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ORIGINAL ARTICLE

Impact of ranibizumab on visual impairment in patients with bilateral diabetic macular edema

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Abstract

Aims Diabetic macular edema (DME) frequently presents bilaterally. In case of bilateral retinal disease, the visual impairment (VI) and the visual acuity (VA) are strongly correlated to the better eye. The aim of this study was to assess the impact of ranibizumab intravitreal injections (IVR) on VI in patients with simultaneous VA loss due to DME.

Methods This was a retrospective two-center study including consecutive DME patients with visual loss treated with ranibizumab since November 2011 and with a minimum follow-up of 6 months. Patients with bilateral visual decrease from DME undergoing IVR within 6 months of each other were included.

Results Twenty-nine DME patients who received bilateral IVR within a 6-month interval in the second eye were included. At baseline, 82.8% ($n=24$) of patients had a VA < 20/40 in their better eye versus 44.8% ($n=13$) of patients at the end of follow-up, i.e. a reduction by 45.9% of VI. In the better eye, the mean VA was 57.3, 65.0 and 65.5 ETDRS letters, respectively, at baseline, month 3 and month 6 (mean VA gain +8.2 letters). In the worse eye, the mean VA was 44.2, 53.5 and 53.8 ETDRS letters, respectively, at baseline, M3 and M6 (mean VA gain +9.6 letters).

Conclusions In patients with bilateral DME, subsequent ranibizumab IVR reduced VI frequency.

Keywords Bilateral diabetic macular edema · Anti-VEGF · Disability · Visual impairment

Introduction

Diabetes is the leading cause of visual impairment [1] in active patients. This impairment mainly results from a macular edema. Moreover, this condition frequently presents bilaterally and may lead to disability. During the last decade, anti-VEGF treatments have become the first-line therapy for this disease [2]. To date, previous treatment, i.e. laser photocoagulation, allowed stabilizing visual acuity (VA) but did not improve visual outcomes [3]. Phase III studies assessing anti-VEGF have shown a significant VA gain [4–6], and anti-VEGF contributes to decrease the frequency of visual impairment (VI). In "real-world" studies, ranibizumab allows achieving a visual gain between 4.4 and 10.7 letters after 1 year of intravitreal injections [7–9].

Previous studies have assessed the impact of VI on participation in daily activities in diabetic patients. Lamoureux et al. [10] have reported major restrictions for the Leasure and Work, Mobility, and Consumer and Social Interaction domains. Previous "real-world" studies have already assessed the use of ranibizumab in diabetic macular edema (DME) patients. However, to our knowledge, no published "real-world" study has assessed the effect of anti-VEGF on the prevalence of visual disability in diabetic patients with bilateral involvement. Only the PRIDE study [6] has shown that the percentage of improved/maintained VA is similar in patients with unilateral or bilateral DME. As diabetes often

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affects both eyes and younger patients, it is valuable to assess whether an anti-VEGF intervention is associated with a trend towards reduced impairment in DME. The aim of this study was to assess whether ranibizumab intravitreal injections (IVR) could reduce the frequency of VI.

Methods

A retrospective study was conducted at two centers specialized in retinal disease imaging and treatment (Avicenne hospital, Bobigny and centre d'imagerie et de Laser, Paris). All patients diagnosed with DME due to Type 2 diabetes, and treated with ranibizumab with a minimum follow-up of 6 months were included between November 2011 and October 2015.

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and an informed consent was obtained from all patients. Approval was obtained from the France Macula Federation ethics committee.

Inclusion criteria were: (1) patients with DME-induced simultaneous bilateral VA decrease. (2) Intravitreal treatment-naive patients. (3) Simultaneous VA decrease, defined as a visual loss that required IVR with less than 6-month interval between the treatment of the right and left eyes. (4) Bilateral VI. There are two main definitions of VI: according to the World Health Organization (WHO) [11, 12], VI occurs with a VA less than 6/18 in the better eye while according to the United States criteria, VI is defined as a VA less than or equal to 20/40 in the better eye [13]. (5) Central retinal thickness ≥ 300 µm.

Exclusion criteria (1) Intravitreal hemorrhage or diabetic tractional retinal detachment. (2) Ischemic maculopathy, assessed by a blinded grader (GC). (3) Previous intravitreal steroids or anti-VEGF injections or prior retinal surgery. (4) Cardiovascular event < 3 months before. (5) Pregnancy. (6) Uncontrolled glaucoma (intraocular pressure > 24 mmHg on medication or neovascular glaucoma). (7) Uveitis, cataract, refractive errors or other vitreoretinal disease, or other conditions that could contribute to the visual loss.

All patients underwent a complete bilateral ophthalmological examination including: best-corrected visual acuity (BCVA) based on the ETDRS chart (to compare our results to theses definitions, we converted ETDRS BCVA into Snellen BCVA), slit-lamp and non-contact fundus examination (Superfield, Volk, Ohio, USA). Fluorescein angiography (FA) (Topcon TRC-50DX Retinal Camera, Topcon Medical Systems, Inc, Japan) and OCT (Cirrus 5000, Zeiss Meditec, Jena, Germany) were performed at baseline. DME was defined as a central retinal thickness (CRT) ≥ 300 µm. FA was performed at baseline to rule out ischemic maculopathy. In case of VA < 20/40, IVR was initiated. All patients received a loading dose of three monthly IVR, followed by re-treatments on an as-needed basis (PRN regimen) until no further improvement in VA and a reduction in macular edema were observed. This treatment protocol was in accordance with the "real-world" practice at the time of this study based on the phase III RESTORE study [14]. Retreatment decision was based on two criteria: VA (decrease > 5 ETDRS letters) and/or a CRT > 300 µm. Patients were examined every 4 weeks for 6 months. At each visit, the BCVA was measured, fundus photography and SD-OCT were performed (CRT is presented as mean ± SD) and the need for IVR was assessed. The VA and OCT were monthly assessed bilaterally after treatment initiation in the first affected eye. When the VA in the second eye decreased below 20/40 due to DME, treatment was initiated in the second eye. Patients with an interval of less than 6 months between treatment initiation in the first and second eyes were included in this study.

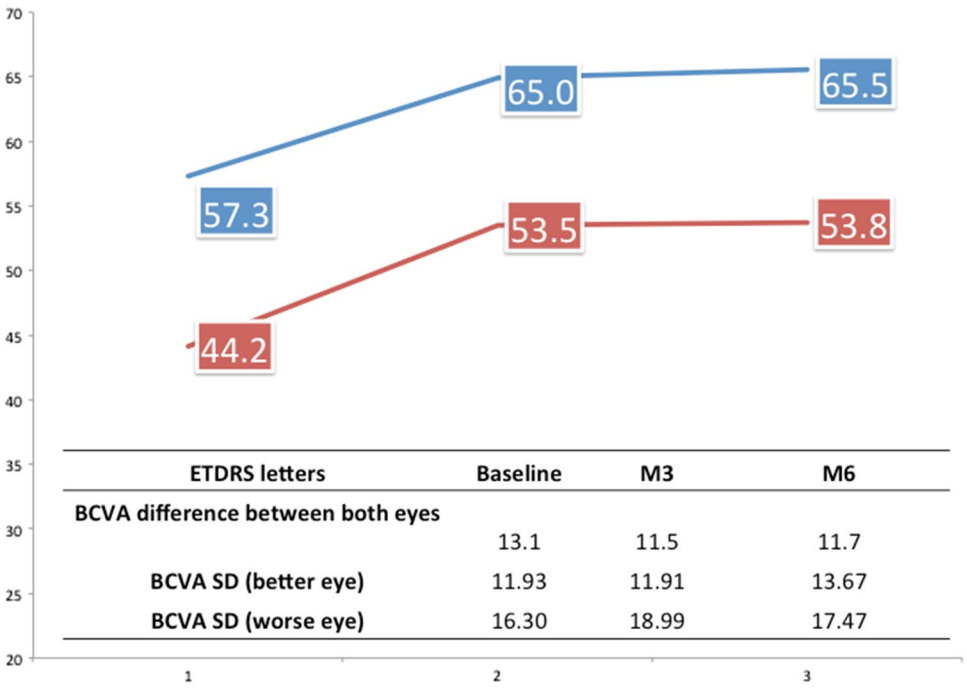
The primary endpoint was to assess the reduction in VI associated with ranibizumab treatment in patients with bilateral DME. This endpoint was evaluated 6 months after initiation of treatment in the second eye. For the second eye (better eye), initiation of treatment was set as baseline. In each group, we have collected baseline visual acuity (before any treatment) and BCVA at months 3 and 6 after the initiation of treatment. The percentage of VI reduction was defined according to the formula: (baseline percentage − final percentage)/baseline percentage.

Secondary endpoints were to assess the time interval to achieve a VA > 20/40 (impairment recovery), and the VA gain in the better eye and in the worse eye.

Statistical analysis was performed using the McNemar test for VI reduction analysis with Prism 7 software (GraphPad) and a linear random-effect model was used to compare the overall VA and the CRT evolution with R software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). We estimate the inter-eye correlation with a nested analysis of variance. A p value < 0.05 was considered statistically significant.

Results

A total of 138 patients were treated with 0.5 mg ranibizumab in the two centers during this study. Among these patients, 49 patients (35.5%) underwent bilateral IVR. In 30 patients (21.7%), IVR were performed with an interval < 6 months between the first and second affected eyes (Fig. 1). The only patient with Type 1 diabetes was excluded. These 29 patients represented our study group. No case of ischemic maculopathy was observed among these patients. Baseline characteristics of the 29 patients meeting the definition of bilateral treatment are presented in Table 1. In all cases, the



ETDRS letters	Baseline	M3	M6
BCVA difference between both eyes	13.1	11.5	11.7
BCVA SD (better eye)	11.93	11.91	13.67
BCVA SD (worse eye)	16.30	18.99	17.47

Fig. 1 Change in visual acuity over the 6-month follow-up for the better eye (blue line), and for the worse eye (red line). *X* axis: time (*1* baseline; *2* M3, and *3* M6), *Y* axis: visual acuity (ETDRS letters). *M3* month 3 and *M6* month 6. The mean difference in best-corrected visual acuity (BCVA) between both eyes at each time point and the standard deviations (SD) are presented. ($p < 0.001$ between M6 and baseline for both eyes)

Table 1 Baseline characteristics of patients with bilateral and simultaneous diabetic macular edema ($n = 29$ patients)

	Mean (standard deviation) or percentage (*n*)
Age, mean ± SD (years)	65.8 ± 10.5
Type 2 diabetes, % (*n*)	100% (29 patients)
Diabetes duration, mean ± SD (years)	12.8 ± 2
HbA1c, % ± SD	7.5 ± 1.3
Sex (male), % (*n*)	58.6 (17 males)
Stage of diabetic retinopathy, % (*n*)	
NPDR	62 (36 eyes)
RDP	38 (22 eyes)
ME duration, mean ± SD (months)	19.4 ± 22
Previous PRP, % (*n*)	41.4 (24 eyes)
Previous macular laser, % (*n*)	41.4 (24 eyes)
Pseudophakic, % (*n*)	27.5 (16 eyes)

NPDR non-proliferative diabetic retinopathy; *RDP* proliferative diabetic retinopathy; *PRP* pan retinal photocoagulation

better eye was the second treated eye. The estimate of inter-eye correlation was 0.12 ($p = 0.04$).

Visual outcomes

Among the 29 patients with bilateral treatment at baseline, 24 patients (82.8%) met the US visual impairment definition and had a BCVA < 20/40 in their better eye. At the end of follow-up, 13 patients (44.8%) had a BCVA < 20/40 in their better eye, i.e. a reduction in VI by 45.9% ($p = 0.0056$).

Among the 29 patients with bilateral treatment at baseline, 17 patients (58.6%) met the WHO visual impairment definition and had a BCVA < 6/18. At the end of follow-up, six patients (20.7%) had a VA < 6/18, i.e. a reduction in VI by 64.7% ($p = 0.0067$).

Functional outcomes

Among the 29 patients who received a bilateral treatment, 58.6% improved their BCVA by > 15 letters in one eye, and this improvement occurred in the better eye in 30% of cases. No patient experienced a loss > 5 letters in their better eye.

The reduction in VI was already observed at month 3. The percentage of patients with VA < 6/18 was of 58.6% at baseline, 34% at M3 and 21% at M6. Among patients with VA over 20/40 at the end of follow-up, the mean interval to achieve a VA > 20/40 was 3.44 months after treatment initiation (range 3–6). The BCVAs measured in both eyes are summarized in Fig. 1. In the better eye, the visual gain was + 8.2 letters and + 9.6 letters in the worse eye, 6 months after treatment initiation. The mean VA difference between both eyes was 13.1 letters at baseline and 11.7 letters at the end of follow-up.

Anatomical outcomes

In the worse eye, the mean CRT was of 536 ± 157 µm before any treatment, 332 ± 107 µm 3 months after initiation of

treatment and 351 ± 124 µm, 6 months after initiation of treatment (Comparison between M6 and baseline, $p < 0.01$).

In the better eye, the mean CRT was of 499 ± 135 µm at baseline, 327 ± 177 µm at M3 and 348 ± 176 µm at M6 (Comparison between M6 and baseline, $p < 0.01$).

Injections

The mean number of RBZ injections was 4.03 in the better eye and 4.27 in the worse eye within the first 6 months ($p = 0.62$).

The mean time to treatment initiation in the second eye was 2.74 months (range 0–6). The mean follow-up duration was 8.74 months (range 6–12).

Discussion

In our series, we showed a reduction in VI in patients with DME treated with ranibizumab.

Our study confirmed the beneficial effect of ranibizumab on functional and anatomical outcomes in DME patients. At M6, we observed a visual gain between 8.2 in the better eye and 9.6 letters in the worse eye and a decrease in CRT between − 185 and − 151 µm from baseline, respectively. These results are consistent with other studies, since Wykoff et al. [15] have recently confirmed that in DME, there is a strong relationship between BCVA and CRT. Other studies [7–9] have already assessed the visual outcomes of DME patients treated with ranibizumab injections in "real-world" conditions. In the PRIDE study [6], in terms of decimal score, the mean (± SD) VA gain in unilateral and bilateral patients was 1.5 ± 2.38 and 1.22 ± 1.67 at M5, respectively, compared to baseline VA. However, most patients were not naive of treatment before study inclusion. The aim of our study was to assess the visual outcome taking into account both affected eyes.

In our study, 21% of patients (30/138) experienced a bilateral simultaneous visual decrease. This rate is consistent with others reported in the literature. In the DRCRnet protocol I, a bilateral and simultaneous treatment was administered in 24% of cases [16].

A bilateral disease has severe impacts on the quality of life. Man et al. [17] have studied the impact of unilateral better eye and bilateral categorizations of diabetic retinopathy (DR) and DME and the vision-related quality of life (VRQoL). They have found that a bilateral involvement led to significant decrements in VRQoL that occurred only when both eyes had either DR or DME, and worsened when both eyes were affected by DME. In their study, they have shown that patients with only one affected eye had a VRQoL similar to that of patients without DR.

Many studies have confirmed that a unilateral visual loss is not associated with limitations in daily activities unlike a bilateral visual loss. In a recent paper by Daien et al. [18], the authors have confirmed the possibility of successfully performing all instrumental activities of daily living when using only one eye with a normal VA. The capability of performing daily activities is closely related to the VA in the better eye [19]. It has been shown in an exudative AMD study that the activity limitations occurred when VA was less than 20/40–20/50 [18]. The 20/40 threshold is the most frequently used criterion for safe driving [12].

We assessed the ability of ranibizumab to decrease VI in patients with bilateral DME. We found a decrease in VI ranging between 45.9 and 64.7% according to the US definition and WHO definition, respectively. To the best of our knowledge, it is the first evaluation of VI reduction associated with anti-VEGF treatment in DME patients both in "Real-World" studies and in clinical trials. To date, the only study that has assessed this issue is a population-based model [13] simulating VA outcomes over 2 years after diagnosis and treatment of DME. In their study, the authors have used the following definition: VI was defined as a VA worse than 20/40 in the better-seeing eye. Compared to no ranibizumab treatment, the model predicted that 0.3 mg ranibizumab every 4 weeks could reduce the number of patients with VI from 11,438 [95% simulation interval (SI), 7249–16,077] to 6,304 (95% SI 3921–8981), corresponding to a 45% (95% SI 36–53%) reduction at 2 years. Thus, our findings support this result.

However, our study has some limitations, including its retrospective design, the relatively small size of our cohort, and the short follow-up that may have underrepresented the potential for some patients to have improvement of visual impairment. But, the PRIDE study has shown that a greater improvement in median VA change was observed 3–4 months after ranibizumab therapy initiation. Also, we did not explore the correlation between diabetes duration, age and VA/CRT outcomes. However, previous studies have observed that the predictors of improvement in BCVA > 15 letters in ranibizumab-treated patients were a poor baseline BCVA, a young age and a short diabetes duration [20].

In conclusion, this study showed that ranibizumab significantly reduces disability in DME patients by at least 45.9% at 6 months. This reduction occurs early in the course of the treatment from month 3, and is maintained with a close follow-up and under treatment. We could assume that the reduced disability could improve the quality of life of diabetic patients while most of these patients still have a professional activity.

Compliance with ethical standards

Conflict of interest Dr. Franck Fajnkuchen, Dr. Sylvia Nghiem-Buffet, and Dr. Audrey Giocanti-Aurégan report having received personal

fees from Novartis, Bayer, Allergan, outside the scope of the submitted work. Dr. Dante Pieramici is consultant for Genentech, Regeneron, Thrombogenics, Novartis, and reports having received research Genentech, Regeneron, Ophthea, Regenerative Patch, RegenX Bio, Clearside Biomedical. Dr. Typhaine Grenet reports having received personal fees from Novartis, Bayer, outside the scope of the submitted work. Dr. Linda Hrarat, Dr. Anne-Laurence Best, Dr. Corinne Delahaye-Mazza and Prof. Bodaghi have nothing to disclose. Dr. Gabriel Quentel reports having received personal fees from Novartis outside the scope of the submitted work. Prof. Salomon Y. Cohen reports having received personal fees from Novartis, Bayer, Allergan, Alcon, Thea, outside the scope of the submitted work.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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