2011. Novartis and Bayer opposed the policy on four grounds. They said that the supply of bevacizumab was unlawful because “it was not licensed for ophthalmic use; it undermined drug regulation; it undermined patients’ right to have a NICE approved drug; and the patient information sheet accompanying the policy was misleading”.16

The case is also made more complex by the fact that Avastin and Lucentis were developed by Genentech, a company that belongs to the Roche group. Genentech assigned the commercial exploitation of Lucentis to the Novartis group by way of a licensing agreement; however, Roche markets Avastin. Added to this, there were a series of investigations by the BMJ that claimed that doctors had been deterred from prescribing off-label bevacizumab through legal threats, misinformation, anticompetitive behaviour and lobbying.17

In the High Court, Mrs Justice Whipple dismissed the application for judicial review on all grounds and found in favour of the CCGs. She said that the companies’ arguments that the NHS could not prescribe bevacizumab for AMD unless Roche applied for a licence for ophthalmic use was an “absurd proposition”. She added: “It would give unbounded power to the pharmaceutical companies to decide which medicines to make available for which purposes... that would be seriously detrimental to the wider public interest in maintaining a cost effective public health system.”

Mrs Justice Whipple’s summing up

Unsurprisingly, the claimant companies are seeking to appeal. The High Court refused permission to appeal on 26 October 2018; however, the parties may still apply direct to the Court of Appeal and Bayer has indicated its intention to do so.

Clinical practice and guidance

In Holland, bevacizumab is approved as first-line treatment for AMD. In Italy, Roche/Novartis were fined 180 million Euros for trying to “channel demand toward the much more expensive drug Lucentis, through an artificial distinction between the two products”, ie Lucentis and Avastin.20 In the USA, bevacizumab is the most popular anti-VEGF drug.24

In the UK, guidance from NICE on the treatment of wet AMD was published in January 2018.3 The guidance clarifies that there are no clinically significant differences in the effectiveness and safety of anti-VEGF medications that are licensed for treating AMD and those that are not licensed, such as bevacizumab. However, the guidance also states that “the prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented... The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.”

In terms of guidance for prescribers, the GMC welcomed the High Court’s decision on the Avastin case. They stated: “It’s important that doctors work in partnership with patients and give them sufficient information about the medicine they propose to prescribe to allow them to make an informed decision. We expect doctors to follow clinical guidance and make prescribing decisions in good faith on the basis of evidence and experience.”22 However, the GMC also pointed out the risks of dividing up Avastin vials in a clinical setting, stating that “there is greater chance of infection, contamination, or incorrect dosage”. The GMC has supported NICE’s revised view and has removed the possibility that any doctor who prescribes Avastin for ophthalmic treatment will be charged with professional misconduct.23

Future implications

This case raises some interesting questions around drug research and development, marketing and licensing systems. Concerns have been voiced around the potential risks of pharmaceutical companies exploiting the system to prevent access to cheaper alternatives in order to boost their profits. The pharmaceutical industry in turn has responded by continuing to work within the regulatory system that was designed in a post-thalidomide world to protect the patient.

What is clear is that prescribers can prescribe with confidence when they have good evidence and clear policies in place to optimise medicines for their patients. The 2018 ruling and other cases across Europe support this action when issues around cost have been raised. The judicial review clearly stated that CCGs and NICE are competent to assess clinical effectiveness, including issues of safety and cost. EU member states are also permitted to adopt measures that are aimed at saving costs in order to ensure that only the most effective medicines are available for which purposes... that would be seriously detrimental to the wider public interest in maintaining a cost effective public health system.”
costs, in order to ensure the financial stability of their domestic healthcare systems. Furthermore, Mrs Justice Whipple concluded that regulatory bodies such as the MHRA and EMA do not have “exclusive competence to determine whether Avastin is clinically effective and safe for ophthalmic use”. At the point of publication, the MHRA has not issued any further comment on their position.

As the UK moves toward Brexit, future relationships with the EMA and medicines regulation will need to be established. A government policy paper, Collaboration on Science and Innovation, published in September 2017, stated that the UK will look to continue working closely with the EMA, and that existing agreements between the EMA and third countries such as Switzerland, the USA and Canada provide a precedent that the UK could build on. It is also hoped that the UK will retain access to established Europe-wide pharmacovigilance systems, which successfully monitor medicines and their side-effects in order to inform continued safe prescribing.

For the vast majority of medicines and medical devices, the regulatory system works well. Licensed products provide prescribers and patients with the reassurance that the medicine has been tested to the appropriate level of safety. However, prescribing outside of a licence is and always has been lawful when the prescriber works in collaboration with the patient and prescribes with due diligence on the basis of evidence and experience.

References

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Declarations of interest
None to declare.

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