Review Article

Intravitreal therapeutic agents in noninfectious uveitic macular edema

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The management of uveitis is challenging for most treating ophthalmologists. The treatment of uveitis often requires the use of high dose of systemic corticosteroid and immunosuppressive agents, which are almost always associated with potential side effects. Intravitreal medications have become a popular mode of drug administration in uveitis patients as they provide high volume of drug to the target tissues, eliminating the risk of systemic toxicity. There has been tremendous development in the intravitreal therapeutics over the last few years. With the advent of sustained-release technique, increasing patient compliance, biodegradable nature of the implant, and introduction of newer agents with better safety profile, the intravitreal medications have become more popular in recent years. This review presents evidence in the scientific literature supporting the use of intravitreal medications for the management of uveitis and its complications.

Key words: Anti-vascular endothelial growth factor agents, dexamethasone, fluocinolone acetonide, intravitreal agents, methotrexate, noninfectious uveitis, sirolimus, triamcinolone acetonide

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Uveitis is one of the major causes of visual morbidity, with a reported prevalence of 38–714 cases per 100,000.[1] It is responsible for 10%–15% blindness in the developed world.[2] It predominantly affects the younger population, and the consequent economic blindness imposes a greater burden on society and healthcare.[3,4]

Posterior uveitis is the major cause of visual morbidity among patients with uveitis.[5] Visual loss in posterior uveitis is usually secondary to macular edema (ME), choroidal neovascularization, glaucoma, optic nerve involvement, vitreous opacification, and cataract formation.[1,6] ME is the most common structural complication causing visual morbidity in about 40% of patients diagnosed with uveitis.[7] It is more commonly seen in cases of posterior uveitis and intermediate uveitis as against anterior uveitis and may persist despite adequate control of intraocular inflammation due to prolonged damage to the blood–retinal barrier or persistent low-grade inflammatory cytokines.[7,8] Cystoid ME (CME) may progressively damage the macular photoreceptors and may lead to complications such as macular ischemia, macular cyst, or hole formation.[1,9]

Pathophysiology of uveitic ME has not been fully understood, and the dysfunction of blood–retinal barrier is attributed in majority of cases.[10] ME occurs when there is a disturbance in the balance between fluid entering the tissues and the function of metabolic pump, leading to the accumulation of fluid intra- or extra-cellularly.[11] Chronic ME may be associated with significant vision loss.[12]

Treatment of uveitis remains a challenge with a host of treatment options – nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and more recently biological agents.[9] Each agent can be administered through various drug delivery routes with each route having its own merits and demerits.

Use of topical corticosteroids, though better tolerated than systemic administration, is effective only for the treatment of anterior uveitis due to poor reach of the drug to the posterior segment of the eye.[2,13,14] Periocular injection of depot corticosteroid, though minimally invasive, provides only a short-term effect with uncertain therapeutic concentration due to partial absorption of drug by highly vascular choroid before it reaches target site.[3] Furthermore, periocular injections are associated with their own side effects – ptosis, extraocular muscle injury, globe penetration, subdermal fat atrophy, or skin depigmentation.[1,15] Systemic use of corticosteroids and immunosuppressive agents may not achieve effective concentration in vitreous cavity due to physiological properties of the blood–retinal barrier, leading to the requirement of higher doses of these agents which again in turn are associated with potential side effects.[2,14] Intravitreal route allows relatively lower doses of the drug to be administered while achieving high concentration in the target areas, avoiding the risk of side effects associated with systemic use of the drug[13] Local side effects such as cataract, glaucoma, sterile and infectious endophthalmitis, hypotony, intravitreal hemorrhage,

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and retinal detachment have been reported with the use of intravitreal injection although incidence of such complications is relatively low.[6,13]

Over the past few years, there has been tremendous improvement in intravitreal therapeutics – many immunomodulatory agents have been added in the armamentarium of intravitreal medications against uveitis with the development of various new formulations to attain rapid yet controlled release of drug molecule in vitreous cavity. Intravitreal drugs are now considered as a safe and effective treatment option for the management of noninfectious uveitis, especially in patients with unilateral disease without any systemic component.[15,16] This article reviews the various intravitreal drugs used for the treatment of ME secondary to noninfectious uveitis.

Literature Search

A detailed review of the literature on PubMed was conducted using such terms as intravitreal [MeSH], macular edema [MeSH], cystoid macular edema [MeSH], uveitic macular edema [MeSH], corticosteroid [MeSH], anti-VEGF [MeSH], immunosuppressive [MeSH], biologicals [MeSH], intraocular injection. Additional studies were identified from the bibliographies of the retrieved articles. For non-English literature, English abstracts were reviewed when available. Foreign-language articles without English abstract were excluded.

Corticosteroids

Corticosteroid remains the first-line therapy for the management of uveitis.[2,12] Corticosteroids are effective in treating ME due to its potent anti-inflammatory properties by preventing leukocyte migration, stabilizing endothelial cell tight junctions which reduces cellular and fluid extravasation, and also inhibiting synthesis of vascular endothelial growth factor (VEGF), prostaglandins, and proinflammatory cytokines.[13] Intravitreal administration of corticosteroids aids to circumvent a host of adverse effects which are otherwise associated with their systemic administration.[17]

Intravitreal Triamcinolone Acetonide Injection

Triamcinolone acetonide (TA) is the most widely used corticosteroid for the treatment of uveitic CME. When injected intravitreally, TA has a mean half-life of 18.6 days in nonvitrectomized eyes and 3.2 days in postvitrectomized eyes.[18] A single dose of 4 mg when injected as a suspension in vitreous cavity of a nonvitrectomized human eye is known to maintain a desirable drug concentration for approximately 3 months because of its decreased water solubility.[19] It has been estimated that a single intravitreal injection of TA can yield a concentration of 0.22 ± 0.24 μg/ml.[20]

Various studies conducted to evaluate the efficacy of intravitreal TA (IVTA) have shown that IVTA 4 mg is effective in reducing the CME and leads to improvement in visual acuity (VA) in 50%–70% of patients, but repeated injections are required to maintain the effect over a period. In their study to evaluate the outcome of IVTA in the treatment of uveitic ME, Kok *et al*.[21] found that TA was effective in reducing CME with significant improvement in best-corrected VA (BCVA) (0.65–0.39 logMAR), especially in patients ≤60 years of age, but rise in intraocular pressure (IOP) was observed in 43% of subjects. Factors favoring better response to IVTA included in their study were CME of < 1-year duration, younger age, and nonvitrectomized eye.[21] Cataract formation and increased IOP remain a concern for intravitreal corticosteroid. About 40%–70% of patients experienced rise in IOP following a single intravitreal injection of TA, but majority of these were transient and could be effectively managed by antiglaucoma medications.[21-24] In uveitic eyes, the risk of development and progression of cataract increases with multiple injections, almost all patients developing cataract after five injections.[24]

Endophthalmitis following IVTA is a serious concern. Culture-positive infectious endophthalmitis following IVTA has a reported incidence of 0.45%–0.87%.[25-27] Pseudoendophthalmitis usually occurs in pseudophakic or aphakic patients or in patients with peripheral iridectomy, when TA particles migrate into the anterior chamber and masquerade as a hypopyon. Sterile endophthalmitis occurs due to an inflammatory reaction to either TA or more likely to its preservative such as benzyl alcohol. Risk factors for developing sterile endophthalmitis following IVTA injection are pseudophakia with breached posterior capsule, CME resulting from Irvine–Gass syndrome, vitrectomized eye, and uveitic eye.[28-30]

Intravitreal Dexamethasone

Dexamethasone (DEX) is a water-soluble, synthetic glucocorticoid that is three times more potent as compared to TA.[31] However, being a small molecule, it is rapidly cleared from the vitreous, with an estimated vitreal half-life of 5.5 h in humans.[32] This limitation in ocular pharmacokinetics of the drug has been overcome with advent of newer sustained-release intravitreal DEX to release corticosteroids over a prolonged duration of time in small doses.[2] DEX was the first corticosteroid to be used as a sustained-release device.[19]

DEX implant (Ozurdex, Allergan, Inc., Irvine, CA) is an intravitreal, biodegradable, sustained-release rod-shaped implant approved by the US Food and Drug Administration (US-FDA) in phase-wise manner for the treatment of ME secondary to retinal vein occlusion, noninfectious uveitis, and diabetic ME.[33] It is composed of polylactic acid and polyglycolic acid polymers that slowly undergoes hydrolysis and gradually releases 700 μg of drug inside the vitreous cavity over a 6-month period, reducing the need for frequent intravitreal injections. The drug–copolymer complex comes in a preloaded applicator with a 22-gauge needle that is inserted in the eye via the pars plana approach. It can be administered in an office-based setting, in contrast to nonbiodegradable implants, which require a surgical procedure in the operating theater. There are two phases of drug release: first phase showing a high concentration of DEX reaching a peak at 2 months, followed by a second phase in which low DEX concentration were released up to 6 months, beyond which the levels fall to below limit of quantitation as most of the implant had fragmented.[32] Subsequently, it forms glycolic acid and lactic acid which are further metabolized to water and carbon dioxide which can be easily eliminated by ocular tissue.[2,19]

It is obvious that drug diffusion and clearance from the vitreous cavity may be more rapid in vitrectomized

(pars plana vitrectomy [PPV]) eyes as compared to nonvitrectomized (non-PPV) eyes, which in turn may limit the drug exposure to the retina and lead to decrease in the efficacy of the drug. However, Chang-Lin *et al*.[32] in their study to understand the pharmacokinetic profile of the DEX implant found no such difference. Pelegrín *et al*.[34] also showed no statistical significant difference in decrease in median central retinal thickness (CRT) and improvement in BCVA between non-PPV and PPV eyes following the implant injection.

In a randomized control trial, Lowder *et al*.[2] in 2011 first reported the safety and efficacy of DEX implant. They found that DEX implant is relatively safe and can reduce inflammation as well as substantially improve vision in eyes with noninfectious intermediate or posterior uveitis. Since then, various studies have documented the efficacy of DEX implant in improving the BCVA and reducing the ME in patients with noninfectious uveitis. DEX implant was also found to be well tolerated in pediatric uveitis eyes and when used bilaterally.[35,36] Results of various studies of DEX implant have been summarized in Table 1.

DEX implant is also associated with IOP which peaks at 2 months postimplantation. However, the SAFODEX study found the raised IOP to be only transient, being effectively managed with topical antiglaucoma medications, and very rarely requiring surgical intervention (<1% eyes).[37] Furthermore, repeated DEX implant injection was not found to be associated with any increase in IOP. Risk factors for IOP rise with DEX implant are young patients, males, type 1 diabetics, patients on 2- or 3-drug antiglaucoma therapy, and those with history of retinal vein occlusion or uveitis.[37] It is independent of the status of the lens (phakic/pseudophakic) or vitreous (vitrectomized or not).[37] In their study to evaluate the IOP rise following steroid injection, Kiddee *et al*.[38] found that ocular hypertension developed in 32% eyes injected with IVTA, 66% and 79% eyes injected with low- and high-dose fluocinolone acetonide (FA) implant, and only 11% and 15% eyes injected with low- and high-dose DEX implant. However, migration of the implant to anterior chamber in aphakic eye, pseudophakic eye with breach of posterior capsule, or eyes with large surgical iridectomy is a major concern, and the implant is not advocated for the use in these eyes.

Intravitreal Fluocinolone Acetonide

FA is a synthetic corticosteroid which is 1/24th as soluble as DEX with an increased half-life in the vitreous even without a special delivery system.[19] RETISERT (Bausch and Rochester, NY, USA) is a nonbiodegradable, sustained-release device available in two doses of 0.59 mg or 2.1 mg. It was approved by the US-FDA for the treatment of chronic noninfectious uveitis in 2005.[5] The implant has an overall dimension of 3 mm × 2 mm × 5 mm and consists of a 1.5 mm central drug pellet surrounded by shells of ethyl vinyl alcohol and 98% hydrolyzed polyvinyl alcohol (PVA). The ethyl vinyl alcohol component partly coats the pellet and is impermeable to the drug restricting the amount of drug release.[19] The 0.59 mg implant releases the drug at 0.6 μg/day initially for 1 month, following which the levels decrease to reach a steady state between 0.3 and 0.4 μg/day controlling the intraocular inflammation for 2.5–3 years.[39] The 2.1 mg implant has a dual release orifice-releasing FA at a rate of approximately 2 μg/day initially and then decreasing to 1 μg/day for a 3-year period.[39] Silicon adhesive is used to attach the silicone-coated drug core to a heat-treated PVA suture tab, and entire assembly is sterilized by γ-irradiation before implantation.[5,40]

The implant is surgically placed through the pars plana incision with a 20G needle and extending 3.5 mm circumferentially, 4 mm posterior to and parallel to limbus. After excising the prolapsed vitreous, the implant is sutured to the sclera.[41] The surgical procedure is performed under local or general anesthesia, and inferior quadrant is the preferred site. An 8-0 nylon or prolene suture is passed through the hole in a suture tab and is used to anchor the implant to the sclera. In case of vitrectomized eyes, a pars plana infusion line can be used to prevent chances of globe collapse.[3,5,42] Having a limited lifespan, Retisert may need re-implantation in patients with chronic uveitis to maintain disease quiescence. Such re-implantation may be done with or without exchange of the old implant.[43] There is a high risk of dissociation of implant during removal/exchange surgery.[44] The prospective, interventional, pilot study conducted by Jaffe *et al*.[42] in 2000 showed a marked reduction in anti-inflammatory medication use and statistically significant improvement in BCVA following implantation of FA implant in seven eyes of five patients.

The Multicenter Uveitis Steroid Treatment Trial was the Phase III, randomized controlled trial conducted to study the relative effectiveness and safety of FA implant against systemic corticosteroids and immunosuppressives in 255 patients (479 eyes) with active noninfectious posterior uveitis. It showed that although eyes with ME treated with FA implant had greater decrease in macular thickness compared to those on systemic therapy, there was no statistically significant difference between two groups in regard to proportion of eyes showing resolution of CME.[45] In addition, risk of adverse outcomes was higher in the implant group with 77.9% requiring IOP lowering medications as against 34% in those systemic therapy group after 54 weeks and nearly 4-fold higher incidence of cataract surgery in the implant group [Table 2].[4]

Retisert implant is associated with numerous complications including increase in IOP, development and progression of cataract, spontaneous dissociation or dislocation of pellet from support strut, hypotony, and cytomegalovirus endotheliitis.[12] Due to high incidence of glaucoma, it is recommended to monitor the IOP every 6–12 weeks after Retisert implantation.[4] Compared to DEX implant, Retisert is associated with high rate of side effects with 45% of patients requiring glaucoma filtering surgery and about 80%–100% of patients requiring cataract surgery within 3 years of implantation.[45-47] On the other hand, a single Retisert 0.59 mg implant can control inflammation for up to 3 years reducing the need for re-implantation, whereas possibility of need for reinjection of DEX implant is 5 times more due to relatively shorter duration of action.[6] Retisert implant may also need explantation in case of the unforeseen circumstance including uncontrolled IOP, depletion of study medication, spontaneous dissociation of implant from anchoring strut, lysis of anchoring suture, endophthalmitis, hypotony, scleral necrosis and melt, and implant protrusion.[5,39,48]

Iluvien (Alimera Sciences, Alpharetta, GA, USA) is another nonbiodegradable intravitreal implant containing FA. The

Table 1: Studies assessing use of dexamethasone implant in noninfectious uveitic eyes

Authors (year)	Dose	Size	Follow-up	Complication		
				Raised IOP (surgical intervention)	Cataract (surgical intervention)	Others
Lowder *et al.*, 2011[2] (HURON) (prospective study) (RCT)	0.7 mg DEX: 0.35 mg DEX: Sham	229 patients (229 eyes)	26 weeks (6 months)			Conjunctival hemorrhage, ocular irritation, eye pain, iridocyclitis
	0.7 mg DEX	77 eyes		7.1% (nil)	15% (1.6%)	Culture-negative endophthalmitis: 1 eye, RD: 2 eyes
	0.35 mg DEX	76 eyes		8.7% (nil)	12% (nil)	
	Sham	76 eyes		4.2% (nil)	7% (nil)	RD: 2 eyes
Yap *et al.*, 2015[13] (retrospective study)	0.7 mg DEX	4 patients (6 eyes)	12-18 months	2 eyes (nil)	1 eye (nil)	Nil
Adán *et al.*, 2013[65] (retrospective study)	0.7 mg DEX	13 patients (17 eyes)	9.6 months (6-17 months)	47.1% (5.9%)	1 patient	Hypotony (11.8%), AC displacement of implant (5.9%), RD (5.9%)
Tsang *et al.*, 2017[16] (retrospective study)	0.7 mg DEX	15 patients (25 eyes)	270 days (101-582 days)	Nil	2 eyes	Intralenticular injection of implant: 1 eye, ERM: 3 eyes
Frère *et al.*, 2017[15] (retrospective study)	0.7 mg DEX	14 patients (20 eyes)		28%	Nil	Nil
Khurana *et al.*, 2017[66] (prospective study) (TAHOE study)	0.7 mg DEX	10 patients (10 eyes)	12 months	1 eye	2 eyes (25%) – both underwent surgery	Nil
Pleyer *et al.*, 2014[3] (prospective study)	0.7 mg DEX	84 patients (84 eyes)	6 months	20%	7/49 eyes (14%) – nil	Conjunctival hemorrhage, Vitreous Hemorrhage: 1 eye
Khurana and Porco, 2015[33] (retrospective study)	0.7 mg DEX	13 patients (18 eyes)	≥3 months	11%	10%	Nil
Bansal *et al.*, 2015[7] (prospective study)	0.7 mg DEX	27 patients (30 eyes)	24 weeks	4 eyes	Nil	Nil
Zarranz-Ventura *et al.*, 2014[67] (retrospective study)	0.7 mg DEX	63 patients (82 eyes)	12 months	40.2% (2.4%)	4 eyes	VH (2.1%), hypotony (2.1%), dislocation of implant in AC (1.4%), endophthalmitis (0.7%)
Cao *et al.*, 2014[68] (retrospective study)	0.7 mg DEX	27 patient (27 eyes)	14.5 months (8-27 months)	18%	Nil	Nil
Nobre Cardoso *et al.*, 2016[46] (retrospective study)	0.7 mg DEX	31 patients (41 eyes)	14 months (2-23 months)	36.2%	3 eyes	VH – 1 patient
Arcinue *et al.*, 2013[69] (retrospective study)	0.7 mg Ozurdex versus 0.59 mg Retisert	25 patients (27 eyes)	>6 months, <2 years	No significant difference in IOP rise ≥10 mmHg within 2 groups	Retisert eyes 4.7 times more risk of cataract progression	
	Ozurdex	9 patients (11 eyes)		0 eyes	50% had progression	1 implant migration in AC, 1 intralenticular injection of implant
	Retisert	16 patients (16 eyes)		44% eyes (3 eyes surgery and 1 eye SLT)	100% had progression	1 hypotony, 1 culture-negative endophthalmitis

Contd...

Table 1: Contd...

Authors (year)	Dose	Size	Follow-up	Complication		
				Raised IOP (surgical intervention)	Cataract (surgical intervention)	Others
Palla *et al*., 2015[70] (retrospective study)	Ozurdex	15 patients (20 eyes)	<1 year	15%	25% cataract surgery	Nil

Authors (years)	Result		
	BCVA	CMT/CRT/CFT (μm)	Others
Lowder *et al*., 2011[2]	15-letter improvement from baseline BCVA seen 2-6-fold greater in DEX implant group Significantly greater mean improvement from baseline BCVA in DEX implant group than sham group throughout the study period	Mean decrease in CMT was significantly greater in DEX implant group compared to sham at week 8, but this benefit was lost at week 26	Vitreous haze score of 0 at 8 weeks was achieved in significantly more number of eyes with DEX implant and the benefit persisted through week 26
Yap *et al*., 2015[13]	Mean ETDRS BCVA improved from 63 letters at baseline to 70 letters at 2 weeks	Mean CMT decreased from 556 μm at baseline to 329 μm at 2 weeks	-
Adán *et al*., 2013[65]	Statistical significance improvement in BCVA at 1 and 3 months, maintained up to 6 months	Statistically significant reduction in CRT at 1 month, maintained at 3 months but lost at 6 months	-
Tsang *et al*., 2017[16]	Significant improvement in VA in 80% eyes at 3 months, sustained till 6 months	91.4% eyes had significant reduction in CRT at 3 months sustained up to 6 months	-
Frère *et al*., 2017[15]	Statistically significant improvement in mean BCVA seen at 1.5 and 4.4 months	Statistically significant decrease in mean CMT noted at 2 and 4.6 months	-
Khurana *et al*., 2017,[66] TAHOE study	Statistically significant improvement in VA as early as 1 month and sustained till 12 months	Complete resolution of CME in 90% eyes at 1 month, 70% eyes at 3 months	2 eyes had worsening of vitreous haze
Pleyer *et al*., 2014[3]	Significant improvement in mean BCVA at 4 weeks (peak), but benefit lost at week 24	Significant decrease in CMT at week 4, maintained throughout the study period	Vitreous haze score of 0 at week 4 in 61% eyes, sustained till week 24, systemic CS could be discontinued in 25% and reduced in 19%
Khurana and Porco, 2015[33]	Statistically significant improvement in BCVA from baseline at months 1 and 3	Significant decrease in CME from baseline at months 1 and 3, resolution of CME in 89% eyes (1 month) and 72% eyes (3 months)	Eyes with ERM had poor prognosis – no significant decrease in CME or improvement in VA, with more frequent and early recurrence
Bansal *et al*., 2015[7]	Significantly improved mean logMAR BCVA at all visits up to week 24	Statistically significant reduced CMT at all follow-up visits up to week 24	-
Zarranz-Ventura *et al*., 2014[67]	Statistically significant improvement in mean VA at all time points, median time to VA improvement – 6 months	Significant decrease in CRT at all time points corresponding to VA at all time points	Median time to vitreous haze score improvement was 1 months
Cao *et al*., 2014[68]	Statistically significant improvement in mean VA at months 1, 2, and 3	Statistical significant reduction in mean CMT with maximum resolution of CME at 1 month	-
	Average BCVA improved from baseline to 2 months but came back to baseline at 6 months	Average CRT significantly reduced from baseline up to 2 months but returned to baseline by 6 months	88% eyes had vitreous haze score of 0 at 2 months compared to 41% at baseline but benefit lost at 6 months All patient reduced or stopped systemic Rx

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Table 1: Contd...

Authors (year)	Dose	Size	Follow-up	Complication		
				Raised IOP (surgical intervention)	Cataract (surgical intervention)	Others
Nobre Cardoso *et al*., 2016[46]	Significant improvement in average BCVA at 1 month, stable at 3 months, but declined at 6 months			Significant decrease in mean CRT in 95.1% eyes, mild relapse at 3 months, with further increase at 6 and 12 months		Vitreous haze score >0.5%-48.8% at baseline, 25% at 3 months (P<0.001)
Arcinue *et al*., 2013[69]	No significant difference in improvement of mean BCVA, incidence of BCVA improvement is two times more in those implanted with Retisert compared to Ozurdex			No statistical significant difference in decrease in mean CRT between two groups		
Palla *et al*., 2015[70]	Statistically significant improvement in BCVA after 6 weeks of implant injection			Statistically significant decrease in mean CRT at 6 weeks sustained till last follow-up		60% eyes had vitreous haze score of 0 at 6 weeks. Reduced to 30% at 52 weeks

RCT: Randomized control trial, IOP: Intraocular pressure, DEX: Dexamethasone, RD: Retinal detachment, AC: Anterior chamber, ERM: Epiretinal membrane, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, CRT: Central retinal thickness, CFT: Central foveal thickness, CME: Cystoid macular edema

implant is a nonbiodegradable cylindrical tube containing a central drug–polymer matrix which releases 0.19 mg of FA into the vitreous cavity over 3 years. It is injected through a 25-gauge injector system in an office-based setting and thus requires no surgical intervention. It releases a lower dose of 0.2–0.5 μg/day for 18–36 months and is FDA approved for the treatment of diabetic ME.[48,49] However, a case report has been published documenting its off-label use in a patient with ME secondary to noninfectious uveitis, in which the patient showed sustained improvement in VA with decrease in inflammatory activity and ME.[49] Iluvien may have a potential role in future for the treatment of uveitic ME.

Despite advent of immunosuppressive therapy and biologics, corticosteroids still are the most preferred agents for treatment of non-infectious uveitic ME. However, due to the myriad of complications associated with the corticosteroid agents, the possibility of an alternate agent targeting different inflammatory pathway is continuously being explored which might be better tolerated.[50]

Intravitreal Anti-Vascular Endothelial Growth Factor

Chronic intraocular inflammation leads to increased production of inflammatory cytokines such as interleukin (IL)-1β and IL-6 which induce VEGF production by Muller cells, which in turn may disrupt the inner and outer blood–retinal barrier and increase vascular permeability, through a protein kinase C-isoform cascade, leading to subsequent ME.[9,51] Fine *et al*.[52] in their study found that the aqueous VEGF concentration is significantly higher in these patients with uveitic CME than those without CME. A study done by Jeon *et al*.[53] showed significant decrease in VEGF levels of aqueous humor following intravitreal injection of anti-VEGF agent. All these suggested a possible role of anti-VEGF agents in treatment of uveitic CME.

Both bevacizumab (BVZ) and ranibizumab (RBZ) have been tried in the treatment on ME associated with noninfectious uveitis. BVZ is a full-length, recombinant, humanized monoclonal antibody against all subtypes of VEGF, and despite having a potentially immunogenic property, it seems to be well tolerated in uveitic eyes with immunogenic predisposition. Available as a preservative-free solution, BVZ is free of any retinotoxic component.[54] RBZ is a recombinant, humanized monoclonal antibody antigen-binding fragment (Fab) which neutralizes all VEGF isoforms and bioactive fragments.[1,9] It has 100 times higher affinity for VEGF than bevacizumab.[55]

Cordero Coma *et al*.[8] published the first retrospective study describing the use of anti-VEGF therapy in the management of 13 patients with recalcitrant uveitic ME in 2007 with documented reduction in central macular thickness (CMT) in six patients (46.15%) and improvement in VA in nine patients (69.2%). Although the improvement in VA was not statistically significant, they encountered no ocular adverse events which are usually seen following intravitreal steroid injection. Since then, many different studies have been conducted showing variable results with anti-VEGF agents in ME associated with noninfectious uveitis. Although these drugs may lead to anatomic and visual improvement in patients with uveitic ME, they have limited potency and their effect is short-lived necessitating frequent reinjections.[8,51,54] Furthermore, they are associated with a theoretical risk of systemic adverse effect such as thromboembolic events, but none of the study found any such risk associated with its use. Table 3 highlights the results of various studies of effect of BVA and RBZ in eyes with noninfectious uveitis.

Although anti-VEGF agents may not be as effective as various steroid agents due to limited anti-inflammatory action, they are associated with significantly lower rate of cataract progression or rise in IOP and thus can be an effective supplementary therapy in patients with persistent uveitic ME, particularly in phakic eyes and in steroid responders.[54]

Intravitreal Methotrexate

Methotrexate (MTX) is another nonsteroidal agent which has been tried in uveitic eyes with reasonably good results. MTX

Table 2: Studies assessing use of fluocinolone acetonide (dose comparative) in noninfectious uveitic eyes

Study (year)	Drug and dose	Sample size	Follow-up	Complication		
				Raised IOP (surgical intervention)	Cataract (surgical intervention)	Others
Callanan *et al*., 2008[5] (prospective study) RCT	0.59 mg FA versus 2.1 mg FA (2:3 randomization)	278 patients (278 eyes), 241 completed study	3 years	Overall 40% eyes required surgery 6 implants removed due to raised IOP	Overall 93% of phakic eyes underwent surgery	Eye pain (22%), conjunctival hyperemia (31%), conjunctival hemorrhage (29%), blurred vision (30%), implant removal in 22 eyes
		0.59 (110)		67% (rise in IOP >10 mmHg)	70%	Hypotony (34%), RD (4%), Endophthalmitis -1 patient
		2.1 (168)		79% (rise in IOP >10 mmHg)	65%	Hypotony (46%), RD (5%)
Sangwan *et al*., 2015[39] (prospective study) RCT	0.59 mg FA versus 2.1 mg FA implant	239 patients (239 eyes), 211 completed study	3 years	Complications in 99.6% eyes		Eye pain, hypotony, conjunctival hemorrhage, hyperemia, implant explanted in 19 eyes
		0.59 (106)		67.8%	94.9% eyes required cataract surgery	
		2.1 (105)		71.3%		
Pavesio *et al*., 2010[47] (prospective study) RCT	0.59 mg FA versus standard of care (SOC) (systemic CS or IS + CS)	140 patients (131 completed follow-up)	2 years			
		0.59 (66)		55.4% (21.2%)	89.6% (87.8%)	Implant removed in 8 eyes, RD in 1 eye (1.5%), hypotony (19.7%), endophthalmitis in 3 cases (4.5%)
		SOC (74)		10.8% (2.7%)	23.2% (19.33%)	RD in 2 eyes (2.7%), hypotony (1.4%), nonocular adverse effects in 25.7% eyes
Jaffe *et al*., 2005[41] (prospective study)	0.59 or 2.1 mg FA implant	36 eyes of 32 patients	683-461 days	56.1% (IOP lowering medications), 7 eyes (19.4%) required surgery	4/8 phakic eyes – required cataract surgery	RD (2 eyes – 5.5%)
Jaffe *et al*., 2006[40] (prospective study)	0.59 or 2.1 mg FA implant	278 patients (110-0.59 mg, 168-2.1 mg)	34 weeks	51.1% required ocular antihypertensive drops, 5.8% underwent glaucoma filtering surgery	9.9% required cataract surgery	Eye pain (27%), hypotony (IOP 7 6 mmHg) – 9.4% endophthalmitis in 1 eye (0.4%), RD in 6 eyes (2.2%)

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Table 2: Contd...

Authors (year)	Result			Recurrence
	BCVA	CMT/CRT/ CFT (μm) or FFA features	Others	
Callanan *et al*., 2008[5]	No significant difference in mean logMAR VA at 1 or 3 years compared to baseline but significant improvement at 2 years post implant Significant difference in mean logMAR VA compared to nonimplanted eye	-	-Significant reduction in area of CME in implanted eyes at 1 and 3 years (seen on FFA), significant reduction in use of adjunctive Rx	Recurrence rate reduced from 1.4 to 0.5 (0.59 mg group) and from 1.1 to 0.7 (2.1 mg group)
Sangwan *et al*., 2015[39]	Mean change in logMAR BCVA significant at 2 and 3 years, gain of >3 lines BCVA more in implanted eyes	Mean area of CME on FFA reduced significantly at 34 weeks and continued to decrease in 0.59 mg group, in 2.1 mg group mean CME area decreased at 34 weeks but relapsed at 3 years	Lower need for adjunctive therapy	0.59 mg – recurrence rate decreased at 1, 2, and 3 years 2.1 mg – recurrence rate decreased at 1 and 2 years but not 3 years postimplant Recurrence rate began earlier for 2.1 mg implant group
Pavesio *et al*., 2010[47]	Mean VA in SOC group stable over 2 years, mean VA in implant group decreased transiently in implant group at 15-18 months but similar to SOC group at 24 months		More VA fluctuation in implant group than SOC group	Delayed onset of recurrence + lower rate off recurrence in implant versus SOC group
Jaffe *et al*., 2005[41]	Statistically significant improvement in VA (1.1 logMAR to 0.81 logMAR) at 30 months		Systemic medication dosage reduction in 68%, Reduction in PST injection from 2.2/year to 0.07/year	No recurrence in 1st 2 years following implantation
Jaffe *et al*.[40] (2006)	VA stabilized or improved in 87% of implanted eyes Significant improvement in mean MCVA from 0.53 logMAR to 0.45 logMAR	Mean baseline hyperfluorescence area was 36.4 mm^2 and decreased to 6.5 mm^2	Reduced need for adjunctive systemic, periocular and topical corticosteroids	Reduced rate of recurrences from 51.4% in the 34 weeks preceding implantation to 6.1% postimplantation

RCT: Randomized control trial, IOP: Intraocular pressure, RD: Retinal detachment, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, CRT: Central retinal thickness, CFT: Central foveal thickness, CME: Cystoid macular edema, FA: Fluocinolone acetonide, CS: Corticosteroids; IS: Immunosuppressives, SOC: Standard or care, FFA-Fundus fluorescein angiography

Table 3: Studies (comparative and noncomparative) assessing use of anti-vascular endothelial growth factor agents in noninfectious uveitic eyes

Authors (year)	Dosage	Sample size	Follow-up	Complication		
				Raised IOP (surgical intervention)	Cataract (surgical intervention)	Others
Ziemssen *et al.*, 2007[71] (prospective study)	IVB (1.25 mg/0.05 ml)	6 patient (6 eyes)	12 months	Nil	Nil	Rupture of retinal cyst (1 eye)
Reddy *et al.*, 2014[72] (prospective study)	IVR (0.5 mg), repeat injection PRN	5 patients (5 eyes)	24 months	1 patient had recurrent uveitis+glaucoma + cataract: required combined surgery		Floaters, eye pain
Mirshahi *et al.*, 2009[73] (prospective study)	IVB (1.25 mg/0.05 ml)	11 patients (12 eyes)	4 months	Nil	Nil	Nil
	Behçet's Disease					
Acharya *et al.*, 2009[9] (prospective study)	IVR (0.5 mg) monthly for 3 months, reinjection PRN	7 patients (7 eyes), 6 completed study	6 months	Nil	Nil	Transient SCH (4 patient)
Bae *et al.*, 2011[54] (retrospective study)	IVB versus IVTA versus PST	31 patients (31 eyes)	22.3 weeks	Mean increase in IOP in TA group >BVZ group	-	
	IVB (1.25 mg)	10 eyes		10%		
	IVTA (4 mg)	11 eyes		45.5% (1 surgery)		
	PST (40 mg)	10 eyes		40%		Blepharoptosis
Mackensen *et al.*, 2008[55] (retrospective study)	IVB 2.5 or 1.25 mg, reinjection PRN	10 patients (11 eyes)	70 days (10-208 days)	-	1 eye	-
		5 eyes – 2.5, 6 eyes 1.25				
Lott *et al.*, 2009[74] (retrospective study)	IVB 1.25 mg	11 patients (13 eyes)	13 months	Nil	Nil	Nil
Lasave *et al.*, 2009[10] (retrospective study)	IVT (4 mg) versus IVB (2.5 mg)	28 patients (36 eyes)	6 months	Increase in IOP in IVTA group significant compared to IVB group at all points	Nil	No systemic side effect in either group

Author (year)	Result			Recurrence
	BCVA	CMT/CRT/CFT/ CST (μM)	Others	
Ziemssen *et al.*, 2007[71]	No significant improvement in BCVA at 1 month postinjection	No significant reduction in CRT at 1 month postinjection	BVZ showed only minor and transient improvement but good tolerability	
Reddy *et al.*, 2014[72]	12.2 letters gained at the end of 12 months – highly significant	Significant decrease in CST at 1st month, maintained at all subsequent follow-up	-	32 injections administered in 5 eyes 1st 6 months – average of 4.6 injections 2nd 6 months – average of 1.8 injections Fewer injections needed with time

Contd...

Table 3: Contd...

Author (year)	Result			Recurrence
	BCVA	CMT/CRT/CFT/ CST (μM)	Others	
Mirshahi *et al*., 2009[73]	Change in VA – statistically significant VA improved in 7 eyes (58%), unchanged in 5 eyes (42%)	No significant difference in CFT and macular volume before and after Rx	-	-
Acharya *et al*., 2009[9]	Gain of 13 letters (2.6 lines) at 3 mos, maintained at 6 months	Statistically significant reduction in mean CRT at 3 months, stable at 6 months	-	Repeat injection – average 0.83 injections given between 3 and 6 months
Bae *et al*., 2011[54]	No statistical significant improvement in VA among study groups	Significant difference in mean CFT reduction compared to baseline Better results with IVTA but not statistically significant	Maximum improvement in VA and reduction in CFT achieved at 4 weeks, worsened till 12 weeks but still better than preinjection	-
Mackensen *et al*., 2008[55]	Improvement in VA in 4/10 patients, unchanged in others Improvement in VA but not statistically significant	Significant reduction in mean CRT at 4 weeks, reduction seen as early as 4 weeks	Patient with higher dosage – faster response and longer Rx effect but overall no significant difference	Repeat injection at 4-week interval 4 patients – 2 injections 5 patients – 3 injections
Lott *et al*., 2009[74]	NO significant change in BCVA/CST during follow-up period		BVZ exerts stabilizing influence on CME	Median of 2 injections
Lasave *et al*., 2009[10]	Significant difference in BCVA from baseline to end of f/u in both groups (IVTA >IVB)	Statistically significant decrease in CMT at 6 months with IVTA but not with IVB	IVTA greater improvement in BCVA and reduction in CMT compared to IVB	-

RCT: Randomized control trial, IOP: Intraocular pressure, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, CRT: Central retinal thickness, CFT: Central foveal thickness, CME: Cystoid macular edema, IVB: Intravitreal bevacizumab, IVR: Intravitreal ranibizumab, IVTA: Intravitreal triamcinolone acetonide, PST: Posterior subtenon, PRN: Pro re nata, SCH: Subconjunctival hemorrhage, TA: Triamcinolone acetonide, CST: Central subfield thickness, Rx: Treatment

is an antimetabolite which competitively inhibits the enzyme dihydrofolate reductase and thus inhibits the production of tetrahydrofolate which in turn inhibits the formation of thymidylate, resulting in the inhibition of DNA replication and RNA transcription. MTX is most commonly used for rheumatoid arthritis and cancer. Systemic MTX is now in common use for various ophthalmic diseases. Intravitreal route for MTX was first used in the management of intraocular lymphoma.[6] Hardwig *et al*.[56] were the first to evaluate the role of intraocular MTX in patients with ocular disease other than lymphoma. In their retrospective case series of 15 patients with various intraocular diseases, all four patients having intraocular inflammation showed a good response to MTX, supporting the possibility of its role in various ocular diseases. MTX exerts its anti-inflammatory action via release of adenosine into the extracellular space, where it acts through the A2A receptor to inhibit neutrophils, macrophage, and T-cell activity in a dose-dependent manner.[57]

Taylor *et al*.[50] conducted a prospective, interventional study to evaluate the use of intravitreal MTX in the treatment of uveitis and uveitic ME using a dose of 400 μg MTX in 0.1 ml in 15 eyes. They showed that 87% patients (13/15 eyes) gained at least 10 letters by the end of 3 months, improving the mean BCVA from 1.06 logMAR preinjection to 0.63 logMAR at 3 months postinjection. However, no statistically significant difference was seen between BCVA post-MTX injection compared to that after previous corticosteroid injection. Further, a statistically significant reduction in vitreous haze score, and decrease in mean CMT was noted. Five patients showed relapse after median time of 4 months and needed reinjections. The only adverse events seen were ocular pain for < 24 h duration and one case of corneal epitheliopathy who was managed symptomatically. Topical folinic acid may be used to treat corneal decompensation.[6]

In another multicenter, retrospective, interventional case series by Taylor *et al*.,[57] 54 intravitreal injections of MTX were given in 38 eyes of 30 patients. Of 38 eyes, 30 (79%) showed effective response with decrease in intraocular inflammation and improvement in VA. None of the patient showed any serious ocular adverse effect. In addition, dosage of systemic corticosteroids could be reduced in eight of 14 patients (57%). Although eight eyes relapsed after a median of 3 months, majority (73%) entered an extended period of remission of up to 18 months. On meta-analysis of both the studies as a whole, a response rate of 80% was noted to intravitreal

Table 4: Level of evidence of various intravitreal therapeutic agents in noninfectious uveitis based on the National Health and Medical Research Council Guidelines[75]

Level	Interventions	Drugs
I	A systematic review of level II studies	
II	A randomized controlled trial	Ozurdex[2]
		Retisert[44,47]
		Sirolimus[58-61]*
III-1	A pseudorandomized controlled trial (alternate allocation or some other method)	
III-2	A comparative study with concurrent controls	
	Nonrandomized experimental trial	
	Cohort study	
	Case–control study	
	Interrupted time series with a control group	
III-3	A comparative study without concurrent controls	Infliximab[63]
	Historical control study	Bevacizumab[54]
	2 or more single-arm study	Ivta[10]
	Interrupted time series without a parallel control group	
IV	Case series with either posttest or pretest/posttest outcomes	Methotrexate[50]

*RCT comparing use of sirolimus via intravitreal and subconjunctival route or compared various dosages of sirolimus. RCT: Randomized control trial

MTX injection. MTX and anti-VEGF agents may offer better alternative to corticosteroid in steroid responders and in phakic patients. Large-scale prospective, comparative trials are required to evaluate the same.

Intravitreal Sirolimus

Sirolimus (rapamycin) is a macrolide antibiotic and a potent immunosuppressant inhibiting mammalian target of rapamycin. Sirolimus is known to interrupt the inflammatory cascade by inhibiting the expression of the IL-2, IL-4, and IL-15, which in turn suppresses T-cell activation and proliferation. It inhibits the production, signaling, and activity of many growth factors and antibodies involved in the inflammatory cascade of uveitis. It has also been shown to downregulate the expression of a number of genes related to inflammation such as IL-8, endothelial monocyte-activating polypeptide II, granulocyte chemotactic protein 2, cyclooxygenase 1 and 2, and inducible nitric oxide synthase.[58]

It is recently being considered for the treatment of noninfectious uveitis. Following intravitreal administration, the formulation localizes in the inferior portion of the vitreous humor as a nondispersive depot in the vitreous. The depot subsequently dissolves slowly over a period of 60 days after single intravitreal administration and diffuses through the vitreous humor to other ocular layers.[58]

Sirolimus as a therapeutic Approach in uVEitis (SAVE) trial in 2003 was the initial study conducted in 30 patients to evaluate the efficacy of intravitreal (352 μg) and subconjunctival (1320 μg) sirolimus. Nguyen *et al*.[58] showed that the drug appeared to be well tolerated via both the routes with reduced vitreous haze scores. While improvement in BCVA was seen in only 30% of the patients, remaining maintained a stable VA with only 20% showing some deterioration. Reduction in CMT was noted at 3 months compared to baseline, but benefit could not be sustained until 6 months, suggesting need for frequent repeat injections. At the end of 1 year of SAVE study, Ibrahim *et al*.[59] reported reduction in vitreous haze in 70% of eyes. Although there was no statistically significant improvement in mean BCVA or change in CRT, SAVE study established that sirolimus was well tolerated in eyes when injected repeatedly. SAVE-2 study to compare the effect of 880 μg of intravitreal sirolimus as against 440 μg administered every 2 months was initiated in 2015. Interim results published by Sepah *et al*.[60] have reported equal efficacy of both the dose groups in reducing vitreous haze, whereas low-dose sirolimus was more effective in reducing uveitic ME.

Systemic use of sirolimus is known to be associated with a number of cytotoxic, especially hematological, adverse effects. However, adverse events, other than those related to the procedure itself, are very rarely seen with intravitreal injections of sirolimus, with vitreous floaters being the most commonly reported adverse events.[59]

SAKURA study was a multicenter, randomized study to evaluate the efficacy and tolerability of 3 doses of sirolimus: 44, 440, and 880 μg. The study results showed that patient using 440 μg of sirolimus demonstrated significant control of ocular inflammation with reduction in the usage of systemic corticosteroid while preserving BCVA. Thus, sirolimus appears to be well tolerated and effective in controlling active uveitic inflammation in the eye, but no significant improvement in BCVA or CMT was seen.[61]

Intravitreal Infliximab

Infliximab is a biological agent and a chimeric monoclonal antibody drug against tumor necrosis factor, commonly being used for many systemic autoimmune diseases such as rheumatoid arthritis, spondyloarthropathy, inflammatory bowel disease, and psoriasis.[62] It is associated with multitude of side effects on systemic administration such as congestive heart failure, reactivation of latent tuberculosis, and increased risk of infections, all of which can be minimized by administering the drug intravitreally. Markomichelakis *et al*.[63] performed a prospective, noncomparative, pilot study in sight-threatening relapsing uveitis in Behçet's disease, studying the effect of single intravitreal injection of infliximab (1 mg/0.05 ml) in 15 eyes. They reported a significant improvement in BCVA by day 7, maintained until follow-up period of 30 days. Further, beneficial effects were noted in all components of intraocular inflammation, except CME. Despite decrease in mean CMT, persistent CME was noted in 80% of the eyes. No ocular or systemic side effects were documented during the study.

However, the risk of autoantibodies against the drug, known to develop after intravenous administration, was not assessed. Moreover, in another study, infliximab was found to have a significantly faster effect when administered via intravenous route as against intravitreal route.[64] Therefore, intravitreal

infliximab can be considered in cases with contraindications to systemic route or in those who manifest systemic side effects.

Although a multitude of drugs have been tried against uveitic macular edema, with new drugs being added with better understanding of the pathogenesis of disease, but very few have been statistically proven to be beneficial in treatment. Table 4 provides the level of evidence of various intravitreal therpeutic agents discussed in this review article. Based on National Health and Medical Research Council guidelines.[75]

Conclusion

Intravitreal therapeutics is slowly becoming the preferred choice of treatment for majority of ocular diseases including noninfectious uveitis due to its efficacy and better safety profile. However, this therapy has its own drawbacks with necessity to treat both eyes separately in cases of bilateral uveitis, need for more frequent follow-ups, and absence of systemic benefits in patients with extraocular manifestations. Intravitreal drugs can be used as a sole therapy or in combination with systemic therapy to treat uveitic ME secondary to noninfectious uveitis, especially in unilateral cases. With a variety of intravitreal therapeutic agents available for treatment of uveitic ME and each drug having its own advantages and disadvantages, the final treatment should be individualized based on the severity of disease, risk/benefit ratio of each therapy, patient tolerance, and choice of the patient. Sometimes, a combination of drugs may be used. In case of refractory ME not responding to any of the above therapy, PPV can be considered as a last resort.

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Conflicts of interest

There are no conflicts of interest.

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