View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Open Access LMU

Original Paper

Ophthalmologica

Ophthalmologica 2015;233:18–26
DOI: 10.1159/000368840

Received: October 7, 2013
Accepted after revision: October 2, 2014
Published online: December 5, 2014

Retrospective, Observational Study in Patients Receiving a Dexamethasone Intravitreal Implant 0.7 mg for Macular Oedema Secondary to Retinal Vein Occlusion

Albert J. Augustin[a] Frank G. Holz[b] Christos Haritoglou[c] Wolfgang J. Mayer[c] Silvia Bopp[e] Alexander F. Scheuerle[f] Matthias Maier[d] Walter Sekundo[g] Dirk Sandner[h] Andrew Shirlaw[j] Lars-Olof Hattenbach[i]

[a]Städtisches Klinikum Karlsruhe, Karlsruhe, [b]Department of Ophthalmology, University of Bonn, Bonn, [c]Klinikum der Ludwig-Maximilians-Universität München, and [d]Klinikum Rechts der Isar der TU München, München, [e]Augenklinik Universitätsallee, Bremen, [f]Universitätsklinikum Heidelberg, Heidelberg, [g]Universitäts-Augenklink Marburg, Marburg, [h]Universitätsklinikum Carl Gustav Carus, Dresden, and [i]Klinikum Ludwigshafen, Ludwigshafen, Germany; [j]Allergan, Marlow, UK

Key Words
Dexamethasone intravitreal implant · Retinal vein occlusion · Macular oedema

Abstract
Purpose: To retrospectively evaluate the re-injection interval, efficacy and safety of dexamethasone (DEX) intravitreal implant 0.7 mg in the treatment of macular oedema (ME) due to retinal vein occlusion (RVO) in Germany in 2009–2012. ***Methods:*** Retrospective, multicentre, anonymised observational study of data collected from the first DEX implant 0.7 mg injection through 3–6 months following the last injection. Data were included if the patient was >18 years old, had a diagnosis of ME secondary to branch or central RVO, and received at least 2 DEX implant 0.7 mg injections during routine practice. ***Results:*** Data from 87 patients were analysed. Mean time to re-injection between first and second treatments was 5.03 months in the total RVO population, and 5.46 and 4.52 months for the branch and central RVO subpopulations, respectively. An intraocular pressure increase of >25 mm Hg was recorded in 20% of patients, and 34% of patients began treatment with anti-glaucoma medication, but surgery was not needed for this condition. ***Conclusions:*** DEX implant 0.7 mg was found to be well tolerated and effective with repeat treatments in clinical practice.

© 2014 S. Karger AG, Basel

Introduction

Macular oedema (ME) is a common sight-threatening complication seen in patients with branch retinal vein occlusion (BRVO) and central retinal vein occlusion

Details of this study were presented by A.J. Augustin et al. at the European Association for Eye and Vision Research (EVER) Congress, Nice, France, October 10–13, 2012, and by L.O. Hattenbach et al. at the 3rd World Congress on Controversies in Ophthalmology (COPHy), Istanbul, Turkey, March 22–25, 2012.

KARGER 125

© 2014 S. Karger AG, Basel
0030–3755/14/2331–0018$39.50/0

E-Mail karger@karger.com
www.karger.com/oph

Andrew Shirlaw
Allergan, 1st Floor, Marlow International
The Parkway
Marlow, SL7 1YL (UK)
E-Mail shirlaw_andrew@allergan.com

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

(CRVO), which can be persistent and difficult to treat [1]. In July 2010, dexamethasone (DEX) intravitreal implant 0.7 mg (Ozurdex®, Allergan Inc., Irvine, Calif., USA) was approved in the European Union for the first-line treatment of ME secondary to BRVO or CRVO, although some patients in Germany have received DEX implant 0.7 mg as part of an early access programme since October 2009. DEX implant 0.7 mg represents a novel intravitreal drug delivery system consisting of a biodegradable copolymer of lactic acid and glycolic acid, which contains micronised DEX. This corticosteroid has been shown to suppress inflammation [2], a key event in the pathophysiology of RVO and development of ME, by inhibiting major inflammatory mediators that are associated with disease severity [3]. DEX implant 0.7 mg delivers 0.7 mg total dose of DEX to the vitreous with gradual release over time allowing for sustained drug levels to the target areas while reducing the potential for side effects typically observed from steroid administration.

The DEX implant 0.7 mg has been shown to be efficacious in clinical trials in patients with inflammation of the posterior segment of the eye in non-infectious uveitis. Its efficacy in patients with ME following BRVO and CRVO has also been demonstrated in clinical trials like the Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Edema (GENEVA) trial and others [4–6], but less is known about the use and injection burden of the DEX implant 0.7 mg in routine clinical practice. This retrospective study was designed to review the re-injection interval, efficacy and safety of DEX implant 0.7 mg in routine clinical practice in Germany in 2009–2012, and therefore enhance knowledge of this treatment option.

Methods

This was a retrospective, anonymised observational data collection study conducted at 10 centres in Germany in 2009–2012 in patients with ME in RVO who were treated according to clinical need at the discretion of each investigator. The total number of patients identified at each separate centre was as follows: Bonn, n = 22; Bremen, n = 7; Karlsruhe, n = 13; Münster, n = 15; Munich/München, n = 17; Dresden, n = 6; Heidelberg, n = 6; Ludwigshafen, n = 4; Marburg, n = 1, and München, n = 5. Of the 96 patients originally identified by the investigators, the case report forms of 9 patients were excluded from the analysis from the Bonn centre (3/22 patients), the Münster centre (2/15 patients) and the first München centre (4/17 patients). These patients were excluded due to the following major protocol deviations: (a) the patient did not receive a DEX implant 0.7 mg at the baseline visit, or (b) the patient did not receive a minimum of 2 DEX implant 0.7 mg injections during the observation period. Data from 87 evaluable patients (~91% of the original patients selected) aged >18 years, who were diagnosed with ME secondary to BRVO or CRVO, who received at least 2 injections of DEX implant 0.7 mg in the study eye, and had follow-up data for 3–6 months following their latest DEX implant 0.7 mg injection were therefore included in the analysis.

As this was a retrospective study of routine clinical practice, there were no specified retreatment criteria, and this was performed at the discretion of each investigator according to clinical need. This also meant that there was no significant delay between a diagnosis of recurrence of ME and the administration of the second DEX implant 0.7 mg injection. Data from patients who received DEX implant 0.7 mg as part of a clinical trial were excluded.

The primary endpoint was the mean time between the first and second DEX implant 0.7 mg injection. Secondary endpoints included best corrected visual acuity (BCVA) at 7–12 weeks after injection and central retinal thickness (CRT) measured by optical coherence tomography. Individual BCVA values were recorded in Snellen, but for the statistical analysis, the formula from Gregori et al. [7] was used to convert Snellen to approximate early treatment diabetic retinopathy study (ETDRS) values. The time point of 7–12 weeks was chosen for the secondary analysis based on the results of other clinical trials that suggested that after 7–12 weeks the chance of a relapse occurring is highest at this time point. In patients whose follow-up visits were not performed within 7–12 weeks, the follow-up visit closest to this time window was chosen for analysis.

Safety measures included adverse events monitoring, intraocular pressure (IOP), biomicroscopy and ophthalmoscopy. Data were collected and entered into a case report form, which was monitored centrally. Data were validated by a contract research organisation, MEDIDATA, and a statistical analysis plan was produced prior to database lock. Statistical analysis of the data was undertaken using statistical analysis software (SAS version 9.1) and MEDIDATA's own software, and descriptive statistics were obtained. This included preparation of data listings and summary statistics (extreme values, interquartile section, mean and median values, standard deviation) or frequency distribution tables as appropriate for each item. In this analysis, baseline was considered to be the patient's first DEX implant 0.7 mg injection.

Results

Baseline Characteristics and Demographics

Data from 87 (46 BRVO, 41 CRVO) patients were included in this retrospective study (table 1). At baseline, past and/or concomitant systemic conditions were reported for 72.4% (63/87) of the patients overall. The most frequent medical conditions were cardiovascular disorders, which were reported by 71.4% (45/63) of patients with medical conditions overall. The frequency of cardiovascular disorders was similar in the BRVO and CRVO subgroups [71.7% (33/46) and 73.1% (30/41)], respectively. Other medical conditions were reported less frequently.

Patient ocular comorbidities are shown in table 1. A history of glaucoma at baseline was reported by 14 pa-

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

Table 1. Patient demographics and disease characteristics at baseline

Characteristics	RVO (n = 87)	BRVO (n = 46)	CRVO (n = 41)
Mean age, years (range)	68 (47–86)	70 (50–85)	66 (47–86)
Sex, n (%)			
Male	58 (67)	30 (65)	28 (68)
Female	29 (33)	16 (35)	13 (32)
Mean BCVA prior to first DEX implant 0.7 mg injection, approximate ETDRS letters	51	59	43
Mean CRT prior to first DEX implant 0.7 mg injection, μm (SD)	594.76 (217.87)	542.45 (198.54)	653.24 (26.41)
Median time from onset of symptoms to first treatment, days (%)	99[a]	81[b]	134[c]
<90 days	29 (33)	14 (30)	15 (37)
90–180 days	6 (7)	3 (7)	3 (7)
181–360 days	5 (6)	3 (7)	2 (5)
>360 days	18 (21)	7 (15)	11 (27)
Previous RVO treatment, n (%)	46 (53)	24 (52)	22 (54)
Bevacizumab	39 (85)	18 (75)	21 (96)
Triamcinolone	16 (35)	6 (25)	10 (46)
Ranibizumab	2 (4)	2 (8)	NA
Other	7 (15)	4 (17)	3 (14)
Lens status of study eye prior to first DEX implant 0.7 mg injection			
Phakic	50 (57.5)	25 (54.3)	25 (61.0)
Pseudophakic	32 (36.8)	17 (37.0)	15 (36.6)
Missing data	5 (5.7)	4 (8.7)	1 (2.4)
Opacity status of study eye prior to first DEX implant 0.7 mg injection			
Opacity	41 (47.1)	20 (43.5)	21 (51.2)
No opacity	6 (6.9)	4 (8.7)	2 (4.9)
Missing data	40 (46.0)	22 (47.8)	18 (43.9)
Ischaemia in the study eye prior to first DEX implant 0.7 mg injection, n (%)	19 (22)	10 (22)	9 (22)
Ocular comorbidities in the study eye prior to first DEX implant 0.7 mg injection, n (%)			
Glaucoma	13 (14.9)	6 (13)	7 (17.1)
Ocular hypertension	1 (1.1)	1 (2.2)	0
Patients with IOP-lowering medications prior to first DEX implant 0.7 mg injection, n (%)	12 (14)	6 (13)	6 (15)

ETDRS value is approximate and calculated based on a formula [7], with n = 78 for RVO overall, n = 39 for BRVO and n = 43 for CRVO. The mean time from the first injection to the last follow-up visit (when the patient may or may not have been retreated) was 273.25 ± 96.06 days (range 98.0–548.0 days) for the RVO population (n = 84), 297.43 ± 95.99 days (range 117.0–548.0 days) for the BRVO subgroup (n = 46) and 243.97 ± 88.80 days (range 98.0–467.0 days) for the CRVO subgroup (n = 38).

[a] Missing data for n = 29 (33%); [b] missing data for n = 19 (41%); [c] missing data for n = 10 (24%).

tients (7 patients each in the BRVO and CRVO subgroups) and prior to the start of treatment with DEX implant 0.7 mg, 14.9% (13/87) of all patients suffered from glaucoma and 1 patient from ocular hypertension. Thirty-four out of the 87 patients had a pseudophakic eye. Concerning past ocular surgeries and treatments, cataract surgery was recorded in 39.0% (34/87) of patients, focal retinal laser treatment in 17.2% (15/87) of patients, panretinal photocoagulation in 14.9% (13/87) of patients, anti-glaucoma medication to treat elevated IOP in 13.8% (12/87) of patients (2 patients with glaucoma/ocular hypertension did not receive treatment for this condition), pars plana vitrectomy in 9.2% (8/87) of patients, laser peripheral iridotomy in 1 patient, with other ocular treatment recorded in 16.1% (14/87) of patients overall. The frequency of these events was similar in the BRVO and CRVO subgroups apart from laser peripheral iridotomy, which was only reported for a single patient in the BRVO subgroup.

As shown in table 1, overall, 67% were men and the mean age was 68 years (range 47–86 years). Mean baseline visual acuity was lower, and mean CRT was greater

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

for the CRVO population at baseline than for the BRVO population. Over half of the patients in this study (53%) had previously received treatment for RVO prior to receiving DEX implant 0.7 mg therapy, and the majority of these (85%) had received anti-vascular endothelial growth factor therapy.

The mean time from the first injection to the last follow-up visit (when the patient may or may not have been retreated) was 273.25 ± 96.06 days (range 98.0–548.0 days) for the RVO population (n = 84), 297.43 ± 95.99 days (range 117.0–548.0 days) for the BRVO subgroup (n = 46) and 243.97 ± 88.80 days (range 98.0–467.0 days) for the CRVO subgroup (n = 38).

Efficacy Results

Data were analysed from 87 patients who received at least 2 injections of DEX implant 0.7 mg and had the required 3–6 months of follow-up data following their last DEX implant 0.7 mg injection. Of these 87 patients, 17 patients (19.5%) received a third injection of DEX implant 0.7 mg and 3 patients (3.4%) received a fourth injection. Sole treatment with DEX implant 0.7 mg was given to 39 out of 46 patients (84.8%) with BRVO and 39 out of 41 patients (95.1%) with CRVO during the course of the observation period.

Primary Efficacy Endpoint of Time to DEX Implant 0.7 mg Re-Injection

The mean time to DEX implant 0.7 mg re-injection between the first and second treatments was 141 days (5.03 months) for RVO overall, 153 days (5.46 months) for the BRVO subpopulation and 127 days (4.52 months) for the CRVO subpopulation, as shown in figure 1. Median re-injection intervals were 135 days [interquartile range (IQR) 99–169], 145 days (IQR 108–178) and 122 days (IQR 84–147) for RVO overall, BRVO and CRVO, respectively.

Secondary Efficacy Endpoints

Mean Change in BCVA from Baseline at Approximately 7–12 Weeks after the Last DEX Implant 0.7 mg Injection (ETDRS Equivalents)

As shown in figure 2, a mean approximate ETDRS letter gain of 9 ± 20.42 letters was observed at a mean time of 77 ± 37.70 days (2.75 months) following the last DEX implant 0.7 mg injection in the RVO population. In the BRVO and CRVO subpopulations, mean gains observed were 6 ± 17.68 letters after 73 ± 29.57 days (2.61 months) and 12 ± 22.67 letters after 80 ± 45.40 days (2.86 months), respectively.

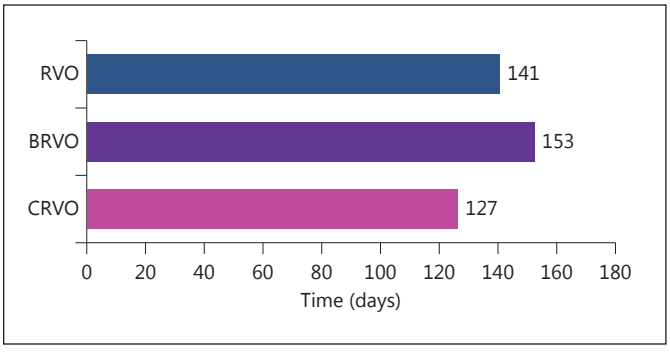

Fig. 1. Mean time between the first and second injection of DEX implant 0.7 mg. 141 days is equivalent to 5.03 months, 153 days is equivalent to 5.46 months and 127 days is equivalent to 4.52 months, if a month is assumed to be 28 days in length. Data available for 85/87 patients in the RVO group (46/46 patients in the BRVO subgroup and 39/41 patients in the CRVO subgroup).

Sub-Analysis Showing Mean Change in BCVA by Baseline Duration of ME at Approximately 7–12 Weeks after the Last DEX Implant 0.7 mg Injection (ETDRS Equivalents)

As shown in figure 3, patients with ME of <90 days' duration at baseline showed greater improvements in BCVA following treatment with DEX implant 0.7 mg compared with the population as a whole (e.g. patients with ME of any duration). In the RVO group of patients with ME of <90 days at baseline (n = 27), the mean change in BCVA from baseline was 15.63 ± 22.88 letters, with a mean time between the last injection and visit of 65.52 ± 41.45 days. The corresponding changes in BCVA from baseline for the BRVO (n = 13) and CRVO (n = 14) subpopulations were 9.62 ± 20.79 letters and 21.21 ± 24.05 letters, respectively, and the mean time between the last injection and visit was 63.46 ± 29.84 days and 67.43 ± 51.05 days, respectively.

Sub-Analysis Showing Mean Change in BCVA by Baseline BCVA of <55 Letters and ≥55 Letters at Approximately 7–12 Weeks after the Last DEX Implant 0.7 mg Injection (ETDRS Equivalents)

In a subgroup analysis of RVO patients with a BCVA of <55 letters (n = 36) at baseline, the mean BCVA prior to DEX implant 0.7 mg was 34.58 ± 12.03 letters (range 20.0–50.0) and the BCVA approximately 7–12 weeks after the last DEX implant 0.7 mg injection was a mean of 55.91 ± 14.77 letters (range 35.0–76.0). The change in BCVA for these patients with a baseline BCVA of <55 letters was a mean of 20.91 ± 16.17 letters.

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

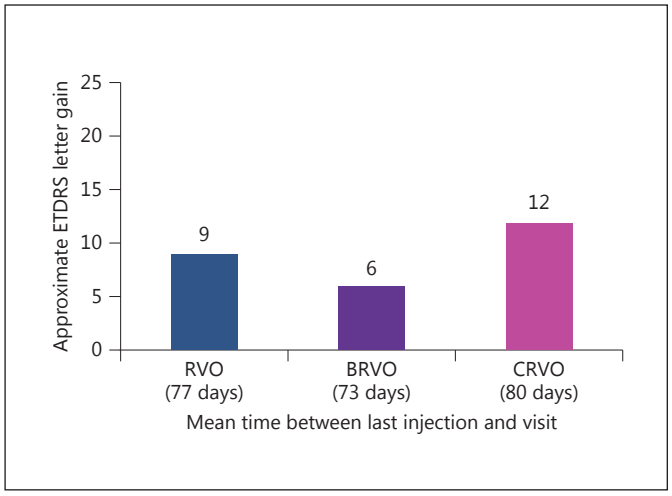

Fig. 2. Mean change in BCVA from baseline. ETDRS value is approximate and calculated based on a formula by Gregori et al. [7].

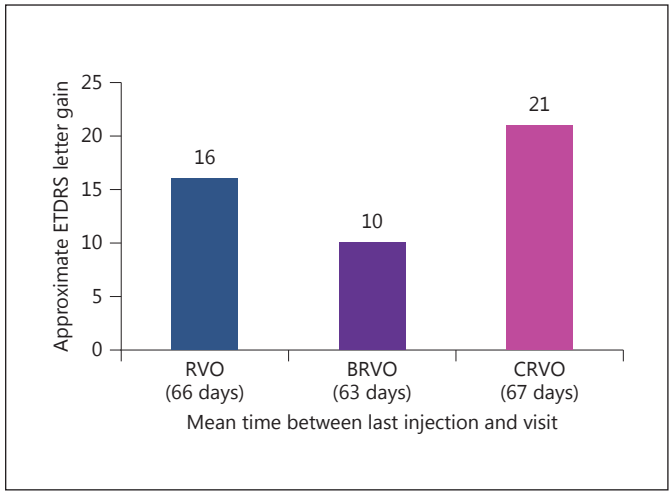

Fig. 3. Mean change in BCVA from baseline for the subgroup with ME of <90 days at baseline. ETDRS value is approximate and calculated based on a formula by Gregori et al. [7].

When RVO patients with a BCVA of ≥55 letters were considered (n = 41), the mean BCVA prior to DEX implant 0.7 mg was 64.51 ± 5.77 letters (range 55.0–76.0) and the BCVA approximately 7–12 weeks after the last DEX implant was 63.32 ± 17.74 letters (range 20.0–85.0). The change in BCVA for these patients with a baseline BCVA of ≥55 letters was a mean of –1.20 ± 18.12 letters.

Results for the BRVO and CRVO subgroups were similar although the data must be interpreted with caution as only a small number of patients were included in each group.

Patients Who Achieved a ≥2- or 3-Line Improvement in BCVA

During the review period, 56.3% (49/87) of RVO patients achieved an improvement of ≥2 lines compared with baseline, in a mean time of 65 days after the first injection (n = 42; range 27–184 days) and 47 days after the second injection (n = 6; range 7–119 days). In the BRVO and CRVO subpopulations, 47.8% (22/46) of the BRVO patients and 65.8% (27/41) of the CRVO patients showed ≥2 lines of BCVA improvement. In the BRVO group, the mean time to a ≥2-line improvement was seen at 69 days after the first injection (n = 17; range 31–184 days) and at 38 days after the second injection (n = 4; range 27–55 days). In the CRVO group, the mean time to this improvement was at 62 days after the first injection (n = 25; range 27–118 days) and at 63 days after the second injection (n = 2; range 7–119 days). While it is expected that the time interval between injections would be approximately the same, the small difference seen could be explained by the small number of patients who required a second or third injection.

In the RVO patients, 50.5% (44/87) showed an improvement of ≥3 lines in comparison to baseline, and this was achieved 69 days after the first injection (n = 35; range 27–208 days) and 50 days after the second injection (n = 9; range 1–160 days). The sub-analyses for the BRVO and CRVO population showed that 41.3% (19/46) of all BRVO patients and 60.9% (25/41) of the CRVO patients achieved an improvement of ≥3 lines compared with baseline. In the BRVO group, the mean time to this improvement of ≥3 lines was achieved 79 days after the first injection (n = 13; range 31–208 days) and 41 days after the second injection (n = 6; range 1–74 days). For the CRVO group, the time to this improvement was 63 days after the first injection (n = 22; range 27–118 days) and 67 days after the second injection (n = 3; range 7–160 days).

Mean Change in Retinal Thickness

Reductions in CRT were seen at all time points during the study. For the 7- to 12-week post-injection time point, reductions in CRT compared with baseline were achieved after the first and second injection of as well as after the last injection of DEX implant 0.7 mg, as shown in table 2.

Safety Findings

Adverse Events and Serious Adverse Events

Adverse events were recorded for 48.3% (42/87) of patients, and table 3 shows the adverse events that were re-

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

Table 2. CRT as assessed by optical coherence tomography during the observational period

	RVO	BRVO	CRVO
Mean CRT at baseline, μm	590.79 (43)	577.68 (25)	609.00 (18)
Change in CRT 7–12 weeks after first DEX implant 0.7 mg injection, μm	–283.37 (43)	–290.56 (25)	–273.39 (18)
Mean CRT at baseline, μm	576.85 (40)	542.18 (28)	657.75 (12)
Change in CRT 7–12 weeks after second DEX implant 0.7 mg injection, μm	–255.53 (40)	–216.11 (28)	–347.50 (12)
Mean CRT at baseline, μm	576.85 (34)	567.70 (23)	596.00 (11)
Change in CRT 7–12 weeks after last DEX implant 0.7 mg injection, μm	–259.21 (34)	–258.52 (23)	–260.64 (11)

Figures in parentheses indicate numbers. Mean CRT: for patients with complete 7- to 12-week data after the first DEX implant 0.7 mg injection. The mean time from the first injection to the last follow-up visit (when the patient may or may not have been retreated) was 273.25 ± 96.06 days (range 98.0–548.0 days) for the RVO population (n = 84), 297.43 ± 95.99 days (range 117.0–548.0 days) for the BRVO subgroup (n = 46) and 243.97 ± 88.80 days (range 98.0–467.0 days) for the CRVO subgroup (n = 38).

Table 3. Adverse events recorded during the observational period

Adverse event	RVO (n = 87)	BRVO (n = 46)	CRVO (n = 41)
IOP increase	16 (18.4)	4 (8.7)	12 (29.3)
Glaucoma	10 (11.5)	9 (19.6)	1 (2.4)
Eye laser surgery	9 (10.3)	6 (13.0)	3 (7.3)
Cataract operation[1]	6 (6.9)	3 (6.5)	3 (7.3)
Retinal degeneration	6 (6.9)	2 (4.3)	4 (9.8)
Cataract	3 (3.4)	1 (2.2)	2 (4.9)
Conjunctival irritation	3 (3.4)	1 (2.2)	2 (4.9)
Retinal detachment	3 (3.4)	2 (4.3)	1 (2.4)
Conjunctival haemorrhage	2 (2.3)	1 (2.2)	1 (2.4)

Results are expressed as numbers with percentages in parentheses. The mean time from the first injection to the last follow-up visit (when the patient may or may not have been retreated) was 273.25 ± 96.06 days (range 98.0–548.0 days) for the RVO population (n = 84), 297.43 ± 95.99 days (range 117.0–548.0 days) for the BRVO subgroup (n = 46) and 243.97 ± 88.80 days (range 98.0–467.0 days) for the CRVO subgroup (n = 38).

[1] One operation took place after the end of the formal data collection period.

Table 4. Mean IOP recorded during the observational period for the RVO population (n = 87)

	Mean IOP after first DEX implant 0.7 mg injection, mm Hg (n)	Mean IOP after second DEX implant 0.7 mg injection, mm Hg (n)
Time point		
Baseline	15.3 (74)	
0–6 weeks	16.9 (36)	15.4 (30)
7–12 weeks	16.1 (42)	16.3 (30)
13–17 weeks	15.4 (24)	18.3 (24)
18–22 weeks	16.0 (16)	15.8 (21)
23–26 weeks	15.3 (13)	14.6 (5)
>26 weeks	14.1 (12)	14.5 (2)

When the DEX implant 0.7 mg injections were performed during a visit, pre-injection pressures have been included for the mean calculation. The mean time from the first injection to the last follow-up visit (when the patient may or may not have been retreated) was 273.25 ± 96.06 days (range 98.0–548.0 days) for the RVO population (n = 84), 297.43 ± 95.99 days (range 117.0–548.0 days) for the BRVO subgroup (n = 46) and 243.97 ± 88.80 days (range 98.0–467.0 days) for the CRVO subgroup (n = 38).

ported in >1 patient. The most frequently recorded adverse event was IOP increase, which occurred in 18.4% (16/87) of all RVO patients. Other adverse events reported by more than 10% of patients included glaucoma (11.5%, 10/87) and eye laser surgery (10.3%, 9/87).

During the review period, 6.9% of patients (6/87) reported a serious adverse drug reaction; however, if cataract progression or surgery are excluded, as these events were not related to the injection procedure itself, this drops to 2.3%.

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

Table 5. Comparison of efficacy data from this and other real-life studies

	Number of patients with RVO	Mean time to re-injection, months	≥2 line improvement, %	≥3 line improvement, %
This study	87	5.03	56.3	50.5
Papathomas et al. [8], 2013	76	4.2	NR	NR
Querques et al. [9], 2013	33	4.7	NR	30.3
Pommier and Meyer [10], 2012	220	5.35	61.5	50.8
Capone et al. [12], 2014	289	5.6	49.8	35.0
Ferrini and Ambresin [13], 2013	15	4.6	55.0	33.0
Coscas et al. [14], 2013	128	5.9	NR	39.0

NR = Not reported.

Out of the 6 events reported, the following were assessed by the investigator as having a casual or possible causal relationship with DEX implant 0.7 mg: 1 case of bulbar hypotension with choroidal detachment, which later resolved, 1 case of increased lens opacity and 2 cases of cataract surgery. One further cataract surgery and 1 hospitalisation due to suspected glaucoma were reported as serious adverse events, but due to the retrospective nature of this study, it was not possible for the investigator to assign a causal relationship.

Special Interest Adverse Events – IOP, Glaucoma and Cataract Surgery

Table 4 shows the mean IOPs that were recorded at each time point. Anti-glaucoma medication, prescribed at the investigators' discretion, was taken by 43.7% of all patients (38/87) during the observation period with 34.5% of all patients (30/87) initiating anti-glaucoma medication while receiving treatment with DEX implant 0.7 mg. No surgery for glaucoma was reported. An IOP >25 mm Hg was seen in 19.5% (17/87) of patients. Of these patients, 17.6% (3/17) were taking anti-glaucoma medication prior to the start of treatment with DEX implant 0.7 mg, whereas 82.4% (14/17) of patients began anti-glaucoma medication during the observation period.

Lens opacity was recorded in 47.1% (41/87) of patients at the baseline visit and 9.8% (4/41) of these patients had cataract surgery due to cataract progression during the mean observation period of up to 548 days (mean 273.25 ± 96.06 days). A fifth patient also had cataract surgery during the study, but data were not available on this patient's lens opacity status at baseline.

Discussion

Data from this retrospective, observational data collection study in Germany show that with repeat usage of DEX implant 0.7 mg in clinical practice, the mean time interval between the first and second injection is 5.03 months for patients with RVO (5.46 and 4.52 months in the BRVO and CRVO subpopulation, respectively). This time period of approximately 5 months is similar to data from the published GENEVA randomised controlled clinical trial [4, 5] and comparable to data from more recent real-life retrospective studies using the DEX implant 0.7 mg for ME in RVO carried out in the UK, Italy, France and the USA [8–12] (table 5). In these retrospective real-life studies, as well as a prospective study from Switzerland and a European multicentre study, re-injection intervals in both treatment naïve and previously treated patients were typically between 5 and 7 months, with a trend towards a longer injection interval for subsequent injections [8–14]. Many patient-specific factors are likely to impact on the need for retreatment and therefore treatment should be individualised for each patient with the retreatment decision based on clinical judgement. Regular monitoring of the patient is therefore recommended especially as for some patients the optimum retreatment interval for the DEX implant 0.7 mg may be <5 months. This approach is aligned with that suggested by Coscas et al. [14], who recently published a retreatment algorithm for the retreatment with DEX implant 0.7 mg for ME secondary to RVO and recommend monthly examinations from 3 to 6 months following injection.

As also shown by the data obtained, repeat DEX implant 0.7 mg treatment results in lasting improvements in visual acuity and corresponding reductions in CRT in both BRVO and CRVO patients. Visual acuity improve-

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

ments were more marked in the CRVO population than in the BRVO population. However, mean baseline visual acuity in the BRVO population was higher than in the CRVO population (59 vs. 43 approximate ETDRS letters). As previously reported in randomised clinical trials, patients with a lower visual acuity at baseline had greater improvements following treatment presumably due to a ceiling effect [4, 15] and therefore this finding is not surprising.

Data from the subgroup analysis of patients with ME of shorter duration (<90 days) and lower BCVA (<55 letters) at baseline conducted in this study indicated that these patients had greater improvements in BCVA following treatment compared with the population as a whole. This finding is consistent with the results of the GENEVA trials, Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion (BRAVO) studies, and the Standard Care versus Corticosteroid for RVO (SCORE) study [4, 5, 16, 17]. Therefore, data obtained in this observational study of German clinical practice supports the growing evidence base that early treatment is beneficial.

Expected side effects of intraocular steroid treatment include cataract formation and IOP increases as observed in previous studies with triamcinolone and fluocinolone acetonide [18–21]. Over the course of this study, a low rate of cataract was reported with only 5 cataract operations performed, 4 of which were in patients who had lens opacity recorded at baseline. The majority of patients did not experience substantial IOP rises and the mean IOP at the expected peak effect for the DEX implant 0.7 mg (e.g. 7–12 weeks after injection) was 16.1 mm Hg after the first injection. The mean IOP after the second DEX implant 0.7 mg injection was 16.3 mm Hg, thereby indicating that IOP rises were similar for repeat treatment. While 34.5% of patients began anti-glaucoma medications at the investigators' discretion during the observation period, no surgery for this condition was reported. As IOP increases are known to occur with intravitreal steroids, regular monitoring and appropriate pharmacotherapy is recommended to control IOP [19, 20, 22]. As alternative treatments to intravitreal steroid implant in patients with RVO may be associated with an increased injection frequency or side effects that are less easily managed, the advantages of treatment with the DEX implant 0.7 mg may outweigh the disadvantages of steroid-related side effects such as cataract and moderate IOP increase [23, 24].

Limitations of this study include the small number of centres and hence, patients who had data analysed (10 centres; n = 87), and its retrospective and observational nature. It is likely, however, that data obtained were reflective of clinical practice in Germany between 2009 and 2012. Larger prospective observational studies are currently underway to more fully elucidate the usage patterns of the DEX implant 0.7 mg in clinical practice, and they will allow comparisons with the results of the study reported herein.

In conclusion, the findings of this retrospective study on the efficacy and safety of DEX implant 0.7 mg in routine clinical practice in Germany in 2009–2012 are in line with those reported in similar length or long-term studies in other European and US clinical practices [8–14, 25]. A summary of the main findings from this study in comparison with other real-life studies is provided in table 5. As confirmed in this retrospective study, treatment with DEX implant 0.7 mg had a positive effect on the final visual function and had a favourable long-term safety profile in patients with RVO. In particular, while IOP changes were seen in some patients, these could be easily controlled with medications, did not generally prevent retreatment, and surgery was not performed for IOP increase and/or glaucoma. This study demonstrated that the main benefit of treatment with the DEX implant 0.7 mg over other treatment modalities is its acceptable risk-benefit ratio and the long interval between injections. There are also likely to be cost savings from the use of the DEX implant 0.7 mg as well as an improvement in patient compliance, but further research is needed to establish this. In addition, data are awaited from the COMO study, which will allow the comparison of the relative safety and efficacy of DEX implant 0.7 mg and ranibizumab 0.5 mg, an anti-vascular endothelial growth factor medication. These are two different pharmacologic approaches that have very different mechanisms of action, and the findings of the COMO study should improve our understanding of the relative role of managing multiple inflammatory mediators in RVO. Data will also be available on the potential benefits of the different treatment schedules and the burden of the number of injections on patients and health care systems. Coupled with the findings of this retrospective, real-life study, data obtained should help determine future management choices in patients with RVO.

Acknowledgments

Project monitoring, data management and the statistical analysis of this study was provided by MEDIDATA GmbH and funded by the sponsor, Allergan Pharmaceuticals, Ireland. Editorial support was provided by Synergy Medical Communications, Richmond, Surrey, UK.

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM

References

1 Rehak J, Rehak M: Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. Curr Eye Res 2008;33:111–131.

2 Nehme A, Edelman J: Dexamethasone inhibits high glucose-, TNF-α-, and IL-1β-induced secretion of inflammatory and angiogenic mediators from retinal microvascular pericytes. Invest Ophthalmol Vis Sci 2008;49:2030–2038.

3 Scholl S, Augustin A, Lowenstein A, Rizzo S, Kuppermann BD: General pathophysiology of macular oedema. Eur J Ophthalmol 2011;21(suppl 6):S10–S19.

4 Haller J, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM; Ozurdex GENEVA Study Group: Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134–1146.

5 Haller J, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jiao J, Li XY, Whitcup SM; Ozurdex GENEVA Study Group: Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve month study results: twelve-month study results. Ophthalmology 2011;118:2453–2460.

6 Haller JA, Dugel P, Weinberg DV, Chou C, Whitcup SM: Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. Retina 2009;29:46–51.

7 Gregori NZ, Feuer W, Rosenfeld PJ: Novel method for analyzing snellen visual acuity measurements. Retina 2010;30:1046–1050.

8 Papathomas T, Tsagkataki M, Kumar I, Kamal A: Safety and efficacy of dexamethasone intravitreal implant in macular edema due to retinal vein occlusions – 1 year follow-up. Poster presented at the 2013 ARVO Congr, Seattle, May 2013.

9 Querques L, Querques G, Lattanzio R, Gigante SR, Del Turco C, Corradetti G, Cascavilla ML, Bandello F: Repeated intravitreal dexamethasone implant (Ozurdex) for retinal vein occlusion. Ophthalmologica 2013;229:21–25.

10 Pommier S, Meyer F: Résultats d'une étude multicentrique de l'implant de dexaméthasone dans l'oedème maculaire des oblitérations veineuses rétiniennes: étude REMIDO. Réalités Ophtalmol 2012;195:1–4.

11 Dodwell DG, Krimmel DA: Intraocular pressure in patients after multiple Ozurdex implants for retinal vein occlusion. Poster presented at the 2012 ARVO Congr, Fort Lauderdale, May 2012.

12 Capone A Jr, Singer MA, Dodwell DG, Dreyer RF, Oh KT, Roth DB, Walt JG, Scott LC, Hollander DA: Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (SHASTA study). Retina 2014;34:342–351.

13 Ferrini W, Ambresin A: Intravitreal dexamethasone implant for the treatment of macular edema after retinal vein occlusion in a clinical setting. Klin Monatsbl Augenheilkd 2013;230:423–426.

14 Coscas G, Augustin A, Bandello F, de Smet MD, Lanzetta P, Staurenghi G, Parravano MC, Udaondo P, Moisseiev E, Soubrane G, Yatziv Y, Loewenstein A: Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion. Eur J Ophthalmol 2014;24:1–9.

15 Yeh WS, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P, Whitcup SM, Kowalski JW: Effect of duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. Ophthalmology 2012;119:1190–1198.

16 Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, Murahashi WY, Rubio RG; for the BRAVO Investigators: Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1102–1112.

17 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;127:1101–1114.

18 Royal College of Ophthalmologists: Cataract Surgery Guidelines. Royal College of Ophthalmologists, 2007.

19 Ramezani A, Entezari M, Moradian S, Tabatabaei H, Kadkhodaei S: Intravitreal triamcinolone for acute central retinal vein occlusion: a randomized clinical trial. Graefes Arch Clin Exp Ophthalmol 2006;244:1601–1606.

20 Ip MS, Gottlieb JL, Kahana A, Scott IU, Altaweel MM, Blodi BA, Gangnon RE, Puliafito CA: Intravitreal triamcinolone for the treatment of macular edema associated with central retinal vein occlusion. Arch Ophthalmol 2004;122:1131–1136.

21 Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, Garretson B, Gupta A, Hariprasad SM, Bailey C, Reichel E, Soubrane G, Kapik B, Billman K, Kane FE, Green K; for the FAME Study Group: Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125–2132.

22 Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, Whitcup SM; for the Dexamethasone DDS Phase II Study Group: Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 2007;125:309–317.

23 Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG: Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:1594–1602.

24 Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG: Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 2011:118:2041–2049.

25 Moisseiev E, Goldstein M, Waisbourd M, Barak A, Loewenstein A: Long-term evaluation of patients treated with dexamethasone intravitreal implant for macular edema due to retinal vein occlusion. Eye 2012;27:65–71.

Downloaded by:
UB der LMU München
129.187.254.47 - 8/27/2018 3:45:14 PM