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

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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 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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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.4

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.4,6 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 Ltd20 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.
recommended that practitioners should discuss the off-label 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. 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.’

Ranibizumab was developed after bevacizumab and is a small portion of the bevacizumab molecule, which has helped to lower the overall costs such as arterial thrombo-embolic events.

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.

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 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.

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. 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.
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.34

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 UK29 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 to treat infected chronic wounds. The ophthalmic community, led 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.5,7,27-29

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 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. 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.

References


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