

Clinical outcomes of sub-tenon injection of corticosteroids

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RESUMO

Introdução: As uveítes não tratadas de forma adequada podem cursar com perda visual. Apesar das novas terapêuticas, os corticoides (CCT) continuam a ser a principal arma terapêutica, apresentando contudo inúmeros efeitos laterais a nível sistémico ou local. Para controlar a actividade inflamatória, minimizando estes efeitos, a sua administração periocular, nomeadamente de triamcinolona subtenon, apresenta um interesse renovado. Existe pouca informação recente disponível na literatura, pelo que é nosso objectivo avaliar os efeitos funcionais e anatómicos deste tipo de terapia nas uveítes crónicas ou recorrentes, complicadas por vitrite grave ou edema macular, reportando a sua eficácia, duração de efeito, e efeitos laterais, propondo-a como uma alternativa válida

Material e Métodos: Estudo retrospectivo de todos os casos de uveíte não infecciosa que receberam pelo menos uma injeção subtenon de CCT, entre Setembro 2013 e Maio 2015, estendendo-se o follow-up até Setembro de 2015. A indicação para a injeção de triamcinolona foi edema macular, vitrite ou necessidade de titular CCT sistémicos. Foram analisados os eventos favoráveis (melhoria da acuidade visual (AV), edema macular ou vitrite) e adversos (catarata, hipertensão ocular, necessidade de cirurgia).

Resultados: Nos 48 olhos estudados, 44.7% foram classificados como tendo uma uveíte anterior, 4.3% intermédia, 31.9% posterior e 19.19% como uma panuveíte. O follow-up mediano foi de 14 meses [5; 15]. No grupo injectado por edema macular, a espessura diminuiu 75.00 μm [23.50; 104.75], tendo 83.3% dos doentes ficado melhor. No subgrupo de doentes com vitrite, 53.8% melhorou muito, 23.1% melhorou pouco e 23.1% não obtiveram melhorias; a resposta foi melhor no grupo etiológico por tuberculose e melhor em casos idiopáticos e por artrite/espondiloartrite ($p=0.049$). No subgrupo injectado para poupar CCT sistémica o objectivo foi conseguido em todos os casos. Como grupo, existiu uma tendência para melhor AV ($p=0.103$). A pressão intra-ocular foi significativamente mais elevada no pós injeção ($p<0.001$), com 12.8% dos doentes acima dos 22 mmHg, mas sem alterar significativamente o número de fármacos para o controlar ($p=0.467$). Nenhum doente necessitou de cirurgia ao glaucoma ou catarata. Uma segunda injeção foi necessária em 29.8%, numa mediana de 305 dias [227.50; 331].

Conclusões: As injeções de CCT subTenon apresentaram bons resultados anatómicos nas uveítes não infecciosas complicadas com edema macular ou vitrite, auxiliando a poupar CCT sistémica. Estes resultados são sustentados, com um longo tempo de acção. Contudo, os resultados funcionais continuam a necessitar de melhorar. Os efeitos laterais desta terapia são mínimos, apresentando-se portanto como uma opção válida, segura e eficaz no controlo da inflamação intraocular activa.

Background: Suboptimal uveitis treatment may lead to visual loss. In spite of new therapies, corticosteroids (CCT) are still the mainstay of therapy, but associated with numerous side effects. To improve inflammation control, minimizing adverse effects, Sub-Tenon's triamcinolone

acetamide (STTA) injection may be an alternative of renewed interest. There is few recent information available, so we aim to evaluate functional and anatomic outcomes of this therapy in chronic or recurrent uveitis, reporting its efficacy, duration of effect and side-effects.

Methods: Retrospective study of patients with noninfectious uveitis who received at least one STTA injection due to cystoid macular edema (CME), vitritis or need to spare systemic CCT, between September 2013 and May 2015, with the follow-up period extended to September 2015. Favorable (improvement of visual acuity, CME or vitritis), and adverse outcomes (ocular hypertension, cataract progression, surgeries) were recorded.

Results: 48 eyes were classified as anterior uveitis in 44.7%, intermediary in 4.3%, posterior in 31.9%, and panuveitis in 19.1%. They were followed by a median of 14 months [5; 15]. CME improved in 83.3%, with thinning of macular thickness by 75.00 μm [23.50; 104.75]. In vitritis group, 53.8% experienced major, 23.1% minor and 23.1% no improvement; response was worst for tuberculosis and better for idiopathic and arthritis/spondyloarthritis ($p=0.049$). To spare systemic CCT, there was 100% success. As a whole group, ST TA injection resulted in a tendency towards better vision ($p=0.103$). Intraocular pressure (IOP) was higher ($p<0.001$), with 12.8% above 22 mmHg, but not significantly different number of drugs to control it ($p=0.467$). No patient needed glaucoma or cataract surgery. A second injection was needed 29.8%, at a median of 305 days [227.50; 331].

Conclusion: STTA injection may help to spare systemic CCT in the treatment of active forms of intraocular inflammation, exhibiting interesting long-term results and a very good safety profile, with a small risk of increasing IOP to manageable levels and negligible cataract progression. Functional results still need to improve. It may represent a valid, safe and efficient alternative in uveitis management.

INTRODUCTION

Uveitis is an ocular inflammatory condition that occurs most commonly in working age people and can lead to severe visual dysfunction, bearing serious therapeutic challenges for the ophthalmologist in view of its socioeconomic burden.^{1,2}

Significant vision loss is estimated to occur in 10% to 25%,^{3,4} and it is the fifth commonest cause of visual loss in the developed world, accounting for about 10-15% of the cases of blindness.⁴ Cystoid macular edema (CME) is a major cause of decreased visual acuity in patients with uveitis.^{2,3,5,6}

Treatment of inflammatory CME edema requires control of primary disease by means of anti-inflammatory treatment.⁷ Although newer drugs acting as immunomodulatory steroid-sparing agents are increasingly available, corticosteroids (CCT) are still the mainstay of therapy.^{7,8} However, systemic therapy may cause significant morbidity because of its dose-dependent side effects, an ominous concern in these patients.⁹

Local treatments, topical or intravitreal, are also available to reduce the need for systemic drugs and their related side effects.^{6,8} However, ocular side effects such as cataract, elevation of intraocular pressure or endophthalmitis, as well as their relatively short-lasting action for chronic/recurrent cases, may also limit these therapies.^{10,11}

The unsatisfactory visual acuity in patients with uveitis underlines the need for improved management with better and long-lasting control of the ocular inflammation, preventing it from becoming persistent and leading to irreversible damage, while at the same time attempting to avoid CCT-related side effects.⁵ In this concern, periocular administration of steroids, as sub-Tenon's triamcinolone acetamide (ST TA) injection, which was proposed many years ago,¹²⁻¹⁴ may be a case of renewed interest.¹⁵ Recent data on the impact of this therapy on different uveitis entities is, however, scarce. In this regard, the aim of this study was to evaluate the anatomical and functional outcomes of ST TA in recurrent or chronic noninfectious uveitis complicated by severe vitritis, retinal vasculitis or CME, aiming to reduce systemic steroid use. A report on its efficacy, duration of effect, repeatability and side-effects is made, proposing it as a valid therapeutic alternative for improving outcomes and tolerance to therapy.

METHODS

In this retrospective study, we included all patients with a diagnosis of noninfectious uveitis from our hospital, a tertiary health care center, who received at least one

ST TA injection at any time between September 2013 and May 2015, with the *follow-up* period extended to September 2015.

All patients underwent a screening protocol for etiology, depending on the anatomic classification of the inflammation, which briefly included blood cell counts, HLA-B27 typing, angiotensin converting enzyme and lysozyme levels, syphilis serologic analysis, chest x-ray, purified protein derivative (PPD) testing and antinuclear antibody levels. Systemic diseases were diagnosed according to current diagnostic criteria. Only presumed noninfectious ocular inflammatory diseases were analyzed.

Data from each eye with ocular inflammation were abstracted from all clinic visits, including demographic information, associations with systemic diseases, medications, ocular inflammation activity status (based on clinical evaluation using slit-lamp and fundus evaluation), anatomic site and its sequelae. Systemic anti-inflammatory medications in use also were recorded. Best corrected visual acuity (BCVA) was measured by Snellen charts, but for statistical analysis, values were converted into logarithm of the minimal angle of resolution.

Indications to perform a ST TA injection were presence of CME defined by spectral-domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg) or fundoscopically as the primary cause of vision loss, fundoscopic important vitritis or need to spare systemic CCT.

ST TA was performed at operating room in every case, preceded by topical anesthesia injection with lidocaine 2% plus adrenaline. Then, gentle conjunctival dissection and Tenon's capsule breaching in the inferior temporal quadrant was undertaken. Posterior injection of 40 mg crystalline TA (concentrated to a syringe volume of 20 units) in the ST space using an appropriate curved long cannula with a blunt edge was then performed.

Improvement of CME was defined either by SD-OCT or in the cases that SD-OCT was not available as ≥ 0.2 logarithm of the minimum angle of resolution of improvement in BCVA after injection. Improvement in vitritis was categorized as 1) "no improvement" if terms as "active", "uncontrolled" or "worsening inflammation" were used in the medical records; as 2) "slightly better" if "mild", "few", "trace cells" or "trace activity" were described, and as 3) "major improvement" when descriptors such as "quiet," "quiescent," or "no cells" were used.

Adverse outcomes were also recorded: cataract affecting BCVA, cataract surgery, rise in intraocular pressure (IOP), change in number of antihypertensive or glaucoma surgery.

Statistical analysis was performed using SPSS software, version 20 (IBM, Chicago, USA). The sample did not obey

to a normal distribution, so median and interquartile range were used to describe continuous variables and rates and percentages for categorical ones. Non parametric tests were performed – Wilcoxon Paired Samples, Kruskal-Wallis and Chi-square test, as appropriated. A time-to-event approach was used to quantify the incidence of second injection need using a Kaplan-Meier method. $P < 0.05$ was considered significant.

The study complied with the Declaration of Helsinki.

RESULTS

We identified 48 eyes from 41 patients who received at least one ST TA injection.

The median age was 45 years [38; 61] and 76.6% were females. There was no laterality preference (57.4% left eyes and 42.6% right eyes). 21 (44.7%) patients were already pseudophakic. Other baseline characteristics are listed in table 1. Median follow up time was 14 months [5; 15].

Table 1 | Characteristics at Baseline.

Characteristics	Total (%)
Systemic Pathology	
Idiopathic	18 (38.3)
Latent Tuberculosis	7 (14.9)
Sarcoidosis	6 (12.8)
Arthritis/Spondyloarthritis	10 (21.3)
Behçet Disease	4 (8.5)
Harada Disease	1 (2.1)
Lymphoma	1 (2.1)
Uveitis Primary Site	
Anterior	21 (44.7)
Intermediate	2 (4.3)
Posterior	15 (31.9)
Panuveitis	9 (19.1)
Injection Indication	
Macular edema	24 (51.1)
Vitritis	13 (27.7)
Vitritis + macular edema	5 (10.6)
Spare Systemic CCT	5 (10.6)

CCT – corticosteroids

In the group of patients that underwent the injection because of CME, the macular thickness became thinner by a median of 75.00 μm [23.50; 104.75], with a maximum of 954 μm in a patient with a pre-injection macular thickness of 1282 μm ; in only one case the macular thickness rose by

14 µm. In the 24 patients with CME, 20 (83.3%) become better, measured by OCT or rise in BCVA; in the 5 that had CME and vitritis concomitantly, 3 (60%) become better. There was no association of response with age (p=0.622), neither with anatomic main site of inflammation (p=0.145) or systemic pathology (p=0.440).

In the group of 13 patients that underwent the injection because of vitritis, 7 (53.8%) experienced a major improvement, 3 (23.1%) were slightly better and 3 (23.1%) had no improvement; in the subgroup in which vitritis coexisted with CME, 2 were slightly better (40%) and 3 had a major improvement (60%). Again, there was no association of response with age (p=0.255), or anatomic main site of inflammation (p=0.620), but systemic pathology tended to influence the response to ST TA injection (p=0.049), being worst for tuberculosis and better for idiopathic and arthritis/spondyloarthritis cases.

In the 5 cases whose indication for injection was sparing of systemic CCT, success was achieved in all of them.

As a whole group, subTenon injection resulted in a tendency towards better BCVA, but not at significant levels (p=0.103). It also resulted in higher IOP (p<0.001), but not in a median value of ocular hypertension or a significantly different number of drugs (p=0.467); 6 cases (12.8%) had a register of IOP > 22 mmHg post-injection. Age was not correlated with this rise (p=0,209; r=-0,187). No patient needed glaucoma or cataract surgery at present follow-up time. In table 2 is the comparison between pre and post injection characteristics, measured at a median of 24 days [19; 42] after the injection.

Table 2 | Comparison of some clinical characteristics before and after injection.

Characteristics	Pre-injection	Post-injection	p
BCVA (n=47)			
	0,60 [0,30; 1,00]	0,50 [0,16; 0,90]	0,103
IOP (n=47)			
	14 [11; 17]	17 [13; 21]	<0,001
Number of anti-hypertensive drugs (n=47)			
0	44 (93,6%)	42 (89,4%)	0,157
1	1 (2,1%)	3 (6,4%)	
2	1 (2,1%)	1 (2,1%)	
3	1 (2,1%)	1 (2,1%)	
Macular Thickness (n=22)			
	354,50 [287; 556]	279,50 [227,25; 354,75]	<0,001

BCVA – Best Corrected Visual Acuity; IOP – Intraocular Pressure

A second injection was needed in 14 (29.8%) eyes, at a median of 305 days [227.50; 331], as it is possible to see in figure 1. No substantial rise in IOP was noticed (p=0.407). A third injection was needed in 2 patients. Systemic pathology had no influence on second injection need (p=0.432)

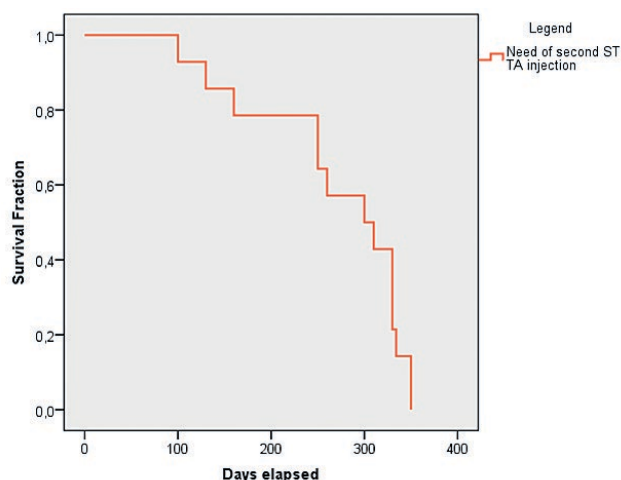


Fig. 1 | Kaplan-Meier estimation of global incidence of need of second ST TA injection. ST TA – Sub-tenon’s Triamcinolone Acetonide.

DISCUSSION

In spite of recent advances in uveitis treatment, there is still the need to improve control of the ocular inflammation, making it long-lasting and avoiding CCT-related side effects,⁵ which are particularly concerning because uveitis usually strikes relatively young people. In the past, it was stated that ST TA injection was a good option, then abandoned towards newer therapies. However, our clinical impression was that it may work well, so we aimed to report its efficacy, duration of effect, repeatability and side-effects on the uveitis management, proposing it as a valid therapeutic alternative.

Indeed, our results are suggestive of long-term efficacy of this medication. It was 100% successful enabling us to spare systemic CCT. Success rates were also optimal in treating the CME (83.3%), and we may hope a median of 75.00 µm decrease in retinal thickness when undertaking a ST TA injection; however, it is noteworthy that response is variable, and values as high as 954 µm may be achieved. For vitritis group results were slightly worst, but still reasonable (53.8% major improvement). Direct comparison to other studies is difficult, due to different inclusion criteria, definitions and follow-up. However, ST TA efficacy was already documented in the past.¹⁶ In one study, clinical resolution of CME was

reported in 57% of patients at 3 months after a single periocular CCT injection,¹⁷ while other had “clinical resolution of inflammation” in 48% at 3 months.¹⁸ More recently, 72.7% of the eyes achieved “complete control of Inflammation” and 49.7% showed an improvement in BCVA.¹⁹

Despite our lack of results in improving BCVA, it was reported by other series, in 50 - 59.4%.^{16,17,20} It is unclear why we didn't find this difference in our sample, perhaps the number of cases was not enough to achieve statistical significance, or damage was severe because of prolonged duration of disease which then prevented anatomic improvement to result in a functional one. It is also worth pointing out the injection's main objective was to ensure control of the inflammatory process thus avoiding systemic CCT, that being also this study's primary outcome.

We have not found any factors predictive of better effectiveness, but anterior uveitis, younger age and shorter duration of uveitis were already pointed out.^{13,19} Prior studies, however, as us, have not found these potentially predictive factors of outcome.^{17,18} Instead, we found that systemic pathology may be associated with response and we may speculate that it is due to a spectrum of severity in the various uveitis etiologies.

Regarding safety profile, median IOP rose from 14 to 17 mmHg, but this value is not representative of ocular hypertension; a value superior to 22 mmHg occurred in 12.8%. This was in accordance to previous studies, in which ocular hypertension ranged from 11-36%.^{18,19,21} However, 0.9-2.4% of patients needed glaucoma surgery,^{19,21} while in our sample some patients were started on anti-hypertensive drugs, at non-significant levels and this medical therapy was enough, with no glaucoma surgery performed. It may reflect the adverse impact of intraocular inflammation and its sequelae themselves. Age role is controversial, as younger age is proposed as a risk factor for CCT-induced ocular hypertension^{20,21} but as other authors¹⁹ we did not find any association between ocular hypertension and age. Multiple injections were also not a risk factor, but subsequent injection was avoided whenever possible if IOP elevation was found after the first injection.

Cataract progression is also one of the most commonly reported complications, present for 12-20%,^{18,19,21} with 6.7-13.8% of the initially phakic eyes being operated on within a year.^{19,21} In our sample, cataract surgery was not needed in this *follow-up* period, but 44.7% of patients were already pseudophakic. Ideal data was not available, since the definition of cataract adversely affecting BCVA is subjective, and it is possible that some cases of BCVA not improving following anatomic resolution may, in reality, be due in part to cataract impact on one or two lines of visual acuity but not severe enough as a cause of low vision. Also, we may

speculate that by controlling the factors concurring to cataract formation, as intraocular inflammation and sparing systemic CCT, this progression to significant cataract may overall be halted. In addition, as other authors refer, patients may be waiting to quiet the inflammation before surgery in a way that would result in an overestimation of the real risk of cataract surgery in their studies.¹⁹

We did not find other complications associated with ST TA injections, but small number of ptosis cases are reported,¹⁸ as well as hypopigmentation and globe perforation. However, the type of cannula used was different, and nowadays a blunt curved cannula is employed.²²

Repeatability is a feature of ST TA injections. In our study, it was needed in 29.8% eyes, which is a very good rate when compared to previous studies;^{17,18} however, these authors performed a second injection to improve control also in patients that didn't respond to the first, so it may be overestimated.

Perhaps the more interesting point of our analysis was the long-term results: besides this efficacy within the timeframe of 14 months, when a recurrence occurred, it was in a median of 305 days (10 months approximately). This represents an extended rate when compared to 20.2 weeks¹⁷ (5 months) or 7.6 months¹⁸ previously reported. We believe this longer duration of action may be explained by the extreme concentration attained by our method (40 mg crystalline TA in 20 units syringe volume), thus allowing for longer drug delivery to intraocular tissues.

The main limitations we faced are the retrospective character, absence of a set protocol with standardized assessment of severity and outcomes, and the small number of patients included. Also, not finding an improvement in BCVA is a major drawback, but possible explanations were aforementioned. Large randomized trials would be ideal – currently there seems to be a preference for intravitreal over ST route, because it is assumed that direct injection of CCT into the vitreous allows for more effective and sustained release of the drug, avoiding the various barriers (static, dynamic, metabolic) that exist between the sclera and posterior pole; however these ocular barriers that may hinder drug efficacy, can also limit the adverse effects of intraocular steroid treatment.²² Intravitreal placement of drugs, although maximizing effect, may limit duration of action because of the smaller concentrations needed to avoid intraocular side effects. We believe such limitation is easily overcome by periocular (ST) placement of a higher drug concentration, ensuring a long lasting therapeutic effect without loss of efficacy.

In summary, the management of uveitis is a worldwide challenge for ophthalmologists and delayed and suboptimal treatment causes irreversible visual sequelae. CCT use is

still the mainstay of treatment, and our results suggest that ST route for delivering this medication is effective and may address some of the current therapy drawbacks. In conclusion, ST TA injection may thus help to spare systemic CCT in the treatment of active forms of intraocular inflammation, as CME or vitritis, exhibiting long-term results and a very good safety profile, with a small risk of increasing IOP to manageable levels and negligible cataract progression.

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