

Current Role of the use of Corticosteroids in the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion

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Before the introduction of antagonists of vascular endothelial growth factor (anti-VEGF), intravitreal corticosteroids were the main treatment of the macular edema (ME) secondary to central retinal vein occlusion (CRVO). It has been shown that panretinal photocoagulation was only efficacious in the prevention and treatment of the neovascular complications of CRVO. With the discover of the anti-VEGF agents, they became the actual first-line of treatment of the ME associated to CRVO.

Bevacizumab is an off-label agent for the treatment of ME, whereas ranibizumab is an approved option for this treatment. The more recent introduction of aflibercept had increased the options of treatment, including to the refractory cases to older anti-VEGF agents.(1,2,3)A Cochrane meta-analysis concluded that repeated intravitreal injection of anti-VEGF agents in eyes with CRVO macular oedema improved visual outcomes at six months, compared to no treatment. (4) Participants receiving intravitreal anti-VEGF treatment were 2.71 times more likely to gain at least 15 letters of visual acuity at six months compared to participants treated with sham injections. Anti-VEGF treatment was associated with an 80% lower risk of losing at least 15 letters of visual acuity at six months compared to sham injection. This meta-analysis also showed that all agents were relatively well tolerated with a low incidence of adverse effects in the short term. (4)Campochiaro et al. (CRUISE study) have shown that ranibizumab treatment for ME following central retinal vein occlusion results in sustained benefits. (5)The 0,3 and 0,5 mg ranibizumab groups received monthly injections for 6 months and after this period, intravitreal ranibizumab was given as needed, if the following criteria were met: BCVA<20/40 and CRT >250um. The sham/0,5mg group which has received sham injections in the first 6 months, and 0.5 mgranibizumabrecue injections as needed, if the described criteria were met. Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 13.9 (11.2-16.5) and 13.9 (11.5-16.4) in the 0.3 mg and 0.5 mg groups, respectively, and 7.3 (4.5-10.0) in the sham/0.5 mg group (P<0.001 for each ranibizumab group vs. sham/0.5 mg). The percentage of patients who gained ≥15 letters from baseline BCVA at month 12 was 47.0% and 50.8% in the 0.3 mg and 0.5 mg groups, respectively, which was significantly greater than in sham/0,5mg group (33,1%).(5)The RETAIN study studied the long-term outcomes in patients with retinal vein occlusion treated with ranibizumab and showed that most patients with CRVO (56%) required frequent injections of ranibizumab, had reduced visual potential, and a guarded prognosis. (6) So a novel approach to refractory cases was needed.

The better understanding of the role of inflammation in the pathophysiology of the ME secondary to several retinal diseases, including CRVO, led to a renewed interest relative to the use of the corticosteroid in the treatment as intravitreal implants, taking advantage of his well-known anti-vascular, anti-inflammatory and anti-permeability properties. .(1-3,10-15)Pharmaceutical industry had supported these ideas and the world of options for the treatment of ME have increased, with the introduction of the steroid intravitreal implants, like dexamethasone and fluocinolone implants. Several studies were done in order to evaluate the efficacy of these new treatment options in ME associated to retinal vein occlusions (10-15).

In the anti-VEGF era, the older option of intravitreal injections of triamcinolone have only been done only in special cases, or as an optional treatment or as a last resort option, considering the less appealing safety profile of these injections compared to anti-VEGF (secondary glaucoma or hypertension, cataract formation, among others). (1-9) Some studies have shown only a transitory benefit of intravitreal injections of triamcinolone in this clinical setting. (2)Gregori NZ *et al* have found an improve of at least 15 letter in best-corrected visual acuity (BCVA) in only 21% of the 40 studied eyes with CRVO after 1 month of treatment, having this beneficial effect decreased to 12% of

all eyes after 12 months. (7) BCVA was unchanged after this treatment in the majority of the eyes (71%) between 6-12 months, being necessary more than 1 injection (mean 1,6; range of 1-4 injections). Intraocular pressure increased more than 10mmHg in 24% and secondary cataract and glaucoma was noted in 63% and 30%, respectively. (7)

The main study about intravitreal injections of triamcinolone is the SCORE study (*Standard Care versus Corticosteroid for Retinal Vein Occlusion Study*) and this study found that treatment with intravitreal triamcinolone, in both 1mg and 4mg dosing, increased 5-times the probability of BCVA improvement. (8) In fact, with a mean of 2,2 injections during 12 months, a 15-letter improvement in BCVA was achieved in 27% of eyes with the 1mg dose and 26% with the 4mg dose, which were significantly greater than the 7% improvement observed in the no treatment arm of the study. As side effects were greater with the 4mg dose, the 1mg dose of triamcinolone was recommended by this study as a safer option. This study concluded that intravitreal injections of triamcinolone were superior to standard of care in the treatment of ME secondary to CRVO.(8) The meta-analysis of Jin ZY *et al.* has found higher incidence of adverse effects associated with the use of intravitreal injections of triamcinolone compared to the use of intravitreal anti-VEGF agents, despite similar improvements on BCVA and central retinal thickness (CRT) at 4, 12 and 24 weeks of follow-up. (9)

Advanced biotechnological techniques and new polymers have led to the development of many innovative intravitreal drug delivery systems. (10) Actual therapeutic options for corticosteroid use for the ME associated to CRVO include the recent intravitreal steroid implants, like the dexamethasone orfluocinoloneacetoneimplants. Their advantage over treatment with steroid injections and the anti-vascular endothelial growth factor ranibizumab is the long-term control of inflammation and ME with a reduced frequency of administration. Their potential side effects are cataract and glaucoma, therefore, careful patient selection and monitoring is essential. (10)

The Geneva Ozurdex Study Group has evaluated the effect of 0,35 mg and 0,70 mg dexamethasone implants compared to “sham” injection on retinal vein occlusion, and included CRVO eyes. (11) The percentages of eyes that achieved a 15-letter improvement in BCVA at 30th, 60th and 90th days after treatment were significantly higher on both dexamethasone implant treatment groups than in “sham” group ($p<0,001$), but no differences were observed at 180th day, which could be related to study design. The occurrence of 15-letter loss in BCVA was significantly less with 0,70 mg dexamethasone implant ($p<0,036$). At the end of follow-up period, the gain of 15-letters in BCVA was higher with 0,70mg DEXAI (41%) and 0,35mg DEXAI (40%) than in sham group (23%) ($p<0,001$). The reductions in CRT were also higher on 0,70mg ($208\pm 201\mu\text{m}$) and 0,35mg ($177\pm 197\mu\text{m}$) than sham group ($85\pm 173\mu\text{m}$, $p<0,001$), but the differences were not significant at 6months after treatment. At 12month, only 17% of CRVO needed only one intravitreal implant injection. This study has concluded that dexamethasone implants lowers the risk of visual loss associated to ME of retinal vein occlusions and could improve the speed and frequency of visual recovery, being a good therapeutic option. (11) Coscas and colleagues showed the efficacy of multiple intravitreal injections of dexamethasone implants, which are relatively safe, considering the beneficial effects on BCVA and CRT, which occurred even after the second injection. (12)

In 2015, Bakri and colleagues showed that repeated, as needed, dexamethasone implant injections, for ME associated with retinal vein occlusions, may be performed. (14) In the mean follow-up period of 344.94 days, fourteen patients (45%) developed ocular hypertension (≥ 22 mmHg), and 40% of phakic patients required cataract surgery. Mean interval of OCT fluid resolution was 52 days (range, 28-245; SD, ± 8), and mean retreatment interval was 119 days (range, 42-309; SD, ± 9). No patients required glaucoma surgery or developed endophthalmitis. Multiple dexamethasone injections require a close follow-up for early treatment of adverse effects. (14) In 2015, Campochiaro *et al.* showed that dexamethasone implants reduce several pro-permeability proteins providing a multi-targeted approach in retinal vein occlusions. (15) Persephin, hepatocyte growth factor, and VEGF are among the target proteins that were reduced by this treatment modality. (15)

Corticosteroid implants are promissory treatments with proven efficacy, even in cases refractory to anti-VEGF. Dexamethasone implants are now officially approved for the treatment of ME secondary to retinal vein occlusion, when it is refractory to anti-VEGFs agents. There is a lack of studies that directly compare the efficacy of anti-VEGFs to novel corticosteroid intravitreal implants and these direct comparisons of efficacy are needed. As the experience with these novel treatments increase and new implants arise, retinal physicians will have more options to give to non-responders to conventional treatment of ME secondary to CRVO.

REFERENCES

- [1] Aref AA, Scott IU: Management of Macular Edema secondary to Central Retinal Vein Occlusion: An Evidence-Based Update. *AdvTher* (2011) 28(1):40-50.
- [2] J. Jonas, M. Paques, J. Monés, and A. Glacet-Bernard, “Retinal vein occlusions,” *Developments in Ophthalmology*, vol. 47, pp. 111–135, 2010.
- [3] Goldman DR, Shah CP, Morley MG, Heier JS.: Venous Occlusive Disease of the Retina. In Yanoff M, Duker JS.: *Ophthalmology*. Elsevier, 2014, 4th Ed, pp 226-234.
- [4] Braithwaite T1, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*. 2014 May 1; 5:CD007325. doi: 10.1002/14651858.CD007325.pub3.
- [5] Campochiaro PA1, Brown DM, Awh CC, Lee SY, Gray S, Saroj N et al.: Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011 Oct; 118(10):2041-9. doi: 10.1016/j.ophtha.2011.02.038. Epub 2011 Jun 29.
- [6] Campochiaro PA1, Sophie R2, Pearlman J3, Brown DM4, Boyer DS5, Heier JS6, Marcus DM7, Feiner L8, Patel A3; RETAIN Study Group. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology*. 2014 Jan; 121(1):209-19. doi: 10.1016/j.ophtha.2013.08.038. Epub 2013 Oct 7.
- [7] Gregori NZ1, Rosenfeld PJ, Puliafito CA, One-year safety and efficacy of intravitreal triamcinolone acetonide for the management of macular edema secondary to central retinal vein occlusion. *Retina*. 2006 Oct; 26(8):889-95.
- [8] Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, et al.: A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *ArchOphthalmol*. 2009; 127(9):1101.
- [9] Jin ZY, Zhu D, Tao Y., Wong IY, Jonas JB.: Meta-analysis of the effect of intravitreal bevacizumab versus intravitreal triamcinolone acetonide in central retinal vein occlusion. *Journal of Ocular Pharmacology and Therapeutics* 2013; 29(9):826-831.
- [10] Lambiase A1, Abdolrahimzadeh S2, Recupero SM3. An update on intravitreal implants in use for eye disorders. *Drugs Today (Barc)*. 2014 Mar; 50(3):239-49. doi: 10.1358/dot.2014.50.3.210375
- [11] Haller JA, Bandello F., Belfort R. et al.: Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion. *Ophthalmology*. 2010 Jun; 117(6):1134-1146.e
- [12] Coscas G., Augustin A.; Bandello, F. et al.: Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion. *Eur J Ophthalmol*. 2014; 24(1):1-9.
- [13] Parodi, M.B.; Iacono, P.; Cascavilla, M.; Zucchiatti, I.; Bandello, F.: Compassionate use of dexametasone implant for the treatment of macular edema secondary to central retinal vein occlusion in a clinical setting. *ActaOphthalmol* 2012 Jun; 90(4):e322-3.
- [14] Bakri SJ1, Omar AF, Iezzi R, Kapoor KG. Evaluation of multiple dexamethasone intravitreal implants in patients with macular edema associated with retinal vein occlusion. *Retina*. 2015 Sep 28. [Epub ahead of print].
- [15] Campochiaro PA1, Hafiz G2, Mir TA2, Scott AW2, Sophie R2 et al.: Pro-Permeability Factors After Dexamethasone Implant in Retinal Vein Occlusion; the Ozurdex for Retinal Vein Occlusion (ORVO) Study. *Am J Ophthalmol*. 2015 Aug; 160(2):313-321.e19. doi: 10.1016/j.ajo.2015.04.025. Epub 2015 Apr 20.