National PBM Drug Monograph

Ranibizumab (Lucentis®)

November 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Ranibizumab is a humanized antibody fragment directed towards vascular endothelial growth factor A (VEGF-A).
- Ranibizumab is indicated for the treatment of patients with neovascular (wet) AMD.
- The pivotal trials of ranibizumab contain double blinded, sham or active control studies. There were a total of 1323 patients enrolled in these trials. Disease type included classic, occult and mixed AMD. Ranibizumab injection has been shown to statistically reduce the risk of loss of vision and increase the chance of improved vision when given in monthly doses.
- Ranibizumab was shown to significantly improve visual acuity over results from treatment with verteporfin PDT.
- Adverse events with ranibizumab are minimal and commonly may include conjunctival hemorrhage, eye pain, vitreous floaters, intraocular inflammation, eye irritation, cataract, foreign body sensation, increased lacrimation, itching, visual disturbance, blepharitis, ocular hyperemia, blurred/decreased vision, and retinal exudates.
- Safety and efficacy data for up to two years has been demonstrated to include a durable treatment response with minimal adverse events. Ongoing trials are evaluating these results over longer time periods.
- Ranibizumab may be effective in the treatment of diabetic macular edema as shown by results of two Phase I trials. The results need further clarification to determine appropriate dosing and treatment durations.

Introduction

The purposes of this monograph is to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ranibizumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Ranibizumab is a humanized antibody fragment directed towards vascular endothelial growth factor A (VEGF-A). Activation of VEGF-A on epithelial cell membranes promotes cell proliferation, vascular leakage and new blood cell formation. Ranibizumab displays high affinity binding of the VEGF-A receptor. Blockage of these receptors by ranibizumab reduces neovascularization and leakage, thus effectively decreasing the progression of neovascularization in the "wet" form of age related macular degeneration (AMD).

In animal trials using the intravitreal injection of ranibizumab, maximum concentrations appear to be reached by 24 hours post injection with a half-life of approximately three days. During the Phase II/III trials of ranibizumab further pharmacokinetic information in humans was described. The average serum concentration following monthly intravitreal injections of ranibizumab was in the range of 0.3ng/ml to 2.36 ng/ml. These levels were attained one day following intravitreal injection. The estimated vitreous elimination of ranibizumab is approximately 9 days. In humans, the expected serum concentrations are expected to be in the order of 90,000 fold lower than vitreal concentrations.

FDA Approved Indication(s) and Off-label Uses[1]

Ranibizumab is indicated for the treatment of patients with neovascular (wet) AMD. Additionally, anecdotal information has demonstrated efficacy in diabetic macular edema, proliferative diabetic retinopathy, neovascular glaucoma and central venous occlusion.

Current VA National Formulary Alternatives

There are currently two agents approved by the FDA for the treatment of wet AMD, pegaptanib is and verteporfin in conjunction with photodynamic laser therapy (PDT). Neither agent is currently on VANF. There are criteria for non-formulary use of pegaptanib. Additionally, there are anecdotal and case series reports of the off label use of bevacizumab in wet AMD.

Dosage and Administration[1,3-5]

Ranibizumab is available in a 10mg/mL single use vial and 0.05 mL is given by intravitreal injection. It is withdrawn from the vial using aseptic technique through a 5-micron 19-gauge filter attached to a 1-cc tuberculin syringe. The filter needle is replaced with a sterile 30-gauge x 1/2-inch needle for the intravitreal injection. 0.05 ml is injected into the eye under aseptic conditions using sterile gloves, a sterile drape, and a sterile eyelid speculum. The eye is ordinarily prepared with Betadyne and adequate anesthesia. Each vial is used for only 1 eye. Ranibizumab should be refrigerated at 2° - 8° C and not frozen.

Ranibizumab is usually injected once per month and has been used for as long as 24 consecutive months. Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to uninterrupted monthly dosing, dosing every three months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. When used in conjunction with verteporfin PDT, treatment monthly may not be necessary after the first few months. There are ongoing studies (SAILOR [Safety Assessment of Intravitreal Lucentis for AMD] and PrOTECT)[3] assessing whether treatment can be interrupted if the condition of the eye is monitored with noninvasive ocular coherence tomography (OCT). Patients should be evaluated regularly.

Efficacy Measures

Primary outcome measures were visual acuity, improvement and stabilization. This was measured by visual acuity (VA). Each line of VA is equivalent to 5 letters in the study. 20/20 vision is normal, 20/40 vision allows driving a car, 20/60 vision allows some reading, and 20/200 vision is considered the threshold of "legal blindness." Secondary endpoints related to morphologic lesion characteristics. These included changes in size of classic CNV (optic disk area), alterations in the size of leakage from CNV plus staining of the retinal epithelium, absence of new retinal hemorrhage, reduction in retinal thickening on optical coherence tomography (OCT), and prevention of worsened fluroscein angiography(FA) leakage.

The primary endpoints of the studies involved vision measured as best-corrected (best glasses) visual acuity (VA).

Efficacy[6-14]

The pivotal trials of ranibizumab contain double blinded, sham or active control studies. There were a total of 1323 patients enrolled in these trials.[7-8] Disease type included classic, occult and mixed AMD. Ranibizumab injection has been shown to reduce the risk of loss of vision and increase the chance of improved vision when given in monthly doses. Treatment with ranibizumab, on the average, resulted in improved vision. Ranibizumab is superior to sham treatment in all forms of exudative (wet) AMD and superior to verteporfin PDT (laser treatment after intravenous injection of photosensitizing verteporfin) used alone in predominantly *classic* wet AMD. *"Classic"* means that a definite pattern of abnormal CNV blood vessels is visible on FA.

In MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration)[7] patients with *minimally classic or occult (without classic)* choroidal neovascularization (CNV) received monthly ranibizumab injections. The results show significantly less visual loss and more visual improvement in ranibizumab-treated patients at 1 and 2 years. These results can be considered revolutionary because no on-label treatment, on the average, improves vision or even prevents loss.

In a second pivotal trial, ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration),[8] patients with *predominantly classic*, subfoveal CNV received monthly ranibizumab intravitreal injections and sham verteporfin PDT (photodynamic treatment) or sham intravitreal injection and active verteporfin PDT every 3 months if fluorescein angiography showed leakage. Ranibizumab treatment was superior to verteporfin PDT treatment.

In the PIER[10] (A Phase IIIb, Multi-center, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration) trial, patients with subfoveal CNV *with or without classic* CNV received either ranibizumab (0.3 mg and 0.5 mg intravitreally) or sham injection administered once a month for three months and every 3 months thereafter for 24 months. On the average, the patients in the ranibizumab group improved the first 3 months then returned to baseline. The sham treated group significantly worsened below baseline.

In the FOCUS[9] (RhuFab V2 Ocular Treatment Combining the Use of Visudyne(R) to Evaluate Safety) study, patients with predominantly *classic* subfoveal CNV received either ranibizumab 0.5 mg intravitreally + verteporfin PDT or sham injection + verteporfin PDT. Injections (ranibizumab or sham) were given monthly, and PDT was given at Day -7 and every 3 months

thereafter as determined necessary. The mean change in VA over the first year showed a gain in vision in the group receiving ranibizumab + verteporfin PDT and a loss in vision in the group receiving sham injection + verteporfin PDT.

In the PrONTO (Prospective OCT imaging of neovascular AMD patients treated with intraocular ranibizumab) trial[13,14] involved an open label design which employed specific OCT criteria assessed monthly in deciding the need for further ranibizumab therapy. Patients received ranibizumab 0.5 mg at months 0,1,2 and were then followed by OCT. Forty patients were enrolled in the trial. A total of 222 injections were given during the 12 month period. The mean time to retreatment was 4.3 months. The mean VA demonstrated a gain of 9.3 letters at 12 months with 95% of patients stable or improved. The study is continuing another 12 months and results will be described at a future date.

A comparison of the trial results can be found in **Table 1**.

There are potential off label uses of ranibizumab. The use of this agent in diabetic macular edema (DME) has been explored in two phase I trials.[12, 15] The first, READ-1(Ranibizumab for edema of the macula in diabetes), was an investigation involving 20 eyes with refractory DME and foveal thickness > 250 µm. Nine visits occurred over a twelve month period, with ranibizumab 0.5mg at months 1,2,4 and 6. Visual acuity and retinal thickness as measured by OCT were primary outcomes. Data is available for all 20 patients at month 3 and demonstrates a 50% decrease in foveal thickness from baseline and increase in VA by 11 letters.
A single center open label trial investigated ranibizumab 0.3 mg (N=5) and 0.5 mg (N=5) in patients with clinically significant macular edema. Interim safety data is available which demonstrates no adverse events. In 10 patients who have received three injections, clinical improvement in VA has been noted.

Table 1: Results of clinical trials with ranibizumab

	MARINA[7]		ANCHOR[8]		PIER[10]	FOCUS[9]	PROTECT[11]
design	Prospective, multicenter,randomized, double blind		Prospective, multicenter,randomized, double blind		Prospective, multicenter,randomized, double blind	Prospective, multicenter,randomized, double blind	Open label multi center
Patient population	*minimally classic or occult (without classic)* choroidal neovascularization (CNV)		with *predominantly classic*, subfoveal CNV		subfoveal CNV *with or without classic* CNV	predominantly *classic* subfoveal CNV	Predominately classic or occult CNV
N	716		423		184	162	32
Drug regimen	monthly ranibizumab injections, 0.3 mg and 0.5 mg. Sham control group		Ranibizumab 0.3 and 0.5 mg with sham PDT to sham injection and verteporfin/PDT		Ranibizumab 0.3 and 0.5 mg vs. sham injection for first three months followed by doses every 3 months for a total of 24 months	Ranibizumab 0.5 mg with PDT versus sham injection and verteporfinPDT	Ranibizumab 0.5 mg followed with same day PDT
Patients completing at 12 months	664 (93%)		386 (91%)		184 (93%)	162 (91%)	NA
Patients completing at 24 months	615 (86%)		NA		NA	NA	NA
Primary efficacy	*R 0.5 mg*	*sham*	*R 0.5 mg*	*sham*			
<15 letters loss in VA (%)	94.6*	62.2	96.4*	64.3	83*	90.5*	
Secondary efficacy endpoints							
Gain ≥15 letters of VA (%)	34*	4	40.3*	5.6	12	23.8*	at 3 months +3.7
Change in VA over time	+7.2*	-10.5	NA	NA	-1.6*	NA	

All trails utilized intent to treat analysis for primary and secondary endpoints

NA- not available

R-ranibizumab

* p<0.001 vs. sham

Adverse Events (Safety Data)[1,12]

Serious Adverse Events

Serious adverse ocular events occurred in < 0.1% of intravitreal injections, including endophthalmitis, retinal detachment, and traumatic cataract. Less serious adverse ocular events occurred in < 2% of patients, including intraocular inflammation and increased intraocular pressure.

Non-ocular arterial thromboembolic events occurred in 2.1% (18 of 874) of ranibizumab treated

patients in the first year compared to 1.1% (5 of 441) of control patients. In the second year, the incidence in MARINA was 3.0% of patients (14 of 466) treated with ranibizumab and 3.2% of patients (7 of 216) in the control arm. The differences between the treatment and the sham groups were not statistically significant in MARINA or ANCHOR.

Common Adverse Events

Common adverse ocular events include conjunctival hemorrhage, eye pain, vitreous floaters, retinal hemorrhage, vitreous detachment, intraocular inflammation, eye irritation, cataract, foreign body sensation, increased lacrimation, itching, visual disturbance, blepharitis, subretinal fibrosis, ocular hyperemia, maculopathy, blurred/decreased vision, detachment of the retinal pigment epithelium, dry eye, ocular discomfort, conjunctival hyperemia, posterior capsule opacification, and retinal exudates. Some of these adverse events were more common in control eyes as compared to ranibizumab treated eyes, and were equally common in both groups for others.

Other non-ocular events included hypertension, nasopharyngitis, arthralgia, headache, bronchitis, cough, anemia, nausea, sinusitis, URI, back pain, urinary tract infection, influenza, arthritis, dizziness, and constipation. The rates of these events were comparable in the ranibizumab and the control eyes.

Tolerability

Pre-treatment immunoreactivity to ranibizumab was present in 0% - 3% of treatment groups. After monthly dosing with ranibizumab for 12 to 24 months, antibodies were detected in 1% - 6% of patients. The clinical significance of immunoreactivity to ranibizumab is unclear, although some patients with the highest levels of reactivity were noted to have iritis or vitritis.[12]

Precautions/Contraindications

Precautions

- Ranibizumab should not be given to patients with a bacterial ocular or periocular infection because of the risk of endophthalmitis.
- Proper aseptic injection technique should be used when administering ranibizumab and patients should be monitored during the week following injection to permit early treatment should endophthalmitis develop.
- Injection into the eye raises the intraocular pressure, usually just temporarily. This pressure rise and perfusion of the optic nerve head should be monitored and managed appropriately. Insert text here

Contraindications

- Pregnancy Category C. Animal reproduction studies have not been conducted with ranibizumab and it is not known whether it can cause fetal harm when given to a pregnant woman. Ranibizumab should be given to a pregnant woman only if clearly needed.
- Nursing mothers. It is not known if ranibizumab is excreted in human milk, so caution should be exercised when it is administered to a nursing woman.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name ranibizumab

Moderate severity

- Bevacizumab
- Daclizumab
- Efalizumab
- Rituximab
- pegaptanib

LA/SA for trade name Lucentis®

Moderate severity

- Lumigan
- Livostin

Minor severity

- Lantus
- Lunesta
- Luveris

Drug Interactions

There are no known Drug-Drug Interactions or Drug-Lab Interactions for ranibizumab at this time.

Acquisition Costs

Drug	Price/dispense unit	Dose	Cost/Month/Pt	Cost/Year/Pt
Ranibizumab (Lucentis®, Genentech, Inc.)	$1,450 per vial (1 dose per vial)	0.5 mg intravitreally every 4 weeks	$1,450	$17,400
Pegaptanib* (Macugen®, Pfizer, Inc.)	$760 per syringe (1 dose per syringe)	0.3 mg intravitreally every 6 weeks	$507	$6,080

* Pegaptanib, on average, does not improve or stabilize vision in treated eyes.

Pharmacoeconomic Analysis

There are no currently available pharmacoeconomic trials for ranibizumab. The manufacturer reports a Markov model is in development.

Data Compilation Tables

The NNT for the primary outcome of rate of visual acuity loss (measured as the loss of fewer than 15 letters) is shown in the following table:

	pegaptanib	ranibizumab
(OUTCOME ON DRUG)	70%	82%
(OUTCOME ON PBO)	55%	53%
Treatment duration	54 weeks	24 months
Relative Risk Reduction	27%	
Absolute Risk Reduction	15%	29%
NNT	7	3

Conclusions

Ranibizumab is the first FDA approved agent for neovascular AMD that has demonstrated improvement in patient's VA over time. It has been shown to be effective for all subtypes of AMD; minimally classic, occult and predominately classis lesions. Ranibizumab has been demonstrated to be superior to verteporfin therapy. The safety profile of ranibizumab use, in clinical trials, demonstrates a low incidence of serious ocular events. The efficacy and safety of ranibizumab has been demonstrated over a two year time period. The ability to dose ranibizumab in a modified fashion based on patient response has been demonstrated in a small scale trial but requires further investigation to prove the durability of response. Additional Phase III trials are underway investigating further long term safety and efficacy beyond a two period in addition to a trail evaluating 0.3 mg and 0.5 mg of ranibizumab dosed once monthly for three months with retreatment based specific criteria. The early results of two Phase I trials in DME appear promising however; further trials will be needed to define the appropriate dose and duration of treatment in this indication.

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