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Intravitreal Dexamethasone as a Rescue for Anti-Vascular Endothelial Growth Factor Therapy in Neovascular Age-Related Macular Degeneration with Persistent Disease Activity and High Treatment Demand

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Abstract

Purpose: To assess the impact of switching to, or adding, an intravitreal dexamethasone implant (Dex; Ozurdex®) in anti-vascular endothelial growth factor (VEGF) therapy on disease stability and treatment intervals in eyes with neovascular age-related macular degeneration (nAMD) and persistent disease activity and high treatment demand.

Methods: This retrospective noncomparative multicenter longitudinal case series included pseudophakic eyes with nAMD and persistent retinal fluid despite regular anti-VEGF therapy (ranibizumab or aflibercept) that received at least 1 intravitreal Dex implant. Visual acuity, central retinal thickness (CRT), and intraocular pressure were recorded before, and after, the addition of Dex to anti-VEGF therapy.

Results: Sixteen eyes of 16 patients met the inclusion criteria of persistent fluid despite anti-VEGF therapy, under treatment intervals of ≤7 weeks in 14 instances. Patients were 80.9 ± 7.4 years old and had received 25.5 ± 17.4 anti-VEGF injections before Dex over a period of 36.4 ± 21.9 months before switching. The treatment interval increased from 5.5 ± 3.2 weeks between the last anti-VEGF and first Dex injection to 11.7 ± 7.3 weeks thereafter ($P = 0.022$). CRT remained stable (385.3 ± 152.1, 383.9 ± 129.7, and 458.3 ± 155.2 μm before switching as well as 12 and 24 months after switching; $P = 0.78$ and $P = 0.36$, respectively). An insignificant mean short-term early increase in visual acuity was not sustained over time.

Conclusions: The addition of Dex resulted in a relevant and sustained increase in treatment intervals, whereas CRT and visual acuity remained stable in these difficult-to-treat eyes. It may be discussed whether inflammation or other steroid-responsive factors play a significant role in cases of nAMD with nonsatisfactory responses to anti-VEGF.

Keywords: neovascular age-related macular degeneration, intravitreal anti-VEGF therapy, dexamethasone implant, Ozurdex, disease stability, burden of treatment

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Introduction

Macular degeneration is the most frequent cause of irreversible vision loss in the aging population, affecting nearly 200 million individuals globally. Moreover, it is anticipated that it will increase by 50% by 2040.[1,2] Of the 2 types of macular degeneration, the dry form progresses quite slowly, whereas exudative or neovascular age-related macular degeneration (nAMD) develops with more rapid visual deterioration, if left untreated.[3–5]

The pathophysiological mechanisms underlying vascular leakage and proliferation include, among others, an upregulation of vascular endothelial growth factor (VEGF). This is a key driver, which can be controlled by intravitreal anti-VEGF antibody injections. These not only prevent severe vision loss but may result in a relevant visual gain in the majority of cases.[6–8] Although the anatomic response to these intravitreally injected biologics is generally favorable in the majority of instances,[9,10] the durability of their effect is limited in a reasonable proportion of eyes as evidenced by the need for anti-VEGF injections for up to every 4 weeks because of persistent retinal fluid indicating insufficiently controlled disease activity.[11–15] In the long term, insufficiently controlled disease activity will result in progressive macular fibrosis or atrophy and secondary vision loss despite intensive therapy.[16]

Depending on the anti-VEGF drug used, insufficient response in the face of a high treatment density has been reported in 20%–40% of patients.[17] With the increase in treatment density, socioeconomic costs of treatment rise dramatically, and patient adherence declines in line with visual deterioration.[18–20] Switching of therapy to another drug on the market may, but must not go along with stabilization of visual acuity and a reduced, although in selected cases still unsupportable, treatment burden.[21] It thus seems that other disease mechanisms, not directly related to VEGF, may play a predominant role in these cases.

The role of inflammatory processes has been established in the development and progression of AMD and the growth of submacular neovascularization.[22] Inflammatory cytokines were found to be increased in nAMD with an insufficient anti-VEGF response.[23] Because corticosteroids are well-known for their ability to reduce inflammation and inhibit angiogenesis, their ocular application was investigated long before the use of anti-VEGF drugs.[22,24,25] Although the role of corticosteroids in diabetic maculopathy is well established,[26,27] these have only sporadically, and in small case series, been used in eyes with nAMD that do not respond sufficiently well to anti-VEGF drugs.[28–30] Under intravitreal triamcinolone acetonide, most patients demonstrated a short-term benefit with increased visual acuity, whereas its side effects, namely increased intraocular pressure (IOP)[24,25] and cataract progression,[24] inhibited a systematic research in this direction.

The intravitreal dexamethasone implant (Dex; Ozurdex®; AbbVie, Inc.), in contrast, has received anecdotal attention as an addition to anti-VEGF drugs for the long-term control of disease activity and visual acuity in selected cases. Previous research found that Dex might be of benefit in eyes with persistent disease activity despite switching from one anti-VEGF to another in maintaining visual function over 3 to 12 months. In addition, it seems that fewer anti-VEGF injections may be needed.[28] Therefore, this study was set up to further explore the effect of Dex in difficult-to-treat anti-VEGF-pretreated eyes on morphological and functional outcomes over a longer follow-up time of 24 months.

Patients and Methods

This retrospective noncomparative multicenter case series includes patients from 5 specialized eye centers in Switzerland (Berner Augenklinik, Bern; Jules Gonin Eye Hospital, University Hospital Lausanne, Lausanne; Pallas Kliniken, Olten; Swiss Visio Montchoisi, Lausanne; and the Centre Ophtalmologique de la Colline, Geneva). It was approved by the Ethics Committee of the canton of Berne (registration number 2022-00510) based on the general consent of all included patients to use their coded data for this retrospective analysis and performed in accordance with the International Council for Harmonisation E6 Good Clinical Practice Guideline, the Declaration of Helsinki in its latest version, and federal laws.

All patients presented with a long-standing and persistent nAMD as indicated by the presence of intra- and subretinal

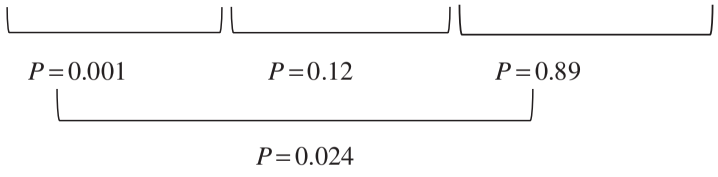
Table 1. Demographics for the Series of 16 Eyes (16 Patients)

Age (years; mean ± SD)	80.9 ± 7.4
Gender, *n* (%)	9 (56.3%) female 7 (43.7%) male
Time interval between first anti-VEGF injection and first Dex (months; mean ± SD, range)	36.4 ± 21.9; 10.3–76.3; Median: 31.5 (IQR: 16.1–53.8)
Follow-up after first Dex (months; mean ± SD)	39.1 ± 32.0 Median: 31.7 (IQR: 12.1–66.2)
Reason for switch to or addition of Dex	Persistent fluid (*n* = 13; 81.3%) High treatment demand (*n* = 3; 18.7%)
anti-VEGF injections before Dex (*n*)	25.5 ± 17.4 (range 10–71) Median: 18.0 (IQR: 12.0–30.8)
Treatment before first Dex	Aflibercept and ranibizumab (*n* = 8) Aflibercept (*n* = 3) Ranibizumab (*n* = 3) Aflibercept and bevacizumab (*n* = 1) Ranibizumab and Triamcinolone (*n* = 1)

IQR (25%–75%).
IQR, interquartile range (25%–75%); VEGF, vascular endothelial growth factor; SD, standard deviation.

Table 2. Injection Intervals Between Last Anti-Vascular Endothelial Growth Factor and First Dex, First and Second Intervals After Switch to Dex and Persistent Fluid (Intra- or Subretinal Fluid)

Eye	*No. of Dex implants*	*Mean interval before Dex (weeks)*	*Interval between last anti-VEGF and first Dex (weeks)*	*Interval between Dex and first injection thereafter (weeks)*	*First interval after first Dex (weeks)*	*Second interval after first Dex (weeks)*	*Presence of fluid at switch to Dex*	*Presence of fluid 12 months after first Dex*
1[a]	1	5.8	4.0	6.0	6.0	5.0	Yes	Yes
2	1	7.3	5.0	12.0	24.0	10.0	Yes	Yes
3[a]	1	10.1	5.0	4.0	13.0	11.0	Yes	Yes
4	1	5.6	4.0	14.3	7.0	5.7	Yes	Yes
5	1	5.8	6.3	16.7	8.3	12.7	Yes	Yes
6[b]	1	10.9	6.4				Yes	Yes
7[b]	1	4.3	4.1				Yes	Yes
8	1	6.8	7.1	24.0	4.0	6.0	Yes	Yes
9[a]	2	7.4	1.1	4.0	4.0	4.0	Yes	Yes
10	3	5.9	3.0	27.0	25.0		Yes	No
11	4	4.6	4.3	19.6	18.9	12.4	Yes	Yes
12	5	5.0	5.0	15.4	14.6	19.4	Yes	Yes
13	6	4.0	7.0	17.0	15.0	21.1	Yes	Yes
14	10	8.4	1.4	10.0	6.0	10.0	Yes	Yes
15[c]	1	5.0	13.6	31.4	4.0		Yes	Yes
16[c]	5	5.4	11.3	18.0	13.0	12.0	Yes	Yes
Total (mean ± SD; weeks)		6.4 ± 2.0 (median: 5.8, IQR: 5.0–7.4)	5.5 ± 3.2 (median: 5.0, IQR: 4.0–6.9)	15.7 ± 8.2 (median: 16.1, IQR: 9.0–20.7)	11.6 ± 7.2 (median: 10.7; IQR: 5.5–16.0)	10.8 ± 5.4 (median: 10.5; IQR: 5.8–12.6)		



[a]Combination therapy with Dex and anti-VEGF agents required because insufficient control of disease activity under a high anti-VEGF treatment demand.
[b]Desease stability in the first year after first Dex, treatment continued with anti-VEGF later.
[c]Dex was considered in 2 eyes because both patients were unable to further support regular injections owing to their general health condition.

fluid that was insufficiently controlled by intravitreal ranibizumab and/or aflibercept in treatment intervals below 8 weeks. According to medical judgment, these qualified for rescue therapy to prevent further visual deterioration. All included eyes had been switched from their primary anti-VEGF therapy to an approved alternative anti-VEGF drug and failed to stabilize the disease (absence of intra- and absence or stability of subretinal fluid) over at least 6 months following a treat-and-extend protocol. Dex is not approved for use in nAMD. In the absence of further approved options, its off-label use was considered in the here reported instances in addition to insufficiently responsive anti-VEGF treatment. All eyes were pseudophakic and had a well-controlled IOP (≤20 mmHg) before the first Dex implantation.

All eyes received at least 1 Dex implantation in addition to, or following, their current anti-VEGF therapy with the aim of reducing their anti-VEGF treatment demand. Given the unpredictable response to Dex, patients were seen monthly and treated on an as-needed or pro re nata basis after switch based on change in visual acuity and central retinal thickness (CRT).

The following exclusion criteria were applied: phakic eyes; anti-VEGF treatment duration of <1 year; structural damage to the fovea without reading potential (defined as a distance Snellen visual acuity <0.1); relevant subfoveal hemorrhage (>1/2 optic disc diameter); any previous treatment using photodynamic therapy, radiotherapy, vitreoretinal surgery, or triamcinolone injections; other underlying ocular diseases (ie, diabetic maculopathy, advanced diabetic retinopathy, end-stage glaucoma, uveitis, vitreoretinal traction and/or tractional epiretinal membrane); aphakia; complicated cataract surgery within 6 months before Dex implantation. The primary outcome was the impact of adding a corticosteroid on treatment intervals. Key secondary outcomes included the impact of Dex on disease activity, as measured by change in CRT, long-term treatment demand, and change in visual acuity after the addition of Dex.

Data were retrospectively collected from electronic medical records before the initiation of anti-VEGF therapy (baseline), 3, 6, and 12 months after beginning anti-VEGF therapy, 6 months before switching, at the time of switching therapy, and 3, 6, 12, and 24 months thereafter. The following data were retrieved: best-corrected Snellen visual acuity (BCVA), IOP, CRT, and the presence of foveal intra- and subretinal fluid in optical coherence tomography. For statistical analysis, BCVA was converted to Early Treatment of Diabetic Retinopathy Study (ETDRS) letter scores, where a Snellen BCVA of 1.0 is defined as 85 ETDRS letters.[31] Along with the total number of injections per eye, the last interval before switching as well as the injection intervals following switching and number of injections per year after switching were recorded.

Descriptive statistics were applied for descriptive data. The Shapiro–Wilk test was applied to control for the data distribution pattern and revealed that the data were not normally distributed. Data are presented as mean ± standard deviation as well as median with 25% and 75% interquartile ranges (IQRs). The Wilcoxon signed-rank test was applied to compare longitudinal data over time (this test can be considered the nonparametric equivalent of the paired-sample *t*-test), and the Friedman test for related samples to compare multiple time points (nonparametric alternative to the 1-way repeated-measures analysis of variance). A group comparison was calculated using the Mann–Whitney *U*-test. All statistical analyses were performed using the SPSS software package V.27 (SPSS, Inc., Chicago, IL) and R (version 3.2.4; R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, 2016).

Results

This retrospective multicenter study included a total of 16 anti-VEGF pretreated eyes (15 patients). Of these, 14 presented an insufficiently controlled nAMD despite injection intervals ≤7 weeks, whereas 2 patients (2 eyes) did not tolerate their treatment density despite intervals of >10 weeks because of their general health condition. Demographic data on this cohort are given in Table 1. Table 2 provides the number of Dex implantations, the individual intervals between the last anti-VEGF and the first Dex, the first and second intervals after switching to Dex, and the change in CRT between the switch and 1 year after. Of the 16 eyes, 9 (56.3%) had only 1 Dex implant, after which they continued with anti-VEGF only; 2 eyes continued therapy only with Dex, whereas the remaining 5 continued with ranibizumab or aflibercept in addition to Dex. ''A'' and ''B'' in Table 3 show the number of anti-VEGF injections per year after the first Dex.

The main outcome was that visual acuity slightly improved within the first 3 months after implantation and remained widely stable thereafter over the following 2 years [Fig. 1A, change in BCVA over time (total sample); Friedman test for related samples: $P = 0.15$; Fig. 1B, the same results for eyes that received 1 Dex only, change over time: $P = 0.61$]. CRT correspondingly improved after Dex implantation across the whole sample, but this effect was lost 6 months after the first Dex (Fig. 2, change over time: Friedman test for related samples, total sample, and for eyes

Table 3. Number of Anti-Vascular Endothelial Growth Factor Injections Per Year After The First Dexamethasone Implant, A. For All Eyes and B. For Eyes After 1 Dex Injection Only

	n	*Mean ± SD*	*Median*	*IQR*
A.				
First year	16	3.8 ± 3.9	4.0	0–5.8
Second year	14	4.1 ± 3.8	3.5	0–7.3
Third year	13	4.8 ± 4.6	5.0	0–8.0
Fourth year	12	3.5 ± 4.6	0	0–8.8
Fifth year	12	3.0 ± 3.9	0	0–7.3
	n	*Mean ± SD*	*Median*	*IQR*
B.				
First year	9	4.2 ± 3.6	4.0	1–5.5
Second year	8	5.3 ± 4.1	6.0	0.8–7.8
Third year	9	4.2 ± 4.6	3.0	0–8.0
Fourth year	8	3.4 ± 4.7	0	0–8.8
Fifth year	8	2.6 ± 3.7	0	0–7.3

IQR (25%–75%).

that received 1 Dex only, $P = 0.44$). When comparing CRT at switch to the timepoints after first Dex, based on the extended treatment intervals none of the single comparisons was significant (Wilcoxon signed-rank test >0.05).

At the switch, all 16 eyes presented intra- and/or subretinal fluid in the central retinal perimeter while the presence of pigment epithelial detachment was not recorded. Of these, 1 eye became completely dry within 12 months, whereas fluid persisted in 15 eyes (Table 2).

IOP increased after switching to Dex in the total sample from 12.6 ± 3.7 (median 12.0, IQR: 10.0–16.0) mmHg to 16.3 ± 4.7 (median 17.0, IQR: 10.8–20.5) mmHg 1 month

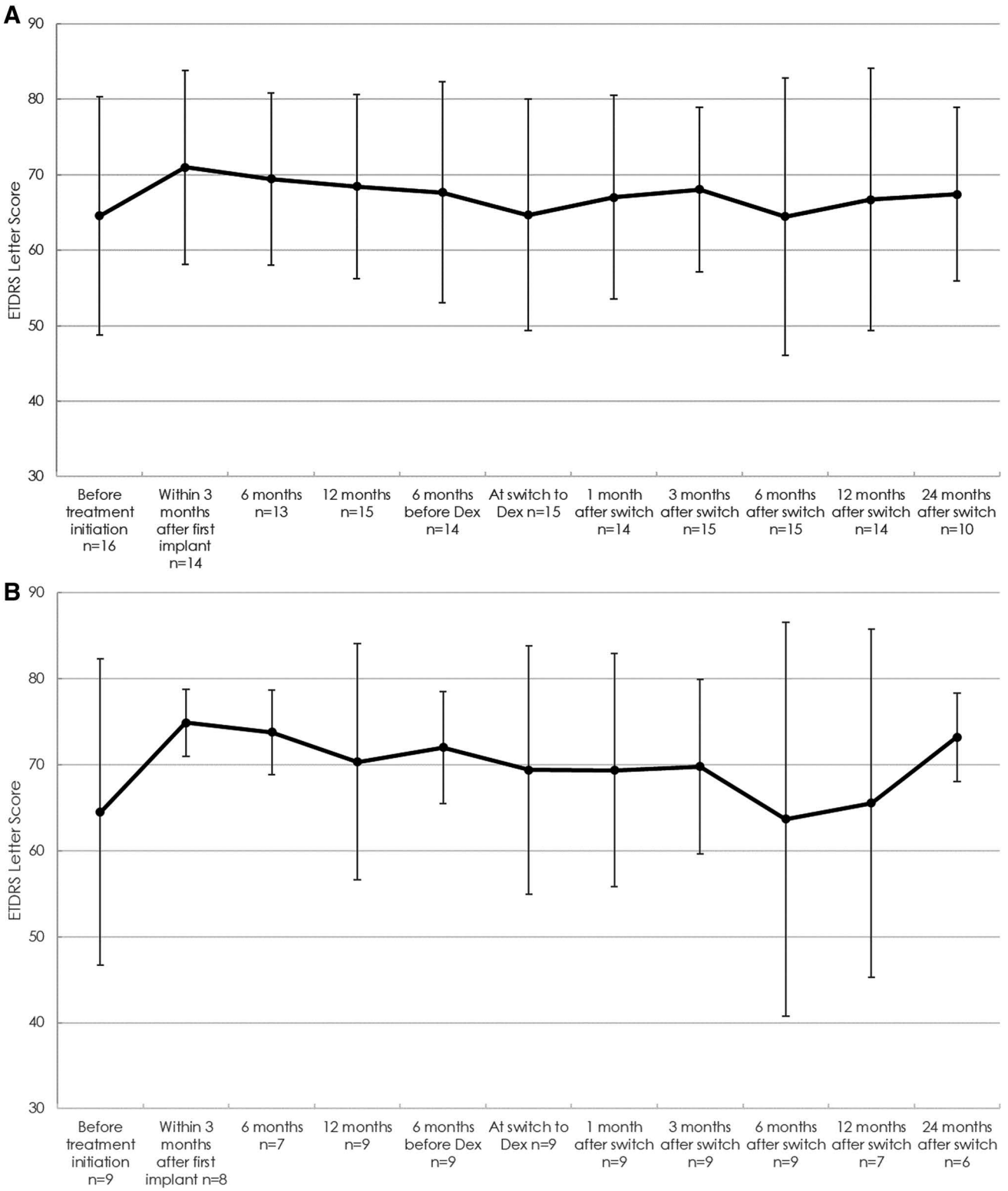


FIG. 1. Evolution of best-corrected visual acuity for all eyes **(A)** and for eyes with 1 implantation only **(B)**. Friedman test $P > 0.05$. ETDRS, Early Treatment of Diabetic Retinopathy Study.

after the first Dex ($P = 0.006$), and thereafter decreased again to baseline values after 12 months (12.9 ± 4.2, median 11.5 mmHg, IQR: 9.8–16.5, $P = 0.40$; Fig. 3).

The interval between the last anti-VEGF injection and the first Dex was 5.5 ± 3.2 weeks (median 5.0, IQR: 4.0–6.9), which increased to 11.7 ± 7.3 (median 10.7, IQR: 5.5–16.5) weeks from the first Dex to the next injection (Wilcoxon signed-rank test: $P = 0.022$).

In eyes receiving >1 Dex, the injection intervals could significantly be extended compared with the last interval before the switch, whereas this extension was not significant for eyes with only 1 Dex (Table 4).

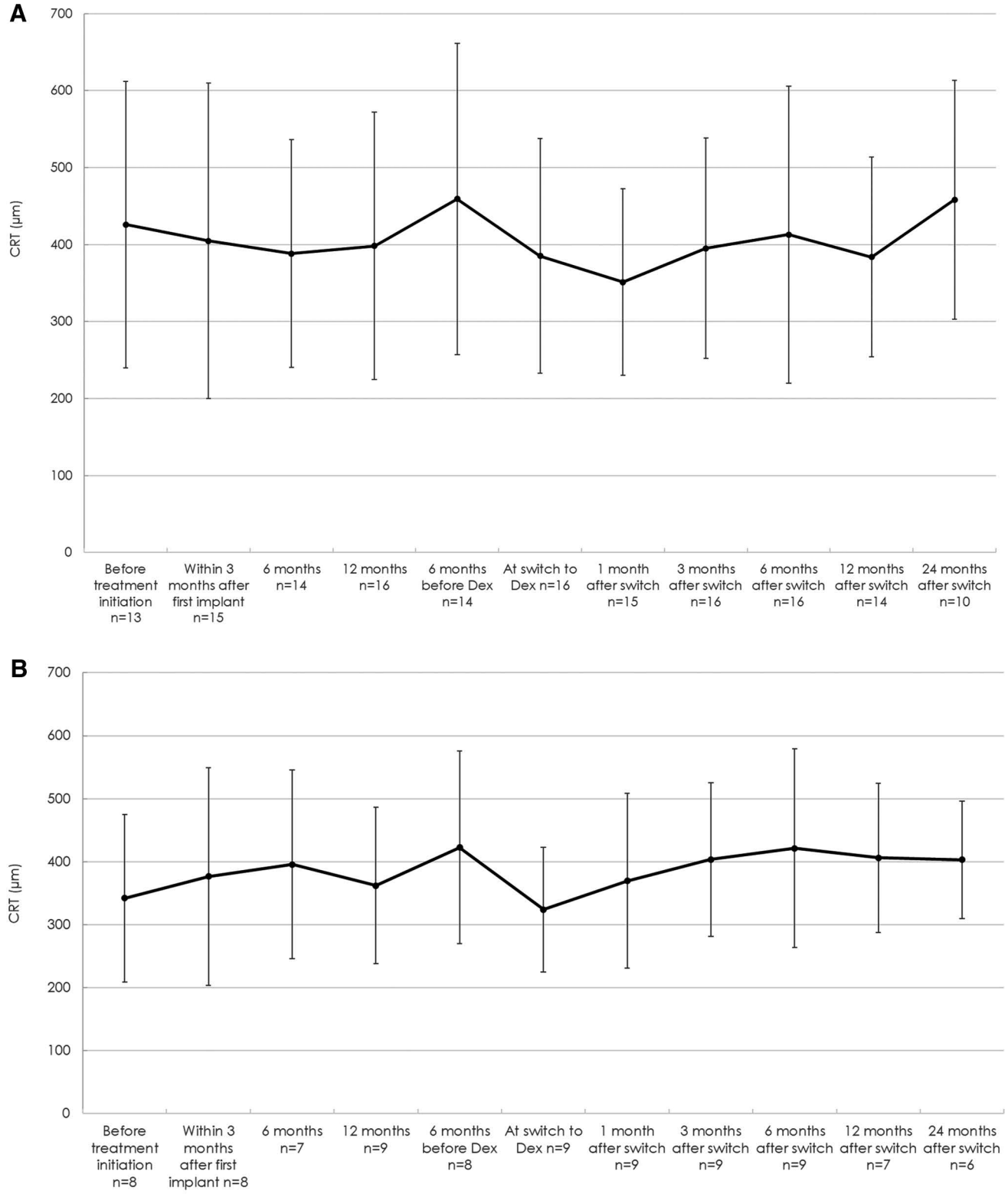


FIG. 2. Evolution of CRT for all eyes **(A)** and for eyes with 1 implantation only **(B)**. CRT, central retinal thickness.

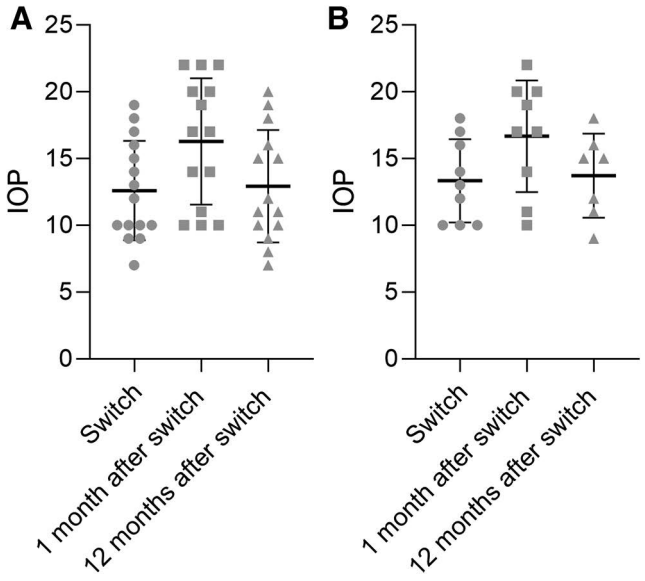


FIG. 3. IOP at switch to Dex and at 1 and 12 months of follow-up for all eyes **(A)** and for eyes with 1 implantation only **(B)**. For all eyes IOP from switch to 1 month after switch: $P=0.006$; from switch to 12 months after switch: $P=0.40$ **(A).** For eyes with 1 implantation only: from switch to 1 months after switch: $P=0.044$; from switch to 12 months after switch: $P=0.25$ **(B)**. IOP, intraocular pressure.

Discussion

From a clinical perspective, this real-life study provides interesting insights into the handling of eyes with nAMD that is insufficiently controlled under anti-VEGF therapy: The addition of Dex resulted in a relevant and sustained increase in treatment intervals and a reduced treatment burden, while it stabilized, but did not improve, visual function in the long term. Disease stability, that is, the absence of retinal fluid, was achieved in only 1 eye (6%). Obviously, corticosteroids were used late in the course of treatment when structural damage prevented a visual gain. The aim of adding Dex treatment was to reduce the treatment burden for the affected patients and to maintain their residual visual function. It seems that persistent disease activity despite dense anti-VEGF treatment is a rare finding, probably, because many patients have already stopped treatment because of futility before being offered this off-label treatment option.

Although we have not formally undertaken a cost-effect analysis, the use of Dex seems to be anti-VEGF drug-sparing and thus cost-effective, although a ''game changer effect'' was not observed. Of interest, this effect was similar in eyes that received a single Dex implant to that of those under ongoing Dex treatment. Adding to earlier reports with a shorter follow-up,[28,32] our study shows that the effect on treatment intervals was maintained over 2 years, although the majority of eyes in this series received a single Dex injection only. It is worth noting that the potential for interval extension was already detectable soon after the first Dex, which facilitates the further treatment decision as to whether or not to proceed with Dex.

It is conceivable that the number of eyes showing a benefit from Dex would increase if it were used less reluctantly, and we cannot predict whether some of the eyes that received 1 single Dex implant would have developed a more pronounced response under consecutive Dex therapy. A potential benefit to maintaining disease stability could be the retinal thickness. As has been known that visual acuity decreases with time in nAMD patients under the treatment regimen of anti-VEGF, the retinal thickness fluctuates, which may cause this decrease. This could play an important role for maintaining visual acuity and be of possible benefit when considering treatment options, as studies have investigated the outcome of retinal thickness fluctuations on visual acuity during therapy with anti-VEGF and showed that intraretinal fluid fluctuations caused a significant decrease of visual acuity.[33,34]

Furthermore, the absence of a standard retreatment protocol for Dex in our series prevents the evaluation of potential long-term benefits from adding Dex to, or replacing, anti-VEGF therapy. In line with previous reports, our patients achieved stability, but not improvement, of their visual function under Dex.[28,35] The fact that this treatment was generally well tolerated may provide an argument in favor of Dex if, under a treat-and-extend protocol, a treatment interval of 8 weeks cannot be exceeded in the long term.

Table 4. Injection Intervals (Weeks) Between Last Anti-Vascular Endothelial Growth Factor and First Dex, First and Second Intervals After Switch to Dex in Eyes With Only 1 Dex Compared With Eyes With >1 Dex

	Eyes with 1 Dex (n=9) Mean±SD Median, 25%–75% IQR	*Eyes with >1 Dex (n=7) Mean±SD Median, 25%–75% IQR*	P[a]
Interval between last anti-VEGF and first Dex [1]	6.2±3.0 5.0, 4.1–6.8	4.7±3.6 4.3, 1.4–7.0	0.35
First interval after first Dex [2]	9.5±7.1 7.0, 4.0–13.0	14.0±7.3 15.0, 6.0–19.6	0.26
Second interval after first Dex [3]	8.4±3.2 8.0, 5.5–11.4	13.4±6.2 13.3, 8.5–19.5	0.18
Change within the group (Wilcoxon signed-rank test, *P* values):			
[1] vs. [2]	0.50	0.018	
[1] vs. [3]	0.08	0.028	
[2] vs. [3]	0.67	0.69	

IQR (25%–75%).
[a]Mann–Whitney *U*-test for group comparison.

As an inherent weakness of this retrospective multicenter study, the limited sample size, which is associated with the off-label use of this treatment in nAMD, does not allow robust conclusions to be drawn. On the contrary, we provide a homogeneous sample of patients and proper follow-ups. We have recorded the last treatment interval but have not documented the evolution of treatment intervals before switching. Furthermore, there was no unified protocol regarding retreatment criteria after the addition of Dex to the anti-VEGF therapy. The reasons for not proceeding with Dex in more than half of the eyes were manifold and include, among others, patient wishes, physician estimation of the impact of Dex on disease, and cost coverage for this off-label therapy for nAMD by the health insurance companies in Switzerland. The mean follow-up time of 2 years, on the contrary, adds to the strengths of this cohort study because it shows a potential long-term impact of Dex on disease activity in selected cases.

Clearly, newer, stronger, and longer acting anti-VEGF therapies such as brolucizumab (FDA approved in 2020 for nAMD) and faricimab (FDA approved in 2022 for nAMD) have been added to our armamentarium in eyes with insufficiently controlled disease activity and probably contributed to a reduction in the proportion of eyes with persistent disease activity. Nevertheless, still >10% of eyes present with persistent disease activity despite treatment intervals of <8 weeks, and according to our experience, this percentage slowly increases as the treatment lasts longer. There is, thus, still an unmet therapeutic need in these eyes, which may be linked to lesion size or different disease pathomechanisms in addition to the upregulation of VEGF.[6,36] The most broadly discussed among these is chronic inflammation linked to the subretinal and sub-retinal pigment epithelium (RPE) deposits associated with a limited phagocytotic capacity of the RPE and consecutive free oxygen radical accumulation in the outer retina as a consequence of mitochondrial dysfunction.[37,38]

On pathophysiological grounds, this clearly supports the use of corticosteroids.[39] This contrasts, however, from a clinical perspective with their limited effect. The latter could be explained by the advanced stage of chronic neovascular disease and the increase in large and thick fibrovascular submacular tissue. Arguably, an earlier addition of corticosteroids might evoke a stronger and longer lasting effect on disease activity and treatment demand.[32] The latter consideration might be included in the conceptualization of a prospective study in this field. And indeed, in diabetic maculopathy, better functional and anatomic outcomes have been achieved with the use of Dex as a rescue therapy in insufficiently controlled instances.[40] Moreover, a reduction in the burden of treatment has proven to be favorable with regard to treatment adherence and patient compliance.[30,41] A combination of anti-VEGF with other therapies may reduce the number of intravitreal anti-VEGF injections in nAMD as in retinovascular diseases.[29,32]

In conclusion, the addition of Dex in our series contributed to a reduction in the number of intravitreal anti-VEGF injections over up to 2 years, and it improved, but did not fully control, persistent fluid and disease activity. Its potential side effects, that is, increased IOP, conjunctival or vitreous hemorrhage, as well as cataract progression have to be balanced against the benefits in each given case,[39] which were not responsible for a change in treatment in any of our patients. A larger sample size as well as randomized controlled studies would be required to evaluate the role of Dex as an adjunct in routine treatment for difficult-to-treat eyes with persistent disease activity owing to nAMD.

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Author Disclosure Statement

J.G.G., A.A. and I.M. act as advisors to, and speaker for, several pharmaceutical companies (AbbVie, Bayer, Novartis, and Roche) and have contributed to several international studies, which have no bearing on the outcomes presented here. The authors received neither direct nor indirect support for this study, or do they have any conflicting interests regarding the data presented in this report. M.P., C.T., D.N., I.B.P., and C.S. do not report any competing activities or interests.

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