



Clinical, legal and ethical implications of the intra-ocular (off-label) use of bevacizumab (Avastin) – a South African perspective

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Choroidal neovascularisation is a potentially visually devastating element of various forms of eye pathology. Recent research has focused on neurovascular age-related macular degeneration (AMD) as a cause. AMD can be classified as being exudative (wet) or atrophic (dry). Wet AMD is characterised by a pathological process in which new blood vessels develop in the choroids, causing leakage of fluid and haemorrhage under the retina and leading to localised serous detachment and loss of central vision. Vascular endothelial growth factor (VEGF) stimulates growth of neovascular membranes. Treatments have until recently yielded disappointing results.

Ophthalmologists are using intra-ocular injections of bevacizumab (Avastin), an anti-VEGF, to treat AMD. Avastin appears to be safe and effective in the short term, but its intra-ocular administration is entirely off-label. Avastin is registered for treating metastatic colorectal and breast cancer.

The off-label use of medication is an important part of mainstream, legitimate medical practice worldwide. Lawyers representing plaintiffs injured by drugs increasingly encounter off-label use claims. From a legal/ethical point of view the off-label use of medication represents a delicate balance between the statutory regulation of medication and

a physician's prerogative to prescribe medication that in his or her medical opinion will be beneficial to the patient. The main reason for the controversy created by the off-label use of Avastin is that there are anti-VEGF drugs on the market that have formal approval for the treatment of AMD (and other eye conditions). Lucentis, for example, is extremely expensive, with treatment cost approximately 50 times that of Avastin. Many patients suffering from AMD and macular oedema cannot afford the registered product.

The off-label use of Avastin has passed the innovative or experimental stages, as ophthalmologists have used it regularly and openly for a long time, with good success. Such use therefore cannot be considered careless, imprudent or unprofessional. We submit that an ophthalmologist who omits to inform a patient of the availability of Avastin for this form of treatment may be found to be negligent.

Protocols developed by the South African Vitreoretinal Society and endorsed by the Ophthalmological Society of South Africa for administering Avastin and other intra-ocular medication intravitreally should be strictly adhered to.

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Clinical background

Bevacizumab (Avastin) is registered for the treatment of metastatic colorectal and breast cancer. Avastin blocks vascular endothelial growth factor (VEGF) and was the first clinically available angiogenesis inhibitor in the USA. Blocking or inhibiting VEGF prevents further growth of blood vessels, thus impeding the tumour's blood supply.¹

Ophthalmologists are using intra-ocular (intravitreal) injections of Avastin to treat neurovascular age-related macular degeneration (AMD). Choroidal neovascularisation

is a potentially visually devastating element of various forms of eye pathology. Research has focused on AMD as a cause and has attracted significant funding in Europe and the USA because of their ageing populations.

AMD can be classified as exudative (wet) or atrophic (dry). Dry AMD is slowly progressive and rarely leads to total blindness. Wet AMD is characterised by a pathological process in which new blood vessels develop in the choroids,² causing leakage of fluid and haemorrhage under the retina and leading to localised serous detachment and loss of central vision. AMD is the leading cause of blindness in people over 50 years of age. Wet AMD may initially be reversible, but without treatment permanent loss of vision may be quick and severe.³

Treatment options have until recently yielded disappointing results. Treatment with Argon laser can cause shrinkage and atrophy of the offending choroidal vessels, but with unacceptable collateral damage.⁴ Photodynamic therapy with verteporfin only slows down disease progression. Surgery, involving removal of the sub-foveal neovascular complex or rotation of the whole or part of the retina to effectively



translocate the macula, has had disappointing results and significant complications.⁵

Enter the anti-VEGFs. VEGF stimulates growth of neovascular membranes. The intravitreal injection of anti-VEGF antibodies reduces the amount of VEGF and interrupts the pathological process.

Intra-ocular administration of bevacizumab (Avastin) is entirely off-label. It is formulated for intravenous infusion, not intravitreal injection, and the Food and Drug Administration (FDA) approved its use for colon cancer in February 2004. In 2005 Philip Rosenfeld first injected Avastin into a human eye and two case reports showed benefit; the first patient had neovascular AMD and the second had central retinal vein occlusion. After this its intra-ocular use spread rapidly around the world.⁶

However, there is no long-term safety and efficacy information for intravitreal bevacizumab based on large randomised trials and no true dose escalating/ranging studies. There is therefore no scientifically determined optimal dose and dose frequency,¹ but bevacizumab appears to be safe and effective in the short term.⁶⁻⁹ Besides, ophthalmologists frequently use medications off-label. Intra-ocular triamcinolone is a typical example.

Pegaptanib (Macugen) and ranibizumab (Lucentis) were two anti-VEGF contenders in the race to get a registered drug on the market via the obstacles of the FDA.

Legal implications of the off-label use of medication

'Off-label' means that the medicine is used in another way or for an indication other than those specified in the conditions of its registration and reflected in its labelling.¹⁰ This does not necessarily imply that the medication is not effective or is unsafe to be used in this way.¹¹ Off-label use is an important part of mainstream, legitimate medical practice and is a worldwide phenomenon.¹² According to the American Medical Association, 40 - 60% of all prescriptions in the USA are off-label. The off-label use of medication is common practice, especially in oncology, obstetrics, paediatrics, infectious diseases (notably HIV) and rare diseases.¹³ Lawyers representing plaintiffs injured by drugs increasingly encounter off-label use claims.¹⁴ Off-label use of medication can vary from being experimental or controversial to standard practice and even state-of-the-art treatment.¹²

When will off-label use of medication be negligent and when not?

From a legal/ethical point of view the off-label use of medication represents a delicate balance between the statutory regulation of medication (to safeguard patients) and the physician's prerogative to prescribe medication that in his or

her medical opinion will benefit the patient.¹⁵ This freedom to prescribe is not unsupervised; fear of delictual liability and medical malpractice claims are a check on the prescribing of physicians, who must balance the benefits against the risks.¹¹

Physicians learn about off-label uses of medication through professional medical literature, presentations and peer lectures at conferences, medical research and advice from colleagues. They cannot prescribe or administer medication off-label with the same confidence as with registered medication. Information regarding possible side-effects, correct dosage and route of administration is normally unavailable, and anecdotal evidence is not the equivalent of clinical tests.¹⁵ Side-effects occur more often where medication is used off-label.¹⁶

Prescribing or administering medication off-label is acceptable medical practice when done by an informed, competent and experienced physician. Reasonable and acceptable medical practice was described as follows:¹⁷ 'In deciding what is reasonable the court will have regard to the general level of skill and diligence possessed and exercised at the time by the members of the branch of the profession to which the practitioner belongs.'

A patient may successfully sue the practitioner if it can be proved that the off-label use of the medication in the circumstances was negligent, namely that harm was reasonably foreseeable and preventable. If off-label use of the specific medication has taken place regularly and openly and colleagues have also been doing it, over a period of time, with a reasonable degree of success and without patients being harmed, it would be almost impossible for a prospective patient to establish that harm was reasonably foreseeable.¹⁰ 'Physicians may be found negligent if their decision to use a drug off-label is sufficiently careless, imprudent or unprofessional.'¹⁸

In a law-suit the defendant doctor is required to provide sound scientific evidence, from medical literature and expert evidence, that the off-label use is acceptable, effective and without known harmful side-effects. Strong scientific evidence for the safe use of off-label uses of medication exists in only 28% of cases; in 72% there is little or no scientific evidence.¹⁹ The risk of liability is heightened when the medical practitioner relies exclusively on his own experience and the experience of his or her colleagues. These cases often end up as a battle of experts. Experts for the plaintiff will try to prove that the defendant's conduct deviated grossly from the standard practice set out in the labelling. Experts for the defendant doctor will try to demonstrate conduct in accordance with what other doctors are doing and therefore in accordance with ordinary protocol.¹⁴ In *Durr v. ABSA Bank Ltd*²⁰ the Supreme Court of Appeal emphasised that although the court will pay much attention to the views of the profession, it is not bound to adopt them. The court must ultimately decide what is reasonable in the circumstances.



The court will take the package insert and other information, such as that in the *South African Medicines Formulary*, into consideration when determining the proper use of the medication. There is no case law in South Africa where a finding on the evidentiary value of the package insert and other labelling was made. We submit that because medical discovery runs ahead of the Medicines Control Council (MCC)'s registration process, the labelling should not *per se* be regarded as an indication of standard practice. As in most judgments in the USA¹⁸ it should, however, be an important factor to take into account.

Where off-label use is the standard of care, failure to follow this standard may be grounds for malpractice claims.¹¹

It is highly recommended that medical practitioners keep a separate file of the latest professional information and medical literature regarding the off-label use of medication.

Must the patient be informed that the medication is used off-label?

The doctrine of informed consent requires the medical practitioner to give a patient the *material* information regarding the proposed treatment, alternatives, potential risks and benefits of each potential treatment, and the result of no treatment. Most judgments in the USA²¹ view that use of medication off-label pertains to the regulatory status of the medication only and is not relevant medical information that must be disclosed to the patient, but this remains a contentious topic.

The opposing argument is that off-label use lacks the assurances of safety and efficacy that an approved indication has, which is important information the reasonable patient would want to know before making a decision.¹⁵ Because there is no case law on this in South Africa the court may hold that a finding of lack of informed consent cannot be based solely on the off-label status of the medication not being revealed. Circumstances may also play a deciding role: if a medication is prescribed at a higher than approved dose, and it is standard practice to do so, it will be difficult to convince the court that this was material information. However, this will differ when the medication is used for a different condition and in a different manner to that approved, even if it is regarded as standard practice to do so, e.g. the intravitreal injection of a medication to treat AMD that was approved to be given intravenously for the treatment of metastatic cancer of the colon.

Generally speaking it would be good medical practice to reveal the off-label use of medication. If not revealed it could, for instance, confuse the patient should he or she read the package insert. This information can also be important to determine whether the medical aid fund will pay for the treatment. To safeguard against possible litigation it is highly recommended that practitioners should discuss the off-label

use of medication with their patients and document the discussion. Informed consent is imperative if there is little research or other evidence of current practice, or if the use of the medicine in this way is innovative.

The 'off-label' use of bevacizumab (Avastin)

The 'off-label' use of bevacizumab (Avastin) for medical, retinal and vitreo-retinal treatment has been controversial mainly because two anti-VEGF drugs are on the market, specifically developed and with formal approval (e.g. USA, Switzerland and South Africa) for treating AMD (and other eye conditions), namely ranibizumab (Lucentis) and pegaptanib (Macugen).

Genentech developed bevacizumab (Avastin) and ranibizumab (Lucentis), and because of lack of economic incentive has little interest in getting Avastin registered for ophthalmic use. Bevacizumab is derived from the same mouse monoclonal antibody precursor as ranibizumab. It neutralises VEGF when injected into the eye at a dose of 1.25 mg, normally in 0.05 ml.⁶ The company has explained its position on the use of intra-ocular Avastin: 'We have a huge database suggesting that Lucentis is very effective and very safe, so we are just not sure of the value of taking something that is not formulated for the eye and subjecting patients to a randomized trial when there is, in our opinion, a very low likelihood of it being superior ...', but acknowledged: 'If people have a hypothesis that it would be better or safer, one could certainly test that.'⁶ Ranibizumab was developed after bevacizumab and is a small portion of the bevacizumab molecule, which has helped to lower the overall risks such as arterial thrombo-embolic events.^{1,6}

However, the cost of treatment with Lucentis is approximately 50 times that of treatment with Avastin. Costs can effectively make certain drugs unavailable to patients. In South Africa the price difference between drugs of comparable efficacy is significant in the choice of drug.^{1,3,6}

Avastin is produced in 100 mg vials. For colorectal cancer a dosage of 5 - 10 mg per kg body weight every 14 days is prescribed. A person weighing 60 kg would therefore receive 3 - 6 vials every 14 days. The commonly used dose for the treatment of AMD is 1.25 mg per injection. It can be injected into an eye repeatedly, at intervals of 1 month to 6 weeks, or as clinically indicated. Most patients need only 2 or 3 injections.²² The larger Avastin ampoule is often fractionated for use in multiple eyes, and the cost to the ophthalmologist per injection then varies between US\$17 and US\$50. The cost of a single vial of Lucentis (0.5 mg in 0.05 ml) is US\$1 950.⁶ The view has been expressed that Avastin might well be safer than the multiple injections used with Lucentis or Macugen. Injections carry the inherent risk of causing glaucoma, endophthalmitis, damage to the structures of the eye and bleeding.^{6,23}



Genentech raised concerns about the compounding of Avastin into smaller doses for intra-ocular use, as it was unapproved and patients could accordingly be at a higher risk, and notified physicians that it would not sell Avastin to compounding pharmacies. The ophthalmic community, led by the American Academy of Ophthalmology and the American Society of Retinal Specialists, reached an agreement with Genentech whereby the company would provide Avastin to retinal surgeons, who could get compounding pharmacies to 'cut' the dose to the appropriate ophthalmic dosage.²⁴

The need for large randomised control trials is obvious. Trials comparing the efficacy, safety and optimal dosing of Avastin and Lucentis are underway in the UK²⁵ and the USA.²⁶

Conclusion and recommendations

Ophthalmologists have access to a reportedly effective and safe drug to treat a serious disease, but without the backing of randomised controlled trials, without the blessing of the manufacturer of the drug, and without registration for intra-ocular use by the MCC. In the event of a complication, would the ophthalmologist have a legal leg to stand on? On the other hand, if a patient lost sight due to AMD, could negligence by the ophthalmologist who had access to Avastin be suggested?

Off-label use of medication carries a higher risk for the patient and the practitioner than its registered use, so extra care should be taken. The off-label use of Avastin has passed the innovative or experimental stages, and its use by ophthalmologists is widespread in South Africa and elsewhere in the world. It has been used regularly and openly over a long time, with a high degree of success and without undue harm to patients. The off-label use of Avastin for AMD and macular oedema is also well documented.^{3,6,7,27-29} The off-label use of Avastin cannot therefore be branded as careless, imprudent or unprofessional. It is submitted that an ophthalmologist who omits to inform a patient of the availability of Avastin for this form of treatment may be found to be negligent.

The protocols developed by the South African Vitreoretinal Society and endorsed by the Ophthalmological Society of South Africa for administering Avastin and other intra-ocular medication intravitreally cover aspects such as informed consent, possible complications such as endophthalmitis, the off-label use of the drug, and pre-injection management.³ If it is affordable, patients should be given the option of choosing Lucentis. These protocols should be strictly adhered to.

From a legal/ethical point of view, patients suffering from AMD and macular oedema who cannot afford the registered product should be given the opportunity to be treated with the off-label product, especially to prevent functional blindness.

Funders should cover the costs associated with the off-label use of Avastin. Owing to financial pressures many funders in the UK commission 'Avastin only' services for these eye conditions. To act in the best interests of their patients, ophthalmologists must be empowered by having this cost-effective alternative medication available.

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