·Letter to the Editor·

Intravitreal triamcinolone acetonide: a "real world" analysis of visual acuity, pressure and outcomes

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Dear Sir,

Triamcinolone acetonide (TA) is worldwide available therapeutic agent that is commonly used throughout medicine. TA remains a safe and important ophthalmic therapeutic agent even after the advent of angiogenesis inhibitors [1-2]. Intravitreal TA effectiveness has been demonstrated either alone or combined with other treatment options [3-4]. Several commercially available TA formulations are being used for intravitreal injection. TA formulations vary in pH value, particle size, crystallinity, solubility, dissolution, and flow kinetics both during and after intravitreal injection[5-9]. All of which are important for the clinical understanding of the therapeutic effects and safety profile of the TA preparation being used.

Triesence (Alcon Pharmaceuticals, Ft. Worth, TX, USA) is a Food and Drug Administration (FDA) approved preservative-free TA formulation. Triesence use has increased mainly due to concern over potential toxicity of TA formulations that have a preservative (*e.g.* Kenalog)[10-11]. However, safety and efficacy of intravitreal Triesence remain poorly elucidated. The present study was designed to compare visual acuity and intraocular pressure (IOP) before and after intravitreal Triesence for the treatment of cystoid macular edema. Complication profile was also evaluated.

An institutional review board-approved (LCH-3-012015) retrospective cohort study of 1631 consecutive intravitreal TA (Triesence) injections was undertaken at an ocular oncology and retina practice. The study included 370 patients that were treated with 0.1 mL of TA 40 mg/mL due to cystoid macular edema detected by spectral-domain optical coherence tomography (SD-OCT; Heidelberg Spectralis, Germany). Patients with neovascular glaucoma were excluded from our study. All patients that underwent treatment with intravitreal TA were refractive to treatment with at least 2 intravitreal bevacizumab 2.5 mg/0.1 mL injections separated by a 4-week interval. Patients with intraretinal fluid were treated every 6-8wk. Patients were treated with topical glaucoma medications if IOP was above 18 mm Hg at any clinical evaluation. If IOP was elevated at any evaluation, the patient underwent intravitreal bevacizumab 2.5 mg/0.5 mL plus addition of a topical glaucoma agent with follow up in 4wk.

The mean age of the population was 68 years of age (range 12-89). Sixty-five percent of patients were male and 35% were female. Radiation maculopathy (50%) was the most common diagnosis associated to treatment. Mean follow up time was 8.0±1.4mo. Mean time between injections was 6.7wk. Mean visual acuity at initiation of treatment was 1.08±0.64 logMAR (20/240). Mean visual acuity at last follow up was 0.76±0.58 logMAR (20/115). Mean IOP at initiation of treatment was 14.64±4.0 mm Hg. Mean IOP at last follow up was 14.70±4.1 mm Hg.

Statistical analysis was performed using Student's *t* test. There was a statistically significant improvement in best-corrected visual acuity from initiation of treatment to last follow up ($P<0.05$). No significant change in IOP was detected in the study ($P=1.00$). A significant proportion of the patients (61%) had IOP below 21 mm Hg without treatment. All patients who developed IOP over 21 mm Hg (39%) during treatment were controlled (IOP below 21 mm Hg) with topical treatment only. Patients using topical treatment were controlled with a mean 1.3±0.6 agents. Mean IOP in patients under topical treatment was 14.00±4.0 mm Hg. Thirty percent of patients that were on topical glaucoma treatment during intravitreal TA therapy had prior diagnosis of glaucoma. All patients with glaucoma had primary open-angle glaucoma and were controlled with a mean 1.1±0.5 topical agents. No patient in the study developed uncontrolled glaucoma that required filtrating or laser surgery. Endophthalmitis, retinal tears, retinal detachment, pseudoendophthalmitis, and toxic anterior segment syndrome did not develop in any of our patients.

TA has been extensively studied and used in ophthalmology to treat a variety of vitreoretinal disorders including macular edema, angiogenesis, and intraocular inflammation [12-14]. Various preservative-free TA preparations (*e.g.* Triesence, Alcon Laboratories, Inc.; Trivaris, Allergan, Inc.) have been developed due to concerns over retinal toxicity from the preservative and bactericidal agent benzyl alcohol [10-11]. Triesence use has increased significantly because it is the only FDA approved preservative-free TA commercially available.

A recent study performed at the Bascom Palmer Eye Institute, Miami, FL USA showed that Triesence has different flow rates from TA with benzyl alcohol[6]. Triesence has also demonstrated a significantly slower dissolution profile and lower free drug level in the vitreous than TA with benzyl alcohol [5]. These results suggest that intravitreal Triesence may provide a longer therapeutic duration and less steroid-related complications, such as cataract and IOP elevation, when compared to an equivalent intravitreal injection of TA with benzyl alcohol, because these complications are free TA level-dependent [5]. Retinal cytotoxicity of TA is also crystal size dependent, with larger aggregates being more cytotoxic [9]. TA with benzyl alcohol has the largest cytotoxicity and crystal aggregates [9]. These studies suggest that different TA formulations have different safety and efficacy profiles.

Previous reports on acute infectious endophthalmitis have been a concern for ophthalmologists using intravitreal TA[15-16]. Noninfectious endophthalmitis has also been reported with multiple TA formulations including Triesence [17]. In our study, endophthalmitis was not present. Intraocular inflammation, vitreous opacification, and synechia in the absence of angle rubeosis were not identified.

Previous studies have also reported the annual incidence of severe IOP rise (defined as needing laser or filtrating surgery) between 3.6 and 9.5 per 1000 TA injections [18]. However, data regarding Triesence IOP rise remains scarce. No patient underwent laser or filtrating surgery in the study. IOP showed no statistically significant variation under our treatment protocol. IOP stability might be related to slower dissolution profile and lower free drug level[5].

Multiple studies have reported best-corrected visual acuity improvements after treatment with intravitreal TA alone or in combination for macular edema[19-20]. There was a statistically significant improvement in best-corrected visual acuity from initiation of treatment to last follow up in our study. Future studies may elucidate if the effectiveness among TA preparations are comparable for cystoid macular edema.

Alternatives to newer TA preparations are also available in the market. Intravitreal implants offer the comfort of extended treatment interval; however, intravitreal injections give physicians the ability to more effectively titrate the treatment to the individual. Triesence also allows the physician to treat patients with less associated cost than newer generation cortocosteroids implants. However, Triesence continues to be more expensive that other TA preparations.

Limitations in our study include: large proportion of patients with macular edema due to radiation retinopathy, differential follow up schedule, and retrospective nature. Cataract progression was not evaluated in our study. Prospective studies are needed to assess for these variables.

TA continues to be an important therapeutic agent in the management of cystoid macular edema. Different formulations may have different clinical impact. This study reports favorable visual outcomes with stable IOP. Close follow up and low threshold for treatment may have significantly affected IOP control. Randomized studies are needed to compare Triesence to other TA preparations.

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