

Prescribing outside of a drug's licence: issues and implications

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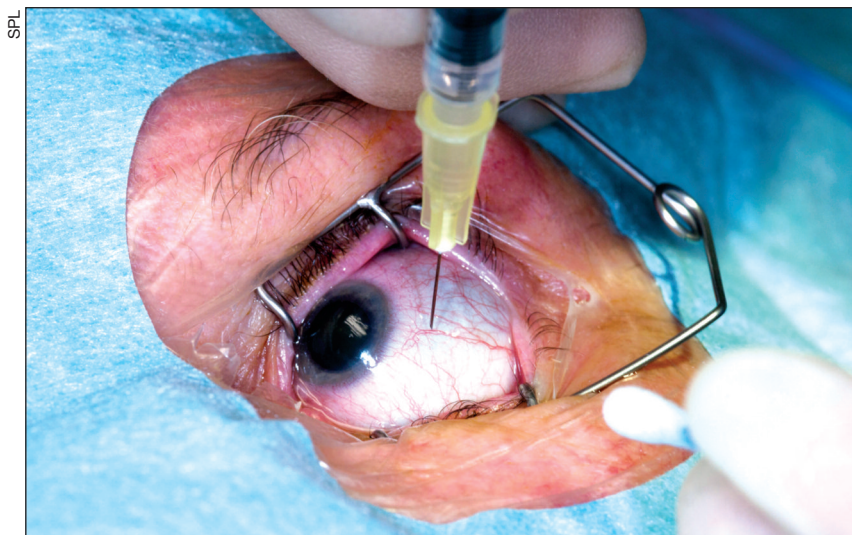


Figure 1. Despite there being three licensed treatments for wet AMD, one of which is NICE approved, bevacizumab is sometimes used off-label because it is cheaper

The GMC recently published updated guidance on prescribing outside of a medication's licence. Here, we examine the drivers and implications for off-label prescribing, with a particular focus on the issues surrounding the prescribing of bevacizumab in wet AMD.

An estimated 1000 specific off-label drug use requests are made to NHS commissioners in England every year. Indeed, the high use of off-label medicines within the NHS has prompted the Department of Health to commission expert assessments into the magnitude of the practice and its potential clinical implications.¹

It is not only the clinical implications but also the drivers for off-label drug prescribing that are of interest and importance at a time of escalating budgetary pressures and increased focus on cost-effective prescribing within the NHS. This article looks at the issues around off-label prescribing, and in particular the prescribing of drugs for age-related macular degeneration (AMD).

The GMC position

The GMC recently published updated prescribing guidance. It

advises prescribers that they 'may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient'.²

Circumstances in which prescribing an unlicensed medicine may be necessary include where:

- there is no suitably licensed medicine that will meet the patient's need
- a suitably licensed medicine that would meet the patient's need is not available
- prescribing forms part of a properly approved research project.

The guidance also states that prescribers should be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy.

They must also take responsibility for their prescribing decision

and oversee the patient's care, monitoring and any follow-up treatment (or arrange for another doctor to do so).

The updated guidance has been welcomed by the Association of the British Pharmaceutical Industry (ABPI), which had opposed a draft form of the guidance that suggested a more relaxed stance acknowledging that prescribers may choose to use off-label, or unlicensed, therapies if there is no appropriately licensed alternative available, or if the prescriber is satisfied on the basis of authoritative clinical guidance that it is as safe and effective as an appropriately licensed alternative.

The ABPI commented: 'Decisions on the prescribing of unlicensed medicines are never easy, and this is why it is so critical to get this guidance right. The GMC has listened to stakeholders

Characteristic	Ranibizumab	Bevacizumab
Target	VEGF	VEGF
Product	monoclonal antibody fragment	monoclonal antibody
Epitope	receptor-binding region	receptor-binding region
Molecular weight	48.39kDa	149kDa
Half-life	3 days	17–21 days
Glycosylate	no	yes
Expression system	<i>Escherichia coli</i>	Chinese hamster ovary cells
Effectiveness	strong	strong
Safety	uncertain	uncertain
Cost	£742/injection	£60/injection
Use for wet AMD	approved	not approved

Table 1. Comparison of the main properties of ranibizumab and bevacizumab; after reference 17

and taken an open and constructive approach to engaging with us. The new guidance reaffirms that patient need should beat the heart of clinical decisions.³

Unlicensed vs off-label

The terms unlicensed and off-label are commonly used, sometimes interchangeably, but they are not synonymous.

In Europe an unlicensed medicinal product is one that has not been evaluated by a competent regulatory authority as having an appropriate risk-benefit profile and granted a marketing authorisation (sometimes simply because no regulatory submission has been prepared and considered).

In contrast, off-label medicine use refers to use of a medicine for an indication or population other than that defined by the marketing authorisation.

Off-label drug use in ophthalmology

A high-profile example of such off-label prescribing is the use of bevacizumab for the management of wet (neovascular) AMD.

Vascular endothelial growth factor (VEGF) is considered critical in both the physiological and pathological processes involved in wet

AMD and its inhibition has been shown to markedly slow disease progression and vision loss for a large number of such patients.⁴ Aflibercept (Eylea), pegaptanib (Macugen) and ranibizumab (Lucentis) are VEGF inhibitors licensed for the treatment of wet AMD. However, NICE does not recommend pegaptanib⁵ and is currently appraising aflibercept.

Bevacizumab (Avastin) is also a VEGF inhibitor approved for use in the treatment of a number of cancers in combination with other agents and in appropriate patient subgroups; nowhere in its licence is approval given for intraocular use.

The similarities and differences between ranibizumab and bevacizumab are outlined in Table 1. Of particular clinical note is the difference in half-life of the two drugs: around 20 days for bevacizumab compared with about three days for ranibizumab. Also of note is the substantial difference in treatment cost – £742 per injection for ranibizumab compared with approximately £60 for bevacizumab.⁶

A recent editorial in the *BMJ* noted that ‘with around 25 000 new cases of this disease diagnosed in the UK annually, replacing ranibizumab with bevacizumab as

standard treatment for these cases could save close to £300 million a year’.⁷ In 2008 bevacizumab accounted for 58 per cent of all injections for the treatment of wet AMD in the USA.⁸

The Quality and Outcomes Framework (QOF) indicators encourage GPs to make efficiency savings in prescribing.⁹ The targets require NHS practices to review their current prescribing behaviour to assess its clinical and cost effectiveness. Against this backdrop there are concerns that physicians may face increasing pressures to prescribe cheaper therapies irrespective of their licence status.

Legal review

The recent case of Southampton, Hampshire, Isle of Wight and Portsmouth (SHIP) PCT cluster Board highlights some issues of cost and cost-effectiveness playing an increasing role in ophthalmic prescribing decisions and local policy.

In September 2011, the SHIP cluster agreed a policy that would allow reimbursement of ranibizumab or off-label bevacizumab for the treatment of wet AMD. Regarding bevacizumab NICE notes: ‘The use of bevacizumab in the eye is considered “unlicensed” rather than “off-label”. The pharmaceutical quality of the product when used for eye conditions needs consideration; to use the product for eye conditions it needs to be manipulated to produce a formulation of a strength and volume suitable for intravitreal use’.¹⁰

Novartis, who hold approval for ranibizumab in the UK, asked for the legal situation around such local policy to be reviewed over concerns that it may place NHS clinicians under pressure to use an off-label medicine where a licensed NICE-approved alternative exists. Novartis spoke of fears that local

policies to reimburse off-label drugs could undermine the drug regulatory process, a process intended to safeguard patients,⁹ and that clinicians were being pressurised to prescribe off-label.

The SHIP cluster initially defended their policy on the basis that it offered clinicians choice rather than mandated use of bevacizumab, and because there is growing anecdotal evidence for the use of bevacizumab in wet AMD.¹¹ However, SHIP later revoked their policy because of a number of circumstances that allegedly 'made the policy difficult to implement'.

Such circumstances included guidance from the Royal College of Ophthalmologists, which supported the continued use of ranibizumab until there was a regulatory review of the role of bevacizumab in wet AMD.¹² Moreover, Novartis agreed a discount with the PCT as part of a new National Patient Access Scheme that made ranibizumab somewhat more affordable.

Implications of off-label prescribing

Safety

The SHIP PCT cluster referred to data suggesting bevacizumab and ranibizumab were both effective and broadly comparable, but also noted that further comparative evidence would not be available for another 12–18 months.

The evidence referred to was that from the IVAN (Inhibit VEGF in Age-related choroidal Neovascularisation) and CATT (Comparison of AMD Treatments Trials) studies – clinical trials designed to evaluate the comparative safety and efficacy profiles of the two VEGF inhibitors in wet AMD.¹³

IVAN is on-going at the time of writing and is a noninferiority trial in which 651 wet AMD patients have been randomised to one of

four treatment groups – ranibizumab or bevacizumab monthly (continuous treatment), or ranibizumab or bevacizumab as required (discontinuous treatment). Interim one-year outcome data were published in 2012.¹³

One year after randomisation no clinically important differences were measured in terms of efficacy (distance visual acuity) or safety (serious systemic adverse events; see Figure 2). However, within the trial setting, the patient per year treatment costs were significantly lower for bevacizumab than ranibizumab for both monthly and discontinuous regimens. Continuous and discontinuous treatment costs (including the costs of monitoring, adverse events and drugs) were £9656 and £6398, respectively, per patient per year for ranibizumab and £1654 and £1509, respectively, for bevacizumab ($p < 0.0001$).¹³

The IVAN investigators concluded that the one-year bevacizumab *vs* ranibizumab visual acuity comparison was inconclusive but that other outcomes were broadly consistent, suggesting the two drugs and treatment regimens as having similar efficacy and safety.

Pharmacovigilance

Concerns around pharmacovigilance and longer-term drug monitoring exist wherever therapies are used outside their licence. It is a legal requirement, under EU directive 2001/83, for medication manufacturers to design a pharmacovigilance framework to ensure on-going monitoring of adverse events.¹⁴ While such manufacturers have a responsibility to record and report adverse events, safety reports resulting from off-label usage will not be evaluated as part of a formal risk management plan. As a result, important emerging safety signals may be missed.

Degradation of licensing practice

When launching judicial proceedings against the SHIP PCT cluster, Novartis voiced concerns around local endorsement of off-label prescribing undermining the drug regulatory process. This is a concern that may strike at the heart of the matter.

To obtain a marketing authorisation manufacturers must carry out extensive clinical trials to satisfy regulatory bodies of the medicine's positive safety profile and efficacy. Furthermore, as part of the submission, the manufacturer must also demonstrate an optimal formulation and specify the production techniques and presence of a robust supply chain.

Encouraging and incentivising physicians to prescribe therapies on the basis of price rather than robust trial data arguably undermines the value of the regulatory process and may affect patient safety. In the long term, this may discourage pharmaceutical manufacturers from investing in research and lead to a reduction in the number of new medications available for treatment of disease coming to market.

An editorial in the *BMJ* notes: 'Despite evidence that it [bevacizumab] works in macular degeneration, the manufacturers and marketers (Roche in the USA, Novartis in the UK and elsewhere) are actively discouraging its use for this condition, even going so far as taking legal action to prevent such off-label use.' And adds: 'the company [sic] has done all it can to limit the use of bevacizumab outside cancer, most notably by not applying for regulatory approval for use in patients with macular degeneration'.

However, the article concedes that: 'the safety of bevacizumab remains a worry. Concerns relate to its greater systemic absorption and the fact that it has to be decanted

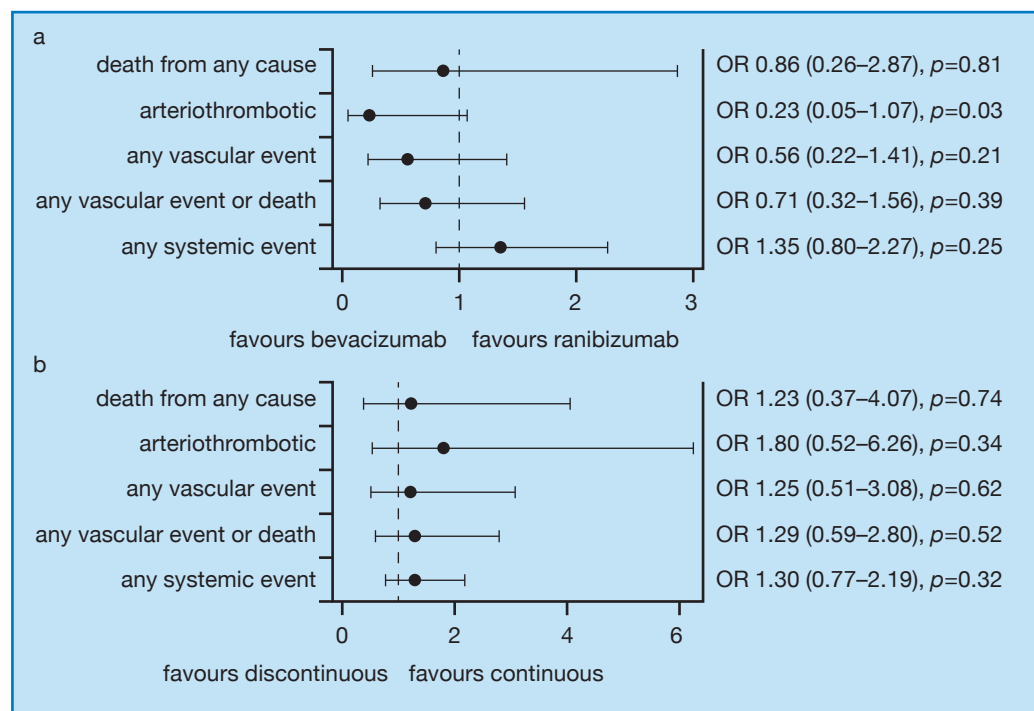


Figure 2. a: Differences between ranibizumab and bevacizumab and b: between continuous and discontinuous treatment regimens in safety outcomes at one year. Circles indicate odds ratios (ORs) and bars indicate 95% confidence intervals. ORs <1 reflect fewer serious adverse events during the first year in the bevacizumab or discontinuous (as required) treatment groups; after reference 13

into smaller quantities for intravitreal injection, which introduces the risk of infection'.¹⁵

Patient trust and physician confidence

A questionnaire-based study (commissioned by Novartis) – *Exploring UK Attitudes Towards Unlicensed Medicines Use* – sought to evaluate physicians' prescribing decisions, priorities and attitudes to off-licence prescribing and also the public's knowledge of, and attitudes towards, the medication licensing system.¹⁶

In this survey 81 per cent of patients expressed at least some concern about safety if prescribed an off-label treatment and the majority (76 per cent) of physicians were at least somewhat concerned about the legal risks, lack of robust safety data and safety monitoring of unlicensed prescribing.

Participating patients and physicians agreed that safety and efficacy

were the most important factors to consider when making prescribing decisions, and off-label prescribing on the basis of cost raised concerns for both groups.

Only 17 per cent of physicians indicated they would be very comfortable to prescribe an unlicensed therapy over a licensed alternative, but more than 90 per cent said they expected cost to become an increasingly important factor when prescribing. The patients generally placed a high degree of trust in their physicians' prescribing decisions and the majority believed prescribing decisions were made collaboratively between themselves and their physician and were driven by clinical appropriateness rather than cost.

Conclusion

The complexities of off-label prescribing are many and ramifications extend far beyond the ophthalmic

example discussed here. The medicines regulatory and licensing process exists to safeguard patients, yet cost pressures may challenge the integrity of the system.

The best prescribing decisions are based on patient need and a full evaluation of the clinical evidence base available. Commissioners and payors postulate that it is unethical to deny patients access to therapies that could offer similar safety and efficacy profiles at significantly lower cost. The counter argument is that it is unethical to prescribe an unlicensed medicine where a proven, licensed alternative exists.

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