BULLETIN 211 : Ranibizumab or Bevacizumab for the Treatment of Juxtafoveal Telangiectasia

**JPC recommendation:**

- The use of anti-VEGF agents (i.e. ranibizumab or bevacizumab) for the treatment of Juxtafoveal Telangiectasia is **not** supported.

<table>
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<th>Medicine</th>
<th>Intravitreal ranibizumab (Lucentis®) or Bevacizumab (Avastin®) for the treatment of Juxtafoveal Telangiectasia</th>
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**Introduction / Background**

The following background information has been extracted from a review by Nowilaty et al (Idiopathic Juxtafoveal Retinal Telangiectasis: A Current Review, Middle East Afr J Ophthalmol. 2010 Jul-Sep; 17(3): 224–241)

Idiopathic juxtafoveal retinal telangiectasis (IJFT) (also known as idiopathic parafoveal, perifoveal or macular telangiectasia or telangiectasis), refers to a heterogeneous group of well-recognized clinical entities characterized by telangiectatic alterations of the juxtafoveal capillary network of one or both eyes, but which differ in appearance, presumed pathogenesis, and management strategies. Classically, three groups of IJFT are identified.

**Group I** - This is a congenital or developmental form of IJFT, which occurs predominantly in males and is typically unilateral (97% of cases). Onset of symptoms can occur at any age and the mean age at presentation is 40 years. It has easily visible telangiectasis and causes visual loss as a result of macular edema.

**Group II** - This is the most common type of IJFT, and differs completely from IJFT I. It is acquired, not congenital. Affected patients are middle-aged or older (mean 55 years). Males and females are affected equally. This disorder is bilateral, but may be asymmetric appearing as unilateral in its early stages. Similarly, patients may have visual loss in only one eye. It presents with telangiectasis that is more difficult to detect on biomicroscopy, but with characteristic and diagnostic angiographic and
optical coherence tomography features. Vision loss is due to retinal atrophy, not exudation, and subretinal neovascularization is common.

The natural course of IJFT IIA has been subdivided by Gass and Blodi into five stages. Although this staging has been simplified recently, the main observations remain identical.

In Stage 1, patients are generally asymptomatic. A slight loss of the retinal transparency, typically grayish and usually in the temporal juxtafoveolar area, where this condition most often starts, may be the only biomicroscopic clue to the presence of the telangiectasis. Fluorescein angiography is required for detection and shows no evidence of capillary dilation, but mild late retinal staining of the outer juxtafoveolar retina surrounding part or all the foveolar border but sparing the foveola itself.

In Stage 2, patients may be asymptomatic or have minimal disturbances in central vision such as blurred vision, metamorphopsia, or paracentral positive scotoma. A slight graying of the parafoveolar retina approximately one disc diameter in size, confined temporally or forming a partial or complete horizontal oval around the foveal center exists. The foveal center is spared and may appear thinned. The telangiectasis is minimally or not visible, hence the term “occult” as opposed to the easily visible telangiectasis of IJFT I. Superficial crystals may be seen. There is little or no thickening. Stereoscopic FA demonstrates early rapid staining of the thickened walls of the outer capillary network, mostly temporally, followed by diffuse late staining primarily in the middle and outer retina.

In Stage 3, patients may experience decreased vision, which is slow in onset and progression. Paracentral vertically oriented slightly dilated right-angled venules draining the telangiectatic area are evident biomicroscopically. These vessels have been recently attributed both a venular and arteriolar origin that leads to a network of proliferating vessels in the deep retinal layers. These right-angled vessels typically develop temporally. Prominent dilation of the capillaries may be seen clinically. The foveolar depression may simulate macular hole. Stereo FA often shows unusual capillary dilation and permeability change in the outer retina beneath the right-angled vessels causing the retinal staining. However, there is no fluid causing ballooning or cystic spaces in the outer plexiform layer (as occurs in eyes with IJFT I).

In Stage 4, as a result of RPE migration into the retina along the course of the right-angled vessels, one or more loci of black retinal pigmented epithelial hyperplasia or clumps may be seen around the parafoveal right-angled vessels. In some cases, the pigment extends into the inner retina and forms an irregular or stellate plaque enveloping the right-angled vessel. Some patients develop a pseudovitelliform lesion within the fovea.

Stage 5 is marked by the onset of sub-retinal neovascular membrane (SRNV) which occurs as a result of retinal capillary remodeling, proliferation, and invasion of the outer retina which has progressively atrophied. A subretinal network, often with a clearly discernible retino-retinal anastomosis (RRA) or retinal-subretinal anastomosis is evident. Retino-choroidal anastomosis may exist. The SRNV usually occurs temporally, often in the vicinity of the intraretinal pigment epithelial migration or unrelated to the latter. Rapid visual decline ensues as the SRNV causes exudation, neurosensory elevation, intra and subretinal hemorrhage, and fibrovascular proliferation. These features are easily evident clinically and angiographically. On FA, the SRNV has angiographic features similar to classic neovascularization demonstrating early hyperfluorescence which increases and leaks in the late phases of the angiogram. However, it is not associated with RPE detachment and its final size is generally smaller compared to classic choroidal neovascularization in AMD and visual acuity does no deteriorate much further. The fibrovascular tissues tend to
remodel over time, leading to retinal vascular distortion and dragging of neighboring venules and arterioles into the tissue itself.

At any stage (Stages 2–5), tiny golden crystals may be seen near the retinal surface often anterior to the retinal vessels over the area of telangiectasis. They are characteristic although an inconsistent feature. According to Yannuzzi et al., the intraretinal and subretinal pigmented plaques may also occur variably throughout the course of the disease and may persist without visual consequence for years.

Group III is very rare characterized predominantly by progressive obliteration of the perifoveal capillary network, occurring usually in association with a medical or neurologic disease.

- Juxtafoveal telangiectasia (IJFT) is also sometimes termed perifoveal telangiectasia and more often known as idiopathic macular telangiectasia (MACTEL).
- Two types of telangiectasia are seen. Type 1 MACTEL occurs in middle age persons; the condition is usually unilateral and exhibits exudative features. Type 2 MACTEL occurs in older people and is usually bilateral. MACTEL type 2 is mainly divided into 2 stages. Type 1 IJFT has easily visible telangiectasis and causes visual loss as a result of macular oedema. Type 2 IJFT telangiectasis is more difficult to detect and visual loss is due to retinal atrophy, not exudation and subretinal neovascularisation (SRNV) is common. There are 5 stages of Type 2 IJFT. Stage 1-4 are a non-proliferative stage whereas stage 5 is classified as a proliferative stage marked by the onset of SRNV.
- Non-proliferative type 2 IJFT is associated with a progressive visual decline in association with outer retinal atrophy and can occur over at least a decade.
- Rapid vision decline can occur in proliferative type 2 IJFT (stage 5) as SRNV causes exudation, neurosensory elevation, intra and subretinal haemorrhage and fibrovascular proliferation.
- Ranibizumab is a recombinant humanized monoclonal antibody fragment (lacking an Fc region). Ranibizumab is the first VEGF inhibitor specifically designed for use in the eye to bind to and inhibit VEGF-A, a protein that is believed to play a critical role in the growth of new blood vessels (angiogenesis) and the hyperpermeability (leakiness) of the vessels.
- Ranibizumab is approved by NICE for the treatment of Age-related macular degeneration, diabetic macular oedema, visual impairment caused by macular oedema secondary to retinal vein occlusion and treatment of choroidal neovascularisation associated with pathological myopia.
- Ranibizumab is not licensed for the treatment of juxtafoveal telangiectasia and it is therefore, unlikely that it will be assessed by NICE for this condition.
- Bevacizumab is not licensed for use by the intravitreal use. It is licensed for a variety of cancer indications.
- The evidence for use of Ranibizumab (Lucentis®) or bevacizumab (Avastin®) for the treatment of juxtafoveal telangiectasia consists of case reports, case series, chart reviews and 2 open label non-randomised trial.
- Evidence indicates that when intravitreal bevacizumab is used in non-proliferative type 2 IJFT, there can be some anatomical responses, however there is no improvement in visual acuity.
- There is some evidence to support that intravitreal bevacizumab can cause involution of neovascularisation and improve visual acuity in patients with proliferative type 2 IJFT. The proliferative stage is reportedly successfully
treated with photodynamic therapy, intravitreal anti-vascular endothelial growth factor (VEGF) injections, and combination therapies.

- The information is more mixed with intravitreal ranibizumab. Combined with reduced-fluence PDT in non-proliferative MACTEL type 2, ranibizumab may slow down disease progression, although when used on its own it is not recommended. Use of ranibizumab in 4 patients with proliferative type 2 idiopathic MACTEL indicated it was as effective in improving visual acuity as bevacizumab although the sample size is too small to conclusively prove this.
- Intravitreal ranibizumab with laser photocoagulation in type 1 MACTEL improved both visual acuity and macular oedema in 1 patient.

### The intervention

#### Mechanism of action

**Mechanism of action (with regards Ag-related Macular degeneration (AMD) - NICE TA 155)**

AMD occurs in two forms, dry and wet AMD. Dry AMD (non-neovascular) is a form of extensive atrophy (wasting) of cells that progresses slowly, whereas the wet form can lead to a rapid worsening of vision. Wet (neovascular) AMD is characterised by the development of immature blood vessels that grow between the retinal pigment epithelial cells and the photoreceptor cells in the centre of the retina, a process known as choroidal neovascularisation (CNV). These vessels easily haemorrhage and cause lesions on the macula, leading to visual impairment. A protein known as vascular endothelial growth factor (VEGF), which induces new blood vessel formation (angiogenesis), vascular permeability and inflammation, has been implicated in the development and progression of CNV. CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. A mixture of classic and occult CNV can occur in the same lesion. CNV can also be described in terms of its location: the fovea is the central part of the macula, and CNV that develops below the foveal area is termed ‘subfoveal CNV’

Ranibizumab is a recombinant humanized monoclonal antibody fragment (lacking an Fc region). Ranibizumab is the first VEGF inhibitor specifically designed for use in the eye to bind to and inhibit VEGF-A, a protein that is believed to play a critical role in the growth of new blood vessels (angiogenesis) and the hyperpermeability (leakiness) of the vessels.

In wet AMD, the abnormal blood vessels grow under the surface of the retina and leak blood and fluid, causing rapid damage to the macula, the portion of the eye responsible for fine, detailed central vision. (6)

**Mechanism of action (with regards Ranibizumab for treating Diabetic Macular oedema (Rapid Review of TA 237) – NICE TA 274)**

Ranibizumab (Lucentis®) belongs to a class of drugs that blocks the action of vascular endothelial growth factor A (VEGF-A). In diabetic macular oedema, VEGF-A causes blood vessels to leak in the macula, the area of the retina responsible for the clearest vision. The accumulated fluid causes swelling, or oedema, which impairs vision. By inhibiting the action of VEGF-A, ranibizumab reduces oedema and limits visual loss or improves vision.

**Mechanism of action (with regards Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. – NICE TA 283)**

Ranibizumab (Lucentis®) belongs to a class of drugs that block the action of vascular endothelial growth factor (VEGF) A. Retinal vein occlusion (RVO) is a common cause of reduced vision as a result of retinal vascular disease. Thrombosis in the retinal veins causes an increase in retinal capillary pressure, resulting in increased capillary permeability and the discharge of blood and plasma into the retina. This leads to macular oedema and varying levels of ischaemia through reduced perfusion of capillaries. These changes trigger an increase in VEGF, which increases vascular
Evidence published in literature

**Permeability and new vessel proliferation.** By inhibiting the action of VEGF A, ranibizumab reduces edema and limits visual loss or improves vision.

**Mechanism of action (with regards Ranibizumab for treating choroidal neovascularisation associated with pathological myopia- NICE TA 298)**

Ranibizumab (Lucentis, Novartis) belongs to a class of drugs that blocks the action of vascular endothelial growth factor (VEGF) A. By blocking the action of VEGF A, ranibizumab prevents abnormal blood vessels developing, thereby limiting visual loss and improving vision.

**Mechanism of action (with regards treating juxtafoveal telangiectasia)**

Requesting clinicians on previous IFR requests have stated that this condition has a similar pathology to Age related Macular Degeneration (NICE TA 155)

A Medicine Information request asking for a critical review of the evidence of clinical and cost effectiveness for the use of ranibizumab or bevacizumab for the treatment of Juxtafoveal Telangiectasia was sent to Ipswich Medicine Information Department. The following is a summary of the information found as a result of this search.

The Royal College of Ophthalmologists Age –Related Macular Degeneration: Guidelines for Management (Published in 2013) states the following:

“A number of disorders can result in macular lesions which have to be distinguished from AMD.

Macular telangiectasia. Idiopathic macular telangiectasia (MACTEL) also sometimes termed perifoveal or juxtafoveal telangiectasia may be difficult to distinguish from nAMD, particularly with the RAP form of n AMD. In Two types of telangiectasia have been described in the MACTELstudy Type 1 MACTEL occurs in middle age persons; the condition is usually unilateral and exhibits exudative features as the vessels are leaky and intraretinal fluid accumulation occurs with a cystic maculopathy and surrounding exudates. Type 2 MACTEL occurs in older people and is usually bilateral with evidence of crystalline deposits, pigmentary charges, and right angled venules evident temporal to the fovea and extending to the entire perifoveal region. While leakage is detectable on fluorescein angiography, there is no evidence of increased retinal thickening. Cystic spaces are evident within the retina using OCT and these spaces are thought to reflect the loss of retinal tissue. Occasionally, sub-retinal neovascularization develops and arises from the retinal circulation.” (3)

There are no published guidelines on the treatment options regarding juxtafoveal telangiectasia provide by the Royal College of Ophthalmologists.

A total of 14 references regarding the use of either intravitreal bevacizumab or ranibizumab, dating between 2010 and 2013 were found by Medicines Information. There are more published reports of intravitreal bevacizumab than ranibizumab and there is more information on type 2 idiopathic macular telangiectasia than type 1.

**Type 2 Idiopathic macular telangiectasia**

A summary each reference is provided below:


This paper describes a retrospective case series of 19 German patients/38 eyes with symptomatic type 2 idiopathic macular telangiectasia (IMT) followed up for a mean of 81 months (range 15-188 months). 6 eyes were treated with intravitreal bevacizumab. There was no significant difference in visual acuity between eyes receiving no treatment, intravitreal bevacizumab or laser treatment after 3 and 5 years. The
authors concluded that the data, although small in size, indicates clearly that non-proliferative IMT type 2 is associated with a progressive visual decline over at least a decade and that their results showed that the use of intravitreal bevazicizumab or laser treatment did not improve visual outcome.


This paper describes a case report of a 47 year old Turkish female patient who presented with non-proliferative macular telangiectasia type 2 in in two eyes. After 4 months one eye transformed to proliferative macular telangiectasia type 2 and 3 consecutive monthly injections of intravitreal bevazicizumab 1.25mg were administered. Visual acuity improved.

The discussion section states that - In spite of different classifications, MacTel type 2 is mainly divided into 2 stages, in case of treatment. The first stage is the non-proliferative stage, which is characterized by slow, progressive visual loss in association with outer retinal atrophy. The second stage is the proliferative stage, which is characterized by the presence of subretinal neovascularisation (SRN). Several treatment options have been studied for the non-proliferative stage; however, most are reported to be ineffective because of the degenerative and progressive nature of this disease. In contrast, the proliferative stage is successfully treated with photodynamic therapy, intravitreal anti-vascular endothelial growth factor (VEGF) injections, and combination therapies.


Retrospective case series of 10 eyes in 5 Brazilian patients (1 male, 4 female) with type 2A idiopathic macular telangiectasia. RESULTS: Four weeks after the third Intravitreal bevazicizumab injection, Visual acuity (VA) remained stable for all patients. All eyes showed some decrease in fluorescein leakage, and there was a mild decrease in central macular thickness. One year later, VA, optical coherence tomography (OCT) and fluorescein angiography (FA) findings returned to the baseline levels. The authors concluded that intravitreal bevazicizumab lead to mild and temporary decrease in central macular thickness, total macular volume and perifoveal hyperfluorescence, it does not result in any best corrected visual acuity improvement.


Retrospective, consecutive, interventional case series of 28 American patients (13 males, 15 females; 56 eyes) with type 2 idiopathic macular telangiectasia (Mactel). 15 eyes received intravitreal bevazicizumab, 33 observation and 8 had pars plana vitrectomy with internal limiting membrane removal. No significant difference in best corrected snellen visual acuity was observed between the 3 groups. Intravitreal bevazicizumab and pars plana vitrectomy with internal limiting membrane removal appear ineffective in improving visual outcome in eyes with non-proliferative type 2 idiopathic macular telangiectasia.


A retrospective chart review of 16 eyes in 16 consecutive Indian patients (9 females, 7 males) with treatment naive subretinal neovascularization secondary to macular telangiectasia type 2. 4 eyes were treated with intravitreal ranibizumab, 12 had intravitreal bevazicizumab. The mean number of injections was 1.9. Patients were followed up for 12 months. Results: A total of 16 eyes of 16 patients were included in the study. Of 16 eyes, 4 were treated with intravitreal ranibizumab monotherapy and 12 with intravitreal bevacizumab monotherapy. The average follow-up duration was 12 months (range, 3–43 months). The mean baseline visual acuity was 0.17 ± 0.16 (Snellen equivalent 20/120)
(range, 0.001–0.5), and the mean final visual acuity was 0.27 ± 0.14 (Snellen equivalent 20/70) (range, 0.05–0.66), and this difference was statistically significant (P = 0.02). The mean number of intravitreal injections was 1.9 (range, 1–3), and there were no injection-related complications.

Conclusion: Intravitreal anti–vascular endothelial growth factor monotherapy appears to be effective and safe in treatment-naive SRNVM secondary to Mactel.

Roller AB et al. Intravitreal bevacizumab for treatment of proliferative and nonproliferative type 2 idiopathic macular telangiectasia. Retina 2011; 31 (9)

Retrospective chart review of 14 eyes (9 proliferative, 5 non-proliferative) in 10 American patients (4 females, 6 males) with type 2 idiopathic macular telangiectasia.

RESULTS: Fourteen eyes of 10 patients were included. In 5 eyes with nonproliferative macular telangiectasia Type 2, average follow-up was 17 months (+ 7 months), and no eye demonstrated improvement in visual acuity or decrease in central macular thickness at final follow-up compared with baseline. In 9 eyes with proliferative disease, follow-up averaged 17 months (+ 9 months). At 6 weeks, central macular thickness decreased 63 mum (+ 58 mum), and acuity improved 1.7 lines (+ 2 lines). At final follow-up, central macular thickness decreased 48 mum (+ 89 mum) and acuity improved 1.1 lines (+ 3 lines). Subretinal neovascularization resolved in eight of nine eyes with proliferative disease after treatment. CONCLUSION: Bevacizumab did not improve acuity or reduce retinal thickness in nonproliferative macular telangiectasia Type 2 at final follow-up. In proliferative macular telangiectasia Type 2, bevacizumab caused involution of neovascularization and improved visual acuity.

Zehetner C; Haas G; Treiblmayr B; et al. Reduced-fluence photodynamic therapy combined with ranibizumab for nonproliferative macular telangiectasia type 2. Ophthalmologica; 2013 229 (4): 195-202

Non-comparative, retrospective, consecutive, interventional case series of 5 eyes from 4 Austrian patients (1 female, 3 male) with macular telangiectasia type 2.

Intravitreal ranibizumab with reduced-fluence photodynamic therapy slowed down disease progression in 3 out of 5 eyes. 2 patients gained visual acuity during 12 months of follow up. 2 patients who lost vision after 6 months treatment received a second treatment cycle. Slight visual recovery occurred in 1 case and the other case stabilised. Deterioration of best corrected visual acuity could not be prevented in 2 eyes. The authors concluded that a combination therapy with reduced-fluence PDT and intravitreal ranibizumab might be a valuable treatment option for eyes with progressive vision loss due to nonproliferative MacTel type 2.


Single centre, open label, phase II clinical trial with 5 American patients (5 eyes, 2 females, 3 males) idiopathic macular telangiectasia type 2 with intravitreal ranibizumab. RESULTS: The study treatment was well tolerated and associated with few adverse events. Change in best-corrected visual acuity at 12 months was not significantly different between treated study eyes (0.0 + 7.5 letters) and control fellow eyes (+2.2 + 1.9 letters). However, decreases in the area of late-phase fluorescein angiography leakage (-33 + 20% for study eyes, +1 + 8% for fellow eyes) and in optical coherence tomography central subfield retinal thickness (-11.7 + 7.0% for study eyes and -2.9 + 3.5% for fellow eyes) were greater in study eyes compared with fellow eyes. CONCLUSION: Despite significant anatomical responses to treatment, functional improvement in visual acuity was not detected. Intravitreal ranibizumab administered monthly over a time course of 12 months is unlikely to provide a general and significant benefit to patients with nonneovascular idiopathic macular telangiectasia Type 2.

Prospective, open-label, uncontrolled, nonrandomized interventional clinical trial in 10 eyes in 10 German patients (7 females, 3 males) with non-proliferative macular telangiectasia type 2 (disease stage 2-3). One eye was given a monthly injection of 0.5mg intravitreal ranibizumab for 1 year. Mean visual acuity showed a transient increase in the study eye. However, after 12 months of treatment there was no significant change of visual acuity compared to baseline or compared to the fellow eye. The authors concluded that the angiographic and tomographic effects after intravitreal inhibition of vascular endothelial growth factor (VEGF) using ranibizumab implicate a pathophysiological role of the VEGF pathway in nonproliferative MacTel type 2. As the morphologic response was not associated with a clear functional benefit, and because of the transient nature of the treatment effect, monthly intravitreal ranibizumab is not recommended for the nonproliferative disease stage of MacTel type 2.

Type 1 Idiopathic Macular Telangiectasia

A summary of each reference is provided below:


Retrospective case series of 7 eyes of 7 patients (6 male, 1 female) with type 1 idiopathic macular telangiectasia in Korea. Treatment with intravitreal bevacizumab did not increase visual acuity but did decrease macular thickness and reduce the subretinal fluid level. The authors concluded that the results suggest that the use of an antiVEGF antibody affords only limited morphological and functional improvement to type I IMT patients displaying subretinal fluid accumulation.

Takayama K; et al. Intravitreal bevacizumab for type 1 idiopathic macular telangiectasia. Eye 2010; 24 (9): 1492-7

Retrospective case series of five eyes of five male patients with type 1 idiopathic macular telangiectasia in Japan. The authors concluded that treatment with intravitreal bevacizumab does not appear to improve visual acuity or retinal oedema in Type I IMT.


Case report of use of intravitreal ranibizumab with laser photocoagulation in one eye with idiopathic juxtafoveolar retinal telangiectasia type 1 in a 57 year old Italian male patient. Visual acuity improved after treatment and remained stable for 3 years.

Background: Idiopathic juxtafoveolar retinal telangiectasia (IJRT) type 1 represents an uncommon cause of congenital unilateral visual loss and it typically affects males. Decrease in visual acuity is caused by serous and lipid exudation into the fovea with cystoid macular oedema. In some cases, spontaneous resolution may be observed, but when there is a progressive loss of visual acuity, laser photocoagulation is often necessary. This treatment is not always successful and therapy for this condition is still controversial. Case Presentation: A 57-year-old man referred a 2-month history of blurred and distorted vision in the right eye. Best-corrected visual acuity was 20/50 in
the right eye and 20/20 in the left eye. Fundus examination showed temporal macular oedema, confirmed by optical coherence tomography. Fluorescein angiography showed a localized area of hyperfluorescence probably due to telangiectasia type 1 located below the inferior temporal area of the fovea. A combined therapy of intravitreal ranibizumab injection and laser photocoagulation was performed. Visual acuity improved from 20/50 to 20/32 and the therapy was well tolerated by the patient. After 3 years of follow-up, both visual acuity and fundus examination were stable. Conclusions: This case suggests that the combined use of ranibizumab and laser photocoagulation may be considered an effective treatment for JRT type 1, leading to an improvement in both visual acuity and macular oedema.

**Medicine Information Department (Ipswich) Summary**

Based on the above information, Medicine Information (Ipswich) have provided the following summary:

In summary - the evidence for use of Ranibizumab ([Lucentis®] or bevacizumab (Avastin®) for the treatment of Juxtafoveal Telangiectasia consists of case reports, case series, chart reviews and 2 open label non-randomised trials. Juxtafoveal telangiectasia is also sometimes termed perifoveal telangiectasia and more often known as idiopathic macular telangiectasia (MACTEL). Two types of telangiectasia are seen. Type 1 MACTEL occurs in middle age persons; the condition is usually unilateral and exhibits exudative features as the vessels are leaky and intraretinal fluid accumulation occurs with a cystic maculopathy and surrounding exudates. Type 2 MACTEL occurs in older people and is usually bilateral with evidence of crystalline deposits, pigmentary charges, and right angled venules evident temporal to the fovea and extending to the entire perifoveal region. MACTEL type 2 is mainly divided into 2 stages, in case of treatment. The first stage (2A) is the non-proliferative stage, which is characterized by slow, progressive visual loss in association with outer retinal atrophy. The second stage is the proliferative stage, which is characterized by the presence of subretinal neovascularisation (SRN). Several treatment options have been studied for the non-proliferative stage; however, most are reported to be ineffective because of the degenerative and progressive nature of this disease. In contrast, the proliferative stage is successfully treated with photodynamic therapy, intravitreal anti-vascular endothelial growth factor (VEGF) injections, and combination therapies.

The information above highlights that intravitreal bevacizumab improves proliferative type 2 idiopathic MACTEL but not non-proliferative type 2 or type 1. The information is more mixed with intravitreal ranibizumab. Combined with reduced-fluence PDT in non-proliferative MACTEL type 2, ranibizumab may slow down disease progression, although when used on its own it is not recommended. Use of ranibizumab in 4 patients with proliferative type 2 idiopathic MACTEL indicated it was as effective in improving visual acuity as bevacizumab although the sample size is too small to conclusively prove this. Intravitreal ranibizumab with laser photocoagulation in type 1 MACTEL improved both visual acuity and macular oedema in 1 patient.

**Licensed indication**

Ranibizumab ([Lucentis®]

Indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)

Bevacizumab ([Avastin®]

This is not commercially available as an intravitreal injection and so is not licensed for use in the ophthalmology setting. Bevacizumab is licensed in combination with...
several different chemotherapy treatments for a variety of different cancers including breast cancer, cancer of the colon and non small cell lung cancer.

Usual dosage

To date, the use of either drug has been requested via the IFR route. The dosage regimen quoted by the requesting clinician(s) is:

Loading course of intravitreal anti VEGF (Ranibizumab or bevacizumab) injections x3 every 4 weeks followed by treatment PRN.

The clinician(s) have stated in recent IFR applications that a patient may need 6 injections in the first 12 months.

Treatment alternatives/place in therapy


This article gives a general overview of idiopathic macular telangiectasia type 2 (idiopathic juxtafoveolar retinal telangiectasia type 2A, Mac Tel 2).

Abstract: Macular telangiectasia type 2-also known as idiopathic perifoveal telangiectasia and juxtafoveal retinal telangiectasis type 2A or Mac Tel 2-is an acquired bilateral neurodegenerative macular disease that usually manifests itself during the fourth to sixth decades of life and is characterized by minimal dilatation of the parafoveal capillaries with graying of the retinal area involved, a lack of lipid exudation, right-angled retinal venules, refractile deposits in the superficial retina, hyperplasia of the retinal pigment epithelium, foveal atrophy, and subretinal neovascularization (SRNV). Optical coherence tomography images typically demonstrate intraretinal hyporeflective spaces that are usually not related to retinal thickening or fluorescein leakage. The typical fluorescein angiographic finding is a deep intraretinal hyperfluorescent leakage in the temporal parafoveal area. With time the leakage may involve the whole parafovea, but does not extend to the center of the fovea. Long-term prognosis for central vision is variable and depends on the development of SRNV or macular atrophy. Pathogenesis remains unclear, but Muller cells and macular pigment appear to play a central role. Currently there is no known treatment for the underlying cause of this condition, but treatment of the SRNV may be beneficial.

The following extracts are obtained from the above reference:

- The largest series of case reports (10 eyes) (Park et al) found no improvement or even stabilisation of vision in eyes with macular oedema. Furthermore complications included retinal vascular distortion, proliferation of fibrovascular tissue, choroidal neovascularisation and retinal and subretinal haemorrhage.
- Most cases of SRNV (Group II, stage 5), are not amenable to laser photocoagulation because of the subfoveal localisation, however if the SRNV is located in juxtafoveal area, laser photocoagulation maybe considered.
- Photodynamic Therapy (PDT)
  Prior to the introduction of anti-VEGF agents, PDT was the treatment of choice in diseases complicated by choroidal neovascularisation. PDT with Verteporfin does not seem to be beneficial in Mac Tel 2 eyes.
- Indocyanine green mediated photothrombosis (IMP)
  This is a non invasive laser dye modality used to achieve selective vascular occlusion with minimal or no damage to adjacent neural structures. Arevalo et al reported visual improvement or stabilisation of nine eyes with macular oedema secondary to Mac Tel 2 with the combination of IMP and 4mg of intravitreal triamcinolone acetonide.(2)
- **Anti-VEGF agents**
  
  Although these initial reports are encouraging, caution should be exercised because VEGF plays many roles in the normal eye, including neuroprotection and cellular survival. The long-term safety and efficacy of anti-VEGF therapy are currently unknown. The normal adult retina expresses VEGF without inducing vascular permeability or neovascularization. Both photoreceptors and Müller cells express VEGFR2, the primary VEGF signaling receptor. VEGF inhibition in rodents caused apoptosis of cells in the inner and outer nuclear retinal layers that led to “empty spaces” filled with membranous debris within the neuroretinal layers. Because Mac Tel 2 is characterized by neuroretinal atrophy, it remains unclear if chronic VEGF suppression might lead to an increased rate of apoptosis of retinal ganglion cells and photoreceptors and accelerate the neurodegenerative process. Matt et al reported an eye that developed a lamellar macular hole following treatment with intravitreal bevacizumab. (2)

- **Combination therapy**
  
  Ocular neovascularization is extremely responsive to anti-VEGF therapy. Anti-VEGF therapy is only transiently effective, however, and as the vessels mature they become more resistant to anti-VEGF drugs, requiring multiple injections. In order to decrease the number of injections and deal with the increasing resistance to anti-VEGF monotherapy, combination therapy has been proposed. Both intravitreal bevacizumab and intravitreal triamcinolone in combination with verteporfin photodynamic therapy have been reported for SRNV.

- **Conclusion**
  
  Mac Tel 2 is a primary neuroretinal degenerative disease that affects the vision of patients in a bilateral fashion. The pathogenesis of Mac Tel 2 is not entirely understood, but Müller cells and macular pigment are implicated. New imaging modalities such as CBR, OCT, and blue light FAF allow earlier diagnosis. Currently there is no treatment available to alter the progression of this disease. Although there are some therapies that seem to limit SRNV in the final proliferative stage, previous stages are not treatable. (2)

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**National guidance**

There is no national guidance for the use of anti-VEGF agents for the treatment of Idiopathic Juxtafoveal telangiectasia.

**NICE TA 155- Ranibizumab & Pegaptanib for the treatment of age-related macular degeneration. August 2008, Updated May 2012 due to changes to patient access scheme**

1.1 Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:

- all of the following circumstances apply in the eye to be treated:
  - the best-corrected visual acuity is between 6/12 and 6/96
  - there is no permanent structural damage to the central fovea
  - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
  - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

  and

- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

1.2 It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is
recommended that a national protocol specifying criteria for discontinuation is developed.

1.3 Pegaptanib is not recommended for the treatment of wet age-related macular degeneration.

**NICE TA 247 – Ranibizumab for treating Diabetic Macular oedema (Rapid Review of TA 237). April 2013**

Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.

**NICE TA 283 – Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. May 2013**

Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- following central retinal vein occlusion or
- following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage and
- only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of [NICE technology appraisal guidance 274](#).

**NICE TA 298- Ranibizumab for treating choroidal neovascularisation associated with pathological myopia. November 2013**

Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme.

### Local Guidance

- The use of PDT/Verteporfin for the treatment of juxtafoveal telangiectasia is not supported. (Bulletin 166 – Photodynamic therapy (PDT) with Verteporfin (Visudyne®) Sept 2012.

- There is no local guidance for the treatment of juxtafoveal telangiectasia with either intravitreal ranibizumab or bevacizumab.

### Contraindications and Precautions

**Side effect Profile**

The following information relates to ranibizumab as this is the licensed product for intravitreal use.

**Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with active or suspected ocular or periocular infections.
- Patients with active severe intraocular inflammation

**Precautions**

Intravitreous injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

See SPC for full list of precautions for use.
Systemic effects following intravitreal use
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors.
There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients

Prior episodes of RVO, ischaemic branch RVO and central RVO
There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischaemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended.

Summary of the safety profile
The majority of adverse reactions reported following administration of Lucentis are related to the intravitreal injection procedure.
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.

Drug Interactions*
No formal interaction studies have been performed (see SPC for full details)

Pregnancy and lactation*
Women of childbearing potential/contraception in females
Women of childbearing potential should use effective contraception during treatment.

Pregnancy
For ranibizumab no clinical data on exposed pregnancies are available. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development (see section 5.3). The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Breast-feeding
It is unknown whether ranibizumab is excreted in human milk. Breast-feeding is not recommended during the use of ranibizumab.

Costs
Tariff status
A NETAG appraisal on anti VEGF agents for non-AMD choroidal neovascularisation (CNV) estimated the cost per treatment episode (admission plus drug) to be £1,363 for ranibizumab and £578 for bevacizumab.

Activity costs
(4)

Cost effectiveness
No assessment available.

Potential number of patients in Bedfordshire and Luton
Juxtapfoveal telangiectasia is a rare condition. No estimates of incidence / prevalence included in the references identified.
### Impact per 100,000 population

- **Affordability considerations**

### Decisions from other bodies

Other CCG’s with the East of England region were asked if they have any policies regarding the use of anti-VEGF agents for the treatment of Juxtafoveal Telangiectasia. To date, replies have been received from Herts CCG and Mid Essex CCG. Neither CCG have a policy for this condition and only commission these agents in line with NICE recommendations.

### Evidence strengths and limitations

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

*Consult Summary of Prescribing Characteristics for full prescribing details.

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

**References:-**

2) Lihteh et al. Idiopathic Macular Telangiectasia (Idiopathic juxtafoveal retinal telangiectasis type 2, Mac Tel 2), Survey of Ophthalmology 58 (2013) 536-559
4) NETAG (2009) Bevacizumab and Ranibizumab in the management of non-AMD choroidal neovascular disease.
Bedfordshire and Luton Joint Prescribing Committee (JPC)  
Assessment against Ethical and Commissioning Principles

<table>
<thead>
<tr>
<th>Treatment assessed (February 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JPC Recommendation:</strong></td>
</tr>
<tr>
<td>- The use of anti-VEGF agents (i.e. ranibizumab or bevacizumab) for the treatment of Juxtafoveal Telangiectasia is <strong>not</strong> supported.</td>
</tr>
</tbody>
</table>

1) **Clinical Effectiveness**
   In summary - the evidence for use of Ranibizumab ([Lucentis®) or bevacizumab (Avastin®) for the treatment of Juxtafoveal Telangiectasia consists of case reports, case series, chart reviews and 2 open label non-randomised trials. Juxtafoveal telangiectasia is also sometimes termed perifoveal telangiectasia and more often known as idiopathic macular telangiectasia (MACTEL). Two types of telangiectasia are seen. Type 1 MACTEL occurs in middle age persons; the condition is usually unilateral and exhibits exudative features as the vessels are leaky and intra retinal fluid accumulation occurs with a cystic maculopathy and surrounding exudates. Type 2 MACTEL occurs in older people and is usually bilateral with evidence of crystalline deposits, pigmented charges, and right angled venules evident temporal to the fovea and extending to the entire perifoveal region. MACTEL type 2 is mainly divided into 2 stages, in case of treatment. The first stage (2A) is the non-proliferative stage, which is characterized by slow, progressive visual loss in association with outer retinal atrophy. The second stage is the proliferative stage, which is characterized by the presence of subretinal neovascularisation (SRN). Several treatment options have been studied for the non-proliferative stage; however, most are reported to be ineffective because of the degenerative and progressive nature of this disease. In contrast, the proliferative stage is successfully treated with photodynamic therapy, intravitreal anti-vascular endothelial growth factor (VEGF) injections, and combination therapies. The information above highlights that intravitreal bevacizumab improves proliferative type 2 idiopathic MACTEL but not non-proliferative type 2 or type 1. The information is more mixed with intravitreal ranibizumab. Combined with reduced-fluence PDT in non-proliferative MACTEL type 2, ranibizumab may slow down disease progression, although when used on its own it is not recommended. Use of ranibizumab in 4 patients with proliferative type 2 idiopathic MACTEL indicated it was as effective in improving visual acuity as bevacizumab although the sample size is too small to conclusively prove this. Intravitreal ranibizumab with laser photocoagulation in type 1 MACTEL improved both visual acuity and macular oedema in 1 patient.

2) **Cost Effectiveness**
   No assessment available.

3) **Equity**
   No issues identified.

4) **Needs of the community**
   Juxtafoveal telangiectasia is typically classed as a rare condition in the literature. A cohort study carried out in Australia (2010) reports that although rare, it may be more common than thought as the very subtle nature of the disease in the early stages may lead to misdiagnosis. The authors report a prevalence of between 5 – 23 cases per 100,000 with at least stage 2 or 3 type 2 disease. (7)

5) **Need for healthcare (incorporates patient choice and exceptional need)**
   There is no known proven treatment for the treatment of the underlying cause of juxtafoveal telangiectasia.

6) **Policy drivers**
There are no national or professional guidelines regarding the treatment of juxtafoveal telangiectasia. NICE recommend the use of ranibizumab as a treatment option for age related macular degeneration (TA155), diabetic macular oedema (TA274), macular oedema secondary to retinal vein occlusion (TA283), choroidal neovascularisation associated with pathological myopia (TA298). Local Ophthalmologists regard that juxtafoveal teleangiectasia has a similar pathology to age related macular degeneration.

7) Disinvestment

N/A

The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

N:\Medicines Management\JPC\Approved Bulletins & Papers\from Aug 13\Feb 15\Ranibizumab or Bevacizumab for the treatment of Juxtafoveal Telangiectasia - Bulletin 211.docx
<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 2*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or census)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or poor or non-independent reference standards**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided these are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
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</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table
OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Mochetti, Bob Phillips, Hazel Thomson, Olive Goddard and Mary Hodkinson