Current Eye Research

ISSN: 0271-3683 (Print) 1460-2202 (Online) Journal homepage: http://www.tandfonline.com/loi/icey20

Comparison of Dexamethasone Intravitreal Implant with Conventional Triamcinolone in Patients with Postoperative Cystoid Macular Edema

Georgios Mylonas, Michael Georgopoulos, Panagiotis Malamos, Ilias Georgalas, Chryssanthi Koutsandrea, Dimitrios Brouzas, Stefan Sacu, Christos Perisanidis & Ursula Schmidt-Erfurthon behalf of the Macula Study Group Vienna

To cite this article: Georgios Mylonas, Michael Georgopoulos, Panagiotis Malamos, Ilias Georgalas, Chryssanthi Koutsandrea, Dimitrios Brouzas, Stefan Sacu, Christos Perisanidis & Ursula Schmidt-Erfurthon behalf of the Macula Study Group Vienna (2016): Comparison of Dexamethasone Intravitreal Implant with Conventional Triamcinolone in Patients with Postoperative Cystoid Macular Edema, Current Eye Research, DOI: 10.1080/02713683.2016.1214968

To link to this article: http://dx.doi.org/10.1080/02713683.2016.1214968

Published online: 09 Sep 2016.

CURRENT EYE RESEARCH
http://dx.doi.org/10.1080/02713683.2016.1214968

Taylor & Francis
Taylor & Francis Group

Comparison of Dexamethasone Intravitreal Implant with Conventional Triamcinolone in Patients with Postoperative Cystoid Macular Edema

Georgios Mylonas[a], Michael Georgopoulos[a], Panagiotis Malamos[b], Ilias Georgalas[b], Chryssanthi Koutsandrea[b], Dimitrios Brouzas[b], Stefan Sacu[a], Christos Perisanidis[c], and Ursula Schmidt-Erfurth[a], on behalf of the Macula Study Group Vienna

[a]Department of Ophthalmology, Medical University of Vienna, Vienna, Austria; [b]1st Department of Ophthalmology, "G. Gennimatas" General Hospital of Athens, University of Athens, Athens, Greece; [c]Department of Cranio-, Maxillofacial and Oral Surgery, Medical University of Vienna, Vienna, Austria

ABSTRACT

Aims: To evaluate the efficacy of the treatment with intravitreal triamcinolone acetonide or dexamethasone intravitreal implant in patients with postoperative cystoid macular edema (PCME).

Materials and Methods: Thirty eyes of 29 patients with PCME were randomized into two groups: one group initially received an injection of 4 mg triamcinolone; retreatment after 3 months was dependent on functional and anatomic outcome in a PRN regimen. The second group received a single injection of the dexamethasone intravitreal implant (Ozurdex). Patients were followed for 6 months. The main outcomes were best-corrected visual acuity (BCVA) and central millimeter retinal thickness (CMMT).

Results: Mean BCVA improved significantly in both groups at 3 months ($p \leq 0.05$) and 6 months ($p \leq 0.05$) after treatment. There was no statistically significant difference between the two groups in visual acuity improvement at 3 months ($p > 0.05$) or 6 months ($p > 0.05$). Mean CMMT of both groups also decreased significantly after treatment at 3 and 6 months (both $p \leq 0.05$) and the reduction was significantly superior in the triamcinolone group compared to ozurdex group at 1 week and 6 months ($p \leq 0.05$). All cases with intraocular hypertension were managed with IOP-lowering medication and no surgery was required during the study. One patient was excluded because of endophthalmitis in the triamcinolone group.

Conclusion: Intravitreal triamcinolone and dexamethasone implant are both equally effective in increasing visual acuity in patients with PCME at a 6-month follow-up. However, macular edema seems to respond more rapidly with intravitreal triamcinolone, and 3-monthly repetitive injections maintain the reduction in retinal thickness better than a single dexamethasone implant at the first 6 months of follow-up period.

ARTICLE HISTORY
Received 1 February 2016
Revised 30 May 2016
Accepted 5 July 2016

KEYWORDS
Postoperative cystoid macular edema; intravitreal triamcinolone acetonide; dexamethasone implant; Ozurdex

Introduction

The treatment of chronic, refractory postoperative cystoid macular edema (PCME)/Irvine-Gass syndrome remains controversial and is one of the most common unexpected causes of poor postoperative visual acuity,[1] despite the improvements in surgical techniques.

The dexamethasone implant (Ozurdex; Allergan, Inc, Irvine, CA) is an innovative, biodegradable intravitreal implant containing dexamethasone, a highly potent corticosteroid, administered via a specially designed, single-use applicator.[2,3] Dexamethasone inhibits multiple inflammatory cytokines and has a relatively short half-life (3.5 hours) but it is found to have a five times stronger therapeutic effect than intravitreal triamcinolone. The United States Food and Drug Administration has approved Ozurdex 0.7 mg for the treatment of macular edema associated with retinal vein occlusion, diabetic macular edema, non-infectious ocular inflammation or uveitis affecting the posterior segment of the eye. Due to the extended release of corticosteroids in the intravitreal cavity achieved with this implant, a single injection can offer long-lasting improvement with benefits demonstrated to last for up to 6 months.[4]

At present, there is no standard approach to the treatment of chronic PCME, because there is a lack of randomized clinical trials and comparative effectiveness studies. The lack of large studies is perhaps due to the fact that most patients recover spontaneously (up to 80%) with full restoration of visual function within 3–12 months postoperatively.[5] However, the treatment of refractive PCME remains a challenge.

The aim of this study was to evaluate the functional and retinal morphological changes at 6 months, after a single dexamethasone intravitreal implant (Ozurdex) in patients with PCME and to compare this with intravitreally administered triamcinolone acetonide (VolonA®) in a pro re nata (PRN) regimen after the initial injection.

Patients and methods

The study was designed as a prospective, randomized, comparative interventional case series. All examinations were

CONTACT Michael Georgopoulos michael.georgopoulos@meduniwien.ac.at Department of Ophthalmology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/icey.

conducted at the Department of Ophthalmology, Medical University of Vienna, Austria and at the Department of Ophthalmology, University of Athens, G. Gennimatas. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committees. Before inclusion, all patients signed an informed consent after a detailed discussion explaining the potential risks and benefits of the examination and treatment procedures.

Each of the study patients enrolled had refractory (minimum 3 months) macular edema, developing after cataract extraction or vitreoretinal surgery. Exclusion criteria were a history of branch retinal vein occlusion, central retinal vein occlusion, wet macular degeneration, diabetic retinopathy, epiretinal membrane, uveitis or other inflammatory eye disease that could cause macular edema (ME) and history of previous systemic or intravitreal therapy in the last 3 months.

Patients were required to have a baseline central millimeter thickness (CMMT) of at least 300 μm and best-corrected visual acuity (BCVA) of 20/25 to 20/400 Snellen equivalents in the study eye.

Regimen and follow-up

Patients were randomly assigned to one of two treatment arms: 15 eyes received one initial injection of 4 mg triamcinolone (Triam group) and 15 eyes received one single dexamethasone intravitreal implant 0.7 mg (Ozurdex group). After 12 weeks (±1 week) and application of initial injection of 4 mg triamcinolone, PRN retreatment criteria were defined as follows: (1) intraretinal or subretinal fluid relevant for visual acuity reduction, detected by spectral-domain optical coherence tomography (SD OCT), (2) an increase of 50 μm in central subfield retinal thickness from the thinnest measurement from any prior scheduled study visit, and (3) a decrease in BCVA score ≥5 letters compared with the score from the previous scheduled study visit. If one of these conditions was met, patients received further injections of triamcinolone acetonide. Patients with dexamethasone intravitreal implant were observed for 6 months and then received PRN treatment based on previous criteria.

Retinal morphology scans (Spectralis SD-OCT, Heidelberg Engineering Inc., Dossenheim, Germany), slit-lamp examination including intraocular pressure (IOP) measurement examinations and biomicroscopy were performed at baseline, week 1, months 1, 3, and 6. BCVA testing using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a 4-m distance were performed at baseline, months 1, 3, and 6. Fluorescein angiography (Heidelberg Engineering, Heidelberg, Germany) was performed at baseline in all patients to secure the diagnosis and to exclude other retinal diseases.

Injection technique

In all subjects, intraocular injections were performed under sterile conditions in the surgery unit following standardized procedures.[6]

Volon A (triamcinolone) was withdrawn at a dose of 40 mg/ml into a 1-ml syringe. It was washed three times through a sterile filter with a sterile-balanced salt solution (in order to washout the preservative alcohol). It was then diluted and the volume reduced, to the effect that 4 mg/0.1 ml was injected. Both medications were injected at 3.5 mm distance from the limbus through the inferotemporal pars plana. All the examiners were unmasked to the injected medication used.

Analyses of anatomical and functional results

All statistical analysis of BCVA measurements in ETDRS letters and CMMT measurements in μm values was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and SPSS 17.0 software (SPSS, Inc, Chicago, IL, USA). A mixed model ANOVA was applied for comparison of treatments and a paired *t*-test was applied for comparison time points. For all tests, *P*-values of ≤0.05 were considered significant.

Results

Fourteen patients in Triam group and 15 patients in Ozurdex group were included. The mean ± standard deviation (SD) age of patients was 71 ± 12 and 73 ± 7 years in the Triam and Ozurdex groups, respectively. In total, 10 patients in Triam group and 11 in Ozurdex group were female. Twenty-nine eyes were followed-up until month 6; one patient was excluded because of endophthalmitis five days after triamcinolone injection; both eyes of a patient with bilateral PCME were included in the study.

Baseline characteristics of both groups were similar, with a visual acuity mean ± SD of 63 ± 13 ETDRS letters (20/50 snellen) for the Triam group and 60 ± 10 ETDRS letters (20/63 snellen) for the Ozurdex group and a CMMT of 516 ± 121 μm and 548 ± 110 μm for Triam and Ozurdex group, respectively.

The CMMT showed a significant difference compared to baseline in both groups one week after the initial treatment (difference baseline/1 week: $p < 0.001$ for both groups); however, the reduction was superior in the Triam group compared with Ozurdex group (−166 ± 124 μm and −142 ± 97 μm for Triam and Ozurdex group, respectively; one week intergroup comparison: $p = 0.04$).

One month after the initial treatment, the results were as follows: mean ± SD VA was 73 ± 11 and 73 ± 10 ETDRS letters (20/32 snellen) for the Triam and Ozurdex group sample, respectively (difference baseline/1 month: $p < 0.001$ for both groups); mean ± SD CMMT was 355 ± 59 μm in the Triam and 357 ± 69 μm in the Ozurdex group (difference baseline/1 month: $p = 0.003$ for Triam and $p < 0.001$ for Ozurdex group). No statistical significance between two groups was revealed at this time point (1-month intergroup comparison: $p = 0.86$ for VA and $p = 0.92$ for CMMT).

At 3-month follow-up, VA remained stable in both groups; Triamcinolone: 73 ± 11 ETDRS letters (20/32 snellen); dexamethasone: 72 ± 11 ETDRS letters (20/32 snellen) and with a slightly increase of CMMT to 389 ± 89 μm in the Triam and 391 ± 102 μm in the Ozurdex group. Both parameters showed a statistically significant difference comparing to baseline (difference baseline/3 months: $p = 0.001$ for Triam and $p < 0.001$ for Ozurdex group) and also no statistically significancant difference between the two groups was noted (3-month intergroup comparison: $p = 0.80$ and $p = 0.94$ for VA and CMMT, respectively).

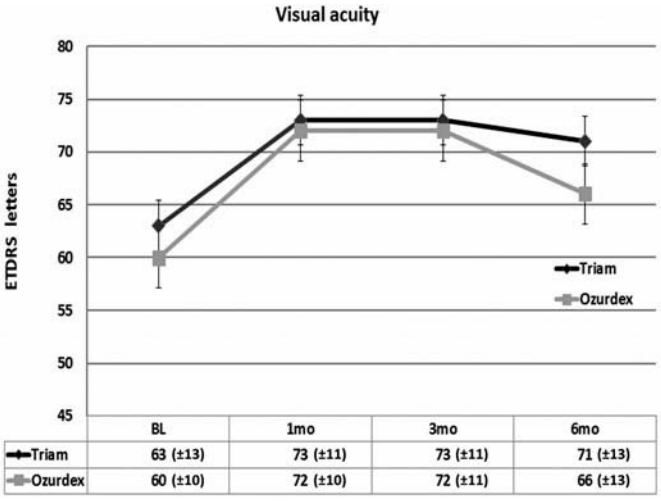

Figure 1. Mean ± standard deviation (SD)/error bars, changes from baseline best-corrected visual acuity (BCVA) of both groups over 6 months in ETDRS. Mean BCVA improved significantly compared with the baseline in both groups at 3 months and 6 months after treatment (both $p \leq 0.05$). At 6-month follow-up visit, BCVA was superior in Triam group; however, statistical analysis revealed no significant difference between two groups (6-month intergroup comparison: $p > 0.05$).

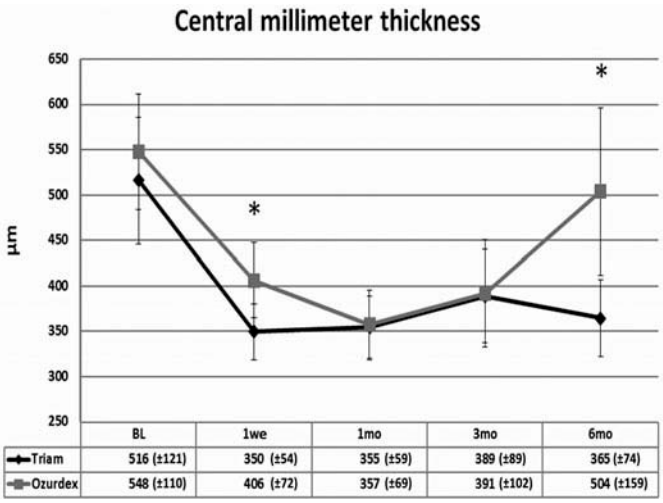

Figure 2. Mean ± standard deviation (SD)/error bars, changes from baseline CMMT over 6-months. Triamcinolone, as well as dexamethasone implant, induced a significant reduction of retinal thickness because of resolution of macular edema. Asterisks indicate a significant difference between groups at 6-month examination ($p \leq 0.05$).

After a follow-up period of 6 months, mean ± SD VA and CMMT remained relative stable in the Triam group [71 ± 13 ETDRS letters (20/32 snellen), 365 ± 74 µm CMMT]. In the Ozurdex group, a decrease in BCVA to 66 ± 13 ETDRS letters (20/40 snellen) and a CMMT increase to 504 ± 159 µm was observed. Compared with baseline, VA improvement and retinal thickness decline were statistically significant in both groups (VA difference baseline/6 months: $p = 0.001$ and $p = 0.009$ for Tiam and Ozurdex group, respectively, and CMMT difference baseline/6 months: $p = 0.002$ and $p = 0.05$ for Tiam and Ozurdex group, respectively). However, the CMMT reduction was superior in Triam group compared with Ozurdex group at 6 months in a statistically significant way (6-month intergroup comparison: $p = 0.01$). BCVA and CMMT measurements changes over the follow-up time are presented in Figures 1 and 2, respectively.

Six patients in Triam and eight patients in Ozurdex group had previous PPV for variable reasons (macular peeling, vitreomacular traction syndrome and retinal detachment). In this subgroup, it was noted in the funduscopy that the triamcinolone was rapidly reabsorbed from the vitreous cavity, so that at 1 week visit only traces of the drug was visible in the vitreous cavity and no drug at 1-month visit. In contrast, in the dexamethasone PPV subgroup the implant was visible in all patients at 1-month visit. In this subgroup analysis, data from patients with previous PPV showed a decrease of CMMT at 1 week visit in triamcinolone group (from 574 µm to 382 µm) and an increase to the following visits (399 µm to 482 µm at 3 and 6 months, respectively). In dexamethasone subgroup we had a reduction of CMMT until 1 month (from 574 µm to 389 µm) and then an increase at 3 and 6 months (438 µm and 550 µm, respectively).

Morphological response to treatment

In all patients, the resolution of subretinal fluid appeared to be faster than dissolution of central cysts and intraretinal fluid. At the 6-month visit, only 5 (5/14) patients in triamcinolone group and 3 (3/15) in dexamethasone group had no evidence of either intra- or subretinal fluid in OCT. Figure 3 shows a characteristic example of retinal thinning and dissolution of central cysts and intra- and subretinal fluid, followed by recurrent CME, with both investigated medications.

In the Triamcinolone group, patients received a mean of 1.4 out of 2 possible injections (19 out of 28). At the 6-month follow-up visit, five patients out of 14 needed an additional injection because of recurrent ME in Triam group and 10 out of 15 patients in Ozurdex group.

Adverse events

Within the observational period of 6 months, one patient in the Triam group was diagnosed with endophthalmitis five days after the injection and was excluded from the study. All cases of IOP elevation were managed readily by observation or topical pressure lowering medications and no glaucoma surgery was necessary. There were no treatment-related cases of retinal detachments or vitreous haemorrhage.

Discussion

This prospective study investigates the functional and morphological parameters of retinal integrity in patients undergoing intravitreal triamcinolone acetonide on an "as-needed" basis or a single dexamethasone intravitreal implant for the treatment of PCME, within the 6-month follow-up, using high-resolution SD OCT imaging.

Intravitreal injections of triamcinolone acetonide are a promising tool for refractory PCME, although there are no prospective randomized studies to date. Conway et al.[7] followed eight treated eyes of eight patients with refractory PCME over a mean follow-up period of 20 months and found that all patients experienced improvement in PCME both angiographically and clinically.

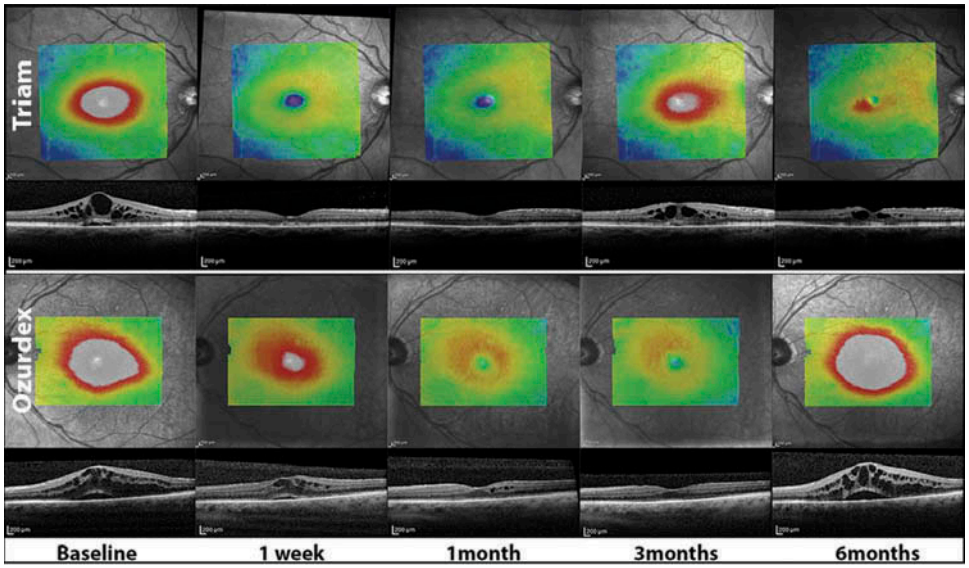

Figure 3. A representative case of topographic images of retinal thickness and SD-OCT B-scan over time in both investigated groups. In triam example (top), the patient initially received one intravitreal injection of triamcinolone and showed a rapid anatomic response with complete resolution of edema only one week later. According to the optical coherence tomography (OCT)-based retreatment regimen, further treatment was required at 3- and 6-month study visits, when pronounced recurrent edema occurred. In ozurdex example (bottom), the patient initially received a single intravitreal injection of the dexamethasone implant and showed a progressive (in contrast to triamcinolone injections) resolution of retinal fluid until 3 months. An additional injection was required at the 6-month study visit, when pronounced recurrent edema occurred.

A number of studies have investigated separately the intravitreal injections of triamcinolone acetonide[7,8] and dexamethasone implant[9] for treatment of PCME and noted the positive effects.

The BCVA and CMMT results were evaluated as the main functional outcome parameters. Both parameters improved during the follow-up period in both investigated groups. However, it seems that the macula edema responds more rapidly and significantly superior in the Triam group, that reached the maximum effect in macular thickness reduction only 1 week after the injection. Thereafter, it increased slightly until the next scheduled injection at 3 months. On the other side, the dexamethasone implant reached the maximum effect 1–3 months after the injection, following an increase in macular thickness at 6-month visit. This difference seems to be due to the pharmacokinetics of the two drugs. Triamcinolone fluid is absorbed faster from the retina in comparison to the slow-release dexamethasone implant. The Ozurdex implant, with its extended release in the intravitreal cavity, is supposed to be beneficial for at least 6 months. Unfortunately, in the present study it has been found to have a peak at the first to third post-treatment months that was not sustained for the entire 6-month observation period. An explanation could be a faster release of steroid-substance from the implant. Some studies have investigated the effect of repetitive intravitreal dexamethasone implant applications in eyes with diabetic ME[10] and ME due to retinal vein occlusion[11,12] and concluded also that repetitive intravitreal Ozurdex on an "as-needed" basis, with a retreatment interval shorter than 6 months, may produce long-term clinically meaningful benefits.

Dang Y et al.[13] also investigated the dexamethasone intravitreal implant and intravitreal triamcinolone acetonide for the treatment of pseudophakic cystoid ME in diabetic patients and showed that both treatments could effectively restore visual function and recover morphological change in this patient population for at least 6 months. However, repeated intravitreal injections are required in the Triam group. In our study, five patients in the Triam group required additional therapy at 3-month follow-up.

In the subgroup of patients with previous pars plana vitrectomy, we noted a rapid reabsorption of triamcinolone within 1 month after treatment, in contrast to the dexamethasone implant that was visible in fundoscopic examination in all patients at 1-month visit. Chin HS et al.[14] investigated the clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes and found that intravitreal triamcinolone acetonide decreases more rapidly in the vitrectomized eye than in the nonvitrectomized eye. Therefore, the faster clearance of intravitreal triamcinolone acetonide must be considered when planning intravitreal injection of triamcinolone acetonide in the vitrectomized eye in patients with postoperative ME.

Adverse events that are of the greatest concern with corticosteroid therapy include postoperative infectious endophthalmitis and increases in IOP.[15,16] In the present study, one treatment-related case of endophthalmitis occurred in the Triam group. All cases with intraocular hypertension were managed with IOP-lowering medication and no surgery was required during the study.

A significant limitation of this study is that it is based on an analysis of a relatively inhomogenous group of patients (with and without PPV) in terms of their response to treatment that may bias the results for the overall subset. The main reason for so many participants with previous PPV was, that current investigation took place mainly in our vitreoretinal department. Another limitation is the relatively small sample size (28 participants completed the study) of our study.

In conclusion, this prospective study suggests that repetitive intravitreal triamcinolone and a single dexamethasone intravitreal implant for the treatment of PCME have similar effects to VA but not to CMMT after 6 months. However, repetitive intravitreal dexamethasone implants on an as needed basis with shorter retreatment intervals may be essential to maintain the initial response.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Drolsum L, Haaskjold E. Causes of decreased visual acuity after cataract extraction. J Cataract Refract Surg 1995;21(1):59–63.
2. Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 2007;125:309–317.
3. 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.
4. Chang-Lin JE, Attar M, Acheampong AA, Robinson MR, Whitcup SM, Kuppermann BD, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci 2011;52:80–86.
5. Bradford JD, Wilkinson CP, Bradford RH. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina 1988;8(3):161–164.
6. Jaissle GB, Szurman P, Bartz-Schmidt KU. Recommendation for the implementation of intravitreal injections–statement of the German Retina Society, the German Society of Ophthalmology (DOG) and the German Professional Association of Ophthalmologists (BVA). Klin Monbl Augenheilkd 2005;222(5):390–395.
7. Conway ME, Canakis C, Livir-Rallatos C, Peyman G. Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg 2003;29:27–33.
8. Konstantopoulos A, Williams CP, Luff AJ. Outcome of intravitreal triamcinolone acetonide in postoperative cystoid macular oedema. Eye (Lond) 2008;22(2):219–222.
9. Williams GA, Haller JA, Kuppermann BD, Blumenkranz MS, Weinberg DV, Chou C, et al. Dexamethasone DDS Phase II Study Group. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. Am J Ophthalmol 2009;147(6):1048–1054, 1054.
10. Scaramuzzi M, Querques G, Spina C, Lattanzio R, Bandello F. Repeated intravitreal dexamethasone implant (Ozurdex) for diabetic macular edema. Retina 2015;35(6):1216–1222.
11. Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, et al. Ozurdex Geneva Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011;118:2453–2460.
12. Querques L, Querques G, Lattanzio R, Gigante SR, Del Turco C, Corradetti G, et al. Repeated intravitreal dexamethasone implant (Ozurdex®) for retinal vein occlusion. Ophthalmologica 2013;229(1):21–25.
13. Dang Y, Mu Y, Li L, Mu Y, Liu S, Zhang C, et al. Comparison of dexamethasone intravitreal implant and intravitreal triamcinolone acetonide for the treatment of pseudophakic cystoid macular edema in diabetic patients. Drug Des Devel Ther 2014;8:1441–1449.
14. Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. Retina 2005;25:556–560.
15. Armaly ME. Statistical attributes of the steroid hypertensive response in the clinically normal eye, I: the demonstration of three levels of response. Invest Ophthalmol 1965;4:187–197.
16. Becker B. Intraocular pressure response to topical corticosteroids. Invest Ophthalmol 1965;4:198–205.