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Anatomical and Functional Outcome of Single Low Dose Suprachoroidal Triamcinolone Acetonide in Macular Edema Secondary to Non-Infectious Uveitis

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Abstract

Background: To study the anatomical and functional outcome following single low dose suprachoroidal triamcinolone acetonide(LD-SCTA) (2mg) injection in non-infectious posterior uveitis.**Material and Methods:**Eleven patients with macular edema more than 300 microns secondary to non-infectious uveitis were included in the study. A single LD-SCTA (0.5 ml) injection was performed in the study eye with the help of a novel suprachoroidalmicroneedle (Pricon, IsconSurgicals, Jodhpur, India). The study parameters were noted at 4- and 12-weeks post LD-SCTA injection.**Results:**Ten of eleven patients had a significant decrease in central macular thickness (CMT). The mean CMT measurement at baseline was 513.6±191.73 μm for the ten patient who responded to the treatment, reduced significantly to 265.1±34.72 μm ($p<0.003$) and 260.6 ±34.72 μm ($p<0.002$) at 4 weeks and 12 weeks respectively. The mean best corrected visual acuity at baseline was 0.84±0.41 logmar unit which improved to 0.52±0.33 ($p<0.001$) and 0.25±0.22 ($p<0.000$)at week 4 and 12 respectively. The mean IOP at baseline recorded was 16.36±2.97 mm of Hg, 19.45±4.80 mm of Hg ($p=0.06$) at 4 weeks and 17.27±2.53 mm of Hg($p=0.35$) at 12 weeks. One eye which did not respond to LD-SCTA was a case of recurrent Vogt-Koyanagi-Harada disease.**Conclusion:**Single LD-SCTA injection is efficacious in reducing CMT in macular edema, improving BCVA and controlling the inflammation in non-infectious posterior uveitis. LD-SCTA can be used as a first line therapy in non-infectious uveitis over other routes of steroid administration with a favourable outcome and safety profile.

Keywords: Non-infectious uveitis, suprachoroidal triamcinolone, macular edema, low dose SCTA (LD-SCTA).

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Introduction

Noninfectious uveitis accounts for 24.9-44.6% of the total number of uveitis patients.[1,2] Macular edema (ME) is the most common complication (8.3%), followed by epiretinal membrane (6.3%) and uveitic glaucoma (4.2%)innon infectious uveitis.[3] The incidence of ME reported in posterior uveitis ranges from 19-34%.[4-7]

The first line treatment for non-infectious posterior uveitis with or without ME includes systemic and local corticosteroids.[8] Systemic steroids have multiple ocular and systemic dose-limiting side effects often associated with development of other co-morbidities.[8] Local steroid includes topical drops, periocular and intravitreal injection. Topical drops have limited penetration hence has modest effect on ME and posterior segment inflammation. Periocular local depot (posterior sub-tenon) injection have been associated with globe perforation and ptosis apart from known steroid complication of increased intra ocular

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pressure (IOP), cataract progression and infection.[9,10]Intravitreal injections have added risk of retinal detachment and endophthalmitis.[11] Apart from various side effects intact blood retinal barrier impedes transport of drugs to choroid resulting in low bioavailability at target sites in posterior uveitis. A lower bioavailability at target tissue with associated side effects through these delivery routes prompts for a targeted drug delivery system with a much higher bioavailability and favourable safety profile.

Suprachoroidal space (SCS) is a potential space between the sclera and choroid. In normal physiological condition this space is collapsed and is around 25-30µ, however it can accommodate and expand upto 150-500µ depending on the viscosity of injected fluid and the equilibrium pressure.[12,13]Suprachoroidal space for drug delivery can be accessed through a transconjunctival approach 3.5-4mm behind the limbus with length of needle matched with for conjunctiva-scleral thickness as demonstrated in various animal trials, Dogwood and Peachtree study.[14-16] The ease of access and a potential space where the drugs can get compartmentalised as a depot provides a lucrative site for drug delivery in posterior segment diseases.

Three-dimensional transport model for intravitreal and suprachoroidal drug injection developed by Zhang et al had simulated that small molecules Like fluorescein sodium and triamcinolone acetonide get compartmentalised in suprachoroidal space and unlike intravitreal injection do not get diluted in the vitreous gel. It rapidly diffuses into the choroid and subsequently crosses the outer blood retinal barrier to achieve higher therapeutic concentration in both choroid and retina with the same dosage due to absence of dilution by vitreous gel.[17]This allows for use of lower drug dose compared to conventional routes of administration as demonstrated in porcine model comparing low dose of SCTA compared to intravitreal triamcinolone acetonide injection with similar efficacy.[18] Steroid molecules compartmentalized in SC space have a more favourable side effect profile due to lower drug concentration at posterior capsule and trabecular meshwork.[19] These advantages make LD-SCTA an attractive alternative for posterior segment disease like posterior uveitis.

Both DOGWOOD and PEACHTREE trials used 4 mg SCTA and demonstrated significant reduction in ME associated with non infectious uveitis with improved signs of inflammation and significant improvement in visual acuity.[15,16] This study aims to evaluate the anatomical and functional outcome of single 2 mg LD-SCTA in macular edema secondaryto non-infectious posterior uveitis.

Material and Methods

This was a prospective and interventional study at a tertiary eye care center in East India. The study adhered to the tenets of the Declaration of Helsinki and has been approved by the institutional ethics committee and research board. Written informed consent was obtained from all the study subjects. Eleven eyes of eleven patients with non infectious posterior uveitis were prospectively enrolled from retina clinic.

Study subjects:

Men and non-pregnant women above 18 years of age with diagnosed case of non infectious uveitis were eligible for the study. Demographic data, best corrected visual acuity (BCVA), Intraocular Pressure (IOP) by Goldmannapplanation tonometry were recorded. BCVA was measured using Snellen chart and converted to equivalent logmar units. Slit lamp biomicroscopy and indirect ophthalmoscopy was done to grade anterior chamber cell, flare and vitreous haze according to SUN criteria.[20,21] All patient underwent optical coherence tomography (OCT) Macula (3D OCT-1 Maestro, Topcon Medical System, Oakland, NJ, USA) and fundus fluorescein angiography (FFA) (TRC 50 DX, Topcon Medical System, Oakland, NJ, USA) if required. CMT>300µ was considered as significant macular edema.

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Subjects with following ocular conditions were excluded: monocular patients, uncontrolled glaucoma, intraocular pressure of more than 22 mm of Hg, steroid responders, recent fluctuations in IOP of known glaucoma patients, recent change of anti glaucoma medication within 30 days, suprachoroidalhaemorrhage, active ocular infection, anterior staphyloma, co-existing scleral pathology, history of intraocular surgery like filtration surgery, vitreoretinal surgery, cyclodestructive procedure, history of intravitreal injection within 30 days or steroids within 60 days or ozurdex implants within 6 months.

Study Parameters:

The primary objective of this study was to ascertain LD-SCTA (2.0mg) efficacy in cases of non-infectious posterior uveitis associated CME. Secondary objectives were to determine change in BCVA, effect on other inflammatory parameters like vitreous haze, perivascular sheathing and exudation, reduction in size of choroiditis nodule/ granuloma/ foci and resolution of exudative subretinal fluid. Treatment success was defined as >10% reduction in CMT from baseline maintained through 4 to 12 weeks. Other objectives of the study were the percentage of subjects with >20% and>50% reduction in CMT at 4 and 12 weeks. Assessments of safety parameters included evaluation of systemic and ocular adverse events, especially rise in IOP of >10 mm Hg from baseline.

Patients underwent SCTA injection under aseptic conditions under topical anaesthesia. A special microneedle (Pricon, ISCON, Jodhpur, India) [Figure 1d] with a 30 gauge 0.9mm tip length was used to access the suprachoroidal space (SCS). Suprachoroidal needle was passed vertically at 4 mm from limbus after displacing conjunctiva maximally and 2 mg (0.05 ml) of triamcinolone acetonide (TA) was injected. A sudden give away of scleral resistance was an evidence for the tip of needle in SCS. Inability to freely push the 1 ml syringe plunger indicated that the tip had still not traversed the sclera. All eyes underwent indirect ophthalmoscopy after injection to rule out any inadvertent intravitreal injection. Patient were also evaluated after 30 minutes for IOP and presence of TA crystals in suprachoroidal space was confirmed by using AS-OCT.Scheduled examination was done on first post–injection day and all study parameters were evaluated on $4^{th}$and 12^{th}week.

The subjects were injected with a single dose of LD- SCTA at baseline and in case of worsening of disease rescue therapy with local or systemic steroid was administered.

Results

Eleven eyes of eleven patients who completed 12 weeks of follow up were included in the study. Six (54.4%) of the patients were male. The mean age of the patients was 42.36±15.98 years. The mean age of the male and female patient was 37.33±16.30 and 48.4±14.92 years respectively. According to distribution of uveitis four patient had intermediate uveitis/pars planitis, two patients had posterior choroiditis and twopatient had Vogt-Koyanagi-Harada (VKH) syndrome and three had vasculitis secondary to Eales' disease.

10 of 11 eyes were defined as treatment success at 12 weeks follow up. 4 eyes had greater than 6 months of follow up and maintained quiescence in posterior segment inflammatory activity. One patient, a known case of bilateral recurrent VKH on immunomodulator therapy in past presented with single eye recurrence and was subjected to LD-SCTA. The patient complained of further diminution of vision at day 14 and was shifted to oral steroids followed by immunosuppressant.

Efficacy:

Change in CMT:

Ten of eleven eyes achieved treatment success i.e. (>10% reduction of CMT from baseline). The mean CMT measurement at baseline was 513.6±191.73 µm which improved to

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265.1±34.72 µm and 260.6 ±34.72 µm at 4 weeks (p<0.003) and 12 weeks (p<0.002) post LD-SCTA injection for the ten patient who responded to the treatment. The mean CMT remained comparable through week 4 to week 12. 9 out of 10 eyes in the treatment success subgroup had >20% reduction in CMT at 4 and 12 weeks. There was >50% reduction in 3 and 4 eyes at 4 and 12 weeks respectively. One patient of recurrent VKH syndrome with baseline CMT of 410µdid not respond to LD-SCTA and the CMT increased to 880 at 2 weeks. Due to frank exudative detachment patient Macular thickness could not be evaluated at 4 and 12 weeeks respectively. Patient was shifted to systemic rescue therapy. Figure1a shows a line diagram showing individual change in CMT compared to baseline at 4 and 12 weeks respectively.

Change in BCVA:

The mean BCVA at baseline was 0.84±0.41 logmar unit. The mean BCVA significantly improved to 0.52±0.33(p<0.001) and 0.25±0.22(p<0.000) at 4 and 12 weeks respectively. 10 of the 11 eyes had significant improvement in BCVA except 1 eye (Pt 10, Chart 2) of recurrent VKH which was categorised as treatment failure and had to be put on rescue therapy at 2 weeks. Figure1b shows a line diagram showing individual change in BCVA compared to baseline at 4 and 12 weeks respectively.

Grade of Inflammation:

Eight out of eleven patients had clinically relevant vitreous haze at baseline with significant resolution at 12 weeks. The effect of LD-SCTA on other inflammatory parameters has been enlisted in table 1. OCT and fundus photographs of representative patients has been shown in figure 2 and 3.

Adverse events:

Dull aching pain during the procedure and persisting for few hours occurred in almost 45% of study subjects. 36% of the subjects had subconjunctivalhaemorrhage around the injection site. 1 eye (9%) experienced spike of IOP more than 10 mm of Hg and started on topical anti-glaucoma medications (AGM) and was stopped around 12 weeks. The mean IOP at baseline recorded was 16.36±2.97 mm of Hg compared to 19.45±4.80 mm of Hg (p=0.06) at 4 weeks and 17.27±2.53 mm of Hg (p=0.35) at 12 weeks. The IOP was comparable at week 4 and 12 (p=0.08). [Figure 1c] shows a line diagram showing individual change in IOP compared to baseline at 4 and 12 weeks respectively. No other significant ocular adverse events were recorded. [Table 2] enlists the adverse events in the study subjects.

Table 1: Details of the patient undergoing 2 mg LD-SCTA injection and response to the treatment.

S.No	Age	Sex	Diagnosis	Response to treatment (macular edema and other inflammatory parameters)
1.	66	Female	Pars planitis	Resolution of cystoid macular edema with normal foveal contour at 4 weeks and maintained at 12 weeks and improvement in vitritis score.
2.	38	Female	Pars planitis	Resolution of cystoid macular edema with normal foveal contour at 4 weeks and maintained at 12 weeks and improvement in vitritis score.
3.	65	Male	Pars planitis	Resolution of cystoid macular edema with normal foveal contour at 4 weeks

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				and maintained at 12 weeks and improvement in vitritis score.
4.	39	Male	Vasculitis with cystoid macular edema (Eales' disease)	Patient had peripheral vasculitis with CME. CME resolved with resolution of vasculitis and vitritis.
5	26	Male	Vasculitis with cystoid macular edema (Eales' disease)	Patient had undergone targeted photocoagulation earlier and presented with CME. The CME resolved with resolution of vitritis.
6.	23	Male	Vasculitis with cystoid macular edema (Eales' disease)	Resolution of neurosensory detachment and intraretinal fluid. Decrease in size of exudation with resolution of vasculitis and vitritis.
7.	30	Female	Pars planitis	Resolution of macular edema with few pockets of intraretinal cyst with ERM with resolution of disc edema and improvement in vitritis score
8.	48	Female	Choroiditis	Complete resolution of subretinal fluid, choroidal granuloma and outer retinitis at 8 weeks.
9.	25	Male	Multifocal choroiditis	Resolution of intraretinal fluid and choroiditis foci (3 in number)
10.	60	Female	Vogt-Koyanagi-Harada syndrome	Resolution of subfovealsubretinal fluid with normal foveal contour with resolution of disc edema, vitritis and subretinal fluid elsewhere at 4 weeks.
11.	46	Male	Vogt-Koyanagi-Harada syndrome	Increase in loculated pockets of fluid and inflammation with increased exudative retinal detachment at 14 days, classified as treatment failure and was put on rescue therapy.

Table 2: Ocular adverse events.

Adverse Events	**Number of Patients (%) (n=11)**
IOP Rise >10 mm Hg from Baseline	1 (9)
Anterior chamber inflammation	0
Scleritis/NecrotisingScleritis	0
Conjunctival hemorrhage	4 (36)
Conjunctival edema	0
Cataract Formation	0
Retinal artery occlusion	0
Worsening Of Macular Edema	1 (9)
Worsening of vitritis	0
Ocualr pain	5(45)

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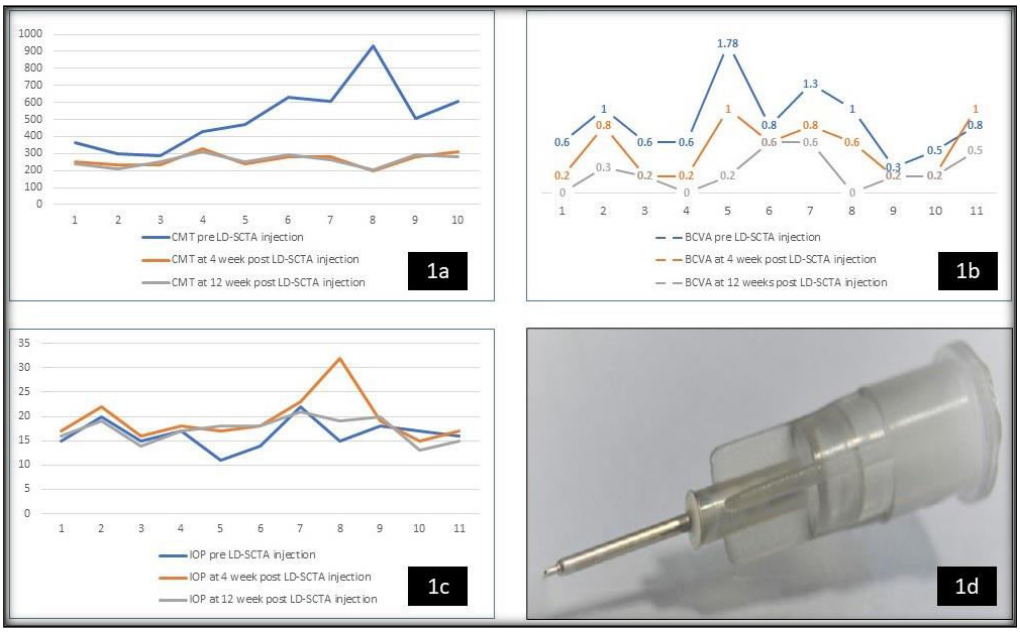

Figure1:1a: Line graph showing central macular thickness in treatment success study subjects at baseline, at 4 and 12 weeks. CMT: central macular thickness Figure 1b: Line diagram showing individual change in BCVA compared to baseline at 4 and 12 weeks respectivelyBCVA: Best corrected visual acuity.1d: The microneedle 30 Gauge needle with a stop and 0.9mm tip length to access the suprachoroidal space

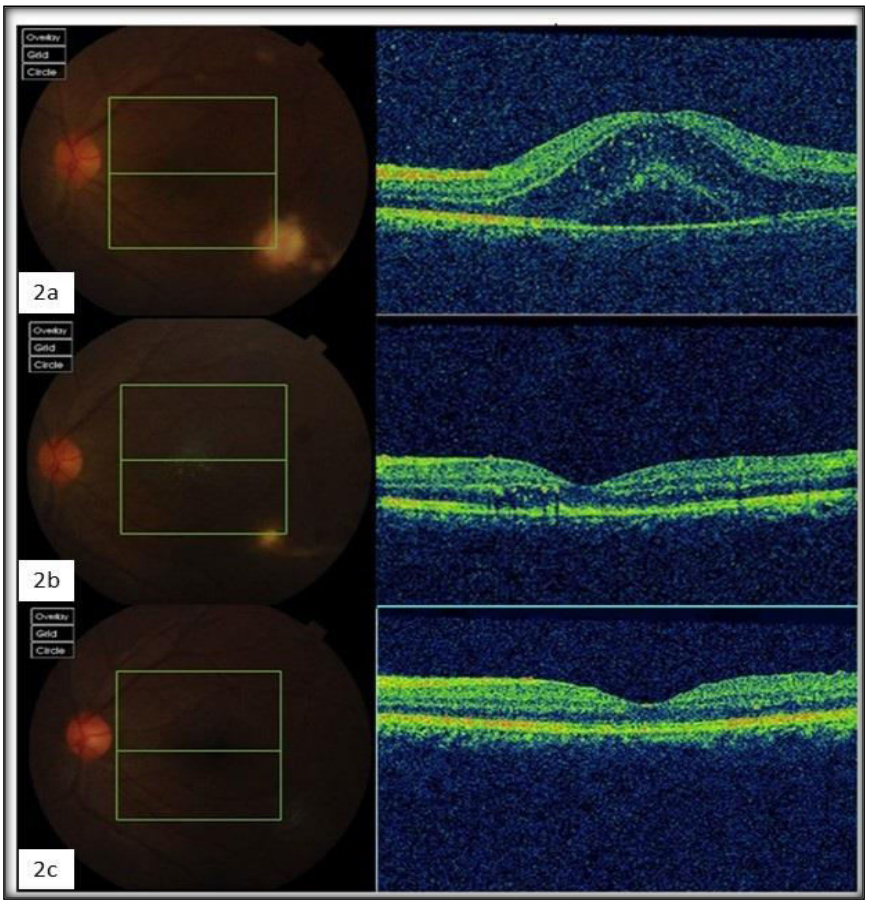

Figure 2: Fundus photograph and OCT of left eye of a 23 year old male patient with Eales' disease with central macular edema. a: At baseline, fundus photo showing exudation and sheathing along the inferotemporal arcade with central macular edema

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(CME) b: At 4 weeks, decrease in size of exudation and sheathing. OCT shows resolution of macular edema with decrease in hyperreflective foci. c: At 12 weeks, complete resolution of exudation and sheathing. The foveal contour is normal on OCT.

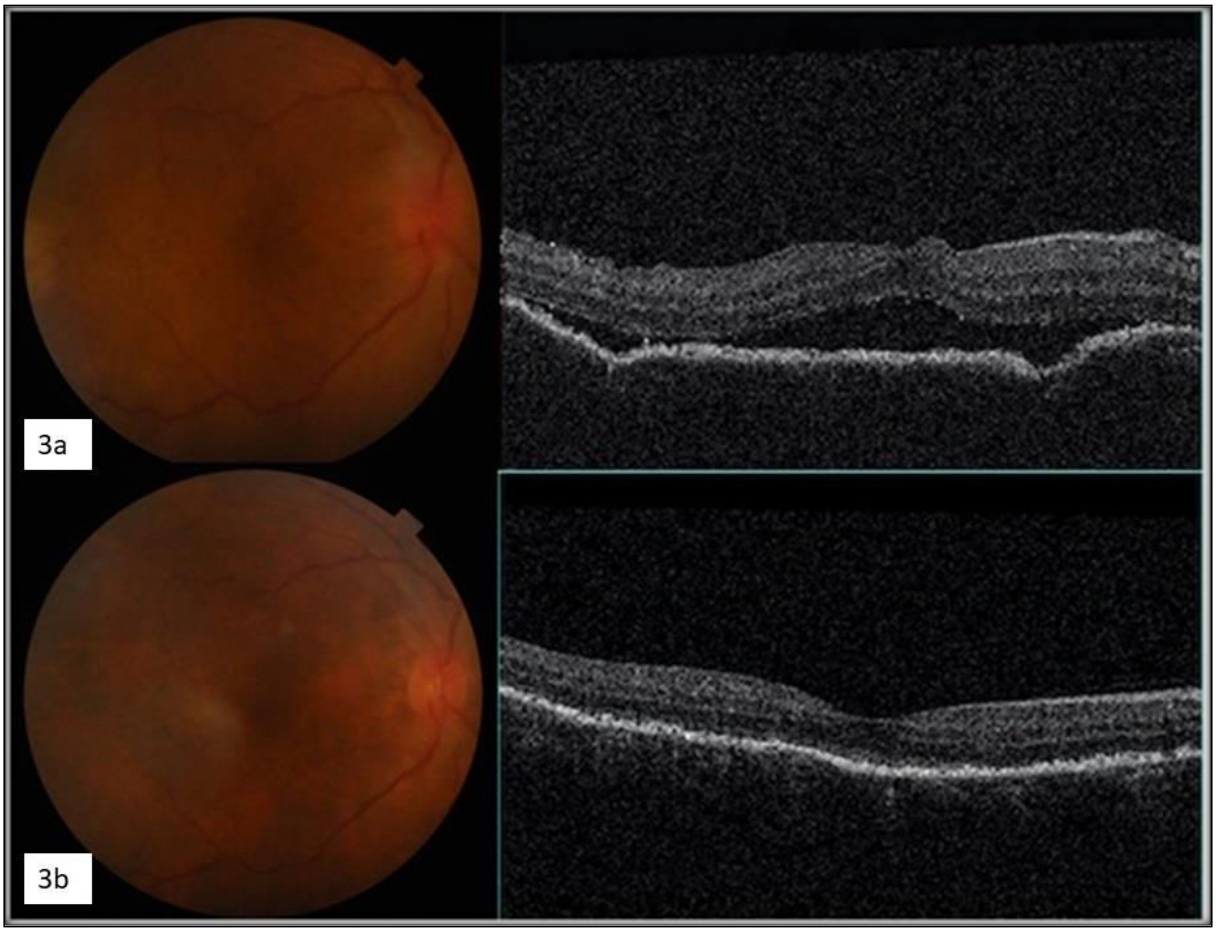

Figure 3: Fundus photograph and OCT of right eye of a 60 year old female with VKH. a: At baseline, fundus photo shows hyperaemic disc with blurring of disc margin suggestive of inflammatory disc edema and obscuration of choroidal vessels due to exudative retinal detachment. OCT shows subretinal fluid at macula. b: At 4 weeks, fundus photo shows resolution of disc edema with resolution of exudative retinal detachment. OCT shows resolution of subretinal fluid at macula.

Discussion

Suprachoroidal triamcinolone injection has been proven safe and efficacious in 4mg dose in recent trials for macular edema secondary to non infectious uveitis. Suprachoroidal space is a potential space for drug administration and ensures high bioavailability to the choroid and retina. The 2 mg dose has not been investigated in human subject but has proven efficacious in porcine and rabbit models.[22,23] The efficacy of 2 mg suprachoroidal dose was evaluated in porcine model of acute posterior segment inflammation and was also compared with intravitreal TA.[22] Mean vitreous humour cells were significantly lower in 2 mg dose of SCTA compared to intravitreal TA group. In another rabbit model of liposaccharide induced uveitis suprachoroidal 2 mg TA was reported to have better efficacy than 20 mg subtenon injection.[23]Three-dimensional transport model for intravitreal and suprachoroidal drug Injection demonstrated that small molecules like fluorescein sodium and triamcinolone acetonide get compartmentalised in SCS and rapidly diffuses into the choroid and crosses the outer blood retinal barrier to achieve higher therapeutic concentration in both choroid and

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retina.[17] Dose sparing can be used to achieve similar efficacy via SCS compared with traditional routes of administration with negligible concentration to the cornea, anterior chamber and lens thus having a favourable side effect profile.[19] TA in SCS also acts as depot and levels are maintained in retina, choroid and vitreous through 90 days.[24] In this study we investigate role of LD-SCTA in improvement in CMT, BCVA and changes in other inflammatory parameters in cases of non-infectious posterior uveitis.

In a preliminary study by Goldstein et al, there was a mean reduction of 154μ in CMT at 8 weeks.[25] All the 7 patients had a reduction in central retinal thickness, 57% had 20% reduction from baseline at week 8 and 43% of the patient did not need any additional treatment.[25] DOGWOOD study, a phase 2 trial investigated effect of 4 and 0.8 mg SCTA for CME associated with non-infectious uveitis in 17 and 5 eyes respectively.[15] The mean CMT reduction was 135 μ at month 1 ($p = 0.0056$) and 164 μat month 2 ($p = 0.0017$) in the 4 mg SCTA group and 78 μ from baseline at month 2 in 0.8 mg group. 69% of the subjects had 20% reduction in CMT and 56% had resolution of macular edema at month 2 after 4 mg of SCTA. In PEACHTREE study, a phase 3 trial, CMT was reduced significantly by 153μ at 24 week compared to controls. 53% of the patients had a resolution of macular edema at week 4.[16] Similarly in our study, after a single 2 mg SCTA dose, the mean CMT reduced significantly to 265.1±34.72 μm and 260.6 ±34.72 μm at 4 and 12 weeks respectively from 513.6±191.73 μm. The mean CMT remained comparable through week 4 to week 12. Our LD-SCTA dosing achieved comparable or better reduction in CMT in comparison to 4mg SCTA used earlier in these studies.

The mean BCVA improvement ranged between 0.17 and 0.28 LogMar and was sustained through the 26-week following 4 mg SCTA in a previous study.[25] All theeleven patient had improvement in BCVA at 12 weeks including the patient who was put on rescue therapy. In DOGWOOD trial also there was statistical significant improvement in BCVA at month 1 and 2.[15] Approximately 49% of the patient had attained BCVA of > 20/40 or better in PEACHTREE trial.[16] In our study also there was significant improvement in BCVA from 0.84 to 0.52 and 0.25 at week 4 and 12 respectively.

Effect of LD-SCTA on other inflammatory parameters apart from CMT was documented. Both Dogwood and PEACHWOOD trials reported resolution of inflammation with improvement in mean SUN scores.[15,16] In the present study LD-SCTA also helped in resolution of vitritis, size of choroidal granulomas/ choroiditis patches thereby controlling all aspects of inflammatory activity. LD-SCTA has effect on disease where choroidal inflammation is one of the primary drivers of the inflammatory process. We also hypothesise that in many case of non-infectious posterior uveitis that a single LD-SCTA can achieve long term disease remission through initial and sustained depot effect of steroid at choroid and retina.

Suprachoroidal Injection through specialised needles are safe. Subconjunctival haemorrhage has been reported in 13.6 % of the patients whereas eye pain was reported in 12.5 % of the patients post SCTA injection.[15,16] In our study post SCTA injection 36% of the subjects had subconjunctival haemorrhage and 42% of the patient had mild dull aching ocular pain which was higher than reported. None of the patient required any medication for these symptoms. In the DOGWOOD trial none of the patient had an elevation of IOP beyond 22 mm of Hg and only one patient had a transient increase in IOP after SCTA injection.[15] Similarly, in PEACHTREE trial none of the patient experienced a spike in IOP.[16] In our study, one patients experienced spike of IOP more than 10 mm of Hg at week 2 and required anti glaucoma medication. There was no significant difference between IOP before injection at day 0 and at week 12. None of the patient had cataract due to 2 mg SCTA injection as against 7.3% in 4 mg SCTA injection in PEACHTREE trial.[16] There were no other ocular and systemic adverse events recorded.

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The present study highlights the efficacy of single dose 2mg LD-SCTA in achieving quiet posterior segment in comparison to 4 mg and 0.8 mg ultra low dose SCTA.Most of the studies have been done on patented Clearsidesuprachoroidal triamcinolone delivery system. The new design suprachoroidal needle by PriconSurgicals can safely deliver drug in Suprachoroidal Space in a reproducible manner [Figure 1d].
Small number of study subjects is the limitation of this pilot study. Initial promising results and comparable results with studies on 4mg suprachoroidal triamcinolone acetonide injection, LD-SCTA can be the first line and sole therapy in patients with posterior uveitis in controlling inflammation and reduction of CMT.

Conclusion

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