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Effectiveness of ranibizumab intravitreal injections in visual impairment due to macular edema secondary to retinal vein occlusion from the French BOREAL cohorts

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Abstract

Background: The French Health Technology Assessment agency requested information on the ranibizumab (RBZ) usage and impact in real-world setting.
Objectives: To assess the effectiveness and patterns of use of RBZ intravitreal injections (IVI) for patients with visual impairment due to macular edema secondary to branch (B) or central (C) retinal vein occlusion (ME-RVO) for up to 24-month follow-up.
Methods: This is a real-world, post-authorization, observational cohort study in adult patients with RBZ intravitreal injections initiation for best-corrected visual acuity (BVCA) loss due to ME-RVO, followed-up for up to 24 months by their ophthalmologist. The primary endpoint was BCVA evolution from baseline to Month 6.
Results: Between December 2013 and April 2015, for B/C cohorts, 223 / 196 patients were enrolled, and 207 / 180 (92.8 / 91.8%) completed the 6-month follow-up. Patient characteristics were: mean (SD) age of 70.3 (11.1) / 70.5 (14.4) years, 47.8 / 50.6% of men, first symptoms onset 4.4 (12.6) / 3.0 (6.0) months, 9.2 / 8.3% previously treated (4.8 / 0.0% macular laser, 6.3 / 7.8% intravitreal corticosteroids; 1.0 / 1.1% other anti-VEGF), 3.9 / 2.8 % with bilateral ME-RVO, mean baseline BCVA of 54.7 (18.9) / 40.5 (25.7) letters, 13.5 / 8.3% with a BCVA > 70 letters, mean central subfield thickness (CSFT) of 558 (178) / 649 (216) µm. During the first three months, 80.7 / 76.1% of patients received the 3 recommended ranibizumab IVI. At 3 ± 1 months, the BCVA mean [95%CI] change from baseline was 14.7 [12.4 to 17.1] / 16.0 [12.1 to 19.8] letters and the CSFT mean change was -240 [-269 to -211] / -323 [-371 to -275] µm. At the end of 6 months of follow-up, the mean number of IVI was 3.8 (1.2) / 3.6 (1.2) with 59.4 / 56.1% patients who had at least one interruption of RBZ IVI, 52.7 / 38.3% for improvement of the pathology and 7.2 / 15.6% for lack of efficiency. After 6 ± 1.5 months of follow-up, the BCVA mean change from baseline was 13.9 [11.5 to 16.3] / 9.5 [5.5 to 13.5] letters, with 43.5 / 30.6% of patients having a BCVA > 70 letters. The CSFT mean change was -223 [-254 to -192] / -264 [-311 to -217] µm.
Conclusions: This study showed a effectiveness of RBZ in daily practice close to the results of the preregistration randomized clinical trial at 3 months, but the effectiveness is limited at 6 months probably due to the fewer number of IVI.

Background

- **Macular edema (ME)** is a complication of **retinal vein occlusion (RVO)** and the most common cause of RVO-associated vision loss. The different RVO forms are related to occlusion location:
  - ✓ Branch retinal vein occlusion (BRVO),
  - ✓ Central retinal vein occlusion (CRVO),
  - ✓ Hemiretinal vein occlusion (HRVO).
- **Ranibizumab** (Lucentis®) is an **anti-VEGF** administered by intravitreal injections (IVI). Ranibizumab had an extent of market authorization for the treatment of visual impairment due to ME secondary to RVO in France in january 2012. At that time, the French Health Technology Assessment agency requested complementary data on the impact of ranibizumab on the change in visual activity.
- The BOREAL ME-BRVO (BRVO) and ME-CRVO (CRVO) cohorts answer to this request.

Conflict of Interest Statement

The study was performed at the request of the HAS, the French Health Technology Assessment agency and funded by Novartis.

Objectives

- **Main objective:** To assess the change in visual activity at Month 6.
- **Secondary objectives:** during the follow-up,
  - ✓ To assess the change in visual activity,
  - ✓ To assess the change in central subfield thickness,
  - ✓ To describe patterns of ranibizumab use.

Methods

- **Design:** This is a real-world, post-authorization, observational cohort study in adult patients with ranibizumab IVI initiation for best-corrected visual acuity (BVCA) loss due to ME-RVO, followed-up for up to 24 months by their ophthalmologist.
- **Data sources:** data collection from patient medical files at inclusion (general characteristics, history of ME-RVO, previous treatments, ophthalmological workup) and at 3, 6, 9, 12, 18 and 24 months (ophthalmological workup, ME-RVO treatments and follow-up modalities).
- **Endpoints:**
  - ✓ Primary endpoint: BVCA evolution from baseline to Month 6 (320 patients expected for each pathology, in order to have a precision of ± 2 letters),
  - ✓ Secondary endpoints: BVCA evolution, central subfield thickness evolution, description of ME-RVO treatments modalities, and ophthalmological workup during the follow-up.
- **This presentation details** results of BRVO cohort and CRVO cohort with **6 months of follow-up.** Patients with OVHR were included in BRVO cohort.

Results

- **Study populations**

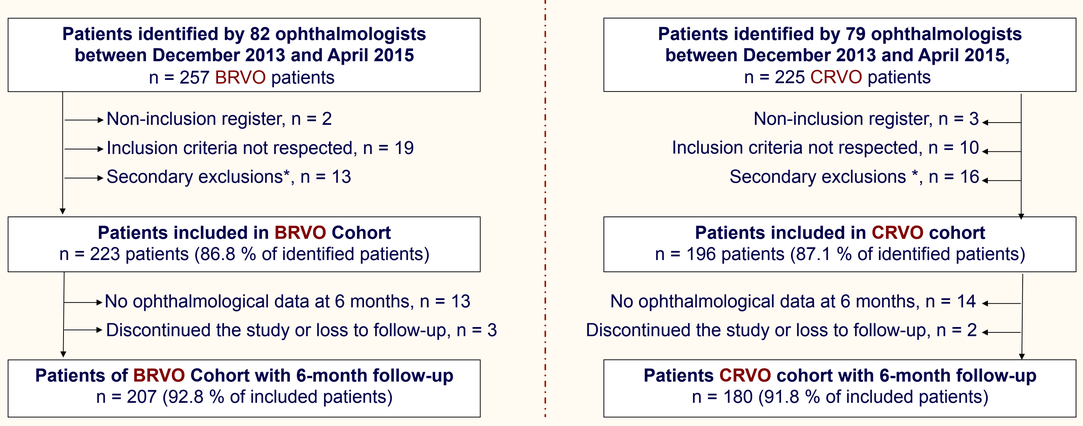

Figure 1 : Flowchart of study populations in BRVO and CRVO Cohorts.
** On Scientific Committee decision: ranibizumab IVI not performed at baseline or not performed within 45 days of study initiation, lack of BVCA measurement at baseline.*

- **Baseline characteristics of patients at inclusion**

Table 1. Patients characteristics at inclusion

	BRVO n = 207	CRVO n = 180
Male, n (%)	99 (47.8)	91 (50.6)
Mean age, year (± standard-deviation)	70.3 (11.1)	70.5 (14.4)
Bilateral RVO, n (%)	8 (3.9)	5 (2.8)
At least one ophthalmic comorbidity, n (%)	114 (55.1)	112 (62.2)
Unoperated cataract	52 (25.1)	51 (28.3)
Pseudophakia	40 (19.3)	35 (19.4)
Glaucoma and ocular hypertension	41 (19.8)	41 (22.8)
Mean duration since first symptoms, month (± standard-deviation)	4.4 (12.6)	3.0 (6.0)
At least one previous ocular treatment received, n (%)	19 (9.2)	15 (8.3)
Macular laser	10 (4.8)	0 (0.0)
Intravitreal corticosteroids	13 (6.3)	14 (7.8)
Other Anti-VEGF	2 (1.0)	2 (1.2)
At least one previous systemic treatment received, n (%)	6 (2.9)	5 (2.8)
Platelet anti-aggregant	6 (2.9)	3 (1.6)
Rheology corrector	1 (0.5)	2 (1.1)
Hemodilution	0 (0.0)	1 (0.5)
Mean BVCA, in ETDRS letter (± standard-deviation)	54.7 (18.9)	40.5 (25.7)
BVCA > 70 letters, n (%)	28 (13.5)	15 (8.3)
Mean central subfield thickness, in µm (± standard-deviation)	558 (178)	649 (216)

- **BVCA evolution**

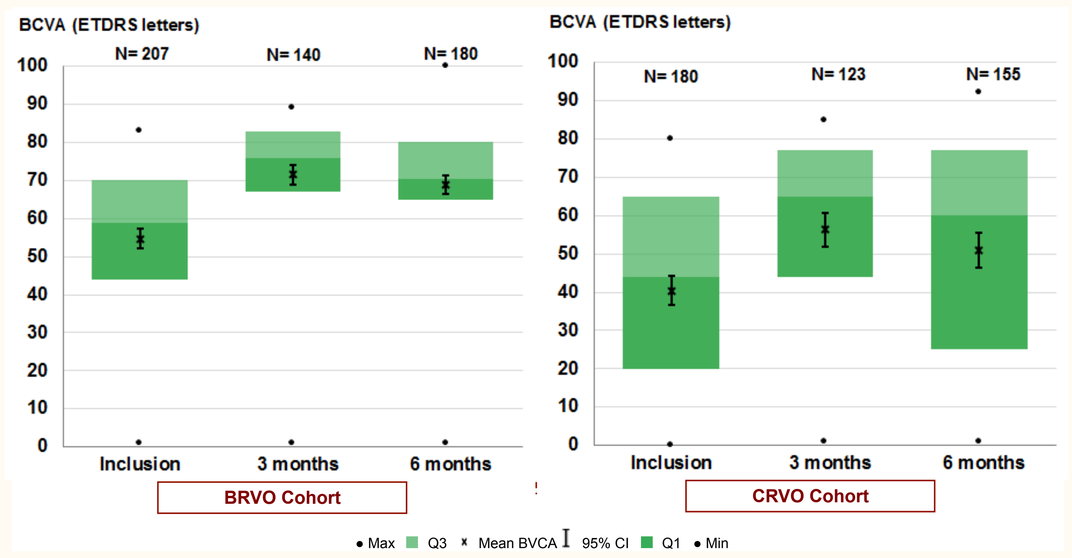

Figure 2 : Evolution of mean BVCA during the follow-up (ETDRS letters) in BRVO Cohort and CRVO Cohort.

- ✓ Overall improvement in BVCA was observed over time with high variability in patients (Figure 2).
- ✓ In BRVO cohort, the mean BVCA change from baseline was:
  - + 14.7 (± 14.0) letters ([95% CI]: [12.4; 17.1]) at 3-month follow-up (± 0.5),
  - + 13.9 (± 16.4) letters ([95% CI]: [11.5; 16.3]) at 6-month follow-up (± 1.5).
- ✓ In CRVO cohort, the mean BVCA change from baseline was:
  - + 16.0 (± 21.4) letters ([95% CI]: [12.1; 19.8]) at 3-month follow-up (± 0.5),
  - + 9.5 (± 25.3) letters ([95% CI]: [5.5; 3.5]) at 6-month follow-up (± 1.5).
- ✓ At 6-month follow-up, 43.5% of BRVO Cohort patients and 30.6% of CRVO Cohort patients had BVCA above 70 letters (Figure 3).

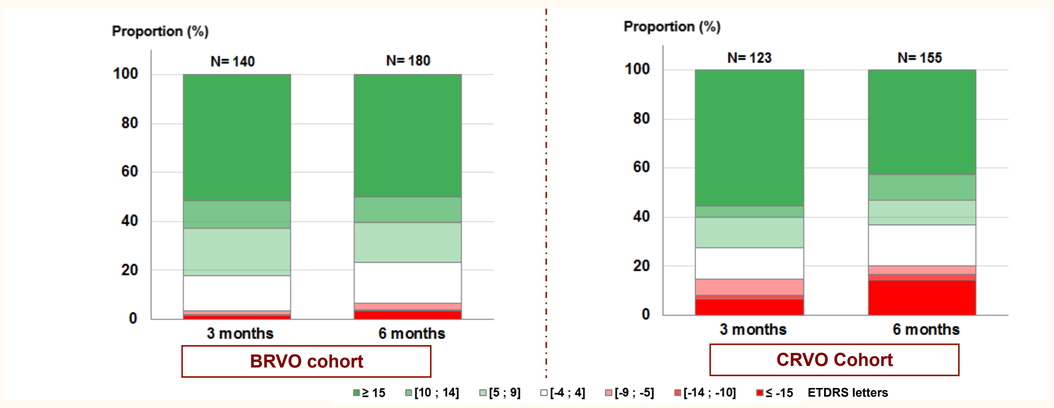

Figure 3 : Evolution of proportion of patients with BVCA gains or losses in EDTRS letters from baseline during the follow-up in BRVO Cohort and CRVO Cohort.

- **Central subfield thickness evolution**

Table 2. Mean central subfield thickness (CSFT) evolution during the 6-month follow-up

	BRVO n = 207	CRVO n = 180
At 3-month (± 0.5) follow-up, n	137	113
Mean CSFT variation [95% CI]	- 240 [-269 to -211]	- 323 [-371 to -275]
At 6-month (± 1.5) follow-up, n	170	129
Mean CSFT variation [95% CI]	- 223 [-254 to -192]	- 264 [-311 to -217]

- **Treatments modalities**
  - ✓ During the first 3 months of follow-up, nearly 80% of patients (BRVO: 80.7%, CRVO: 76.1%) received the initial three recommended ranibizumab injections (induction IVI).
  - ✓ At the end of 6-month follow-up, the mean number of IVI was 3.8 (±1.2) in BRVO Cohort and 3.6 (±1.2) for studied eye in CRVO Cohort.
  - ✓ More than half of patients (BRVO: 59.4%, CRVO: 56.1%) had at least one interruption of ranibizumab IVI:
    - For pathology improvement (BRVO 52.7%, CRVO: 38.3%),
    - For lack of efficiency (BRVO: 7.2%, CRVO: 15.6 %).

Conclusion

This real-world study of patients with ranibizumab IVI treatment initiation in ME-RVO **showed an improvement of visual acuity at 3-month follow-up close to the results of the preregistration randomized clinical trial** (BRVO: 14.7 letters *vs* BRAVO ≈ 15 letters, CRVO: 16.0 letters *vs* CRUISE ≈ 12.5 letters) **and a little more limited at 6-month follow-up** (BRVO: 13.9 letters *vs* BRAVO: 18.3 letters, CRVO: 9.5 letters *vs* CRUISE : 14.9 letters) **with a fewer frequency of ranibizumab IVI in real-world** (BRVO: 3.8 and CRVO: 3.6 in BOREAL *vs* 6 in BRAVO/CRUISE).