REVIEW

Safety and Efficacy of Ranibizumab in Macular Edema following Retinal Vein Occlusion

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Abstract: Macular edema is the leading cause of visual impairment in patients with retinal vein occlusion. Limited improvements may be obtained with laser photocoagulation or intravitreal triamcinolone. However, according to the data provided by randomized clinical trials, intravitreal injections of ranibizumab (Lucentis; Genentech, South San Francisco, CA) constitute a new effective and safe option for the management of these vision-threatening diseases. The aim of the present review is to summarize the clinical evidence of ranibizumab for macular edema due to retinal vein occlusions.

Keywords: retinal vein occlusion, macular edema, VEGF, antiangiogenic therapy, ranibizumab

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Introduction and Background

Retinal vein occlusions (RVO) are the second most frequent major retinal vascular disease after diabetic retinopathy. The affected vein can be the central retinal vein (central retinal vein occlusion, CRVO) (Fig. 1), or more commonly one of its retinal branches (branch retinal vein occlusion, BRVO), mainly the superior temporal BRVO (Fig. 2). Venous thrombus formation leads to poor venous drainage, dilation and tortuosity of the large retinal veins, and increased retinal capillary pressure. These changes result ultimately in exudation of blood, fluid, and lipid into the retina, leading to the development of macular edema (ME). ME is the leading cause of visual impairment in patients with RVO.

Macular grid laser photocoagulation has been considered the gold standard therapy for ME due to RVO through the last three decades. The photocoagulation of the photoreceptors reduces the oxygen consumption of the outer retina and allows oxygen to diffuse from the choroid to the inner retina, where it relieves hypoxia. Clinical trials demonstrated a moderate efficacy of macular photocoagulation in eyes with branch BRVO, but not in cases with central CRVO.

The SCORE trial (Standard Care versus Corticosteroid for Retinal Vein Occlusion) was a phase III multicenter clinical trial that compared standard care versus 1 or 4 mg preservative-free intravitreal triamcinolone (IVTA) for ME due to CRVO and BRVO. In CRVO patients, IVTA was superior to observation, and the 1 mg dose had a better safety profile. In BRVO patients IVTA was not superior to grid photocoagulation and was linked to high negative side effects.

More recently, a sustained delivery biodegradable dexamethasone implant (DEX implant; Ozurdex; Allergan, Inc., Irvine, CA) has been shown to be an effective therapy for ME due to RVO. However, over 12 months, significant cataract progression occurred in 29.8% of phakic patients receiving a second DEX implant. On the other hand, only 15.4% of patients developed a significant intraocular pressure increase, which otherwise was transient and controlled with either topical medication or observation. This means that, with regard to triamcinolone, the new

Figure 1. Branch retinal vein occlusion. (A1) Retinography showing superior temporal branch retinal vein occlusion in a 72-year-old female complaining for blurred vision for the last three weeks. Retinal hemorrhages are located in the superior temporal retinal quadrant with macular involvement; (A2) Horizontal foveal-centered optical coherence tomography scan showing the presence of diffuse retinal thickening, with small cystic intraretinal spaces, and neurosensory foveal detachment. (B1) Retinography after two monthly intravitreal injections of ranibizumab. The visual acuity improved from 20/60 at baseline to 20/20. Important regression of the retinal hemorrhages can be appreciated; (B2) Complete resolution of the macular edema as evidenced in the optical coherence tomography.
dexamethasone intravitreal implant improves relatively the safety profile when considering IOP raise, but there is still a safety concern with cataract progression after the second and further retreatments. Perhaps the only clear indication for the intravitreal DEX implant may be pseudophakic vitrectomized patients.

The huge improvement of visual outcomes achieved by repeated intravitreal injections of ranibizumab (Lucentis; Genentech, South San Francisco, CA) in macular edema due to RVO has changed the therapeutic perspective of this entity. The purpose of the present manuscript is to review the major efficacy and safety concerns of the treatment of macular edema in RVO with ranibizumab.

**Rationale for the Use of Antiangiogenic Agents in the Management of Macular Edema due to Retinal Vein Occlusion**

Following RVO, functional and structural changes in the retinal capillaries, in addition to reduced retinal blood flow, lead to the development of hypoxia. These changes trigger upregulation and intraocular release of several inflammatory factors (mainly interleukin 6 and 8, monokine induced by interferon γ, monocyte chemotactic protein 1, inducible protein 10), and especially a key mediator: vascular endothelial growth factor (VEGF). High levels of VEGF-A have been detected in the ocular fluids of patients with RVO.12–14

VEGF is a disulfide linked homodimer composed of two 23-kDa subunits. VEGF plays a key role in the pathogenesis of ME secondary to retinal vascular diseases as far as it increases the vascular permeability,15 and promotes inflammation.16 Thus, inhibition of VEGF is reasonable and clearly justified when managing ME due to RVO.

Until the approval of ranibizumab for ME due to RVO, intravitreal bevacizumab (Avastin; Genentech, San Francisco, CA) has been widely used for this indication in an off-label fashion, and with a lack of randomized clinical trials ensuring its systemic safety profile. Anyway, we must remember that ranibizumab and bevacizumab are different molecules,17 and a key difference between them is the systemic effect of...
bevacizumab, which induces a significant reduction in VEGF plasma levels following a single intravitreal injection.\textsuperscript{18,19}

There is still controversy over the potential role of ranibizumab in cases with ischemic forms of RVO. While some preclinical studies have hypothesized a harmful effect of this treatment in cases with retinal ischemia, others conclude that there is no increase in the avascular area of the ischemic retina. In our experience, cases with ischemic BRVO and CRVO evidenced an analogous anatomical response in comparison to cases with perfused RVO. Obviously,

Table 1. Summary of the main ocular changes in vision and central subfield thickness in the main clinical trials.

| Reference number | Type of retinal vein occlusion | Follow-up (eyes) | Treated eyes | Injections per patient | Baseline visual acuity | Average visual gain | Baseline CST |
|------------------|-------------------------------|-----------------|-------------|------------------------|------------------------|-------------------|-------------|
| 3                | CRVO                          | 24              | 10          | ND                     | ND                     | 1                 | ND          |
| 20               | CRVO                          | 3               | 10          | 20                     | 23                     | 14                | 297         |
| 20               | BRVO                          | 3               | 10          | 20                     | 20                     | 18                | 288         |
| 21               | CRVO                          | 12              | 20          | 170                    | 45.8                   | 64.3              | 574.6       |
| 22               | CRVO                          | 6               | 129         | 774                    | 48.1                   | 14.9              | 688.7       |
| 23               | BRVO                          | 6               | 130         | 780                    | 53                     | 18.3              | 551.7       |
| 24               | CRVO                          | 24              | 35          | 526                    | 44.2                   | 17.8              | 638         |
| 25               | CRVO                          | 24              | 15          | 64                     | 45                     | 12                | 625         |
| 26               | CRVO                          | 24              | 14          | ND                     | ND                     | 8.5               | ND          |
| 27               | BRVO                          | 24              | 17          | ND                     | ND                     | 17.8              | ND          |
| 27               | CRVO*                         | 24              | 10          | ND                     | 56.6                   | 10                | ND          |
| 27               | CRVO**                        | 24              | 10          | ND                     | 46.5                   | 3.7               | ND          |
| 29               | BRVO                          | 12              | ND          | ND                     | 53                     | 18.3              | ND          |
| 30               | CRVO                          | 12              | ND          | ND                     | 48.1                   | 13.9              | ND          |

Notes: *Pro re nata monthly follow-up; **Pro re nata as needed.

Abbreviation: ND, None described.

Table 2. Summary of ocular and nonocular adverse events in the main clinical trials.

| References | Total |
|----------------|-------|
| Any intraocular inflammation (iritis, iritis, vitritis) | 2 |
| Endophthalmitis | ND ND |
| Lens damage | ND ND ND ND ND ND ND ND ND ND ND |
| Cataract | ND ND 2 4 3 ND ND ND 8 9 24 |
| Iris neovascularization | ND ND |
| Neovascular glaucoma | ND ND ND ND ND ND ND ND 1 2 |
| Rhegmatogenous retinal detachment | ND ND ND ND ND ND ND ND 1 |
| Retinal tear | ND ND ND ND ND ND ND ND 2 3 |
| Vitreous hemorrhage | ND ND |
| Retinal vein thrombosis | ND ND ND ND ND ND ND ND 1 4 |
| Nonocular serious adverse events-related to VEGF inhibition | ND ND ND ND ND ND ND ND ND ND |

Notes: The line on the top shows the reference corresponding to each clinical trial corresponding to the references listed.

Abbreviation: ND, None described.
the visual outcome may be limited to the associated ischemic damage in such cases.

### Ranibizumab for Macular Edema due to Retinal Vein Occlusion: Summary of Clinical Evidences

The terms “retinal vein occlusion” and “ranibizumab” retrieved 51 publications in Pub Med. However, an electronic search limited to “clinical trials” was performed in order to review those manuscripts offering the first level of evidence for the present review. All available data from the selected articles were extracted and tabulated with respect to each study’s identity, its design (prospective or retrospective, randomized or not randomized), protocol treatment, time of follow-up, baseline and final visual acuity, baseline and final central subfield thickness, mean number of intravitreal injection, number of ocular adverse events, number of systemic adverse events.

Twelve clinical trials focusing in ranibizumab for ME due to RVO have been reported.\(^3\)\(^{20-30}\)

Overall, the clear conclusion of them is that ranibizumab is an effective and safe therapeutic approach. The main results are summarized in Table 1.

In those trials reporting results after 24-month follow-up,\(^3\)\(^{24-27}\) the mean visual acuity improved in +15.3 letters (Table 1). Such an impressive visual outcome is achieved both in fixed monthly injections protocols and also in pro re nata retreatment protocols. However, no comparative study between these two regimens has yet been published.

Initially, after a single injection of ranibizumab, there is a rapid increase in visual acuity parallel to a significant decrease in the retinal thickness as measured by optical coherence tomography. Further retreatments achieve small visual gains after this initial one, but contribute to stabilize the ME and the visual acuity.

The proportion of local or systemic adverse events related to the treatment with ranibizumab varies from 0.009 to 0.11. These data evidences the safety of ranibizumab even in cases with associated cardiovascular systemic risk factors, which is the case of patients with RVO (Table 2).

Although no definite recommendation may be delivered with the actual data available, the classical initial management of waiting at least three months to treat patients with ME due to RVO seems to be clearly obsolete due to the results from these trials.

### Conclusion

Nowadays, ranibizumab is the most efficient and safe therapy in the management of ME secondary to both BRVO and CRVO. The intravitreal injection of 0.5 mg of ranibizumab in these cases leads to a rapid

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### Table 1

| Average change CST | Injections per patient | Ocular adverse event per patient | Ocular adverse event per injection | Systemic adverse event per patient | Systemic adverse event per injection |
|-------------------|------------------------|---------------------------------|----------------------------------|----------------------------------|-------------------------------------|
| 119               | 4.5                    | 0                               | 0                                | 0                                | 0                                   |
| 35                | 2                      | 0                               | 0                                | 0                                | 0                                   |
| 51                | 2                      | 0                               | 0                                | 0                                | 0                                   |
| 186               | 8.5                    | 0                               | 0                                | 0.05                             | 0.006                               |
| 452               | 6                      | 0.09                            | 0.02                             | 0.02                             | 0.004                               |
| 345               | 6                      | 0.05                            | 0.009                            | 0.04                             | 0.006                               |
| 164               | 6.6                    | 0.01                            | 0.007                            | 0.03                             | 0.002                               |
| 304               | 4.3                    | 0.2                             | 0.04                             | ND                               | ND                                  |
| 337.7             | 3.5                    | ND                              | ND                               | ND                               | ND                                  |
| 245.8             | 2                      | ND                              | ND                               | ND                               | ND                                  |
| 304               | ND                     | 0                               | 0                                | 0.1                              | ND                                  |
| 282               | ND                     | 0.07                            | ND                               | 0.05                             | ND                                  |
| 374.4             | ND                     | 0.13                            | ND                               | 0.03                             | ND                                  |
| 472.2             | ND                     |                                 |                                  |                                   |                                     |

Note: *Pro re nata monthly follow-up; **Pro re nata as needed.

Abbreviation: ND, Non described.
decrease of the macular thickness and to significant improvements in visual acuity.

It is important to underline that this review focus on ranibizumab, and the results provided by this treatment must not be extrapolated to bevacizumab. These are two different molecules which share the inhibition of VEGF-A as their main mechanism of action; but bevacizumab has not proven its safety in randomized clinical trials, whereas ranibizumab has evidenced an excellent safety profile in several trials of patients with RVO.

Further studies are warranted in order to provide the guidelines that may enable the retinal physicians to optimize the visual outcomes in cases of ME due to RVO, and to establish retreatment protocols looking for less number of injections and visits to the hospital. Until then, we can clearly state that the standard of care for these patients is the intravitreal injection of ranibizumab.

Author Contributions
Conceived and designed the experiments: RGP, MDL. Analysed the data: RGP, RDM, CML. Wrote the first draft of the manuscript: RGP. Contributed to the writing of the manuscript: RGP, RDM, CML, MDL. Agree with manuscript results and conclusions: RGP, RDM. Jointly developed the structure and arguments for the paper: RGP, RDM. Made critical revisions and approved final version: RGP, RDM, CML, MDL. All authors reviewed and approved of the final manuscript.

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References
1. Hayreh S. Prevalent misconceptions about acute retinal vascular occlusive disorders. Prog Retin Eye Res. 2005;24:493–519.
2. Klein E, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion. Arch Ophthalmol. 2008;126:513–8.
3. Pieramici DJ, Rabena M, Castellari AA, et al. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. Ophthalmology. 2008;115:e47–54.
4. Margolis R, Singh RP, Kaiser PK. Branch retinal vein occlusion: clinical findings, natural history, and management. Compr Ophthalmol Update. 2006;7:265–76.
5. Stefánsson E, Landers MB 3rd, Wolbarsht ML. Increased retinal oxygen supply following pan-retinal photocoagulation and vitrectomy and lensectomy. Trans Am Ophthalmol Soc. 1981;79:307–34.
6. Stefánsson E, Machemer R, de Juan E Jr, McCuen BW 2nd, Peterson J. Retinal oxygenation and laser treatment in patients with diabetic retinopathy. Am J Ophthalmol. 1992;113:36–8.
7. Arnarsson A, Stefánsson E. Laser treatment and the mechanism of edema reduction in branch retinal vein occlusion. Invest Ophthalmol Vis Sci. 2000;41:877–9.
8. Shilling JS, Jones CA. Retinal branch vein occlusion: a study of argon laser photocoagulation in the treatment of macular oedema. Br J Ophthalmol. 1984;68:196–8.
9. The Central Vein Occlusion Study Group M report. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. Ophthalmology. 1995;102:1425–33.
10. The SCORE Study Research Group. 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. Arch Ophthalmol. 2009;127:1101–4.
11. Haller JA, Bandello F, Belfort R Jr, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology: 2011;118:2453–60.
12. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480–4.
13. Noma H, Funatsu H, Yamasaki M, et al. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. Am J Ophthalmol. 2005;140:256–61.
14. Pe’er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. Ophthalmology. 1998;105:412–6.
15. Senger DR, Connolly DT, Van de Water L, Feder J, Dvorak HF. Purification and NH2-terminal amino acid sequence of guinea pig tumor-secreted vascular permeability factor. Cancer Res. 1990;50:1774–8.
16. Czeplech FS, Olieslagers S, van Hulten R, Või SA, Waltonberger J. VEGF-A-induced chemotaxis of CD16+ monocytes is decreased secondary to lower VEGFR-1 expression. Atherosclerosis. 2011;215:331–8.
17. Meyer CH, Holz FG. Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab. Eye (Lond). 2011;25:661–72.
18. Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. *Br J Ophthalmol.*, 2010;94:1215–8.

19. Carneiro AM, Costa R, Falcão MS, et al. Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab. *Acta Ophthalmol.* 2011. doi: 10.1111/j.1755-3768.2011.02240.x.

20. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. *Mol Ther.* 2008;16:791–9.

21. Spaide RF, Chang LK, Klancnik JM, et al. Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. *Am J Ophthalmol.* 2009;147:298–306.

22. Brown DM, Campochiaro PA, Singh RP, et al. CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1124–33.

23. Campochiaro PA, Heier JS, Feiner L, et al. BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117:1102–12.

24. Chang LK, Spaide RF, Klancnik JM, et al. Longer-term outcomes of a prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. *Retina.* 2011;31:821–8.

25. Kinge B, Stordahl PB, Forsaa V, et al. Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study. *Am J Ophthalmol.* 2010;150:310–4.

26. Campochiaro PA, Hafiz G, Channa R, et al. Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: two-year outcomes. *Ophthalmology.* 2010;117(12):2387–94.

27. Risard SM, Pieramici DJ, Rabena MD, et al. Intravitreal ranibizumab for macular edema secondary to central retinal vein occlusion. *Retina.* 2011;31:1060–7.

28. Sacu S, Pemp B, Weigert G, et al. Response of retinal vessels and retrolubar hemodynamics to intravitreal anti-VEGF treatment in eyes with branch retinal vein occlusion. *Invest Ophthalmol Vis Sci.* 2011;52:3046–50.

29. Brown DM, Campochiaro PA, Bhistikul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology.* 2011;118:1594–602.

30. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology.* 2011;118:2041–9.