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The Pattern of Recurrence in Diabetic Macular Edema Treated by Dexamethasone Implant: The PREDIAMEX Study

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Purpose: To assess the time to functional and anatomic recurrence of macular edema (ME) after a first intravitreal dexamethasone implant in eyes with diabetic macular edema (DME).

Design: A 6-month observational, prospective, uncontrolled, multicenter, national case series.

Participants: Thirty-seven patients included between January 2015 and June 2016.

Methods: Patients were monitored at baseline and then monthly over 6 months after the first treatment.

Main Outcome Measures: Different patterns of recurrence were defined: qualitative and quantitative anatomic recurrences and functional recurrence.

Results: Median ME duration before the first dexamethasone implant was 2.04 months. All patients received a dexamethasone implant for the first time, but 73% of patients had not undergone any form of treatment previously. The mean time from baseline to qualitative anatomic, quantitative anatomic, and functional recurrence was 4.22 months (95% confidence interval [CI], 3.80−4.65 months), 4.73 months (95% CI, 4.34−5.12 months), and 4.89 months (95% CI, 4.53−5.26 months), respectively. Almost all patients (7/8) who demonstrated a qualitative anatomic recurrence showed a subsequent quantitative anatomic and functional recurrence days later. Mean improvement in best-corrected visual acuity was 10.1 letters (95% CI, 6.7−13.4 letters) and 7.3 letters (95% CI, 4.1−10.6 letters) at months 2 and 6, respectively. The mean reduction in central subfield macular thickness was 206 μm (95% CI, 157−255 μm) and 146 μm (95% CI, 98−195 μm) at months 2 and 6, respectively.

Conclusions: Dexamethasone implant is a functionally and anatomically effective treatment for DME in real-life practice. Qualitative anatomic recurrence seems to be an early sign of quantitative anatomic and functional recurrence. Further studies should demonstrate if early retreatment at the qualitative anatomic recurrence stage could better protect patient visual function. *Ophthalmology Retina 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes.[1] It is the leading cause of vision loss and blindness among adults in developed countries.[2,3] The prevalence of diabetic macular edema (DME) increases from 0% to 3% in individuals with recent diagnoses of diabetes to 28% to 29% in those who have had diabetes for 20 years.[4]

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser as standard care treatment, but the limitations of laser treatment along with intense clinical research over the last 10 years have led to laser treatment being surpassed by intravitreal pharmacotherapy as the first-line treatment for moderate to severe vision loss caused by DME.[5]

Glucocorticoids were the first class of corticosteroids shown by randomized clinical trials to be beneficial for DME.[6,7] However, because of numerous adverse effects, they have been replaced by sustained-release steroid devices made specifically for intravitreal injection, in particular the dexamethasone implant. The implant has been approved for the treatment of macular edema (ME) secondary to retinal vein occlusion,[8] for posterior inflammation such as noninfectious posterior uveitis,[9] and for DME.[10]

Patterns of recurrence have not been yet analyzed in DME after intravitreal injection of dexamethasone implant, as has been done already for ME after retinal vein occlusion (RVO).[11] The objective of this 6-month study was to evaluate the mean time to anatomic and functional recurrence of ME after the first dexamethasone implant (Ozurdex, Allergan, Irvine, CA) injection and also to estimate its efficacy and safety. All parameters were reported prospectively and on a monthly basis throughout the duration of the study.

Methods

A 6-month observational, prospective, uncontrolled, multicenter national case series was conducted in France from January 2015 through June 2016. All patients received clear, detailed prior information on the treatment and on the expected risks and benefits.

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The study was performed with informed consent in compliance with the Declaration of Helsinki and following all the guidelines for experimental investigations on human subjects. We obtained authorization from a national Protection to Persons and Property Committee (institutional review board number, IRB00009118). We certify that this research complies with all the applicable institutional and governmental regulations concerning the ethical use of human volunteers.

All patients in the study were at least 18 years of age and had decreased visual acuity resulting from central DME involvement defined as retinal thickening involving the 1-mm (according to OCT) central subfield macular thickness (CSMT) with subretinal or intraretinal fluid, or both, were eligible. There was no limit regarding the time since the first diagnosis of DME. Patients were not necessarily naïve to treatment for DME, but patients having received previous intravitreal injections of dexamethasone implants in either eye were not accepted. All the previous treatments administered to each patient were identified clearly. For the patients with a history of anti−vascular endothelial growth factor treatment, a mandatory delay of a minimum of 3 months between the last anti−vascular endothelial growth factor injection and the first dexamethasone implant was imposed. We selected 1 eye per patient as the study eye. Eligible patients had to have best-corrected visual acuity (BCVA) of more than 34 ETDRS letters in the study eye. Central subfield macular thickness had to be 275 μm or more in the study eye (thickness of a circular area of 1 mm, concentric to the foveal center). Patients with glaucoma requiring more than 1 topical drug treatment to control intraocular pressure (IOP) were not included in the study.

The main exclusion criteria included the presence of active or acute intraocular inflammation or infection, clinically significant epiretinal membrane, or vitreomacular traction. Patients also were excluded if they had hypertensive retinopathy in either eye or any uncontrolled systemic disease. Patients treated with oral corticosteroids, patients with any of the contraindications for dexamethasone implant set out in the June 2013 marketing approval, patients with uncontrolled diabetes with glycosylated hemoglobin of more than 10%, and patients with a history of steroid-induced IOP increase of 5 mmHg or more also were excluded.

Each patient received a single intravitreal injection of dexamethasone implant at day 0. Only topical anesthetic eye drops (oxybuprocaine hydrochloride 1.6 mg/0.4 ml) were used in the study eye. The intravitreal injections of the dexamethasone implant were performed according to standard clinical practices published by the French Health Authority in January 2011. Given that the main objective of this study was to assess the pattern of recurrence, none of the patients included were injected with a second dexamethasone implant before month 6, unless the rescue criteria were met, to prevent any macular alteration (vision loss >10 letters, increase of CSMT >100 μm, or both).

Each patient underwent a standardized examination at the initial visit and at each monthly follow-up visit, with measurement of BCVA in ETDRS letters, air-puff or applanation tonometer to measure IOP, lens status determination, fundus ophthalmoscopy, and spectral-domain (SD) OCT (Cirrus HD-OCT model 500 Zeiss; Carl Zeiss Meditec, Inc., Dublin, CA) to measure CSMT. Patients who received more than 1 injection received the same follow-up, with a monthly examination and recording of the same clinical and OCT data.

The primary efficacy outcome was evaluation of the mean time to anatomic recurrence (increase in macular edema) or functional recurrence (decrease in BCVA) after treatment. We used the same definitions as previously published,[11] and therefore considered qualitative or strict anatomic recurrence when SD-OCT imaging showed new intraretinal cysts, little subretinal fluid, or both. We also defined quantitative or obvious anatomic recurrence as an increase in CSMT of 50 μm or more identified using SD-OCT imaging. Functional recurrence was defined as a loss of BCVA of 1 line or more in the study eye after treatment. We also assessed the mean change in VA from baseline BCVA at each visit and at 6 months, the mean change from baseline CSMT measured using SD-OCT, and the proportion of eyes with a minimum 3-line improvement from baseline BCVA.

We also defined responder and nonresponder status. Responders were classified as follows: functional responder, BCVA improvement of a minimum of 1 ETDRS lines during follow-up; anatomic responder, central foveal thickness improvement of 20%; and complete responder, both anatomic and functional responder criteria apply.[12−16]

Statistical Methods

Categorical variables were described using absolute and relative frequencies, and quantitative variables were described using median, minimum, maximum, mean, and standard deviation (SD). Linear mixed-effects models were used to study BCVA and CSMT over time. This method allowed us to take into account the within-subject correlation of the repeated observations over time and the inclusion of patients with a varying number of measurements. Best-corrected visual acuity and CSMT were expressed using the absolute measured value or as change from the baseline value. The models gave estimates of the mean BCVA, mean changes in BCVA, mean CSMT, and mean changes in CSMT for each time point, with a 95% confidence interval (CI). The Kaplan-Meier product limit method was used to study the occurrence and delay of anatomic and functional recurrences. Patients contributed to the risk set within the 6 months after the first injection. Patients who did not demonstrate recurrence were considered right censored at the date of their last visit within the period. The R software program (R Development Core Team, Vienna, Austria) was used to perform all analyses, and for each test, the 0.05 significance level was used.

Results

This prospective study was conducted in 3 centers located in mainland France. Thirty-seven eyes of 37 patients were included between January 2015 and June 2016, with a minimum follow-up period of 6 months for all patients.

Patient Characteristics

The population characteristics are shown in Table 1. The mean age was 64.4 years (range, 29.3−84.7 years). The population was made up of more men than women (68% men). There was a small difference in terms of laterality (62% of left eyes). In terms of type of diabetes, 11% of patients had a type 1 diabetes and 90% had a type 2 diabetes. Concerning diabetes treatment, 54% of patients received a combination of oral antidiabetic drugs and insulin, whereas 11% and 35% received only insulin or oral antidiabetic drugs, respectively. In terms of the severity of DR, 14% of patients initially demonstrated mild nonproliferative DR, 46% had moderate nonproliferative DR, 30% had severe nonproliferative DR, and 5% had proliferative DR. Only 2 patients did not have any type of DR. We categorized patients with nonadvanced DR (absence of DR, mild DR, and moderate DR) and patients with advanced RD (severe and proliferative