Functional and Anatomical Outcomes in Patients With Serous Retinal Detachment in Diabetic Macular Edema Treated With Ranibizumab

Audrey Giocanti-Aurégan,[1,2] Linda Hrarat,[1,2] Lise M. Qu,[1,2] Valérie Sarda,[1,2] Marouane Boubaya,[3] Vincent Levy,[3] Gilles Chaine,[1,2] and Franck Fajnkuchen[1,2,4]

[1]Department of Ophthalmology, Hôpital Avicenne, Bobigny, France
[2]Départment Hospitalo-Universitaire (DHU) Vision et Handicap, Department of Ophthalmology, Hôpital Pitié-Salpêtrière, Paris, France
[3]Clinical Research Unit, Paris Seine Saint Denis University Hospitals, Bobigny, France
[4]Centre Ophtalmologique d'Imagerie et de Laser, Paris, France

Correspondence: Audrey Giocanti-Aurégan, Department of Ophthalmology, Hôpital Avicenne, 125 rue de Stalingrad, Bobigny 93000, France;
audrey.giocanti@aphp.fr.

Submitted: October 2, 2016
Accepted: December 26, 2016

Citation: Giocanti-Aurégan A, Hrarat L, Qu LM, et al. Functional and anatomical outcomes in patients with serous retinal detachment in diabetic macular edema treated with ranibizumab. *Invest Ophthalmol Vis Sci*. 2017;58:797–800. DOI:10.1167/iovs.16-20855

Purpose. To assess the effect of serous retinal detachment (SRD) on functional and anatomical outcomes in ranibizumab-treated patients with diabetic macular edema (DME).

Methods. All consecutive ranibizumab-treated patients with SRD were included in this retrospective study. For each patient with SRD, a patient without SRD with the same baseline best-corrected visual acuity (BCVA) was randomly included for adjustment on their baseline BCVA. All patients with SRD were included in group 1 (G1) and those without SRD in G2. The primary endpoint was the mean change in BCVA between baseline and month 12 (M12). Secondary endpoints were the mean change in central retinal thickness (CRT) between baseline and M12, injection number, and proportion of patients who gained/lost ≥15 letters.

Results. Seventy-eight eyes were included, 39 in each group. Baseline BCVA was similar in both groups (45.2 and 45.3 letters). Mean change in BCVA between baseline and M12 was not statistically different: 11 ± 12 letters in G1 and 12 ± 13 letters in G2 ($P = 0.78$). Baseline CRT was 650 ± 130 μm in G1 and 480 ± 79 μm in G2. Mean change in CRT was −235 ± 170 μm in G1 and −130 ± 96 μm in G2 ($P = 0.013$). Patients received 5.2 and 5.5 injections in G1 and G2 ($P = 0.46$). In group 1, 38.5% and 2.6% of patients respectively gained and lost ≥15 letters versus 41% ($P = 0.1$) and 5.1% ($P = 0.1$) in G2.

Conclusions. Similar BCVA gains were observed regardless of the presence of SRD. The higher visual gain usually observed in DME with SRD could be associated with a lower baseline BCVA.

Keywords: diabetic macular edema, ranibizumab, serous retinal detachment

Diabetic macular edema (DME) is the leading cause of blindness in diabetic patients in developed countries.[1,2] In diabetes mellitus, DME has been reported in 4.8% to 6.8% of patients.[3,4]

Serous retinal detachment (SRD) is very common in DME.[5,6] In recent studies, SRD has been reported in 13% to 45% of cases.[6–9] In recent years, intravitreal injections of anti-VEGF have become the first-line therapy for central DME with impaired visual acuity (VA).[10–12] Previous studies have described the natural course,[13] pathogenesis, and visual outcome of SRD associated with DME. However, among the patients treated with ranibizumab for DME, the effect of SRD remains unclear.

We have previously found[9] that SRD was associated with a higher gain of VA 6 months after treatment with ranibizumab. However, in eyes with DME and SRD, the baseline BCVA was significantly lower.

The aim of this study was to determine whether the higher VA gain after DME treatment in the presence of SRD was due to the SRD itself or was a consequence of the lower baseline VA.

Methods

All diabetic patients treated for DME in our department from November 2013 to November 2014 were retrospectively included. An informed consent was obtained from all patients.

Inclusion criteria were age >18 years, type 1 or 2 diabetes with HbA1C <12%, central retinal thickness (CRT) ≥300 μm on the optical coherence tomography (OCT) B-Scan images, best-corrected VA (BCVA) score ≤70 letters based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and patients who had received at least the loading dose of 3 monthly injections. Patients with a history of pan retinal photocoagulation and/or focal/grid laser photocoagulation were eligible. When both eyes of a patient had DME, only the right eye was included.

Exclusion criteria were proliferative diabetic retinopathy, intravitreal hemorrhage or diabetic tractional retinal detachment, ischemic maculopathy, previous intravitreal steroids or bevacizumab injections during the last 6 months, thromboembolic arterial event during the last 3 months, pregnancy, intraocular pressure (IOP) >24 mm Hg on medication, uveitis

Table. Patient Baseline Characteristics

78 Eyes/78 Patients	SRD+ ($n = 39$)	SRD− ($n = 39$)	*P* Value
Age in y, mean (range)	63.3 (31–85)	66.8 (44–82)	0.07
Sex, % men (*n*)	48.7 (19)	61.5 (24)	0.13
Type 2 diabetes, % (*n*)	94.9 (38)	100 (39)	0.08
DR stage (%)			
Mild NPDR, % (*n*)	5.13 (2)	10.26 (4)	0.23
Moderate NPDR, % (*n*)	10.26 (4)	20.5 (8)	0.10
Severe NPDR, % (*n*)	25.64 (10)	7.7 (3)	0.06
PRP, % (*n*)	58.97 (23)	61.54 (24)	0.23
Focal laser history, % (*n*)	41 (16)	64.10 (41)	0.04
DME duration, mean in mo (range)	12.56 (1–72)	29.6 (1–144)	0.001

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PRP, panretinal photocoagulation.

or other vitreoretinal pathology, or other condition that could contribute to the visual decrease.

All patients underwent a complete ophthalmologic examination including BCVA, slit-lamp, and noncontact fundus examination (Superfield; Volk, Mentor, OH, USA). Fluorescein angiography (FA; Topcon TRC-50DX Retinal Camera, Topcon Medical Systems, Inc., Tokyo, Japan) and OCT (OPKO OCT/SLO, OPKO Health, Inc., OTI, Miami, FL, USA) were performed at baseline. DME was defined by a CRT $\geq$300 μm and the absence of foveal pit. Baseline FA was performed to rule out ischemic maculopathy.

The presence of an SRD was confirmed by OCT by the presence of subretinal fluid between the retina and the retinal pigment epithelium.

Patients were divided into two groups: DME with SRD (SRD+ group) and DME without SRD (SRD− group). Patients were adjusted on their baseline BCVA: for each DME patient with SRD, a DME patient without SRD with the same baseline BCVA was randomly included.

All patients received a loading dose of 3 monthly injections of ranibizumab, followed by retreatments with an as-needed basis (PRN regimen). For this pro re nata (RPN) regimen, we performed monthly injections until VA stability was achieved for a period of at least two consecutive visits or until normal VA was achieved. When the stability was reached, treatment with ranibizumab was interrupted. If VA deteriorated (greater than five letters), monthly injections were reinitiated until stability was again achieved.[14]

Patients were examined every 4 weeks. At each visit, the BCVA was assessed using the ETDRS chart, and fundus photography and spectral-domain optical coherence tomography were performed.

The efficacy of the treatment was based on functional and anatomical responses to ranibizumab.

The primary endpoint was the difference in mean BCVA change between the SRD+ and SRD− groups from baseline to month 12 (M12).

Secondary endpoints were the difference in mean CRT change between the SRD+ and SRD− groups from baseline to M12, number of intravitreal injections, and proportion of patients who gained or lost $\geq$15 letters.

Statistical analyses were performed using a *t*-test for numerical values and a χ^2 test for percentages. A *P* value $<$ 0.05 was considered statistically significant. All tests were two-sided at a 0.05 significance level. Analyses were carried out using R statistical software version 2.15.2.

Results

Seventy-eight eyes of 78 patients were included: 39 eyes in the SRD+ group and 39 eyes in the SRD− group. Patient characteristics are presented in the Table.

Functional Outcomes

Baseline BCVA was similar in both groups since this parameter was adjusted: 45.2 letters in the SRD+ group and 45.3 letters in the SRD− group. The mean change in BCVA score from baseline to M12 was +11 letters in the SRD+ group versus +12 letters in the SRD− group ($P = 0.8$; Fig. 1).

Anatomical Outcomes

The mean baseline CRT was 625 ± 130 μm in the SRD+ group versus 480 ± 79 μm in the SDR− group ($P = 0.00001$). The mean CRT change from baseline to M12 was significantly decreased in the SRD+ group (−234 μm) compared to the

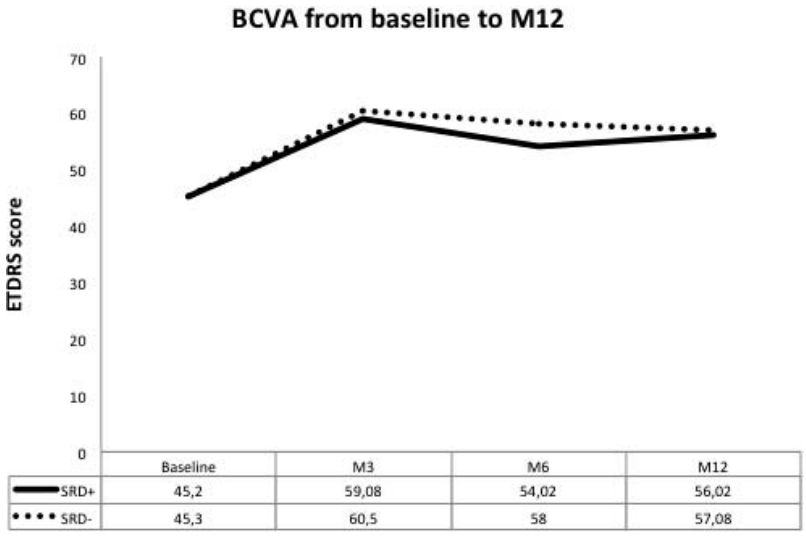

Figure 1. Mean change in BCVA letter score from baseline to M12 (primary endpoint). Bars correspond to SE = standard error, and * corresponds to $P < 0.05$.

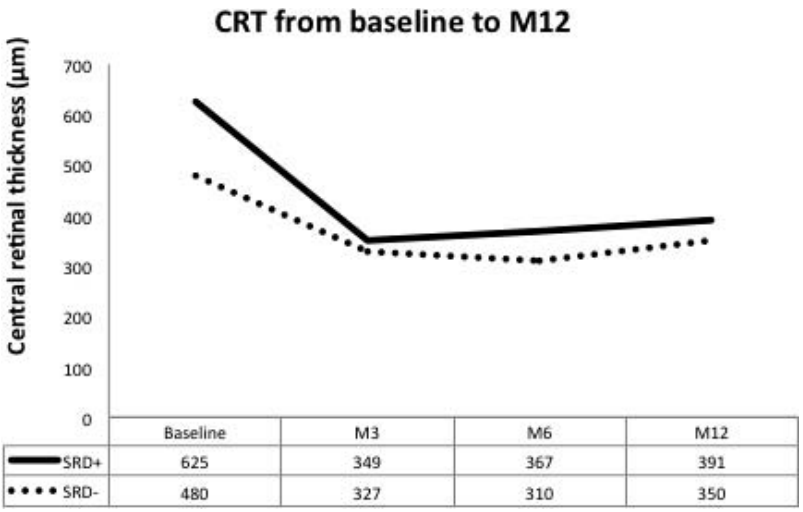

FIGURE 2. Mean change in CRT from baseline to M12 (secondary endpoint). Bars correspond to SE = standard error, and * corresponds to $P < 0.05$.

SRD– group (–130 µm; $P = 0.003$; Fig. 2). The mean CRT at M12 was 391 µm in the SRD+ group versus 350 µm in the SRD– group. At M12, the SRD was not resolved in 25.6% of patients in the SRD+ group.

Number of Ranibizumab Intravitreal Injections

The mean number of ranibizumab injections was similar in both groups: 5.8 in the SRD+ group (range, 3–6) and 5.5 in the SRD– group (range, 3–6) over the first year.

Responder Profiles at M12

The proportion of patients who gained more than 15 letters at M12 was 38.5% ($n = 16$) in the SRD+ group versus 41% ($n = 15$) in the SRD– group ($P = 0.99$). The proportion of patients whose BCVA was >70 letters was 25.64% ($n = 16$) in the SRD+ group versus 41% ($n = 10$) in the SRD– group ($P = 0.75$). The proportion of patients whose CRT was <300 µm at M12 was 33.33% ($n = 13$) in the SRD+ group versus 48.7% ($n = 19$) in the SRD– group ($P = 0.75$). The range of CRT was 170 to 650 µm at 12 months in the SRD+ group and 178 to 646 µm in the SRD– group.

DISCUSSION

Serous retinal detachment is common in DME[5–7] with an incidence of 13% to 45%.[6–8] The presence of SRD has recently been identified as a factor associated with a better prognosis in case of DME treated with monthly ranibizumab.[15] In the present study, we investigated the effect of SRD in DME during ranibizumab treatment with a PRN regimen, on the VA gain at 12 months in a real-life setting and failed to show an association between the presence of SRD and the 1-year visual outcome.

In the literature, a few papers have studied the effect of SRD on DME.[13,16–19] Before anti-VEGFs were indicated for the treatment of DME, Gaucher et al.[13] in 2008 have found that SRD height did not correlate with the VA or retinal thickness in case of DME. Nowadays, there is no clear conclusion about the prognostic value of SRD associated with DME. Shukla et al.[20] have considered SRD as a good predictor of DME resolution on triamcinolone, whereas Shimura et al.[16] in 2011 have not found such an association. Since the introduction of anti-VEGFs for the treatment of DME, some authors have attempted to identify predictive factors for visual outcome based on the different OCT patterns in DME after intravitreal injection of bevacizumab (IVB).[18,21,22] Shimura et al.[21] in 2013 and Kim et al.[22] in 2011 have shown that intravitreal bevacizumab was more effective on the diffuse retinal thickening type than on the cystoid macular edema or SRD type of DME. In contrast, Koytak et al.[18] in 2013 have shown that the SRD type was associated with a greater reduction in central foveal thickness than the diffuse retinal thickening type.

The presence of subretinal fluid during DME treatment with ranibizumab has already been investigated in a post hoc analysis of the RISE and RIDE studies, showing that patients with baseline SRD are more likely to achieve a BCVA >20/40 after 2 years of follow-up on monthly ranibizumab 0.3- or 0.5-mg injections.[15] In a previous study,[9] we have also found that SRD was associated with a higher gain of VA after 6 months of treatment. In this previous study, the visual gain was +21 letters in the SRD+ group versus +7.8 letters in the SRD– group ($P = 0.004$), after the same number of injections. However, the baseline BCVA was significantly different: 39 letters in the SRD+ group versus 52 letters in the SRD– group. The lower baseline BCVA could have, in this study, artificially improved the final visual gain as previously shown by Dugel et al.[23] In the present study, after adjusting the baseline BCVA between both groups, we did not find any difference in VA gain between SRD+ and SRD– patients treated for DME. Taken together, all these findings suggest that SRD is not associated with a higher VA gain but rather with a lower baseline VA that is known in the literature as a negative predictive factor for final VA.[23] Moreover in our series, patients without SRD tended more frequently to achieve a threshold VA of 20/40 at the end of the follow-up than patients with baseline SRD. This result does not support those of the RISE and RIDE subanalysis that has shown a higher proportion of patients with a VA over 20/40 in cases with baseline SRD with odds ratio of 2.88 after 2 years of follow-up on monthly ranibizumab. Furthermore, in our series, patients without SRD also tended to have more often a flat retina at 1 year (<300 µm) despite a longer DME duration before treatment. We could thus assume that SRD associated with DME could be a sign of DME severity, supporting early DME treatment before patients experience a severe vision loss, potentially associated with an increased need for intravitreal injections like in the RISE and RIDE studies to achieve a good visual outcome.

In terms of anatomical features, the mean baseline CRT was significantly higher in the SDR+ group than in the SRD– group

(625 ± 130 μm versus 480 ± 79 μm, $P = 0.00001$). However, after three injections and at the end of the follow-up, the mean CRT was not statistically different between both groups (391 μm versus 350 μm, respectively, $P = 0.15$). Moreover, the percentage of patients with a CRT <300 μm and showing a resolution of the foveal pit was significantly higher in the SDR− group than in the SRD+ group. This supports the fact that patients in the SRD+ group could have required more intravitreal injections, but at the time when patients were treated, the retreatment indications were only based on the VA and not on the presence of fluid.

Further prospective randomized studies on larger patient cohorts are needed to confirm these results since the main limitations of our study are its retrospective design and small sample size.

In conclusion, SRD does not seem to be a good prognostic factor during DME treatment with ranibizumab with a PRN regimen and in a real-life setting. We failed to find better visual outcomes in cases of SRD unlike what has been observed in a post hoc analysis of a large cohort of patients on monthly treatment. We could assume that the previously identified good prognosis associated with SRD could be due to the high frequency of injections, and that we failed to find the same results because patients were injected with a PRN regimen. To achieve the good visual outcomes found in RISE and RIDE in our patients with SRD, we could assume that a more aggressive treatment would have been needed.

Acknowledgments

Presented as a paper at the French Society of Ophthalmology, Paris, May 2015, and Euretina Annual Meeting, Copenhagen, September 2016.

Supported in part by AVOPH, Association for Research and Education, Avicenne Hospital, Bobigny, France.

Disclosure: **A. Giocanti-Aurégan**, Novartis (C), Bayer (C), Allergan (C); **L. Hrarat**, None; **L.M. Qu**, None; **V. Sarda**, None; **M. Boubaya**, None; **V. Levy**, None; **G. Chaine**, None; **F. Fajnkuchen**, Novartis (C), Bayer (C), Allergan (C)

References

1. Romero-Aroca P. Managing diabetic macular edema: the leading cause of diabetes blindness. *World J Diabetes*. 2011; 2:98–104.
2. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102: 7–16.
3. Delcourt C, Massin P, Rosilio M. Epidemiology of diabetic retinopathy: expected vs reported prevalence of cases in the French population. *Diabetes Metab*. 2009;35:431–438.
4. Yau JWY, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556–564.
5. Koleva-Georgieva D, Sivkova N. Assessment of serous macular detachment in eyes with diabetic macular edema by use of spectral-domain optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:1461–1469.
6. Ozdemir H, Karacorlu M, Karacorlu S. Serous macular detachment in diabetic cystoid macular oedema. *Acta Ophthalmol Scand*. 2005;83:63–66.
7. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. *Am J Ophthalmol*. 1999;127:688–693.
8. Shereef H, Comyn O, Sivaprasad S, et al. Differences in the topographic profiles of retinal thickening in eyes with and without serous macular detachment associated with diabetic macular oedema. *Br J Ophthalmol*. 2014;98:182–187.
9. Qu-Knafo LM, Fajnkuchen F, Sarda V, et al. Impact of serous retinal detachment on the efficacy of ranibizumab in diabetic macular oedema [published online ahead of print January 29, 2016]. *Acta Ophthalmol*. doi:10.1111/aos.12973.
10. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013–2022.
11. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118:615–625.
12. Elman MJ, Aiello LP, Beck RW, et al.; for the Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064–1077.e35.
13. Gaucher D, Sebah C, Erginay A, et al. Optical coherence tomography features during the evolution of serous retinal detachment in patients with diabetic macular edema. *Am J Ophthalmol*. 2008;145:289–296.
14. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye Lond Engl*. 2012;26:485–493.
15. Sophie R, Lu N, Campochiaro PA. Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. *Ophthalmology*. 2015;122:1395–1401.
16. Shimura M, Yasuda K, Nakazawa T, et al. Visual outcome after intravitreal triamcinolone acetonide depends on optical coherence tomographic patterns in patients with diffuse diabetic macular edema. *Retina Phila Pa*. 2011;31:748–754.
17. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. *Am J Ophthalmol*. 2006; 142:405–412.
18. Koytak A, Altinisik M, Sogutlu Sari E, Artunay O, Umurhan Akkan JC, Tuncer K. Effect of a single intravitreal bevacizumab injection on different optical coherence tomographic patterns of diabetic macular oedema. *Eye Lond Engl*. 2013;27: 716–721.
19. Shukla D. Re: Sophie et al.: Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab (*Ophthalmology*. 2015;122:1395–401). *Ophthalmology*. 2016;123:e11–e12.
20. Shukla D, Behera UC, Chakraborty S, Mahalakshmi R, Prasad NM. Serous macular detachment as a predictor of resolution of macular edema with intravitreal triamcinolone injection. *Ophthalmic Surg Lasers Imaging*. 2009;40:115–119.
21. Shimura M, Yasuda K, Yasuda M, Nakazawa T. Visual outcome after intravitreal bevacizumab depends on the optical coherence tomographic patterns of patients with diffuse diabetic macular edema. *Retina Phila Pa*. 2013;33:740–747.
22. Kim M, Lee P, Kim Y, Yu S-Y, Kwak H-W. Effect of intravitreal bevacizumab based on optical coherence tomography patterns of diabetic macular edema. *Ophthalmologica*. 2011; 226:138–144.
23. Dugel PU, Hillenkamp J, Sivaprasad S, et al. Baseline visual acuity strongly predicts visual acuity gain in patients with diabetic macular edema following anti-vascular endothelial growth factor treatment across trials. *Clin Ophthalmol Auckl NZ*. 2016;10:1103–1110.