Efficacy of Pegaptanib Sodium on Uveitic Cystoid Macular Oedema

Aim
To evaluate the safety and efficacy of intravitreal pegaptanib Sodium for the treatment of cystoid macular edema (CME) secondary to uveitis.

Study design
A feasibility study, assessing the benefit of 4 intravitreal injections of Macugen 0,3mg at 6 weekly intervals for patients with otherwise controlled uveitis that present with cystoid macular oedema.

Metods
Data (Best-corrected Sneller visual acuity (VA), examination findings, Optical Coherence Tomography (OCT), Fluorescein Angiography and Microperimetry results) of ten patients with macular oedema who received at least 3 intravitreal injection of 0,3 mg of Pegaptanib Sodium at 6 weekly intervals monitored over a period of 54 weeks (1 year) in the Clinical Trial Unit of Moorfields Eye Hospital.

Main Outcome Measures
Change in macular thickness as assessed by OCT at 24 and 54 weeks.
Visual acuity (BCVA): ETDRS letters read at 24 baseline.
Total number of injections required until week 34.
Time to re-injection after (4th standard injection) week 18.
Change in microperimetry at 24 weeks and 54 weeks as compared to baseline.

Results
Seven (70 %) patients were withdradwal from the Study before the 54th week, four of them at week 18 because of no improvement of macular oedema documented by OCT (they did not recived the 4th injection), one of them developed cataract in the study eye and was withdrawal at week 30 to undergo cataract surgery, the last two were withdrawal at week 24 because of lack of efficacy of the Study Drug.
Six (60 %) patients had the standard 4 injections, one of them was re-injected at week 24 (5th injection), the other 4 (40 %) had only 3 injections as they were withrawal from the study at week 18 because of no improvement of macular oedema documented by OCT.
Three (30 %) patients completed the Trial successfully with a decrease in foveal thickness and an improvement of VA by ≥2 lines at the end of the follow-up.

No significant ocular or systemic adverse effects were observed but the tested investigational medicinal product was associated with an adverse side effect already noted in the summary of product characteristics: increased intraocular pressure (in six patients). This adverse effect was related with the drug volume and not with the molecule itself. No other adverse side effects in relation to the investigational medicinal product were observed. There were no dropouts for safety reasons

Conclusions
These results suggest that a four intravitreal injections of pegaptanib Sodium are well tolerated and are associated with short-term improvement in VA and decreased OCT retinal thickness in one third of patients with uveitic CME resistant to conventional

therapy. Further evaluation of intravitreal pegaptanib Sodium for uveitic CME in controlled randomized studies is warranted.

Background

Definition: Cystoid Macular Oedema is the result of accumulation of fluid in the outer plexiform and inner nuclear retinal layers. One of the most common sight threatening complications of uveitis manifests itself not only during the active phase of uveitis, but also over prolonged periods even when inflammation has subsided (11).

Clinical presentation: It presents clinically as an impairment of central vision with the patient often describing a central scotoma, in the affected eye. In the short term, CMO is usually innocuous but in longstanding cases, however, leads to coalescence of the fluid filled microcysts into large cystoid spaces and subsequent lamellar hole formation at the fovea with irreversible damage to central vision.

Pathomechanism and Incidence: Cystoid macular oedema can cause severe visual loss. By compression of retinal neurons, nerve fibres and capillaries, CMO contributes to photoreceptor degeneration and neuronal cell death and to an exacerbation of hypoxic ischemic conditions (10). Below the cysts, the number of photoreceptor cells is decreased.

CMO is one of the major causes of legal blindness in uveitic patients. The overall incidence of CMO in uveitis has been estimated as high as 41% with this varying in different types of uveitis (9). In intermediate uveitis has been estimated as high as 30%, in Behcet's disease 24% and pars planitis 28-52 %(11).

Although the mechanism that produces the oedema in uveitis is not yet fully understood, experimental and human uveitis studies have shown that it is likely to be a result of blood retina barrier (BRB) breakdown (13). There is experimental evidence that BRB breakdown leads to intraretinal fluid accumulation, both extracellularly and intracellularly. Contrary to the belief of most authors in the past, it is been shown that Muller cells contribute to the formation of CMO with accumulation of fluid within their somata, even before the extracellular accumulation (10). At the molecular level, the BRB breakdown is thought to occur due to the secretion of various immunomodulatory mediators from Muller, glial cells and Retinal Pigment Epithelium, such as Tumour Necrosis Factor-α, Transforming Growth Factor-β, b-Fibroblast Growth Factor and Vascular Endothelial Growth Factor (14). VEGF is one of the most important molecules controlling the barrier properties of the vascular endothelial cells. VEGF is secreted within the retina where it plays different roles at the outer and the inner retinal barrier. At the outer barrier of the normal healthy retina, VEGF is produced by RPE cells, preferentially secreted by their basal side, in order to maintain the fenestrated and highly permeable character of the choroidal vascular endothelium. By contrast, the inner blood-retina barrier is exposed to significant levels of VEGF only under hypoxic conditions when Muller cells upregulate their expression and secretion of VEGF. This Muller cell derived VEGF may contribute to the pathological permeability of the barrier, which occurs in the sensory retina under ischemic- hypoxic conditions (10).

The end result of these processes is dysfunctional photoreceptors that if the oedema persists will lead to permanent damage and profound visual loss. However, if the oedema resolves promptly, the majority of the photoreceptors may survive and restore

visual acuity.

Current therapy: Currently, treatment is aimed exactly at the expedition of CMO resolution. Treatment of CMO is usually indicated when the patient is experiencing visual difficulties or visual acuity drops to a level of 6/12 or worse (11). As the fundamental reason for the development of CMO in eyes with uveitis is thought to be the active inflammatory process affecting the integrity of the BRB, initial treatment is aimed at reducing any active inflammation in the eye.

Treatment of choice for the majority of cases is steroids in topical formulation, systemically administered or peri and intraocularly, depending on clinical findings and individual patients. In anterior uveitis topical intensive steroids are usually sufficiently potent to treat the inflammation and CMO, with penetration as far as the anterior vitreous, documented.

The effect of topical non-steroidal anti-inflammatory drugs on CMO has never been evaluated on a large scale. Systemic NSAIDS were found beneficial in one study but their result was comparable to periocular steroids only when administered for several months (12). In posterior uveitis, systemic steroids are the mainstay of treatment, with the exception of recurring cases where, despite aggressive treatment, control of inflammation is not achieved. And where, intolerability to the steroids makes necessary the introduction of other immunosuppressive agents in conjunction or as replacement to the steroids.

Periocular and intravitreal injections of steroid have been shown to be of benefit in CMO resulting from uveitis. Subtenons steroid injections are now widely used to treat asymmetric or unilateral disease. Intravitreal triamcinolone (IVTA) administration is an effective supplementary tool in the management of refractory CMO when standard treatment is inadequate. However the results are often temporary, requiring repeated injections. IVTA is being shown to diminish or dissolve CMO anatomically, as seen on OCT, within six days to three months, but the duration of the effect was between six weeks and six months, which resulted in a recurrence of CMO in up to 76% of treated patients (16). By choosing a local route of delivering the steroid, it relieves the patient from the burden of systemic side effects whilst achieving higher therapeutical levels. Nevertheless, there is evidence that especially in children raised serum steroid levels were noted after periocular dexamethasone injections (12). Injection related complications, although being uncommon, have been reported. These include inadverent perforation of the globe, occlusion of the retinal, choroidal vessels and ophthalmic artery (14). The risk of glaucoma and cataract formation is similar to other routes of steroid administration. However, as these are depot injections the effect may be prolonged, as the drug cannot easily be withdrawn. Endophthalmitis is another significant complication that carries a risk of 0.5 % with IVTA (16). Finally, conditions such as pre-existing steroid induced glaucoma, hypersensitivity to the injection ingredients, active necrotising scleritis and active toxoplasmosis preclude their use. The vitreous body is thought to act as an inflammatory cells reservoir. Vitrectomy is especially helpful in the presence of a tractional component. But it may also, be beneficial by removing the laden with antigens and cytokines vitreous body, which maybe responsible for perpetuating the inflammatory response (15). Vitrectomy may be a safer approach than immunosuppressive therapy when corticosteroids fail but the procedure is not without risks with multiple potential complications such as vitreous haemorrhage, tractional and rhegmatogenous retinal detachment, proliferative vitreoretinopathy (PVR), macular pucker and postoperative CMO (11).

New approaches to treatment: The effort to discover other safer means of treating CMO continues. New anti-cytokine agents such as TNF-α monoclonal antibodies are currently being assessed for uveitis and CMO (11).

Studies with intraocular devices containing steroids and/ or cyclosporine may offer long-term local administration of the drug inside the eye at useful concentrations and with minimal systemic side effects. Initial animal studies with cyclosporine have been promising (15). Similarly, clinical studies of steroid containing implants have shown prolonged beneficial effect, but with a high occurrence of cataract and glaucoma. A clinical study by Jaffe et al, revealed a 2- step increase of lens opacification during the follow-up period, at 27% of the implanted with fluocinolone eyes and an increase of the proportion of eyes requiring antihypertensive agents from 13,6 % at baseline to 49,1%-52,4 % at week 34 after the implantation (17).

VEGF research: Recently, Vascular Endothelial Growth Factor (VEGF) has been found markedly unregulated in the inner retina of animals with experimentally induced autoimmune uveitis and there is evidence that VEGF is over 50,000 times more potent than histamine at inducing vascular permeability. In an experiment conducted by Vinores et al1, eight female Lewis rats and eight female B10.A mice were immunized with S- antigen. Eight days after immunization, a significant up regulation of VEGF positivity was demonstrated in all animals in the ganglion cells, the nerve fibre layer and in some cells of the inner nuclear layer. By 11 days after immunization, VEGF immunoreactivity became even more intense and was seen in more cells in the inner nuclear layer and in the outer retina. Several studies have shown significant retinal vascular leakage with intravitreal injections or slow release implants containing VEGF (3). Luna et al2, in another study attempting to clarify the mechanism of BRB breakdown in experimental autoimmune uveitis, supported the evidence of failure of the tight junctions of retinal pigment epithelium (RPE) and retinal vascular endothelial (RVE) cells. They also verified a parallel transcellular vesicular transport mechanism within the RVE cells. In this study, they demonstrated that TNF-α, IL-1β and VEGF are separately capable of inducing these changes. A study by Fine et al5., measured VEGF in the aqueous humor of twenty uveitic patients. They demonstrated higher VEGF levels in the aqueous humour of uveitic eyes with CMO (152,3pg/ml) compared to uveitic eyes without CMO (109, 5 pg/ml). It is therefore obvious that several lines of evidence exist in the literature to suggest VEGF is involved in the pathogenesis of uveitic CMO, which indicates the possibility of targeting VEGF for the management of uveitic CMO.

Anti- VEGF therapy: Macugen® or pegaptanib sodium is an RNA aptamer with the ability to bind the 165 amino acid form of VEGF in two different domains of the molecule and render it inactive. Aptamers6 are nucleic acid ligands with small molecular weight. These are highly specific molecules that can be manufactured to target specific proteins in order to modify their activity. They exhibit the ability to discriminate between related proteins that share common sets of structural domains and they display very low to no immunogenicity.

They have low dissociation constants, potentially allowing the use of antidotes if required. They act in the same way as antibodies by folding into a three-dimensional structure based on their nucleic acid sequence. They have molecular weights of between 8-14 kDa and are only about 25-40 nucleotides long, allowing rapid renal clearance.

In vivo experiments in adult guinea pigs revealed that pegaptanib sodium reduced vascular leakage by 58% at a 1 μM dose. Preclinical and clinical studies for the

treatment of exudative AMD and diabetic macular oedema as well as experimental ones on rat corneal angiogenesis and mouse retinopathy of prematurity models have shown significant inhibition of neovascularization with reduction of ROP retinal new vessels by 80%.
Phase I, II and III, safety studies using multiple intravitreal injections of pegaptanib sodium have reported minimal serious side effects6-7-19.
Conclusion: To date, there have been no previous studies evaluating the use of Macugen® (sodium pegaptanib) in the treatment of CMO. Macugen® is however, licensed to treat all types of neovascular age-related macular degeneration, in both the United States and United Kingdom.
The recent VISION study18, using pegaptanib sodium for neovascular ARMD utilised intravitreal doses of 0.3 mg, 1.0 mg, or 3.0 mgs. The injections were administered every 6 weeks over a period of 48 weeks. In the combined analysis of the primary end point (for a total of 1186 patients), efficacy was demonstrated, without a dose-response relationship, for all three doses of pegaptanib sodium.
We feel that there is enough evidence on pathophysiological grounds to advocate the use of pegaptanib sodium in the form of intravitreal injections to control refractory cystoid macular oedema in uveitic patients
°Anticipated benefits of the study
Identify another alternative to steroid injections for the management of refractory uveitic CMO, which will be devoid of glucocorticoid activity, thereby reducing the risk of common complications such as cataract and glaucoma.

Materials and Methods

Ten Patients with different types of uveitis that was in remission but associated with persistent visually significant macular edema despite standard therapy with topical and systemic Steroid, NSAIDs, periocular injections and/or intravitreal triamcinolone were offered 4 intravitreal injections of Pegaptanib Sodium 0,3mg at 6 weekly intervals.

Patients with uncontrolled uveitis or with other causes of CMO were excluded. Patients who had orbital floor, posterior subtenons or intraocular injection of steroids within 3 months from the study enrollment were excluded. Macugen has not been tested in pregnant or lactating women and patients below the age of 18 years old, therefore these groups of patients were excluded from the study. Were also excluded patients with active or suspected ocular or periocular infection, renal clearance less than 20 ml/min and allergy to the excipients.

Pegaptanib Sodium's off-label use and its Food and Drug Administration approval for a different indication, metastatic colorectal cancer, were discussed with each patient, including the potential benefits and side effects. All patients read and signed an informed consent form that included a comprehensive description of Pegaptanib Sodium and the proposed procedure.

The injection procedure was carried out under aseptic conditions, which included the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum and the availability of sterile paracentisis. Before the intravitreal injection,

topical tetracaine and 5% povidone/iodine solution were instilled in the eye to be injected. A single dose pre-filled syringe of 0.09 ml solution containing 1.65 mg of pegaptanib sodium, corresponding to 0.3 mg of the free acid form of the oligonucleotide was injected using a sterile 30-gauge needle. After the injection, patients were instructed to administer topical Chloramphenicol 0.5% ophthalmic solution to the injected eye 4 times daily for 1 week.

Ocular history, topical and systemic medications employed in the treatment of both uveitis and macular edema were recorded at baseline and during the follow-up period.

Data about BCVA testing, slit-lamp examination, dilated funduscopy, and central 1.00 mm measurements by optical coherence tomography (Stratus OCT, Carl Zeiss Jena) were recorded at baseline and follow-up visits at week 1, 4, 6, 8, 12 and every 6 weeks thereafter for at least 12 months.
Microperimetry was performed at baseline and all the follow up visits with the exception of week 1 and 8.
Fluoresceine Angiography was performed at baseline, week 4, week 24 and week 54.

Additional injections were considered under specific clinical criteria, such as, loss of 5 or more letters at the Snellen visual acuity chart, residual intraretinal fluid on OCT, or an increase of 100μm or more in central retinal thickness, following the initial treatment period.

Patient were withdrawal from the study before the exit visit (54^{th} week) in case of Lack of efficacy of study drug after 3 injections (characterised by no improvement of macular oedema documented by OCT), endophthalmitis, retinal ischaemia (documented by the FFA), clinically significant inflammation, severe vitreous haemorrhage, retinal detachment, reduction in visual acuity defined as a doubling of the visual angle, other abnormalities not usually seen in patients with uveitis, persistent eye pain or irritation, hospitalisation or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a life-threatening adverse experience, death.
Outcome measures were VA and OCT recordings at 24 and 54 time point. Improvement was judged by gain in VA >=2 lines and thickness reduction in OCT. Decimal BCVA values were calculated into logMar.

Statistical analyses were performed using……. All tests were two tailed, and a *P* value of less than 0.05 was considered statistically significant..

RESULTS

	AGE	GENDER	STUDY EYE	TYPE OF UVEITIS	ETIOLOGY	DURATION OF UVEITIS (MONTHS)	DURATION OF CMO (MONTHS)
1	64	F	LE	POSTERIOR UVEITIS	BIRDSHOT	90	30
2	55	F	LE	INTERMEDIATE UVEITIS	SARCOIDOSIS	50	36
3	59	F	RE	INTERMEDIATE UVEITIS	SARCOIDOSIS	120	90
4	41	F	LE	ANTERIOR UVEITIS	HLA B27	30	15
5	51	F	RE	INTERMEDIATE UVEITIS	RHEUMATOID ARTHRITIS	84	25
6	37	F	LE	INTERMEDIATE UVEITIS	IDIOPATHIC	78	56
7	19	F	RE	POSTERIOR UVEITIS	IDIOPATHIC	80	20
8	48	F	RE	INTERMEDIATE UVEITIS	IDIOPATHIC	84	43
9	68	F	RE	INTERMEDIATE UVEITIS	IDIOPATHIC	15	15
10	51	M	LE	INTERMEDIATE UVEITIS	IDIOPATHIC	21	20

Table 1 lists demographic and diagnostic information for the 10 patients. Their mean age was 49.9 years (range 19–68). Nine were women and 1 was men.
All patients had been diagnosed previously with uveitis with a variety of etiologies. Seven patients had Intermediate Uveitis, two patients Posterior Uveitis and one patient Anterior Uveitis.
In all cases, CME was confirmed by biomicroscopy, OCT and FA. The mean duration of Uveitis was 63 months (range 15-120) and the mean duration of the CME was 37.2 years (range 15–90).
Patient 7 and patient 9 were not followed for the planned 54 weeks as they decided not to attend any further visit after week 18 (patient 7) and after week 36 (patient 9)
Only patients 8 from all the injected eyes had been vitrectomized previously.

Seven (70 %) patients were withdradwal from the Trial before the 54th week, four of them at week 18 because of no improvement of macular oedema documented by OCT so they did not recived the 4th injection, one of them developed cataract in the study eye and was withdrawal at week 30 to undergo cataract surgery, the last two were withdrawal at week 24 because of lack of efficacy of the Study Drug.

Six (60 %) patients had the standard 4 injections, one of them was re-injected at week 24 (5th injection), the other 4 (40 %) had only 3 injections as they were withrawal from the study at week 18 because of no improvement of macular oedema documented by OCT.

Uveitis was inactive (max 1+ anterior chamber cells and trace vitreous haze) as judged by SUN criteria in all patients at the time of treatment, but all patients had CME with a mean central retinal thickness of 481 µm (range 288–887 µm).

The patients'concurrent treatments for uveitis and macular edema are listed in Table 2

	Systemic Steroid	Topical Steroid	Topical NSAID	Periocular Steriod Injection*	IVTA*
1	x		x	x	x
2		x		x	
3	x	x	x	x	x
4	x	x	x		
5		x	x	x	
6	x	x	x	x	x
7				x	
8	x	x	x		
9		x	x		
10		x	x		

* orbital floor, posterior subtenons or intraocular injection of steroids were not performed within 3 months from the study enrollment.

Five patients were receiving systemic steroid therapy, the other five patients were only on topical steroid/NSAID. These therapies were not altered at the time of treatment with intravitreal macugen.
Six patient had previously periocular Steoid injections and three patients had previously intravitreal steroid injections.

The baseline VA and OCT measurements and change in these parameters at Baseline, week 6, 12, 18 and 24 are provided in **Table 3**.

	BASELINE		WEEK 6		WEEK 12		WEEK 18		WEEK 24	
	OCT	BCVA	OCT	BCVA	OCT	BCVA	OCT	BCVA	OCT	BCVA
1	377	20.63	233	20.40	181	20.40	165	20.50	179	20.50
2	465	20.32	489	20.80	459	20.50	296	20.32	260	20.40
3	401	20.63	515	20.100	495	20.80	394	20.80	381	20.80
4	887	20.125	971	20.80	749	20.80	733	20.80	274	20.60
5	640	20.80	551	20.80	557	20.80	653	20.63	232	20.60
6	306	20.40	384	20.32	386	20.32	386	20.40	521	20.40
7	389	20.50	429	20.32	474	20.32	530	20.32	NA	NA
8	524	20.50	529	20.50	611	20.50	538	20.80	566	20.63
9	537	20.40	557	20.63	501	20.40	600	20.63	NA	NA
10	288	20.80	205	20.40	203	20.25	195	20.32	198	20.25

BCVA = best-corrected visual acuity; OCT = optical coherence tomography.

Table 3: Baseline Visual Acuity, Optical Coherence Tomography, and the Change of These Parameters at week 6, 12 and 24.

Patient 1 and 2 were two of the three patients reaching the exit visit. Patient 1 had a decrease in foveal thickness of 198 μm (from 377 to 179 μm) and an improvement of BCVA from 20.63 to 20.50. Patient 2 had a decrease in foveal thickness of 205 μm (from 465 to 260 μm) but, as she developed visual significant cataract, there was no improvement of the BCVA at week 24 and a deterioration of it at week 54 when her BCVA was 20.200 (**Tab 4**).
Patient 3 developed visual significant cataract early during the Study, was withdrawal at week 30 and underwent cataract surgery + IVTA between week 24 and 52.
Patient 4 and 5 were withdrawal from the study at week 18 and the same day received, instead of the Macugen intravitreal injection, an IVTA with an improvement of both central macular thickness and BCVA.
Patient 6 was withdrawal at week 24 because of lack of efficacy of the Study Drug and had IVTA at week 36.
Patient 7 and patiet 9 were lost at the follow up before week 24 and their BCVA and OCT data for week 24 are not available.
Patient 10 was the last of the three patients reaching the exit visit. He had a decrease in foveal thickness of 90 μm (from 288 to 198 μm) and an improvement of BCVA from 20.80 to 20.25.

Only three (30 %) patients completed the Trial as showed in **Table 4.**

	BASELINE		24 WEEKS		52 WEEKS	
	BCVA	OCT (µm)	BCVA	OCT (µm)	BCVA	OCT (µm)
1	20.60	377	20.50	179	20.40	165
2	20.30	465	20.40	260	20.200	236
10	20.80	288	20.25	198	20.25	189

BCVA = best-corrected visual acuity; OCT = optical coherence tomography.

Table 4: Baseline Visual Acuity, Optical Coherence Tomography, and the Change of These Parameters at week 24 and 54 as per Main Outcome Measures of the Trial.

Patient 1, 2 and 10 completed the Trial successfully. They had the standard 4 injections and reached the exit visit (week 54) with a decrease in foveal thickness. Patient 1 and 10 had also an improvement of VA by ≥2 lines at the end of the follow-up. Patient 2 developed visual significant cataract in the late stage of the Study and underwent surgery only after the end of the Study. This cataract can explain the poor VA at week 54 despite the reduction of central macular thickness.

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The other seven (70 %) patients were withdradwal from the Study before the 54th week, four of them at week 18 because of no improvement of macular oedema documented by OCT (they did not recived the 4th injection), one of them developed cataract in the study eye and was withdrawal at week 30 to undergo cataract surgery, the last two were withdrawal at week 24 because of lack of efficacy of the Study Drug.

No significant ocular or systemic adverse effects were observed: there were no signs of active inflammation after the injection attributable to pegaptanib sodium in any patient. There were no thromboembolic events in any patient during the follow-up period. We did not detect safety concerns.

Six patients developed intraocular pressure higher than 25 mmHg after the injection. This adverse effect was related with the drug volume and not with the molecule itself. In four cases because of the high IOP (higher then 50 mmHg) and NLP (that last more then 2 minutes), anterior chamber paracentesis were performed from the sclerocorneal limbus, usually in the upper temporal quadrant. All these cases resolved without effects.

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