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Review Article

Therapeutic Potential of Steroids in Ocular Vasooclusive Disorder

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Abstract

Retinal vein occlusion as a vasooclusive disorder of the retinal vein is the most common visually disabling disease affecting the retina after diabetic retinopathy, and is a frequent cause of vision loss and even blindness. Although it is more common in the middle-aged and elderly population, no age group is immune to it. The retinal vein occlusion pathogenesis has varied systemic and local implications that make it difficult to elaborate treatment guidelines. The disease entity has long been known, but there is a great deal of confusion regarding its management. Various new therapeutic approaches have been developed in the past few years. The objective of this review is to evaluate the treatments by steroids, emphasizing evidence-based ones, in the light of our current scientific knowledge of retinal vein occlusion.

Keywords: Retina, Retinal vein, Vasoocclusion, Steroids

1. Introduction

Retinal vein occlusion as a vasooclusive disorder of the retinal vein is the most common visually disabling disease affecting the retina after diabetic retinopathy, and is a frequent cause of vision loss and even blindness (Shahid et al., 2006).

Although it is more common in the middle-aged and elderly population, no age group is immune to it (Hayreh et al., 1994).

In spite of the fact that the clinical entity of RVO has been known since 1878 (Michel, 1878) its management still remains highly controversial. The pathogenesis of RVO is multifactorial with both local factors and systemic diseases being etiologically important.

Many case-control studies have examined the clinical features and risk factors in this disorder (The Eye Disease Case-Control Study, 1996; Lang and Spraul, 1997; Sperduto et al., 1998; Shahsuvaryan and Melkonyan, 2003; Koizumi et al, 2007).

Known risk factors for RVO include systemic vascular disease, hypertension, diabetes mellitus, hyperlipidemia and glaucoma. Hypercoagulable states are associated with RVO.

Depending on the location of the obstruction, the RVOs can be divided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

In CRVO the obstruction is located in the central vein, at the level of the optic nerve, so most of the retina is affected. Anatomic features make the central retinal vein vulnerable to occlusion at this location. As the optic nerve and the accompanying central retinal artery and vein pass through the sieve-like connective

tissue of the lamina cribrosa, the central retinal vein normally narrows, and the dense connective tissue of the lamina cribrosa limits any expansion of the traversing optic nerve and vessels within. Any thickening of the central retinal artery, which shares a common fibrous tissue sheath with the vein, might easily compress the lumen of the adjacent central retinal vein and start in motion the sequence of events that lead to thrombus formation (Arakawa et al., 2011).

In BRVO, the obstruction is located in one of the branches of the central vein, affecting only part of the posterior pole and the portion of the peripheral retina drained by occluded branch (Rehak and Rehak, 2008).

There are still gaps in understanding the aetiology and pathogenesis of circulatory disorders of the central retinal vein and its branches.

Although various new therapeutic approaches have been developed in the past few years, existing therapy forms are subject to controversy and available data to same extent inconsistent.

Over the years, many treatments have been advocated enthusiastically and success has been claimed. Except for a few prospective studies, all the reports are based on retrospective collection of information or on limited personal experience. Most of the reported studies have a variety of limitations, which make it hard to evaluate the claimed benefits.

The objective of this review is to evaluate the treatments by steroids, emphasizing evidence-based ones, in the light of our current scientific knowledge of retinal vein occlusion.

Glucocorticosteroids

Glucocorticosteroids have multiple specific and non-specific effects. They are used in particular for their anti-inflammatory, anti-edemic, anti-proliferative and anti-angiogenic properties. In ophthalmology, steroids are administered topically, as periocular injections, or systemically. However, the problem with topical ocular application of drugs is that it does not allow for sufficient delivery to the posterior segment of the eye while long-term systemic administration of steroids is often associated with serious side effects. Given that the eye constitutes only 0.01% of body volume, that its sclerotic membrane makes it a relatively self-containing organ and that a substance works best when directly administered to the target area, intravitreous local administration by injection recommends itself as a means of high dosage local corticosteroid treatment.

2. Triamcinolone Acetonide

Triamcinolone acetonide is a crystalline, synthetic glucocorticoid with potency approximately five times that of cortisol. Since soluble triamcinolone is washed out of the eye within 24 hours of intravitreous injection, the crystalline form is preferable.

2.1 Intravitrealinjection of triamcinolone acetonide

Recent studies have reported successful treatment of macular edema secondary to CRVO and BRVO with intravitreal injection of triamcinolone acetonide. In patients with non-ischaemic CRVO and macular edema, improvement of macular edema and VA was reported .Meanwhile, Cekic et al. (2005), Ozdek et al. (2005) ,Gelston et al. (2006) and Jonas et al. (2006) stated that patients with non-ischaemic CRVO may respond more favourable than patients with ischaemic CRVO, and re-treatment may be necessary in some patients. The general consensus, however, is that improvement is not permanent and usually persists for a maximum of 3-6 months following one intravitreal injection (Ladjimi et al., 2005;Jonas ,2005;2006; Goff et al.,2006; Gunnlaugsdottir et al., 2006;Moschos et al.,, 2007; Oh et al., 2007).

Gregori et al. (2006) in a retrospective review of 40 eyes with CRVO (not differentiated into ischaemic and nonischaemic types) treated with IVTA claimed that some patients demonstrated visual improvement after injection and this improvement was maintained over one year with re-injections of TA. However, most patients did not have such favourable course. They stated that it is difficult to make any generalized prediction on how an individual patient will respond to IVTA even if the edema resolves, since it depends on the degree of macular ischaemia, the amount of retinal haemorrhage and the extent of irreversible

photoreceptor damage, and also an initial positive response could be lost with future treatments if the ischaemia progresses.

Some authors have advocated the use of intravitreal triamcinolone acetonide in patients with macular edema due to BRVO, claiming significant improvement in VA (Cekic et al., 2005; Krepler et al., 2005;, Chen et al., 2006, Jonas,2005,2006;Ozkiris et al., 2006), however, the significant effect was not permanent and persisted for only one month. Oh et al. (2007) found that intravitreal triamcinolone is more effective in patients with BRVO who are treated earlier – after onset of or<or=3 months. In addition, optical coherence tomography (OCT) has demonstrated significant anatomic improvement in the majority of patients with macular edema due to CRVO (Degenring et al.,2003;Ip et al., 2003; Moschos et al., 2007) and BRVO (Cekic et al., 2005;Krepler et al., 2005; Chen et al.,2006; Oh et al., 2007). Although systemically safe, intravitreal steroids have significant ocular side effects.

Among the side effects mentioned are development of ocular hypertension (requiring antiglaucoma therapy including surgery) in about 50% of eyes after about 1-2 months (Park et al., 2003;Cekic et al., 2005; Jonas, 2005;2006;Goff et al., 2006), progression of cataract in some (Jonas, 2005;2006) and rarely endophthalmitis. In the elderly population of patients with RVO, intravitreal injection of TA leads to clinically significant posterior subcapsular cataract and nuclear cataract in about 15 to 20 % of eyes within one year of the intravitreal injection (Jonas, 2005; 2006). Repeated intravitreal injection of TA could also result in primary open-angle glaucoma, particularly since, in patients with RVO there is already high incidence of glaucoma and ocular hypertension (Jonas, 2005; 2006). Gregori et al. (2006) have found that patients with pre-existing open angle glaucoma had an IOP elevation at a higher rate than eyes without glaucoma, suggesting that this population may be at a higher risk for glaucoma surgery after intravitreal TA treatment. The authors stated that this potential risks need to be seriously considered and discussed with the patient given the transient and modest visual benefit of steroids.

Jonas reported that, after intravitreal injection, triamcinolone acetonide can be detected in the aqueous humour for up to 1.5 years (2004) with earlier findings (2002) indicating up to 6 months. That may be responsible for the reported high incidence of markedly elevated intraocular pressure following intravitreal TA, as well regression of iris neovascularization (2001). Dosages of TA used for intravitreal injection range from 4 to 20 mg. Thus far, there are no stadies on the optimal dose under various conditions. Moreover, the intravitreal method of delivery poses injection-related risks (Jager et al., 2004) of vitreous haemorrhage, retinal detachment and infections such as endophthalmitis with a rate of about 1:1000 (Jonas, 2005;2006) and also conjunctival necrosis (Srinivasan and Prasad ,2005)and macular hole (Lattanzio et al., 2007). Recently more prevalent are non-infectious endophthalmitis and pseudoendophthalmitis with TA crystals appearing in the anterior chamber (Jonas et al., 2006).

The SCORE (Standard care vs. Corticosteroid for Retinal vein occlusion) study, sponsored by the National Eye Institute (NEI) consists of 2 multicentere randomized, controlled clinical trials comparing the safety and efficacy of standard care with IVTA in either a 1- or 4-mg dose for vision loss associated with macular edema secondary to CRVO or BRVO. In the CRVO trial, standard care therapy is observation. Retreatments are considered for persistent or new macular edema at 4-month intervals.

The SCORE-CRVO study showed that both triamcinolone groups were superior to observation with respect to VA. The visual benefit of IVTA was demonstrated as early as 4 months and continued to 24 months; although there was less power at this point, the benefit appears to persist. However, in all 3 groups (1mg IVTA, 4mg IVTA or observation, there was a reduction of central retinal thickness from baseline to 24 months. Therefore, the visual benefit of IVTA may be due not only to macular edema decrease, but also to other effects, such as anti-inflammatory or neuroprotective effects. The study report 5 also evidenced the superior safety profile of the 1-mg dose compared with the 4-mg dose, particularly with respect to glaucoma and cataract, rendering in the preferred dose in CRVO.

In SCORE-BRVO IVTA injections was not found to be associated with improved VA outcomes compared with grid photocoagulation, being the standard care. The rates of adverse events were highest in the 4mg triamcinolone group. The rates of adverse events in the 1 mg TA group were similar, with respect to surgical intervention for cataract and glaucoma, to the laser group, but laser treatment excluded any

possibility of injection-related adverse events. The SCORE Study Investigative Group concluded that grid photocoagulation should remain the benchmark against which other treatments are compared in clinical trials for eyes with vision loss associated with macular edema secondary to BRVO.

2.2 Posterior sub-Tenon injection of triamcinolone acetonide

Some authors (Iwao et al., 2007; Lin et al., 2007) have recently advocated the posterior sub-Tenon (PST) injection of 40 mg TA under topic anesthesia, based on claims that IOP elevation may be less common after PST injection than after intravitreal injection, however Iwao et al. (2007) have found that PST TA injection is associated with high rates of steroid-induced IOP elevation in eyes with previously normal IOP.

Lin et al. (2007) in a prospective study of 18 eyes with CRVO treated by three biweekly PST TA injections, claimed that this treatment is effective in reversing cystoid macular edema (CME) and improving VA in recent-onset CRVO in the first 9 months before longstanding macular edema results in irreversible photoreceptor damage. No cataract progression or other complications were observed. They stated that patients with nonischaemic CRVO may respond more favourably than patients with ischaemic CRVO and further study with longer follow-up period is necessary.

Recently Mizumo et al. (2007) in the experimental study have found that the periocular injection of TA effectively decreased retinal thickness and inhibited leukocyte-endothelium interactions in the retina after ischemia. Down regulation of adhesion molecules of retinal vascular endothelium induced by TA may play a role in the course.

3. Dexamethasone

The Ozurdex (Allergan Inc., Irvine, CA, USA) dexamethasone drug delivery system (DDS) was recently developed and approved by the FDA as a biodegradable intravitreal implant to provide sustained delivery of 0.7 mg dexamethasone for the treatment of macular edema associated with RVO (Haller et al., 2010; London et al., 2011).

Haller et al. (2010) concluded that for patients who have relatively short duration of macular edema, Ozurdex should be considered a viable treatment option. Increases in IOP were generally transient and similar following each treatment. Cataract adverse events occurred in 26% of patients treated with two injections and in 5% of patients who received no treatment over the 12-month study.

3.1 Dexamethasone in complex therapy

Taken into account that pathogenesis of CRVO is multifactorial with both local factors and systemic diseases being etiologically important we used the combination of different drugs named the therapeutic complex (Shahsuvaryan, 2004) in treatment of CRVO. Each of used drugs influences the specific link in the chain of pathologic changes resulted in RVO. The treatment included mix of Heparin and Dexamethason followed by Emoxypin and Dexamethason local in peribulbar injections, and Doxium, Solcoseryl, Diamox , Troxerutin, Vitamin E systemic during 15 days. The treatment is directed towards normalization the rheologic factors, resorbtion of blood clot in occluded vein, restoration of blood circulation, reducing vascular hyperpermeability and macular edema, activating of retinal oxygen metabolism and decreasing ischemic processes to prevent neovascularization. In CRVO patients with systemic hypertension also were used vasodilating drug to control blood pressure. To evaluate the efficacy of the therapeutic complex treatment we conducted a case-control study. A group of 20 patients treated after 2 weeks of the onset of occlusion was compared with controls without treatment after 1 month of the onset of occlusion. The groups were comparable for age, sex, systemic diseases (mainly presented systemic hypertension, less diabetes mellitus, myocardial infarction, atherosclerotic vascular disease). A statistically significant improvement in visual acuity was found in treated patients compared with control ($t=2.66$, $p<0.01$).

Results of this study revealed that the complex medical therapy in RVO may be more effective than ordinary treatment or spontaneous regression and suggest that a randomized double-masked study should be conducted.

The latest findings of Mataftsi et al. (2012) revealed that intracameral preservative-free dexamethasone in infantile cataract surgery did not seem to cause an increased risk for glaucoma.

4. Conclusion

In spite of enthusiastic claims of success for various therapies, the reality is that the currently available treatments are associated with visual improvement in only a subset of patients and the approach to treatment of RVO is not evidence-based yet. The benefits and risks of therapy should be weighted in all treatment decisions. There is a need for large well-designed prospective randomized controlled trials with a long-term follow-up of new type steroid taken in a non-invasive way.

5. List of Abbreviations

BRVO – branch retinal vein occlusion

CRVO – central retinal vein occlusion

CME – cystoid macular edema

IOP – intraocular pressure

IVTA – intravitreal triamcinolone acetonide

OCT – optical coherence tomography

PST – posterior sub-Tenon injection

RVO – retinal vein occlusion

TA – triamcinolone acetonide

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