

drug information perspectives

Volume 30 (3) 2010

Editor:

Barbara Cadario, B.Sc.(Hon), B.Sc.Pharm., M.Sc.

Contents

Ranibizumab

Barbara Cadario

Chairman, Medical Review

Laird Birmingham, M.D., M.H.Sc., F.R.C.P.(C)

RANIBIZUMAB

Synonym: rhuFabV2

TRADE NAME: Lucentis

CLASSIFICATION: VEGF-A antagonist; antineovascularization agent

ACTION

- Inhibits VEGF-A activity, thereby reducing the formation of new blood vessels (neovascularization) and leakage from blood vessels, which are implicated in neovascular macular degeneration.
- Ranibizumab is a humanized recombinant Fab (antigen-binding) portion of a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF)-A. It consists of a nonbinding human sequence to reduce antigenicity plus a high-affinity binding epitope derived from mice that binds to all isoforms of VEGF-A, preventing it from binding to its receptors.
- Vision loss in neovascular macular degeneration theoretically involves the growth of abnormal blood vessels from the choroid into the subretinal space, with vessel leakage leading to destruction of photoreceptors. VEGF is a major regulator of choroidal neovascularization and also makes vessels permeable, leading to leakage.

PHARMACOKINETICS

- **Half-life:** 10 days in vitreous humour following intravitreal injection; serum half-life may be as short as 2 hours; however, in animals the half-life in serum and vitreous are similar, perhaps because removal from the vitreous is the rate-limiting step.
- **Absorption:** Absorbed systemically to a small degree. Maximum serum concentration occurs approximately 1 day after intravitreal injection, and is below the threshold for 50% inhibition of VEGF but higher than normal physiological levels of VEGF.
- **Distribution:** Reaches the retina in humans after intravitreal injection.
- **Metabolism:** No data. This protein is probably degraded in the liver or kidneys after it reaches the systemic circulation.
- **Elimination:** No data.

B.C. Drug and Poison Information Centre

1081 Burrard Street, Vancouver, B.C. V6Z 1Y6

Phone: (604) 682-2344; Ext: 62126 Fax: (604) 806-8262

- **Special populations:**
 - **Elderly:** No data.
 - **Hepatic impairment:** No data.
 - **Renal impairment:** Mild-moderate renal impairment: Clearance decreased. Severe renal impairment: Clearance reduced by 42%.
 - **Sex difference:** No difference.
 - **Race:** No data.
 - **Pharmacogenetics:** No data.

USES AND EFFICACY

Uses: Effective for the treatment of **neovascular (wet) age-related macular degeneration**. Stabilizes visual acuity at the pretreatment level in up to 90% of patients. It has improved vision in approximately 30% of patients given intensive treatment, e.g once monthly doses, or monthly assessments and variable dosing guided with optical coherence tomography, for at least 12 months.

Clinical course: Visual acuity testing may reveal an improvement within 7 days with continued improvement over the next three months. Central retinal thickness is decreased the day after the first injection and continues to decrease with repeated treatment over the next 3 months.

Major clinical trials

MARINA study 2006: A randomized, double-masked, sham-injection controlled study treated patients with age-related macular degeneration and minimally classic or occult choroidal neovascularization (716 patients, average baseline visual acuity 20/80 with signs of recent progression) with 0.3mg or 0.5mg by intravitreal injection, or a sham injection (similar procedures but used a needleless syringe) once a month for two years. With the 0.5mg dose, 90% of patients had no clinically meaningful loss of vision (lost less than 15 letters of visual acuity), compared with 53% of those given sham injections. Clinically meaningful improvement in vision (at least 15 letters) occurred in 33% of patients after 12 and 24 months, compared with 4-5% of those given sham injections. With this dose, visual acuity increased on average by 7.2 letters compared with a loss of 10 letters in the control group. There were a few cases of culture-negative endophthalmitis and uveitis as well as one retinal tear; stroke occurred in 2.5% of patients given the 0.5mg dose vs. 0.8% in the control group. [New Engl J Med 2006;355(14):1419-1431.] In patients given sham injections, increases in the area of choroidal neovascularization and leaking occurred over time, while treatment decreased leaking and stopped the development of new neovascularization. Better response was seen in patients with worse visual acuity or smaller lesion size at baseline.

PrONTO Study 2007: An open-label, nonrandomized trial investigated a variable dosing regimen in 40 patients with neovascular age-related macular degeneration (all lesion types, mean baseline visual acuity 20/80). Intravitreal injections of 0.5mg were given once a month for three months, then for a further 9 months a reinjection was given only if any one of the following criteria was met at a monthly examination: vision loss of at least 5 letters with optical coherence tomography (OCT) evidence of fluid in the macula; an increase in OCT central retinal thickness of at least 100 micrometres; new macular hemorrhage, new area of classic CNV, or evidence of persistent fluid on OCT at least one month after the previous injection. With these criteria, patients required a reinjection a median of 2 times (range 0-10) over the 9-month period following the initial three injections (average total number of injections 5.6). The most common reason for reinjection was loss of at least 5 letters with macular fluid. After 12 months, average visual acuity had improved by 9.3 letters compared with baseline, and 35% of patients had clinically meaningful improvement (at least 15 letters) in visual acuity. Most patients (95%) avoided a loss of visual acuity of 15 letters over 12 months. [Am J Ophthalmol 2007;143:566-583.] These results are similar to those reported in the MARINA trial (see above) with 13 injections given over 12 months. *Study limitations:* Small, nonrandomized study.

Comparisons

Vs. other therapies:

Versus bevacizumab: Off-label unlicensed use of intravitreal bevacizumab, a full-length humanized monoclonal antibody VEGF inhibitor, has been widespread due to availability and lower cost. Preliminary data, largely from uncontrolled, small case series and retrospective studies, report similar efficacy and toxicity to ranibizumab. Bevacizumab has a longer half-life in the eye and systemically than ranibizumab. Relative efficacy and safety and optimal frequency of treatment are being studied in large, comparative 2-year trials (CATT, IVAN) with results expected in 2011.

Versus Verteporfin: The randomized, double-masked, sham-injection controlled ANCHOR trial in 423 patients with predominantly classic subfoveal age-related macular degeneration compared ranibizumab given every month to verteporfin given every 3 months as needed. After 2 years, 90.0% of patients given 0.3mg ranibizumab and 89.9% of patients given 0.5mg ranibizumab had stable visual acuity (loss of fewer than 15 letters), compared with 65.7% given verteporfin. Improved visual acuity was found in 34.3% and 41.0% of patients treated with ranibizumab, compared with 6.3% given verteporfin. Ranibizumab was statistically significantly better after one month of therapy. The percentage of patients who became legally blind (20/200 or worse) was lower in the ranibizumab group (20-22.9% versus 60.8%). Rates of arterial thromboembolic events were similar, while nonocular hemorrhages were more common with ranibizumab.

Advantages

- High response rate of approximately 90% for stabilization of the disease.
- Improves vision in 30% of patients if monthly treatment is given.
- Patients note an improvement in activities requiring both near and distance vision, and reduced dependency.

Disadvantages:

- Must be given by intravitreal injection by a specialist, which can be uncomfortable for the patient and difficult for patients who do not live near a suitable clinic.
- Expensive.
- The optimal frequency of injection, duration of treatment, and the criteria for reinjection have not been determined. Monthly injections both stabilize and potentially improve vision, but may cause more adverse reactions, more difficulty for the patient, and more cost. Less frequent injections may be safer, more convenient, and less expensive, but with a loss of benefit.
- Most patients do not have a noticeable improvement in visual acuity. Clinically meaningful improvement in visual acuity has been defined as 15 letters (3 lines), but the average increase has been approximately 7 letters compared to baseline. While this compares favourably to the loss of vision if no treatment is given, individual patients may compare their vision to their baseline or “normal” vision.
- Serious adverse reactions are rare but include infectious endophthalmitis and retinal pigment epithelium tears.
- Long-term benefit and toxicities are unknown.

Place in therapy

A major advance in the treatment of wet (exudative; neovascular) age-related macular degeneration.

Investigational/Unapproved Uses

- ***Combination with verteporfin for AMD:*** In theory the combination should be beneficial, since verteporfin occludes vessels and increases VEGF, while ranibizumab acts against VEGF to reduce new vessel formation. In preliminary studies, the combination has been well tolerated; a large-scale randomized trial (SUMMIT) is ongoing.
- ***Diabetic macular edema:*** Consistent with the theory that VEGF is involved in the pathogenesis of diabetic macular edema, small preliminary open and comparative studies have reported improved visual acuity and decreased retinal thickness. Further study is needed.
- ***Idiopathic choroidal neovascularization:*** A single injection has been beneficial in one published case.
- ***Macular edema due to central retinal vein occlusion:*** In an open study of 10 patients, macular edema was reduced and visual acuity improved in some patients.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications:

- **Hypersensitivity**
- **Ocular or periocular infection**
- **Intraocular inflammation**

Precautions:

- Thromboembolism risk (may cause thromboembolism; evaluate risk in patients with a history of stroke or TIA).
- Use proper aseptic technique (ocular infections can occur).
- Monitor for increased intraocular pressure and decreased perfusion of the optic nerve head (may occur within 60 minutes of injection; check immediately after injection).
- **Report** unexpected or serious reactions to Canada Vigilance, Canada's adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

Pregnancy: No animal or human data. IgG can cross the placenta, and angiogenesis is crucial for fetal development. A related drug, bevacizumab, is teratogenic in animals and is contraindicated in pregnancy for these reasons. Consider risk:benefit and use contraception in women of child-bearing age.

Lactation: No data. IgG can enter breast milk. The related drug, bevacizumab, is contraindicated in lactation because of concern that normal development may be harmed. Breast-feeding is not recommended.

SIDE EFFECTS:

Cardiovascular: Stroke (2.5% vs. 0.8% with sham injection, increased risk with a history of stroke; age-related macular degeneration may be a marker for higher risk cardiovascular disease); increased blood pressure (increased 4.4/1.1 mmHg over baseline); nonocular hemorrhage (8.8% vs. 5.5% with sham injection, 6.4% vs. 2.1% with verteporfin). Most studies find no increase in the risk of myocardial infarction.

CNS: Headache (11% vs. 9% with sham injection); dizziness, anxiety (cases).

Endocrine/Metabolic: Gout (2-3% vs. 1-2% with sham injection).

Hypersensitivity:

- Antibodies against ranibizumab (1-6% of patients; may be associated with iritis or vitritis).
- Intraocular antibodies and intraocular inflammation.

Ocular:

- Arcus lipoides (an opaque ring at the periphery of the cornea) (1-2%).
- Blurred vision (3%).
- Cataract (1.3% vs. 0% with sham injection).
- Chalazion (1.6%).
- Conjunctival hemorrhage (71% vs. 58% with sham injection; transient).
- Corneal abrasion (2.5%).
- Dry eye (2.1% vs. 0.8% with sham injection).
- Endophthalmitis, infectious (0.07% per injection, 0.1-0.7% per year; symptoms of vision change, especially floaters).
- Eye irritation (6%).
- Eyelash discoloration (1 case).
- Eye pain (29% vs. 24% with sham injection).
- Foreign body sensation in eye (15% vs. 13% with sham injection).
- Glaucoma (2.5% vs. 0.3% with sham injection).

- Increased intraocular pressure (transient; 19% vs. 4% with sham injection; usually normalized 30 minutes after injection; increased at 1 hour by 2.1-3.4 mmHg vs. 0.8-1.5 with sham injection; 9-18% have intraocular pressure of 30 mmHg or more; in rare cases has been persistent).
- Injection site hemorrhage (4% vs. 1.3% with sham injection).
- Injection site pain (1.3% vs. 0.8% with sham injection).
- Intraocular inflammation (11.7%).
- Iridocyclitis (1.7% vs. 0.4% with sham injection).
- Iritis (5.4% vs. 3.8% with sham injection).
- Lacrimation increased (8%).
- Meibomianitis (1.6% vs. 0.3% with sham injection).
- Ocular discomfort (4%).
- Optic nerve infarct (1 case with IIIrd nerve paresis).
- Posterior capsule opacification (6.4% vs. 4% with sham injection).
- Punctate keratitis (1.3% vs. 0.8% with sham injection).
- Retinal arteriole diameter decreased (VEGF dilates vessels; significance unknown).
- Retinal/subretinal hemorrhage (rare).
- Retinal pigment epithelium detachment (0.4%).
- Retinal tear (RPE tear; usually after first or second injection; symptoms of sudden vision loss, or may be asymptomatic, recovery is uncommon; patients with pigment epithelial detachments (PED) are at risk; may also occur as a natural aspect of CNV).
- Rhegmatogenous retinal detachment (rare).
- Uveitis (0.8-1.3% vs. 0% with sham injection).
- Visual acuity reduced (3%).
- Visual disturbance (7%).
- Vitreous hemorrhage (0.4% over 2 years).
- Vitreous detachment (2%).
- Vitreous floaters (25% vs. 8% with sham injection).
- Vitreous hemorrhage (1.7%) .
- Vitritis (8.4 vs. 1.3% with sham injection).

Respiratory: Bronchitis, influenza (5-12% vs. 3-8% with sham injection); pulmonary embolism (1 case).

Other: Arthralgia (11% vs. 9% with sham injection). Lack of efficacy (cases). Sciatica (2-3% vs. 1-2% with sham injection).

INTERACTIONS:

DRUG	EFFECT	MECHANISM	IMPORTANCE
ASA	Increased risk of subconjunctival hemorrhage	Additive	Caution
Verteporfin	Increased risk of intraocular inflammation?	Unknown	Controversial; more data needed
Warfarin	Risk of ocular hemorrhage?	Additive	Controversial; theoretical

DOSAGE:

Guidelines:

- Given by intravitreal injection only. Must be administered by a qualified ophthalmologist.
- Simultaneous bilateral injections are well tolerated.

Adults:

- Intravitreal injection: 0.5mg once a month for three months. Subsequent dosing frequency requirements are variable and controversial.
- The manufacturer recommends that after three treatments, the injection frequency may be reduced to one injection every three months if monthly injections are not feasible, noting that this will reduce the benefit. Assess vision regularly and re-administer the medication if there is a loss in visual acuity of greater than 5 letters or other evidence of disease activity.
- Monthly injections have produced the best effect, with stabilized vision in most patients and improved vision in some patients (see Uses and Efficacy: Major Clinical Trials: MARINA study). Variable injections based on optical coherence tomography and visual assessment at monthly visits have produced similar benefits (see Uses and Efficacy: Major Clinical Trials: PrONTO Study).
- The PIER study found that injections once a month for three months and then quarterly resulted in stabilization of vision but no improvement. Thus, quarterly injections are less effective than monthly injections or individualized dosing. Treatments “as needed” have produced mixed results, possibly because treating only when disease activity is noticeable and possibly more damage has occurred may make it harder to achieve a benefit.
- Specialists use an “inject and extend” approach: after the first three monthly injections, patients return in 6 weeks; if visual exam and OCT show no new hemorrhage, edema or subretinal fluid, they are injected and rescheduled for a visit in 8 weeks; if they have edema, they are injected and scheduled to return in 4 weeks. The patients who had no fluid at the six week visit are examined at their return visit, and if there is no disease activity they are injected and scheduled to return in 10 weeks; if there is exudation they are injected and they return in 6 weeks. The outcome with this approach has not been tested.

Children: No data.

Elderly: No dosage adjustment needed.

Hepatic impairment: No data.

Renal impairment: Increased systemic exposure; no dosing adjustment has been recommended.

NURSING IMPLICATIONS:

Thus drug is only administered as an intravitreal injection into the vitreous humour of the eye. It must be administered by a qualified ophthalmologist who is experienced in this procedure. To prevent eye infection, the injection is carried out in a sterile environment using aseptic technique and you may be asked to assist. Usually an eye speculum, disinfection of the skin, antibiotic administration and local anesthesia are used.

Before the injection, check that the patient has not experienced any adverse reactions to this medication in the past.

Patients may be anxious and afraid before an injection, especially the first time. Reassurance can be provided that, the day after the injection, 70% of patients have no discomfort, and the remaining 30% have only mild discomfort. Most patients are less anxious before subsequent injections.

Store in the refrigerator. Do not freeze. Keep in the original box to protect it from light. For single use only; discard vial after use.

PATIENT INSTRUCTIONS:

Ranibizumab (ra ni BIZ oo mab) is used for the treatment of age-related macular degeneration to slow the loss of vision. Some patients may have a moderate improvement in their vision.

Before receiving this medication, be sure to inform your physician if you have any pain or infection in your eyes before the injection; or have a history of stroke, transient ischemic attacks (TIA), increased intraocular pressure, glaucoma, or any adverse reactions to this drug. Tell your physician about all other medications that you are taking, including alternative health products and herbal products.

If you are pregnant or considering becoming pregnant, or are breast-feeding, discuss the use of this drug with your physician. Adequate contraception is usually recommended to avoid pregnancy while taking this medication.

This medication is administered by a qualified ophthalmologist as an injection into the eye.

Redness, irritation or eye pain may occur. Inform your physician of any symptoms that you experience. Rarely, this drug can cause an eye infection or other serious ocular effects. Tell your physician immediately if symptoms such as a sudden decrease in vision, an increase in eye floaters (tiny dark spots that float around inside your eyes), flashes of light, or any other new eye symptoms occur.

If you experience any other unusual effects while taking this drug, especially symptoms of a stroke (difficulty walking, difficulty speaking, weakness or paralysis on one side of the body, unusual headache), inform your physician.

This drug can temporarily affect your vision, therefore do not drive or use dangerous equipment if you notice any problems of this type.

Follow carefully any instructions that you have been given for treatment after the injection, such as the use of eye drops.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

PRESENTATION:

Solution for intravitreal injection: 10mg/mL (2.3mg/0.23 mL/vial).

This newsletter is no longer available in print form.

To receive future newsletters by email, healthcare professionals may send an email to info@dpic.ca.