ORIGINAL ARTICLE

Evaluation of the Effect of Suprachoroidal Triamcinolone Injection on Refractory Diabetic Macular Edema

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ABSTRACT

Purpose: To assess the safety and efficacy of supra choroidal triamcinolone injection (SCT) in cases of refractory diabetic macular oedema.

Study Design: Interventional case series.

Place and Duration of Study: Lahore General Hospital, Lahore, from July to December 2019.

Methods: A total of 22 eyes of patients above 18 years of age, with either Type-1 or Type-2 diabetes mellitus and treatment resistant central Diabetic Macular Edema (DME) of 320 um or more (measured on Zeiss Cirrus HD-OCT) and Best Corrected Visual Acuity (BCVA) of less than or equal to 20/40 were included in the study. BCVA, Intra Ocular Pressure (IOP) and Central Subfield Thickness (CST) was recorded. After Supra-Choroidal triamcinolone (SCTA), patients were followed up at one and three months and same clinical parameters were recorded and the results were analysed.

Results: out of 22 patients, 10 (45.45%) were males and 12 (54.54%) were females. Mean pre injection CST was 615.5 ± 200.28 um and Log MAR BCVA was 0.9 ± 0.20. Mean post injection CST at one and three months was 302.45 ± 52.45 and 301.66 ± 55.82 um. Mean post injection Log MAR BCVA at one and three months was 0.52 ± 0.3 and 0.40 ± 0.22. The results were statistically significant for pre and post injection CST at both one and three months (p-value < 0.00001). Pre and post injection BCVA was also statistically significant (p-value < 0.05).

Conclusion: CST is a safe and effective means to reduce refractory diabetic macular edema and improve OCT macular thickness.

Key Words: Diabetic macular edema, Suprachoroidal Triamcinolone, Central sub-field thickness.

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INTRODUCTION

Diabetic Macular Edema (DME) results from hyperglycemia induced breakdown of the blood-retina barrier, which leads to fluid extravasation from the retinal vessels into the surrounding neural retina. A diagnosis of DME is made when retinal thickening that involves the macula is present. Central subfield-involved DME that affects the fovea is a common cause of vision loss in diabetic patients. In contrast, non-center-involving DME is unlikely to affect vision unless it progresses to center involvement. DME can be present in any severity level of diabetic retinopathy. Current algorithms for pharmacologic intervention in DME use a simple, OCT based classification to

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classify DME as center-involved or non-center involved. In center-involved DME, the central retinal subfield appears thickened on OCT scans. DME that does not affect the central subfield is termed non-center-involved.[1]

Anti-VEGF drugs are now the first-line therapy for most eyes with center-involved DME, especially those with vision impairment caused by DME. Commonly used anti VEGF agents are Eylea® (Bayer, Leverkusen, Germany), Lucentis® (Novartis, Basel, Switzerland) and Avastin® (Genentech Inc., San Francisco, CA, USA).[2] Despite their approval by Food and Drug Administration (FDA), not all patients are responsive to this therapy.[3,4]

Corticosteroids are also useful as alternative agents for eyes that are not candidates for anti-VEGF therapy or that were incompletely responsive to previous anti-VEGF treatment.[5] For a long time, Intra-Vitreal Triamcinolone Acetonide (IVTA) has been an alternative drug for cases not responsive to anti VEGF agents; or wherecompliance has been an issue. Although, IVTA has very good effect in reversing macular edema and re-establishing the compromised blood retinal barrier; its use has been plagued by certain non-desirable effects. Most notable among them is the need for repeated injections due to the waning effect of IVTA and rebound macular edema. Its use also leads toelevated Intraocular Pressure (IOP) and cataract formation.[6] The use of locally given steroids has proven their efficacy in certain clinical situations asfirst line treatment. DME with pseudophakia responds equally well to steroids and ranibizumab as illustrated by Protocol I of Diabetic Retinopathy Clinical Research Network (DRCR.net).[7] However, it showed clinically significant rise of IOP in patients receiving IVTA.[7]

Recently, the interest in steroids has increased as the researchers have come up with novel ways of delivering steroids in the eye. The most notable of these are Ozurdex® and Iluvein®. Ozurdex® (Allergan, Inc., Irvine, USA) is a dexamethasone implant designed to stay in vitreous cavity for six months and then biodegrade. It slowly releases the steroid invitreous cavity. It had been approved by FDA and in most European countries for use in patients with DME. Use of Ozurdex® is also associated with increase in IOP and it has been documented by many researchers.[8] Cost and availability are other important issues that limit its use in Pakistan.

Corticosteroids injected into the suprachoroidal space may achieve therapeutic levels in the retina while decreasing the same in the anterior part of the globe. This has the potential to provide efficacy for the treatment of posterior segment pathologies while minimising the risk of intraocular pressure elevation and cataract acceleration associated with intravitreal corticosteroid injection.[9,10]

The rationale of this study was to see the safety and efficacy of supra-choroidal route of Triamcinolone Acetonide in patients with treatment resistant diabetic macular edema.

METHODS

This was a prospective interventional case series conducted in the vitreoretinal department of Lahore General Hospital, Lahore from July 2019 to December 2019.This study was approved by Ethical Committee of the hospital. Informed consent was taken from all the participants. A total of 22 patients were included in this study. The selection of patients was by convenient sampling. All the patients included in this study were 18 years or more ofage, having Type-1 or Type-2 diabetes mellitus. They had treatment resistant central Diabetic Macular Edema (DME) of 320 um or more (Zeiss Cirrus HD-OCT) with Best Corrected Visual Acuity (BCVA) of less than or equal to 20/40. Patient with macular edema secondary to any other cause, IOP of more than 21 mmHg, history of previousintraocular surgery or treatment naïve patientsof DME, uveitis, ocular hypertension, cataractand macular ischemia (documented on fundusfluorescein angiography) were excluded. Patientswho had history of periocular or intravitrealtriamcinolone acetonide treatment within the last6 months and/or prior anti-VEGF treatment within 90 days were also excluded.

Treatment resistance was defined as DMEfailing to respond to three anti VEGF injections (any type) spaced at one month apart. Failureto respond was decided on BCVA and/or Central Subfield Thickness (CST) on Spectral Domain Optical Coherence Tomography (Zeiss Cirrus HD-OCT). At one month after the third anti-VEGF, if BCVA did not improve by 5 letters onEarly Treatment Diabetic Retinopathy Study (ETDRS) chart or the CST did not decrease by 50 um or 10% from baseline, then the case waslabelled as resistant DME. At the timeof initial assessment, all participants underwentcomplete ocular examination that included, IOPmeasurement (Applanation method)

and anterior/posterior segment examination. The patients were followed for three months after injection and their follow up visits were scheduled at oneweek, one month and three months after injection. At each follow-up visit, BCVA, IOP and CST wasrecorded for final data analysis. The primary efficacy end points were change in BCVA and CST from the baseline at the end of three months. Data was analyzed using SPSS 20.0. We used paired t-test and Wilcoxon signed-ranked test astest of significance for normally distributed and skewed continuous data respectively. A p-valueof 0.05 was taken as statistically significant.

A total of 22 eyes of 22 patients were included. Baseline Best Corrected Visual Acuity (BCVA), Intra Ocular Pressure (IOP) and Central Subfield Thickness (CST) were recorded. After SCTA, patient was followed-up at one and three months and same clinical parameters were recorded again and results were analysed.

We used an improvised technique for SCTA injection with 30 gauge1cc insulin syringe (BD Insulin Syringe with BD Ultrafine Needle; Becton, Dickinson and Company, NJ, USA). Other dispensable included 24 gauge intravenous branula and injection triamcinolone acetonide (TA) 40 mg/ml (Kenakort A by Glaxo Smith Kline Brentford, Middlesex, TW89GS, United Kingdom). All patients were dilated before SCTA and indirect ophthalmoscope was placed at hand to examine fundus after injection. Needle was withdrawn from branula and branula was cut in such a way that only 1000 um of insulin syringe was exposed from the edge of branula. TA was filled in the syringe up-to the mark of 0.1 ml. The eye was painted with 10% povidone iodine solution and 5% of this solution was instilled infornices and left there for 30 seconds. The eye was draped in a manner similar to any intraocular procedure. We marked 3.5mm from the limbusin suprotemporal quadrant. After marking, 4 mg of triamcinolone acetonide (0.1 ml) was injected in suprachoroidal space by inserting the needle perpendicular to sclera and bevel pointing backwards at the distance of 3.5 mm from limbus inthe said quadrant. Needle was slowly withdrawn and cotton tipped applicator was applied at the site of injection to ensure minimal reflux. Immediately after this, indirect ophthalmoscopy was performed to ensure patency of central retinal artery and to document any spillage of drug invitreous cavity. In case, central retinal artery was found to be occluded, then anterior chamber paracentesis was performed with 15 degrees' phacoemulsification incision knife. After the procedure, a single drop of routinely used antibiotic was instilled in the eye.

RESULTS

A total of 22 eyes of 22 patients were enrolled in this study. Out of 22 patients, 10(45.45%) were males and 12(54.54%) were females. Mean ageof the patients was 53.2917 ± 6.24 years. Mean number of previous injections received were 5.95. Maximum injections received by a patient was 11 and minimum were four. Mean pre injection CST was 615.5 ± 200.28 um. Mean post injection CST at one and three months was 302.45 ± 52.45 and 301.66 ± 55.82 um. There was statistically significant difference between pre and one-month post injection CST with p-value of < 0.00001. At three months' postinjection, the difference between pre and post injection CST was maintained with p-value of < 0.00001.Mean pre injection and post injection (at one and 3 months) CST is shown in Fig.1.

Mean pre-injection Log MAR BCVA was 0.9 ± 0.20. Mean post injection Log MAR BCVA at one and three months was 0.52 ± 0.3 and 0.40 ± 0.22. The results were statistically significant for pre and post injection CST at both one and three months (p-value < 0.00001). Pre and post-injection BCVA was also statistically significant (p-value < 0.05). Mean pre injection and post injection BCVA (at 1 and 3 months) is shown in Fig.2.

Mean pre injection IOP was 14.25± 3.13 mmHg. Intraocular pressure at one and three months after injection was 14.87 ± 3.41 mmHg and 14.52 ± 3.12 mmHg respectively. The result of BCVA at three months was also statistically significant (p-value < 0.05) from the baseline. There was no difference between pre injection and post injection (one and three months) IOP when measured individually. P-value at one month was 0.131 and at three months was 0.711.We did not encounter any complication or unwanted sequel in our limited follow-up period.

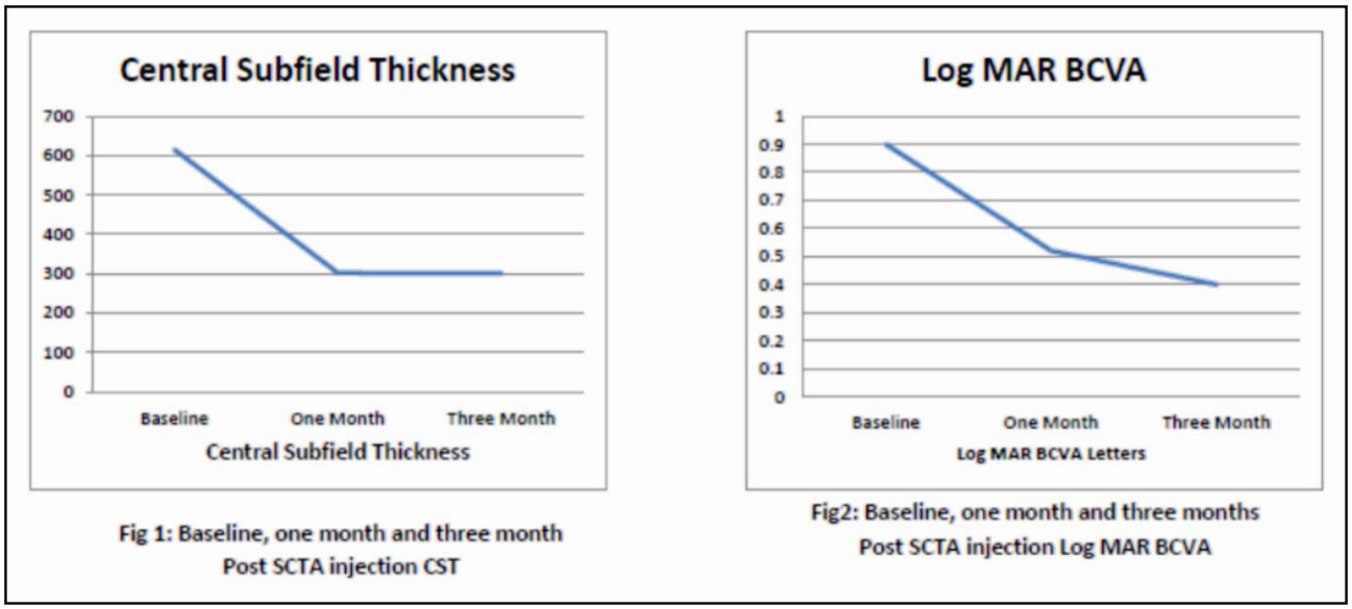

Fig 1: Baseline, one month and three month Post SCTA injection CST

Fig2: Baseline, one month and three months Post SCTA injection Log MAR BCVA

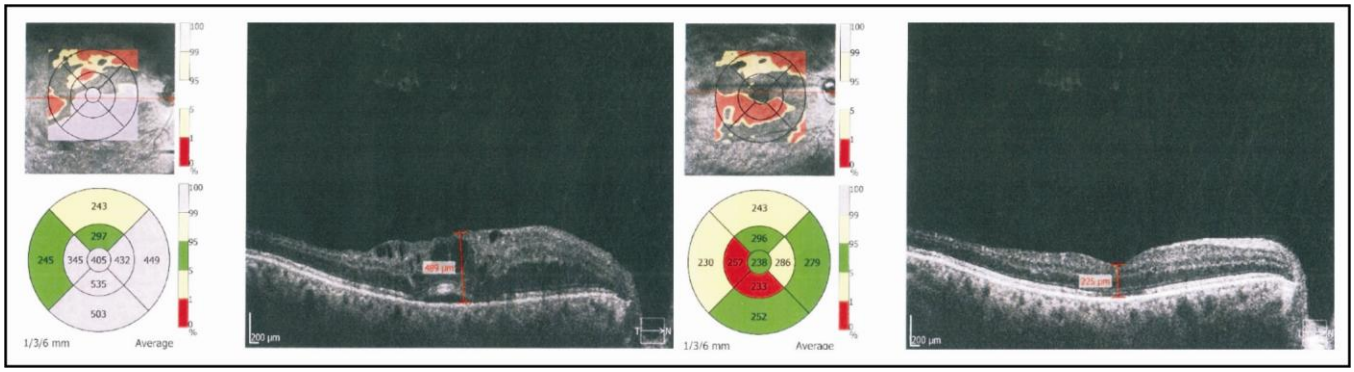

Fig. 3: Pre and post SCTA injection SD-OCTs showing marked reduction in Central Subfield thickness.

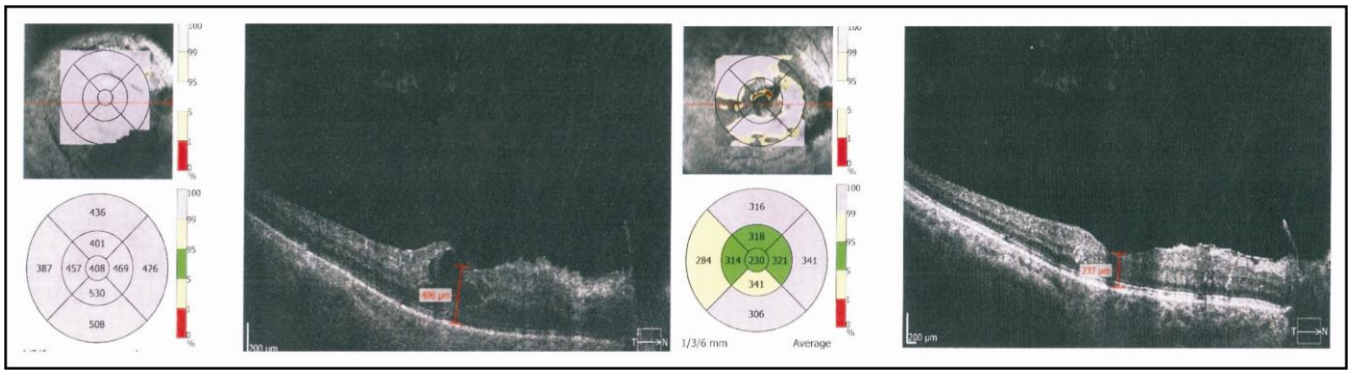

Fig. 4: Pre and post-SCTA injection SD-OCTs showing marked reduction in Central Subfield thickness.

DISCUSSION

Although intravitreal anti-VEGF agents have been very useful for the treatment of diabetic macular edema (DME) but it does not eliminate edema in all patients suggesting that mechanisms other than VEGF are at play in the pathogenesis of DME. Studies have shown that the average number of anti-VEGF injections required for resolution of DME in a single

patient ranged from 9 to 11 in the first year to 17 over five years.[11,12] There has been considerable success in treating both refractory and naive DME with Ozurdex.[13] However, its use has also been plagued with a considerable rise in intraocular pressure (IOP).[14,15]

The efficacy of IVTA in treating DME is well proven over the last several years. However, repeated studies have shown very high occurrence of cataract formation and increased IOP over time.This is especially true when multiple serial injections are used to control chronic DME.[16]

Delivery of corticosteroids to the suprachoroidal space has a therapeutic effect similar to that of intravitreal delivery. However, suprachoroidal delivery is associated with extended half-life and less incidence of IOP rise. The drug has a very low anterior chamber presence as opposed to the intravitreal route.[17,18] Very recently, the HULK trial; N = 20 was carried out which assessed the safety and efficacy of SCTA for DME in treatment naïve and previously treated eyes.[18] In the HULK Trial's previously treated group, the mean number of injections was 21.6 whereas in our study this figure was 7.4. There are certain key differences between our study and the HULK trial. We did not include treatment naïve patients. We also did not combine the first injection of SCTA with Aflibercept. The mean pre-treatment CST in the previously treated arm of the HULK Trial was 473 microns whereas in our study it was 615.5 ± 200.28 um. At 6 months, the mean CST in HULK reduced to 369 um whereas in our study the mean CST at 3 months was 301.66 ± 55.82 um. The initial CST in our study was more than the HULK trial, the CMT achieved at the end of the follow-up period in our study was less than the HULK trial. We did not reinject SCTA in any of our patients as opposed to the HULK trial in which they re-injected SCTA when needed. After a 3-month follow-up, a mean increase of 7 letters from the baseline was reported in the HULK study while our study revealed a mean increase of 11 letters from the baseline. This is probably because the initial BCVA in our study was worse than the HULK trial. The mean IOP was 13.8 mmHg at baseline and it was 14.2 mmHg at 6 months of HULK Trial. The HULK trial reported two cases where IOP was raised and required topical Anti-Glaucoma Treatment. In a similar study, no case of raised IOP was detected.[19] HULK report one incidence of inadvertent intravitreal spillage of triamcinolone where as we had no such incidence. Overall, the efficacy and safety of SCTA are very much comparable in both the studies despite some differences in patient selection and follow-up duration.

In the DOGWOOD Trial SCTA was used for posterior uveitis of non-infectious etiology; there was sustained reduction in terms of Central Subfield Thickness and improvement in BCVA.[20,21]Other studies like PEACHTREE have been conducted to assess the efficacy and safety of SCTA with favourable outcomes.[22]

The suprachoroidal mode of Triamcinolone delivery has also been used in cases of macular edema secondary to Retinal Vascular Occlusion (RVO) and posterior uveitis. In the TANZANITE study, intravitreal Aflibercept efficacy was compared with that of SCTA in cases of macular edema secondary to retinal venous occlusion. The results have been very encouraging in terms of improved visual outcomes with reduced number of injections hence sustained edema resolution.[23] There is a local study conducted by Haroon et al with favourable visual OCT outcomes.[24]

The main advantage of using the suprachoroidal space for delivery of drugs is that it leads to a more posterior distribution with higher concentrations available for the retina, choroid and retinal pigment epithelium with simultaneous lesser exposure to the structures in the anterior segment.[25] This in turn reduces the side effects of triamcinolone in anterior segment like cataract formation and raised IOP.This has been shown in similar studies like HULK, DOGWOOD and TANZANITE studies.

Limitation of this study include a small sample size and lack of a control group. There was short duration of follow-up. However, this novel route of drug administration appears to be effective and safe for pathologies other than diabetic macular edema. However, cautions and controlled use is recommended, that too in carefully selected cases. It is imperative that surgeon is comfortable with the use of this injection technique before venturing on its widespread use.

CONCLUSION

There was anatomical as well as functional improvement following a single injection of Triamcinolone Acetonide (TA). SCT is a safe and

effective means to reduce refractory diabetic macular edema and improve OCT macular thickness.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board.
(AMC/PGMI/LGH/00/06/2021)

Conflict of Interest

Authors declared no conflict of interest.

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Authors' Designation and Contribution

Tehmina Jahangir; Professor: *Concepts, Design, Data acquisition, Data analysis, Manuscript preparation.*

Sidrah Riaz; Associate Professor: *Concepts, Design, Manuscript review,*

Arooj Amjad; Assistant Professor: *Data acquisition, Manuscript preparation.*