Evidence Review for Prescribing Clinical Network
Treatment: Service Development – Intravitreal anti VEGF for uveitis when intravitreal dexamethasone (Ozurdex®) is contraindicated
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Topic Submitted by: Lucy Alexakis
Date: October 2013

Summary page

- How strong is the evidence for claimed efficacy?
  (Grade A = > 1 RCT or meta-analysis; Grade B = 1 RCT or descriptive study; Grade C = expert committee report/opinion)

Grade B

- Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?

Provides patients unable to receive intravitreal dexamethasone a treatment option for uveitis

- Is there a clear place in therapy / treatment pathway?
  (E.g. patient type / characteristics, and relationship to other therapies)

Yes as a 2nd line for patients unable to receive intravitreal dexamethasone due to a contraindication

- Is monitoring for efficacy required?

Yes

- Is monitoring for toxicity required?

Yes

- Is dose titration required?

No

- Traffic light status (ie who will prescribe the drug and any restrictions required)?

RED hospital only

- Role of the specialist (if applicable)?

Administration and monitoring

- Role of GP (if applicable)?

Nil

- Financial implications?

Comparable to currently commissioned treatment

- Other issues

All alternative treatments unlicensed in uveitis

- National Guidance available

No national guidelines available

Recommendations:

To commission the most cost effective intravitreal anti VEGF for the treatment of uveitis as a second line for patients unable to receive currently commissioned intravitreal dexamethasone implant (Ozurdex®) due to a contraindication. This would be for the same patient group as Ozurdex®, non-infectious sight threatening or sight-losing intermediate or posterior uveitis. Ozurdex® is not commissioned for use in anterior uveitis or in uveitis caused by infection.

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1	27/09/13	Lucy Alexakis		

1. Purpose of the Review

A service development has been requested by the Surrey Collaborative Individual Funding Request panel for patients who are unable to receive currently commissioned intravitreal dexamethasone (Ozurdex®) for the treatment of uveitis due to a contraindication. There have currently been 2 individual funding requests for bevacizumab approved by the panel. Moorfields Eye Hospital is the main requesting hospital.

2. Appropriateness

2.1 and 2.2 The patient and the problem:

Patients with uveitis (non- infectious intermediate and posterior) unable to receive currently commissioned Ozurdex® due to a contraindication.

Definition:

Uveitis is a group of intraocular inflammatory disorders affecting the middle layer of the eye (the uvea) which can cause significant visual impairment and may result in partial or complete loss of vision. Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or as a result of trauma to the eye. In many cases the cause remains uncertain.

Uveitis may be classified by the anatomical location of the inflammation; anterior (iris and ciliary body); intermediate (peripheral retina and pars plana of the ciliary body); posterior (retina and choroid) and panuveitis. Uveitis can also be divided based on its aetiology into: infectious, non-infectious, and masquerade syndromes (neoplastic and drug induced). The course of uveitis may be defined as acute, recurrent or chronic (1).

Effects, prognosis, etiology:

Posterior segment uveitis encompasses the terms intermediate and posterior uveitis previously described. It can be localised to the back of one or both eyes. It will typically manifest with 'floaters' and gradual loss of vision, occasional photophobia, but little or no discomfort or redness. Although it is not life-threatening, posterior segment uveitis is a chronic and debilitating condition with a high-risk of permanent vision loss. Uveitis can affect people of any age, but most commonly between the ages of 20 and 59 years. Uveitis is a leading cause of visual impairment with an incidence of impairment of 35% mainly attributable to posterior uveitis. Almost half of people with posterior uveitis develop visual impairment with its attendant socioeconomic impact (1).

It is estimated that non-infectious uveitis of the posterior segment of the eye affects around 3 to 10 persons per 100,000 in the European Union. This would equate to between 1,500 and 5,000 cases per year in England. The true incidence is difficult to determine as many cases will resolve spontaneously and not present clinically (1).

Diagnosis: Slit lamp examination to assess inflammation.

2.3 The Intervention:

Intravitreal bevacizumab or ranibizumab or aflibercept

How does it work: Ranibizumab, bevacizumab and aflibercept are targeted monoclonal antibodies (MABs) which block the action of some or all forms of vascular endothelial growth factor (VEGF) with the intention of reducing new vessel growth and halting the development of the associated pathology. Ranibizumab and aflibercept were specifically developed for ocular use and intravitreal administration whereas bevacizumab was developed for intravenous administration (2).

Care setting: Secondary care, administration by a consultant ophthalmologist.

Frequency:
Dose frequency dependant on response, funding usually applied for 3 doses and then response assessed.

2.4 Alternative treatments:

Intravitreal dexamethasone (Ozurdex®) is currently commissioned by Surrey Heath CCG, Surrey Downs CCG, Guildford &Waverley CCG, East Surrey CCG, Crawley CCG and North West Surrey CCG. Horsham and Mid Sussex CCG will make a decision after review at the Brighton APC.

Ozurdex® is currently commissioned for the treatment of non-infectious sight threatening or sight-losing intermediate or posterior uveitis. Ozurdex® is not commissioned for use in anterior uveitis or in uveitis caused by infection.

Ozurdex® is contraindicated in

- Hypersensitivity to the active substance or to any of the excipients
- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- **Advanced glaucoma** which cannot be adequately controlled by medicinal products alone
- Aphakic eyes with rupture of the posterior lens capsule.
- Eyes with Anterior Chamber Intraocular Lens (ACIOL) and rupture of the posterior lens capsule.

Ranibizumab (Lucentis®) intravitreal injection is a licensed anti VEGF drug for wet age related macular degeneration, retinal vein occlusion and diabetic macular degeneration. It is not licensed for uveitis and would therefore be off label.

Bevacizumab (Avastin®) is not formulated as an intravitreal injection. It is licensed for use in certain cancer treatments. Bevacizumab is not licensed for uveitis and is also not formulated in an intravitreal injection preparation.

Aflibercept (Eylea®) intravitreal injection is a newer anti VEGF drug licensed for wet age related macular degeneration. It is not licensed for uveitis and would therefore be off label. Trial data may also be limited as a newer drug.

3. Effectiveness

3.1 Expected benefits
Maintenance or gain in visual acuity and visual function. Prevention of blindness.

3.2 Is there a plausible biological basis for effectiveness?
Yes, Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation. The anti VEGF's against these processes.

3.3 Side-effects/complications
(3) Bevacizumab
Bevacizumab is not formulated for intravitreal use.

Eye disorders
Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use
A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

(4)Ranibizumab
The most frequently reported ocular adverse reactions following injection of Lucentis are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus.

The most frequently reported non-ocular adverse reactions are headache, nasopharyngitis and arthralgia.

Less frequently reported, but more serious, adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and iatrogenic traumatic cataract.

(5) Aflibercept
The most common adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%).

3.4 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)

Vascular endothelial growth factor inhibition in uveitis: a systematic review.
Gulati N, Forooghian F, Lieberman R, Jabs DA.
Br J Ophthalmol. 2011 Feb;95(2):162-5. doi: 10.1136/bjo.2009.177279. Epub 2010 May 21.
Department of Ophthalmology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA. farzin.forooghian@mssm.edu
Abstract
Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of uveitic complications such as cystoid macular oedema (CMO), choroidal neovasularisation (CNV) and retinal neovascularisation (RNV). The use of intravitreal anti-VEGF therapies, namely bevacizumab and ranibizumab, has recently been described in the treatment of these complications. Evidence describing the use of intravitreal anti-VEGF therapy for these complications consists of case reports and case series, most of which are retrospective and have limitations in design and analysis. As such, the current level of evidence supporting the use of intravitreal anti-VEGF therapy for these complications of uveitis would be rated as very low. Furthermore, blockage of VEGF has not been shown to have an anti-inflammatory effect. Thus, treatment of the underlying inflammatory disease should play a central role in the management of uveitic CMO, CNV and RNV. A two-pronged treatment regimen that focuses on achieving disease quiescence through the use of corticosteroids and/or immunosuppressive agents, while treating complications that arise despite adequate disease quiescence with intravitreal anti-VEGF agents, may be useful. However, further data from prospective controlled trials are needed before the therapeutic role of anti-VEGF therapy in the uveitis treatment regimen can be fully determined.

Bevacizumab

Intravitreal bevacizumab for treatment of uveitic macular edema.
Cordero Coma M, Sobrin L, Onal S, Christen W, Foster CS.
Ophthalmology. 2007 Aug;114(8):1574-1579.e1. Epub 2007 Mar 23.
Massachusetts Eye Research and Surgery Institute, Cambridge, Massachusetts 02142, USA.
Abstract
PURPOSE:
To evaluate the short-term safety and efficacy of intravitreal bevacizumab for the treatment of cystoid macular edema (CME) secondary to uveitis.
DESIGN:
Retrospective, noncomparative, interventional case series.
PARTICIPANTS:
Thirteen patients undergoing treatment for recalcitrant uveitic macular edema at one referral center.

METHODS:
Charts of patients who received one 2.5-mg intravitreal injection of bevacizumab in one eye were reviewed for clinical information including best-corrected Snellen visual acuity (VA), examination findings, optical coherence tomography (OCT) results, and fluorescein angiography results. Kaplan-Meier survival analysis was used to calculate probability success rates. The statistical significance of change in mean retinal thickness and VA was assessed using repeated-measures analysis of variance.
MAIN OUTCOME MEASURES:
Assessments of changes in best-corrected Snellen VA and OCT retinal thickness were made.
RESULTS:
Six (46.15%) patients had a decrease in foveal thickness at the end of the follow-up, whereas 5 (38.4%) patients had an improvement of VA by > or =2 lines 84 days or more after the injection. Mean retinal thickness showed a significant decrease over the follow-up ($P<0.02$). The change in mean logarithm of the minimum angle of resolution VA over the follow-up was not significant ($P>0.05$). Survival analysis showed that the probability of any improvement in VA increased progressively starting at 6 weeks and reached 81% at 14 weeks. No significant ocular or systemic adverse effects were observed.
CONCLUSIONS:
These results suggest that a single intravitreal injection of bevacizumab is well tolerated and is associated with short-term improvement in VA and decreased OCT retinal thickness in a considerable proportion of patients with uveitic CME resistant to conventional therapy. Further evaluation of intravitreal bevacizumab for uveitic CME in controlled randomized studies is warranted.

Intravitreal bevacizumab in refractory uveitic macular edema: one-year follow-up.
Cervantes-Castañeda RA, Giuliari GP, Gallagher MJ, Yilmaz T, MacDonell RE, Quinones K, Foster CS.
Eur J Ophthalmol. 2009 Jul-Aug;19(4):622-9.
Massachusetts Eye Research and Surgery Institution, Cambridge, MA, USA.
Abstract
PURPOSE:
Uveitis is a major cause of ocular morbidity in developed countries. It has been demonstrated that macular edema is a significant cause of decreased visual acuity and macular edema in these patients. In this article, we evaluate the long-term outcome of intravitreal bevacizumab in the treatment of refractory uveitic macular edema.
METHODS:
In this retrospective, noncomparative, interventional case series, uveitic patients with macular edema who were refractory to conventional therapy and who were treated with intravitreal bevacizumab were identified and assessed. Best-corrected visual acuity and optical coherence tomography central macular thickness measurements were collected and analyzed with correlative statistical analysis, including the use of Student paired t-test, Kaplan-Meier, and linear regression analysis.
RESULTS:
Twenty-nine eyes of 27 patients with diverse uveitic etiologies were analyzed and followed up at 1 year. Thirteen patients received a single intravitreal bevacizumab injection. Six patients required a second intravitreal bevacizumab injection, while 10 patients received combination therapy of intravitreal bevacizumab and triamcinolone

acetonide. Baseline mean logMAR visual acuity was -0.59. At 1 year, the mean logMAR visual acuity was -0.42-/+ 0.36 (p=0.0045). Baseline mean central macular thickness was 383.66 microm. At 1 year, the mean thickness was 294.32-/+110.87 (p=0.0007).

CONCLUSIONS:

Intravitreal bevacizumab is a useful and therapeutically beneficial agent in the treatment of refractory uveitic macular edema. Some patients will require adjunctive intravitreal bevacizumab injections or the use of combination therapy with intravitreal triamcinolone acetonide.

Intravitreal bevacizumab (avastin) as a treatment for refractory macular edema in patients with uveitis: a pilot study.

Mackensen F, Heinz C, Becker MD, Heiligenhaus A.

Retina. 2008 Jan;28(1):41-5. doi: 10.1097/IAE.0b013e318156db75.

Interdisciplinary Uveitis Center, Department of Ophthalmology, University of Heidelberg, Germany. friederike.mackensen@uveitiszentrum.de

Abstract

PURPOSE:

: Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) which has been successfully used for the treatment of age-related macular degeneration with choroidal neovascularization. As VEGF is involved in the pathomechanisms of inflammation and endothelial dysfunction the authors used bevacizumab as a last resort treatment in patients with persistent uveitic cystoid macular edema (CME).

PATIENTS AND METHODS:

: Persistent uveitic CME was defined by optical coherence tomography (OCT) measurements >250 mum despite previous treatments. The authors reviewed patients with persistent CME who subsequently had been treated with intravitreous bevacizumab 1.25 or 2.5 mg. Improvement was judged by visual acuity (VA) gain >/=2 lines and thickness reduction in OCT.

RESULTS:

: Eleven eyes of 10 patients were injected since February 2006. Median follow-up was 70 days. Reduction in central retinal thickness could be seen as early as 2 weeks with a mean foveal thickness reduction of 127.2 mum at 4 weeks. Concurrent improvement in VA was seen in 4 of 10 patients, and was unchanged in the others. Four patients received two injections and five patients received three injections. Except for progression of cataract in one eye no ocular or systemic adverse events were recorded.

CONCLUSIONS:

: Intravitreal bevacizumab seems to be an effective and safe treatment in the management of refractory inflammatory CME. The effect is transient, and reinjections may be necessary, although the time until reinjection is needed differs individually

Intravitreal Bevacizumab Versus Triamcinolone Acetonide for Refractory Uveitic Cystoid Macular Edema: A Randomized Pilot Study

Masoud Soheilian , 1,2 Zahra Rabbanikhah , 1 Alireza Ramezani , 1–3 Victoria Kiavash , 1 Mehdi Yaseri , 1 and Gholam A. Peyman 4.

JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS
Volume 26, Number 2, 2010

ABSTRACT

Purpose: To compare intravitreal bevacizumab (IVB) versus intravitreal triamcinolone acetonide (IVT) for treatment of refractory uveitic cystoid macular edema (CME).

Methods: In this randomized clinical trial, 31 eyes with uveitic CME were allocated into the IVB group—eyes that received 1–3 injections of 1.25 mg bevacizumab (15 eyes) and the IVT group—eyes that received 1–3 injections of 2 mg triamcinolone (16 eyes). Primary outcome measure was change in best-corrected visual acuity (VA) at 36 weeks.
Results: Visual acuity improvement compared with baseline values was meaningful in the IVB group at 12, 24, and 36 weeks (−0.35 ± 0.45 logMAR [*P* = 0.016]) and in the IVT group at 24 and 36 weeks (−0.32 ± 0.32 logMAR [*P* = 0.001]). A significant central macular thickness (CMT) reduction was observed only in the IVT group at week 36 (74.6 ± 108.0 μm [*P* = 0.049]). Between-group analysis disclosed no significant difference in any outcome measure. By statistically removing the factor of cataract, the IVT group had more improvement in VA (*P* = 0.007).
Conclusions: IVB was as effective as IVT in refractory uveitic CME regarding VA improvement up to 36 weeks. Irrespective of triamcinolone-induced cataract, a more beneficial effect of IVT may be attainable.

Efficacy and safety of intravitreal bevacizumab compared with intravitreal and posterior sub-tenon triamcinolone acetonide for treatment of uveitic cystoid macular edema.

Bae JH, Lee CS, Lee SC.
Retina. 2011 Jan;31(1):111-8. doi: 10.1097/IAE.0b013e3181e378af.
Department of Ophthalmology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

Abstract

PURPOSE:

To demonstrate the effect of bevacizumab compared with triamcinolone acetonide for the treatment of persistent cystoid macular edema in noninfectious uveitis.

METHODS:

The medical records of 31 eyes of 31 patients with uveitic cystoid macular edema that had persisted despite conventional treatment were reviewed. Ten eyes received 1.25 mg of intravitreal bevacizumab (IVB), 11 eyes received 4 mg of intravitreal triamcinolone acetonide (IVTA), and 10 eyes received 40 mg of posterior sub-Tenon triamcinolone acetonide (PSTA). Changes in visual acuity with a logarithmic minimal angle of resolution and central foveal thickness measured with optical coherence tomography were analyzed.

RESULTS:

The mean follow-up was 22.3 weeks. The best improvement in visual acuity and reduction in central foveal thickness was achieved at 4 weeks in all groups but worsened with time until 12 weeks (visual acuity improved from baseline by 0.19, 0.27, and 0.16 and central foveal thickness decreased from baseline by 167.4 mm, 327.6 mm, and 166.4 mm with IVB,IVTA, and PSTA, respectively; P , 0.001). The results with IVTA were better than those with IVB or PSTA, although the difference did not reach statistical significance. Intravitreal bevacizumab provided a significantly better effect in visual acuity gain in Behcet uveitis than in non-Behcet uveitis (P = 0.045). Kaplan–Meier survival analysis showed that the median period of effect were 16 weeks with IVB, 30 weeks with IVTA, and 12 weeks with PSTA.An increase in intraocular pressure (.5 mmHg greater than baseline) was observed in 1 eye(10%) with IVB, 5 eyes (45.5%) with IVTA, and 4 eyes (40%) with PSTA.

CONCLUSION:

Intravitreal bevacizumab was a well-tolerated and effective supplementary therapy for persistent uveitic cystoid macular edema, especially in Behcet uveitis and **for patients with the risk of an increase in intraocular pressure**. However, reinjection

may be required because of the limited potency and duration of the positive effects of IVB.

Comparison of intravitreal injection of bevacizumab and triamcinolone acetonide in the treatment of uveitic macular edema.

Rahimi M, Shahrzad SS, Banifatemi M.
Department of Ophthalmology and Poostchi Eye Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, e-mail: mrahimi@sums.ac.ir.
Iran J Immunol. 2012 Jun;9(2):136-44. doi: IJIv9i2A7.

Abstract

Background: Cystoid Macular Edema (CME) is one of the most common and sight threatening complications of uveitis. Intravitreal injection of corticosteroids and Anti-VEGF are two routine options for treatment. Objective: To compare the effects of intravitreal injections of Bevacizumab and Triamcinolone Acetonide for the treatment of persistent macular edema in non-infectious uveitis. Methods: In a randomized clinical trial, sixty eyes of 55 patients were enrolled in the study. Patients were divided into two groups with randomized digits table. 29 eyes received 4 mg of intravitreal triamcinolone acetonide, and 31 eyes received 1.25 mg of intravitreal bevacizumab. Two main outcome measures were changes in visual acuity, measured with logarithm of minimal angle of resolution, and central macular thickness, measured with optical coherence tomography. Results: The mean follow-up was 25.3 weeks. The best visual acuities were achieved 6 months after injection in both groups. Improvement in visual acuity at 6 months was achieved in 28/29 (96%) of eyes in Triamcinolone group and in 26/31 (83%) eyes in Bevacizumab group (p=0.196). None of the eyes showed worsening of visual acuity after 6 months. Mean of central macular thickness in the pre-injection time for intravitreal triamcinolone acetonide (IVTA) group was 295.62 µ, and 309.87 µ in intravitreal bevacizumab (IVB) group, which were decreased after six months to 199.27 µ and 221.06 µ, respectively (p<0.001). Conclusion: This study shows that IVT and IVB are both effective in improving vision in uveitic CME. Although effects of triamcinolone on Central Macular Thickness (CMT) are more apparent, this superiority is not seen on Best Corrected Visual Acuity (BCVA).

Changes in the intraocular cytokine levels after intravitreal bevacizumab in uveitic macular edema.

Jeon S, Lee WK, Jung Y.
Ocul Immunol Inflamm. 2012 Oct;20(5):360-4. doi: 10.3109/09273948.2012.709576.
Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seocho-Gu, Seoul, Korea.

Abstract

PURPOSE:

To evaluate the changes in intraocular cytokine after intravitreal bevacizumab (IVB) for uveitic cystoid macular edema (CME).

METHODS:

The authors evaluated 9 eyes of 8 patients who underwent IVB for uveitic CME. The aqueous humor-levels of vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β(2)were measured using suspension array technology at baseline and 1 month after IVB.

RESULTS:
The VEGF level was decreased to insignificant level (p = .008). TGF-β(2) and TNF-α levels increased significantly (p = .008 and .021, respectively). IL-6 and IL-8 showed no significant change (p = .051 and.110, respectively).
CONCLUSION:
IVB resulted in a significant decrease of VEGF levels, which was associated with anatomical improvement of CME at 1 month. Compensatory elevations of proinflammatory cytokines (IL-6 and IL-8) after selective VEGF inhibition were not observed. Marked elevation of TGF-β(2) after IVB seems to play an immunosuppressive role.

Ranibizumab

The LIMO Study, is currently recruiting patients looking at Lucentis(Ranibizumab) for Treatment of Uveitic Patients With Refractory Cystoid Macular Oedema.

Ranibizumab for refractory uveitis-related macular edema.
Acharya NR, Hong KC, Lee SM.
Am J Ophthalmol. 2009 Aug;148(2):303-309.e2. doi: 10.1016/j.ajo.2009.03.028. Epub 2009 May 9.
F.I. Proctor Foundation, University of California, San Francisco, San Francisco, CA 94143, USA. nisha.acharya@ucsf.edu
Abstract
PURPOSE:
To evaluate the effect of intravitreal ranibizumab injections (Lucentis; Genentech Inc, South San Francisco, California, USA) on refractory cystoid macular edema (CME) in patients with controlled uveitis who have failed oral and regional corticosteroid treatment, the mainstays of current medical therapy.
DESIGN:
Prospective, noncomparative, interventional case series.
METHODS:
Seven consecutive patients with controlled uveitis and refractory CME who had failed corticosteroid treatment were studied. One eligible patient chose not to participate and another did not complete follow-up for nonmedical reasons. Intravitreal ranibizumab injections (0.5 mg) were given monthly for 3 months, followed by reinjection as needed. The primary outcome was the mean change in best spectacle-corrected visual acuity (VA) from baseline to 3 months, and the secondary objective was the mean change in central retinal thickness (CRT) on ocular coherence tomography. Six-month outcomes were also assessed.
RESULTS:
At 3 months, the mean increase in acuity for the 6 patients who completed follow-up was 13 letters (2.5 lines), and the mean decrease in CRT was 357 mum. Both VA and CRT improved significantly between baseline and 3 months (P = .03 for each). Although most patients required reinjection, this benefit was maintained at 6 months. There were no significant ocular or systemic adverse effects.
CONCLUSIONS:
Intravitreal ranibizumab led to an increase in VA and regression of uveitis-associated CME in patients refractory to or intolerant of standard corticosteroid therapy. Further studies of this promising treatment are warranted.

Aflibercept

No information available as a newer drug.

4. Summary of Key Points for Consideration

4.1 National guidance:

There is no national guidance available for any of the intravitreal anti-VEGF treatments for uveitis. Ranibizumab has NICE guidance for wet AMD, diabetic macular oedema and retinal vein occlusion. Aflibercept has NICE guidance for wet AMD.

4.2 Efficacy

No evidence or trial data was found for aflibercept in uveitis. Trial data was more limited for ranibizumab than for bevacizumab in uveitis. Although small patient numbers intravitreal ranibizumab in studies has shown to increase visual acuity and lead to regression of uveitis-associated cystoid macular oedema in patients refractory to or intolerant of standard corticosteroid therapy. There have been more published studies looking at the use of intravitreal bevacizumab in uveitis than the other anti VEGF's. The results of these studies have shown intravitreal bevacizumab to improve visual acuity and is well tolerated. The potency and duration of the anti VEGF's compared to intravitreal steroid maybe decreased requiring more frequent re-injection.

4.3 Potential Benefits over existing therapy

- Alternative treatment for uveitis(non-infectious intermediate or posterior) if Ozurdex® is contraindicated
- An option for patients with a risk of increased intraocular pressure rise with steroid administration

4.4 Potential disadvantages

- Unlicensed
- Potentially more expensive depending on anti VEGF drug used
- No national guidance available
- More frequent administration

4.5 Budgetary Impact

4.5.1 Cost:

Bevacizumab

Approximately £60 per injection.

Ranibizumab

List price £742.17 per 0.5mg vial. There is a patient access scheme in place for ranibizumab which is commercially sensitive and cannot be printed in this paper.

Aflibercept

List price £816.00 per 0.1ml vial – 40mg/ml

There is a patient access scheme in place for aflibercept which is commercially sensitive and cannot be printed in this paper.

Tariff codes and prices 13-14
BZ23Z: HRG Code for Intravitreal injection (NICE recognizes this as least complex procedure) **£139**- administration cost per injection

Follow up attendance single professional ophthalmology **£60**

4.5.2 Precedent setting:
Currently since September 2012 there have been 6 patients funded for treatment of uveitis with Ozurdex®.
Surrey Heath CCG – 1 patient
Guildford &Waverley – 2 patients
East Surrey – 2 patients
Crawley – 1 patient

There have been 2 applications and both funded for the treatment of uveitis with bevacizumab via the Individual Funding Request route.

Surrey Downs – 2 patients

The patient numbers for anti VEGF would be smaller as only for patients when 1st line treatment with Ozurdex® is contraindicated. An estimate would be about 1 patient per CCG per year.

5. Conclusions and Recommendations

From the limited study data available anti- VEGF's appear to increase visual acuity in patients with uveitis, although remain unlicensed for this indication. There is more published data for bevacizumab than for ranibizumab or aflibercept. Safety data is available and from the studies bevacizumab and ranibizumab appear to be well tolerated. There are no national guidelines to support the use of any anti VEGF in uveitis. There are no studies available comparing the anti-VEGF's to each other. If comparable bevacizumab is more cost- effective. The patient numbers are likely to be very small.

Recommendations

- To remain a hospital only RED drug
- To commission the most cost effective, in this case bevacizumab as a 2nd line treatment for patients with non-infectious sight threatening or sight-losing intermediate or posterior uveitis who are unable to receive intravitreal dexamethasone (Ozurdex®) due to a contraindication.

Appendix 1: Evidence search

Search terms used: Uveitis, bevacizumab, ranibizumab, aflibercept

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia)	✓

http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References

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Further evidence

INDUCE EXTENDED REMISSION IN SOME PATIENTS IN NONINFECTIOUS UVEITIS

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Purpose: To assess the outcomes of the intravitreal administration of methotrexate in uveitis.

Methods: Multicenter, retrospective interventional case series of patients with non-infectious uveitis. Thirty-eight eyes of 30 patients were enrolled, including a total of 54 intravitreal injections of methotrexate at a dose of 400 mg in 0.1 mL. The primary outcome measure was visual acuity. Secondary outcome measures included control of intraocular inflammation and cystoid macular edema, time to relapse, development of adverse events, and levels of systemic corticosteroid and immunosuppressive therapy.

Results: Methotrexate proved effective in controlling intraocular inflammation and improving vision in 30 of 38 eyes (79%). The side effect profile was good, with no reported serious ocular adverse events and only one patient having an intraocular pressure of .21 mmHg. Of the 30 eyes that responded to treatment, 8 relapsed, but 22 (73%) entered an extended period of remission, with the Kaplan–Meier estimate of median time to relapse for the whole group being 17 months. The eight eyes that relapsed were reinjected and all responded to treatment. One eye relapsed at 3 months, but 7 eyes again entered extended remission. Of the 14 patients on systemic therapy at the start of the study, 8 (57%) were able to significantly reduce this following intravitreal methotrexate injection.

Conclusion: In patients with uveitis and uveitic cystoid macular edema, intravitreal MTX can effectively improve visual acuity and reduce cystoid macular edema and, in some patients, allows the reduction of immunosuppressive therapy. Some patients relapse at 3 to 4 months, but a large proportion (73%) enter an extended period of remission of up to 18 months. This larger study extends the results obtained from previous smaller studies suggesting the viability of intravitreal methotrexate as a treatment option in uveitis.

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Intraocular Methotrexate in the Treatment of Uveitis and Uveitic Cystoid Macular Edema

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Objective: A pilot study to evaluate the use of intravitreal methotrexate (MTX) for the treatment of uveitis and uveitic cystoid macular edema (CME).

Design: Prospective, consecutive, interventional case series.

Participants: Fifteen eyes of 15 patients with a unilateral exacerbation of noninfectious intermediate, posterior uveitis, or panuveitis and/or CME such that visual acuity (VA) was 20/40 or worse, together with a history of increased intraocular pressure (IOP) in response to corticosteroid administration.

Intervention: Intravitreal injection of 400 _g in 0.1 ml MTX.

Main Outcome Measures: The primary outcome measure was VA (using the Early Treatment Diabetic Retinopathy Study chart). Other outcome measures included ocular inflammation scores, time to relapse, levels of systemic corticosteroid and immunosuppressive therapy, and ocular coherence tomography. Potential complications of intravitreal MTX injection, including cataract progression, vitreous hemorrhage, retinal detachment, and corneal epitheliopathy, were assessed.

Results: VA improved at all time points and was statistically significant at the 3- and 6-month follow-up examinations. The mean visual improvement was 4 lines at 3 months and 4.5 lines at 6 months, with no statistical difference between the best VA obtained after MTX injection and after previous corticosteroid treatment, including intravitreal triamcinolone acetate injection. Five patients relapsed after a median of 4 months; a similar improvement was seen

after re-injection. Ocular inflammation scores improved at all time points, and systemic immunosuppressive medication was reduced in 3 of 7 patients taking this at the start of the trial.

Conclusions: In patients with uveitis and uveitic CME, intravitreal MTX can improve VA and reduce CME and, in some patients, allows the reduction of immunosuppressive therapy. Relapse occurs at a median of 4 months in some patients, but reinjection has similar efficacy.

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