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Dexamethasone Inserts in Noninfectious Uveitis

A Single-Center Experience

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Purpose: To report the effectiveness of repeated intravitreal dexamethasone (DEX) inserts in noninfectious uveitis patients.

Design: Prospective, single-center, interventional clinical trial between February 2010 and March 2015.

Participants: Patients with noninfectious uveitis with cystoid macular edema and/or vitreitis.

Methods: Patients were treated with a 700-μg intravitreal DEX insert (Ozurdex; Allergan, Inc., Irvine, CA). Follow-up visits were scheduled 1, 3, and 6 months after injection. Best-corrected visual acuity (BCVA), central retinal thickness (CRT), vitreous haze (VH) score, intraocular pressure (IOP), and adverse events were recorded.

Main Outcome Measures: Primary outcome was the reduction of CRT. Secondary outcome was the improvement in BCVA and reduction of VH.

Results: In total, 109 eyes of 76 patients received 298 DEX inserts. Fifty-two patients were women (68%). The mean age of all participants was 57 years (range, 24–88 years). More than 3 DEX inserts were injected into 44% of eyes. Mean number of injections were 1.54±0.5 (standard deviation [SD]), 1.98±0.84, and 2.46±1.1 over 12, 18, and 24 months, respectively. Central retinal thickness decreased significantly ($P < 0.001$) from 465 μm at baseline to 318, 342, and 388 μm after 1, 3, and 6 months, respectively. Similar trends were seen in eyes receiving a second, third, and fourth DEX insert. Patients with idiopathic uveitis and sarcoidosis benefited well from DEX inserts. The greatest overall benefit was achieved in patients with no systemic treatment and patients receiving antimetabolites and cyclosporin A. A significant VH score reduction was documented in 44% of eyes after 1 month. A gain of more than 3 lines in BCVA was recorded in 31% to 37%, 26% to 39%, and 8% to 32% of eyes after 1, 3, and 6 months, respectively. A transient rise in mean IOP after 1 month ($P < 0.001$) and after 3 months ($P = 0.001$) was seen.

Conclusions: The repeated longer-term administration of DEX inserts in noninfectious uveitis patients, either alone or in combination with other therapies, led to improved CRT, BCVA, and VH. Underlying diseases and concomitant systemic therapy seem to have an impact on overall treatment benefit. Ocular complications were reversible and were managed by local treatment, with exception of cataract formation. *Ophthalmology 2018;■:1–12 © 2018 by the American Academy of Ophthalmology*

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Noninfectious intraocular inflammation or uveitis remains a common cause of vision loss in the developed world. It accounts for 10% to 15% of blindness disproportionally affecting younger individuals.[1] The main cause of vision impairment in uveitis patients includes persistent intraocular inflammation with cystoid macular edema (CME) and vitreous haze (VH). Secondary sequelae can lead to cataract development and increased intraocular pressure (IOP). The treatment of intraocular inflammation of the posterior segment of the eye, including intermediate and posterior uveitis, remains a challenging issue. Initial treatment is based predominantly on corticosteroids, and up to two thirds of patients demonstrate disease control with steroids alone. In fact, there is a need for long-term therapy of chronic noninfectious intraocular inflammation. Many patients are intolerant to long-term application of steroids, and immune modulatory treatment is suggested commonly as a steroid-sparing option. A recently approved drug for noninfectious uveitis is adalimumab, a human anti–tumor necrosis factor α (TNF-α) agent, which is a new steroid-sparing option. But even when this goal can be achieved, introduction of immunosuppressive treatment does not result in better clinical and visual outcomes. Based on these strong effects, use of intraocular steroids has progressed.

In recent years, sustained-release intraocular inserts have been developed as depot devices to deliver steroids into the

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posterior segment.[2–5] Technological advances provide the possibility of administering the agent into the vitreous cavity with an easily injectable device. The most commonly administrated dexamethasone (DEX) insert (Ozurdex; Allergan, Inc., Irvine, CA) is a bioerodible device composed of a mix of polylactic acid and polyglycolic acid polymers that releases 700 μg of preservative-free DEX for up to 26 weeks.[6] Previous studies showed efficacy in treating retinal vein occlusion and uveitis, with effects lasting 3 to 6 months after a single injection.[2,7–9] Also, a meta-analysis based on data from 15 studies and 3859 patients reported on the efficacy of DEX inserts in diabetic macular edema (DME) refractory to anti−vascular endothelial growth factor (VEGF) therapy.[10] The HURON study in uveitis patients demonstrated a significant improvement in intraocular inflammation and visual acuity (VA) persisting for 6 months.[2] Because most of the patients have chronic inflammation with relapsing CME and VH, reinjections are indicated. Also, clinical experience indicates that the beneficial effect often has a shorter duration and subsequently patients require repeated injections. So far, only limited experience exists relating to the use of multiple applications. A retrospective, observational case series reported on a cohort of 27 patients, with 24 eyes receiving multiple inserts over a 17.3±1.8-month follow-up. However, only 7 eyes received more than 3 inserts.[11] In another retrospective, multicenter, noncontrolled study from Spain, a total of 82 eyes (63 patients) received DEX inserts. In this study, merely 15 eyes received more than 3 inserts.[12]

We report our experience to compare with these retrospective and heterogeneous findings. Our data are from a monocentric prospective study presenting long-term outcomes of consecutively enrolled uveitis patients receiving 3 or more DEX inserts within a 5-year study period. In addition, we show the response to treatment of different subgroups, taking into account the issue of adjustments in systemic treatment. Moreover, we highlight complications in long-term outcomes, including progression of cataract and increased IOP.

Methods

This single-center prospective study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the local ethics committee (EA4/093/15). Written informed consent was obtained from each participating patient.

The study included patients with noninfectious uveitis with clinical indications of significant CME, VH, or both who received DEX inserts between February 2010 and March 2015. Patients with birdshot retinochoroidopathy (BSRC) were included, whereas patients with multiple evanescent white-dot syndrome and acute posterior multifocal pigment epitheliopathy were excluded. Previous intravitreal treatments with other off-label corticosteroids or anti−VEGF agents were accepted if they were performed 3 months before the DEX insert was implanted. The retreatment decisions were determined based on the primary and secondary outcome parameters, when compared with baseline values. Although necessity to act on increases in central retinal thickness (CRT) with development of intraretinal fluid was assessed individually and was determined by our specialists (S.W., U.P.), VA improvements of less than 0.3 logarithm of the minimum angle of resolution (logMAR) units and VH decreases of less than 2 units by Standardization of Uveitis Nomenclature score (SUN) were considered retreatment criteria.

Clinical Data

Baseline characteristics for each participant included age, gender, mean follow-up, uveitis anatomic classification (intermediate uveitis, posterior uveitis, or panuveitis), specific diagnosis (cause), current systemic therapy, and previous intravitreal treatment. Two experienced uveitis specialists (U.P., S.W.) were in charge of tracking medical attendance, confirming the diagnosis, identifying indications for treatment, and administering of the DEX insert. In cases of CME or VH recurrences, further inserts were considered. Investigational workup, including serologic testing for syphilis, and Lyme disease, chest radiography, interferon-γ−release assay, and anterior chamber tap for viral antibody titer, in selected cases, was performed to rule out conditions resulting from infectious causes. The DEX inserts were administered under standardized conditions. An additional evaluation was scheduled for the working day after the application to check for injection-related complications.

All patients underwent a comprehensive ocular examination at baseline and prospectively scheduled follow-up visits 1, 3, and 6 months after injection. Data collected included the following: (1) Central retinal thickness (CRT) was measured by spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). (2) Best-corrected VA (BCVA) testing was performed in a routine clinical setting by experienced ophthalmologists with a Snellen chart. Objective refraction was mandatory; subjective refraction was performed as needed. For purposes of statistical analysis and easier comparability with previous results, conversion to logMAR equivalents was performed. In nonnumeric VA grades, denotations were used as follows: counting fingers, 2.0; hand movements, 2.3; light perception, 2.7; and no light perception, 3.0.[13] (3) Slit-lamp examination of the anterior and posterior segments was performed with a focus on recognizing complications. (4) Vitreous haze score was measured using a standardized scale in accordance with Standardization of Uveitis Nomenclature guidelines.[14] (5) Intraocular pressure was measured using Goldmann applanation tonometry. The measurement of CRT was determined as a primary outcome. As a secondary outcome, improvement in BCVA (≥+0.3 logMAR-unit change) and VH (≤−2-unit change or drop to 0) were recorded using the scale in conformance with the SUN guidelines.[15] Furthermore, IOP changes or adverse events were captured.

Statistical Analysis

The Shapiro-Wilk test, Kolmogorov-Smirnov test, and graphical methods using histograms were used to determine normal distribution. The paired-sample t test was used in case of normal distribution; otherwise, the Wilcoxon signed-rank test was performed for comparing medians. The chi-square test was used for comparing proportions of reduction of VH and improvement in BCVA. No missing data substitutions were made; missing data were excluded pairwise in all tests. A P value ≤ 0.05 was regarded as statistically significant. Statistical analyses were calculated using SPSS Statistics for Windows software version 24 (IBM Corporation, Armonk, NY). Figures were created using GraphPad Prism for Mac OS X software version 7.0 (GraphPad Software, La Jolla, CA).