Differential response to intravitreal dexamethasone implant in naïve and previously treated diabetic macular edema eyes

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Abstract

Background: To identify different response patterns to intravitreal dexamethasone implants (IDI) in naïve and previously treated (PT) diabetic macular edema (DME) eyes in a real-life setting.

Methods: 342 IDI injections (203 DME eyes) were included. Number of IDI injections, percentage (%) of eyes with 1, 2, 3 and ≥ 4 injections, time to reinjections, visual acuity (VA), intraocular pressure (IOP) and central retinal thickness (CRT) were evaluated for naïve and PT DME eyes over 24 months.

Results: Mean number of injections was significantly lower in naïve vs PT DME eyes (1.40 ± 0.9 vs 1.82 ± 0.9, p < 0.001). The percentage of eyes receiving 1 injection was significantly higher in naïve vs PT DME eyes (76.1 vs 47.7), (p < 0.001). However, it was significantly lower for 2 (16.4 vs 29.4), or 3 injections (1.4 vs 17.6) (both p < 0.001), with no differences in eyes receiving ≥4 injections (5.9 vs 5.1 respectively, p = 0.80). Mean time to reinjection was not significantly different between both groups for the second, third and fourth injection (9.6 ± 4.0 vs 10.0 ± 5.5, p = 0.75, 13.2 ± 4.0 vs 16.0 ± 3.5, p = 0.21 and 21.7 ± 3.8 vs 19.7 ± 5.8, p = 0.55). VA scores were consistently better in naïve vs PT DME eyes at all studied timepoints, with no significant differences in CRT reduction or adverse effect rates.

Conclusion: Naïve DME eyes received lower number of IDI injections and showed better VA levels than PT DME eyes for 24 months in a real-world setting. This data supports the IDI use in early DME stages and provide further evidence of better IDI response when used as first-line therapy.

Keywords: Diabetic macular edema, Real world setting, Naïve, Previously treated, Refractory, Dexamethasone, Implant, Ozurdex, Audit, Benchmark standard

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Summary statement
Intravitreal dexamethasone implants provide better response in naïve than previously treated diabetic macular edema eyes with better visual outcomes and lower number of injections over 24-months, in a large real-world cohort of eyes treated in routine clinical care outside clinical trial criteria.

Background
Diabetic macular edema (DME) is a complex disease of multifactorial origin in which fluid accumulates in the retinal layers due to the disruption of blood retinal barrier and increased vascular permeability [1–3]. Treatment options to manage DME include intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) or intravitreal corticosteroids (i.e. dexamethasone, fluorocinolone acetonide and triamcinolone acetonide) [4–6]. The intravitreal dexamethasone implant (IDI, 0.7 mg, Ozurdex®: Allergan, Inc., CA, USA) is a biodegradable, sustained-release drug delivery system that releases dexamethasone into the vitreous for up to 6 months, and is currently approved for the treatment of macular edema secondary to retinal vein occlusion [7], non-infectious posterior uveitis [8] and DME, based on the results of the MEAD trial [9]. This study pooled the data from 2 randomized, multicenter, masked, sham-controlled, phase 3 clinical trials (ClinicalTrials.gov identifiers NCT00168337 and NCT00168389), that demonstrated visual and anatomic improvements in DME eyes, which were confirmed in subsequent trials [10, 11].

However, significant concerns appear with regards to the applicability of clinical trials results to real world scenarios. First, in clinical practice, the selection criteria are less strict, usually limited to failure of other therapies. This fact is especially relevant as eyes treated with IDIs in routine clinical practice are often those in which other therapies have primarily failed (laser, anti-VEGFs, etc.) and are at risk of developing chronic macular edema, limiting their potential for greater visual gains. Second, the visit and treatment schedule applied in clinical trials rarely reflects real world clinical conditions. In particular, in the MEAD trial reinjections of the IDI could not be performed prior to 6-months, limiting the potential of the implant to achieve greater visual gains in poor responsive eyes. Third, the potential loss of follow-up visits can produce an overestimation of the benefits and/or an underestimation of its side effects, affecting either way the outcomes reported in comparison to clinical trials. For these different reasons, it is important to evaluate the IDI performance in real-life scenarios.

Currently, anti-VEGF therapies are considered the first-line therapy for DME, and meanwhile the importance of corticosteroid therapy has been recognized it is mainly employed as a second-line therapy. As suggested by the EURETINA guidelines for the management of DME [12], IDIs are only considered as first-line therapy in patients whose medical history excludes the use of anti-VEGF therapies or in specific conditions: history of major cardiovascular events, unwillingness to receive monthly injections, or pseudophakic patients. Nevertheless, there is a growing body of evidence in the last years supporting the benefits of IDIs in naïve DME patients, and several studies have reported better visual outcomes compared to refractory DME eyes [13, 14]. In contrast, very few studies have evaluated specifically the treatment frequency and the number of injections in naïve DME eyes compared to previously treated eyes.

Thus, the purpose of the present study is to audit the use of the IDI in a large series of DME eyes treated in real-life clinical conditions, to identify different treatment patterns in naïve versus previously treated eyes. The study was performed over a 5-year period at two tertiary referral retinal units from a well-defined geographic area that covered a population of 1.8 million individuals. In addition, a specific sub-analysis was carried out to identify differences in baseline characteristics, VA, anatomical outcomes, number of injections and reinjection frequency in naïve eyes (defined as eyes with no prior intravitreal therapies) and previously treated eyes (which previously received intravitreal drugs). The results obtained were compared to those reported in the literature in clinical trials (e.g., MEAD, CHAMPLAIN, BEVOR-DEX) and previous real world published studies, to address the performance of IDI in a large cohort of unselected DME eyes in real-life conditions.

Methods
Study design
This study was approved by the Institutional Review Board (IRB) at the Hospital Clinic of Barcelona and it was conducted in accordance with the Tenets set forth in the Declaration of Helsinki (HCB/2016/0905). Clinical data were collected retrospectively from 2 specialized tertiary referral retina clinics in Barcelona (Spain): Institut Clinic de Oftalmología (ICOF) at Hospital Clinic of Barcelona and Hospital Vall d’Hebrón. No written informed consent was required as data was retrospectively collected from routine clinical care, as approved by the reference IRB. All eyes receiving IDI injections for DME between October 2010 and May 2015 were included in the study. A comprehensive dataset was distributed and completed in both study centers within the predetermined timeframe. Patient identifiers were removed to anonymize the data, and data from the individual centres were collated and merged into a centralized database for analysis.
Clinical data collection
Data collected included demographics (age, gender, etc.), laterality, previous local treatments, number of previous injections, number of injections, surgical details, complications, current topical treatments, visual acuity (VA), intraocular pressure (IOP) and central retinal thickness (CRT) assessed by optical coherence tomography (OCT). This data was collected at all the study timepoints: baseline, 1–2 weeks, 6–8 weeks, and 3, 6, 9, 12, 18 and 24-months post-injection of the first IDI. Additional data was collected at each individual repeated injection during the study, including VA, IOP and CRT data prior to the procedure, and 1–2 weeks, 6–8 weeks, and 3 and 6-months post-procedure.

Data sources/outcome measurements
All original data were gathered in routine clinical care visits. All injections data (i.e. injection date, number of injections, pre and post-injection data) were collected as described above. At each time point, VA was determined as the best VA with habitual correction or pinhole, rather than as the best-corrected refracted VA and presented in logarithm of the minimum angle of resolution (logMAR) units. The analysis of eyes with a low VA was undertaken by substituting counting fingers (CF) and hand movement (HM) with 2.0 and 2.3 logMAR, respectively [15]. IOP measurements were obtained by Goldmann tonometry and presented in mmHg. The CRT was determined by OCT imaging using one of 2 different devices depending on the participating center (Hospital Clinic, Cirrus HD-OCT®, Dublin, CA, USA and Hospital Vall de Hebrón, Spectralis OCT®, Heidelberg Engineering, Germany). No research softwares were employed to control for inter-device measurement differences in CRT. No missing value substitutions were performed in patients where data were not available for a particular visit or were lost during follow-up.

Statistical analysis
Descriptive, frequency statistics and the chi-squared test were used to assess the qualitative variables. The normality of quantitative variables was examined in histograms, and inter-group differences where evaluated with an independent Student’s T-test and Mann-Whitney U-test, when appropriate. A paired t-test was used to compare pre- and post-treatment changes. For VA change analysis, VA values are converted and presented in ETDRS letters. The cumulative probability of IOP events occurring after IDI injection are presented as survival curves using the Kaplan Meier (KM) method [16]. High IOP was defined as an IOP greater than 21 mmHg, 25 mmHg or 35 mmHg, as described elsewhere [17]. The probability of IOP elevation was evaluated for naïve and previously treated DME eyes subgroups, and KM survival curves were compared with the log-rank test. A p-value ≤0.05 was considered significant.

Results
Baseline demographic and clinical characteristics of study cohort
A total of 203 DME eyes from 179 patients treated with IDIs were included in this study. The baseline characteristics of the patients and study eyes are disclosed in Table 1. In this cohort, 67 eyes (33%) were treatment-naïve, whereas 136 eyes (67%) had previously received intravitreal treatment for DME. Previous intravitreal treatments included intravitreal triamcinolone (IVTA) in 27 eyes (13.3%), anti-VEGF drugs in 84 eyes (41.3%), and both IVTA and anti-VEGF treatment in 25 eyes (12.3%). Overall, previous laser treatment was performed in 154 eyes (75.8%), distributed as macular focal/grid laser therapy in 113 eyes (55.6%) and pan-retinal photocoagulation (PRP) in 110 eyes (54.1%). Mean baseline VA of the overall cohort was 0.92 logMAR (equivalent to 39 ETDRS letters) and mean CRT was 498.7 μm. A detailed comparison between naïve and previously treated eyes at baseline is shown in Table 1.

Number of injections and treatment burden
In the overall cohort, a total of 342 IDI injections were administered in 203 eyes, with a mean number of injections of 1.68 ± 0.9 implants in a mean follow-up time of 16.3 ± 7.7 months (Table 2). The percentage of study eyes in the overall cohort receiving 1 injection was 57.1% (116 eyes), 2 injections was 25.1% (51 eyes), 3 injections was 12.3% (25 eyes) and > =4 injections was 5.4% (11 eyes). In this cohort, the mean time to reinjection was 9.95 ± 5.2 months for the 2nd injection, 15.71 ± 4.8 months for the 3rd injection and 20.4 ± 5.1 months for the 4th injection.

When comparing naïve vs previously treated eyes, the mean number of injections was 1.4 ± 0.9 vs 1.82 ± 0.9 (p < 0.001) in a mean follow-up time of 14.5 ± 7.8 vs 17.1 ± 7.9 months (p = 0.02), respectively. The percentage of eyes receiving 1 injection was significantly higher in naïve vs previously treated eyes (76.1% vs 47.7%, p < 0.001), as was significantly lower in eyes requiring 2 injections (16.4% vs 29.4%, p = 0.04) or 3 injections (1.4% vs 17.6%, p = 0.001). No differences were observed in the percentage of eyes requiring > =4 injections (5.9% vs 5.1%, p = 0.80). Interestingly, no differences between groups were observed in the time to reinjection for 2nd injection (9.61 ± 4.0 vs 10.0 ± 5.5 months, p = 0.75), 3rd injection (13.2 ± 4.0 vs 16.0 ± 3.5 months, p = 0.21) and 4th injection (21.75 ± 3.8 vs 19.75 ± 5.8 months, p = 0.55). All these results are presented in Table 2.
The distribution of eyes by VA levels at each individual timepoints is presented in Fig. 1. In the overall cohort, at baseline the percentage of eyes with VA < 0.4 logMAR was 6%, VA ≥ 0.4 – 0.7 was 24%, VA ≥ 0.7 – 1.0 was 42.5% and VA > 1.0 was 27.5%. At 24 months, the percentage of eyes with VA < 0.4 logMAR was 18.5%, VA ≥ 0.4 – 0.7 was 25.7%, VA ≥ 0.7 – 1.0 was 28.5% and VA > 1.0 was 27.1%. The percentage of eyes with good VA levels (< 0.4 logMAR and ≥ 0.4 – 0.7 logMAR) was significantly higher in naïve vs previously treated eyes in all study timepoints (all p < 0.05), as presented in Fig. 1. In the overall cohort, mean baseline VA was 0.92 ± 0.4 LogMAR, at 6–8 weeks was 0.76 ± 0.4 LogMAR and at 24 months was 0.8 ± 0.5 LogMAR (Fig. 2 and Table 3). At 24 months, mean VA improvement was +6 letters at 24 months in the overall cohort, with no significant differences in subgroup analysis in

### Table 1: Patient demographics and clinical characteristics of the study eyes at baseline

| Characteristic                              | Total (N = 203) | Treatment-naïve eyes (N = 67) | Previously treated eyes (N = 136) |
|---------------------------------------------|-----------------|-------------------------------|-----------------------------------|
| Age mean years ± SD (range)                | 66.8 ± 10.3 (43–99) | 66 ± 12.9 (43–99) | 67 ± 8.9 (44–86) |
| Gender, n (%)                              |                 |                               |                                   |
| Female                                     | 87 (42.9)       | 27 (40.3)                     | 61 (44.9)                         |
| Male                                        | 116 (57.1)      | 40 (59.7)                     | 75 (55.1)                         |
| Lens status in study eye, n (%)             |                 |                               |                                   |
| Phakic                                      | 105 (51.7%)     | 41 (61.2)                     | 64 (47)                           |
| Pseudophakic                                | 98 (48.3%)      | 26 (38.8)                     | 72 (53)                           |
| Previous intravitreal therapy, n (%)        |                 |                               |                                   |
| IVTA                                        | 27 (13.3)       | 0 (0)                         | 27 (19.8)                         |
| Anti VEGF                                   | 84 (41.3)       | 0 (0)                         | 84 (61.7)                         |
| IVTA + Anti VEGF                           | 25 (12.3)       | 0 (0)                         | 25 (18.3)                         |
| Previous laser therapy, n (%)               |                 |                               |                                   |
| Any                                         | 154 (75.8)      | 38 (56.7)                     | 116 (85.2)                        |
| Focal/grid                                  | 113 (55.6)      | 25 (37.3)                     | 88 (64.7)                         |
| PRP                                         | 110 (54.1)      | 28 (41.7)                     | 82 (60.2)                         |
| Mean VA, ETDRS letters (Snellen equivalent) | 39 (20/160)     | 42.5 (20/160)                 | 37.5 (20/200)                     |
| Mean CRT, μm (SD)                           | 498.7 ± 136     | 482.1 ± 127.5                 | 506.5 ± 139.7                     |

IVTA Intravitreal triamcinolone acetonide, VEGF Vascular endothelial growth factor, PRP Pan-retinal photocoagulation, VA Visual acuity; *Logarithm of the minimum angle of resolution values are converted into ETDRS letters, CRT Central retinal thickness

### Visual acuity outcomes

The distribution of eyes by VA levels at each individual timepoints is presented in Fig. 1. In the overall cohort, at baseline the percentage of eyes with VA < 0.4 logMAR was 6%, VA ≥0.4–0.7 was 24%, VA ≥0.7–1.0 was 42.5% and VA > 1.0 was 27.5%. At 24 months, the percentage of eyes with VA < 0.4 logMAR was 18.5%, VA ≥0.4–0.7 was 25.7%, VA ≥0.7–1.0 was 28.5% and VA > 1.0 was 27.1%. The percentage of eyes with good VA levels (< 0.4 logMAR and ≥ 0.4 – 0.7 logMAR) was significantly higher in naïve vs previously treated eyes in all study timepoints (all p < 0.05), as presented in Fig. 1. In the overall cohort, mean baseline VA was 0.92 ± 0.4 LogMAR, at 6–8 weeks was 0.76 ± 0.4 LogMAR and at 24 months was 0.8 ± 0.5 LogMAR (Fig. 2 and Table 3). At 24 months, mean VA improvement was +6 letters at 24 months in the overall cohort, with no significant differences in subgroup analysis in

### Table 2: Number of Injections and time to reinjection during the study period

| Total number of Injections, N (%) | 342 (100%) | 94 (27.4%) | 248 (72.6%) |
|-----------------------------------|------------|------------|------------|
| Number of Injections, Mean ± SD (Median-IQR) | 1.68 ± 0.9 (1–1) | 1.40 ± 0.9 (1–0) | 1.82 ± 0.9 (2–1) |
| Follow up time (months), Mean ± SD (Median-IQR) | 16.3 ± 7.7 (16.1–13.8) | 14.5 ± 7.8 (12.4–13.7) | 17.1 ± 7.6 (17.4–13.1) |
| Number of injections, n (% study eyes) |            |            |            |
| 1 injection                        | 116 (57.1%) | 51 (76.1%) | 65 (47.7%) |
| 2 injections                       | 51 (25.1%)  | 11 (16.4%) | 40 (29.4%) |
| 3 injections                       | 25 (12.3%)  | 1 (1.4%)   | 24 (17.6%) |
| ≥4 injections                      | 11 (5.4%)   | 4 (5.9%)   | 7 (5.1%)   |
| Time to reinjection after 1st injection (months), Mean ± SD (Median-IQR) |            |            |            |
| 2nd injection                     | 9.95 ± 5.2 (8–5) | 9.61 ± 4.0 (8–3.75) | 10.0 ± 5.5 (8–5) |
| 3rd injection                     | 15.71 ± 4.8 (15–7.5) | 13.2 ± 4.0 (11–3) | 16.0 ± 3.5 (16–7) |
| 4th injection                     | 20.4 ± 5.1 (19.5–8) | 21.75 ± 3.8 (21.5–5.75) | 19.75 ± 5.8 (18–5.25) |

SD Standard deviation, IQR Interquartile range
treatment-naïve and previously treated eyes (+ 4.5 letters vs. + 6.5 letters, \( p = 0.70 \), Table 3). However, treatment-naïve eyes maintained better mean VA at all timepoints compared to previously treated eyes, with significant differences at 6–8 weeks (mean VA 0.65 ± 0.47 vs. 0.81 ± 0.47, \( p < 0.05 \)) and 3 months (mean VA 0.68 ± 0.53 vs. 0.83 ± 0.46, \( p < 0.05 \)) (Fig. 2).
Central retinal thickness outcomes
The evolution of CRT changes from baseline in the overall, naïve and previously treated eyes cohorts is presented in Fig. 3 and Table 3. Significant improvements were observed in CRT at 6–8 weeks (−181.8 μm, p < 0.05) and at 24 months (−96.1 μm, p < 0.05). In the subgroup analysis, no differences were observed in CRT improvements between naïve and previously treated eyes at 6–8 weeks (−179.7 μm vs −182.8 μm) or 24 months (−141.5 μm vs −79.0 μm, p = 0.46).

Intraocular pressure outcomes
All IOP outcome measures are presented in Fig. 4. The cumulative probability of IOP ≥ 21 / 25 / 35 mmHg at 12 months was 50% / 23% / 6%, and at 24 months was 60% / 30% / 7%, respectively. No significant differences in IOP elevations were observed between naïve and previously treated eyes. At baseline, 41 eyes (20.2%) were already on treatment with topical IOP-lowering drugs. The cumulative probability of requiring IOP-lowering drops was 21.8% at 12 months and 46.2% at 24 months in the overall cohort, with no significant differences between naïve and previously treated eyes. Glaucoma surgery was only required in 1 case (0.49%), that had pre-existing glaucoma and was already on IOP lowering medications prior to first injection. The effect of repeat IDI injections on IOP was also evaluated, and no significant differences were observed in the cumulative

Table 3 Outcome measures before and 24 months after treatment in naïve vs previously treated eyes

|                     | Total (N = 203) | Naïve (N = 67) | Previously treated (N = 136) | p-value |
|---------------------|-----------------|----------------|-----------------------------|---------|
| **Mean VA, ETDRS letters** |                 |                |                             |         |
| Before treatment (mean ± SD) (Snellen equivalent) | 39 ± 61 (20/160) | 42.5 ± 57.5 (20/160) | 37.5 ± 62.5 (20/200) | 0.19    |
| After treatment (mean ± SD) | 45 ± 57.5 (20/125) | 47 ± 60 (20/125) | 44 ± 56 (20/125) | 0.71    |
| Mean Change | 6 | 4.5 | 6.5 | 0.70 |
| **Mean CRT, μm** |                 |                |                             |         |
| Before treatment (mean ± SD) | 498.7 ± 136 | 482.1 ± 127.5 | 506.5 ± 139.7 | 0.25    |
| After treatment (mean ± SD) | 402.6 ± 154.83 | 340.5 ± 88.28 | 427.4 ± 165 | 0.10    |
| Mean Change | −96.1 | −141.5 | −79.0 | 0.46 |

VA Visual acuity, ETDRS Early treatment diabetic retinopathy study, CRT Central retinal thickness, SD Standard deviation, IQR Interquartile range
probability of any IOP level 6 months after the first, second or third injection.

**Discussion**

This study reports better visual outcomes and reduced treatment burden in naïve DME eyes compared to previously treated DME eyes, based on a large cohort of DME patients treated with the IDI in routine clinical care. The results of this study support the use of the IDI in early DME stages in patients who do not qualify for anti-VEGF therapy and provide further evidence of better IDI response when used as first-line therapy compared to its use as second-line therapy, after previous failed intravitreal treatments.

Our real-world cohort of DME patients presented different demographics and baseline clinical characteristics from those reported in clinical trials, overall with a worse mean baseline VA [9, 10, 13, 18, 19] and CRT [9, 10, 18, 19]. In our series, a significant number of study eyes were treated in routine clinical care with VA levels that fall outside the inclusion criteria used in the MEAD trial (33.5% of the study cohort, 6% with VA better than 0.4 logMAR and 27.5% with VA worse than 1.0 logMAR, as presented in Fig. 1). This data is of particular relevance, as reflects more closely the situation in which such a therapy is to be employed in routine clinical care: patients that require a therapeutic option even though they might not conform to the ideal profile, either in terms of specific disease related parameters, prior treatment failure or co-morbidities. In case of our cohort of previously treated eyes, their basal clinical characteristics are generally worse than those reported previously in real-world studies, particularly with lower baseline VA [13, 14, 20–24] and greater CRT [20, 25]. Moreover, more eyes had received prior treatment, particularly with anti-VEGF and/or IVTA, than the study cohorts in these previous series [14, 20, 22, 24–26].

The overall results presented here are somehow comparable with those from previous smaller cohorts. Indeed, previous assessments of the effect of IDI on refractory and treatment-naïve patients showed similar decreases in CRT and improvement in VA in both refractory and treatment-naïve groups. Other real-life studies have also shown similar improvements in VA and CRT without serious adverse events, mainly in smaller series over shorter follow-up periods [27–32]. In our population of DME patients, IDI considerably improved the VA relative to baseline in both treatment-naïve and previously treated patients, suggesting that IDI therapy offers benefits to both types of patient. Nevertheless, naïve eyes maintained a better mean VA than previously treated eyes at all time points studied. A particularly significant improvement was observed in naïve patients during the first 3 months relative to previously treated eyes, suggesting they respond better in terms of VA, consistent with earlier data [13, 14]. Moreover, in our series the percentage of eyes with good VA levels was consistently higher in naïve eyes vs previously treated eyes at all study timepoints, as graphically presented in Fig. 1. Regarding anatomical changes, IDI treatment improves the CRT at all time points during the follow-up, both in treatment-naïve and previously

![Fig. 3 Anatomical outcomes. Evolution of mean central retinal thickness change from baseline to 24 months in the overall cohort (solid line), naïve eyes (stripped line) and previously treated eyes (dotted line). No significant differences were observed between naïve and previously treated eyes at any timepoint.](image-url)
treated eyes, with no significant differences between these subgroups. This discrepancy between functional and anatomical outcomes in DME has extensively been reported in previous studies, that suggest that retinal thinning may also be related with outer retinal layers atrophy preventing visual improvement, more common in chronic DME eyes [33].

The need for frequent injections in DME represents a considerable burden for patients, especially with anti-VEGF drugs [34–36]. In different studies, fewer IDI injections have been shown to be necessary to achieve similar visual and anatomical outcomes in DME patients [10, 11, 37], although the loss of vision mainly due to cataract must be controlled, which may be more common when IDIs are used. Further head-to-head trials will be needed to compare the efficacy of IDI and anti-VEGF therapy based on the patients’ clinical characteristics at baseline and their prior treatments, tailoring the treatment choice individually in a case-by-case basis. Towards this personalized medicine approach, several attempts have been recently reported to shed some light on predictive biomarkers for IDI response, based in retinal imaging (i.e. OCT) or aqueous samples [38–41]. Likewise, recent studies have been directed to identify those patients who don’t respond to anti-VEGF treatment, [42] as well as to determine the synergistic and beneficial effect of IDIs in combination with other treatments [43, 44].

Significantly fewer IDIs were administered to treatment-naïve eyes than to previously treated eyes and indeed, many more treatment-naïve eyes received just 1 injection than previously treated eyes. However, when additional implants were required, the time to reinjection did not differ significantly between the two groups. This is an important point, as suggest that reinjections were timely performed in both groups when required. Such differences have not always been detected when this parameter has been compared between naïve and non-naïve eyes [14, 20]. Our results raise the interesting hypothesis that early treatment may reduce the
treatment burden associated to IDI therapy in naïve DME, beyond the benefit already reported for refractory DME eyes when used as second line therapy. It is well recognized that managing DME with IDIs is generally associated with a need for fewer injections than anti-VEGF therapies, as well as longer periods between the need for treatment. The benefits to be gained from this need for fewer injections have already been recognised in the EURETINA guidelines for DME, whereby IDI use is recommended as a first-line therapy only in specific subgroups of patients. If confirmed in future studies, this finding may offer an additional reason to support the use of IDI as first-line therapy in a wider spectrum of DME eyes.

As found elsewhere, IDI therapy was well tolerated by DME patients. The main adverse event was high IOP but that could typically be managed with medication. Indeed, while nearly a third of patients developed a high IOP, it was controlled with topical antihypertensive drugs. There is no evidence of a previously cumulative effect of multiple injections on increased IOP, irrespective of pre-existing glaucoma or ocular hypertension.

| Study | Indication | Duration (months) | N | Baseline VA (letters) | Baseline CRT (μm) | Baseline %laser | Baseline %anti-VEGF | Baseline %IVTA | Final VA, (letters) | Final CRT (μm) |
|-------|------------|-------------------|---|-----------------------|-------------------|----------------|-------------------|----------------|-------------------|----------------|
| MEAD  | DME-PPV    | 6                 | 55 | 54.5                 | 403.4             | 69.6%           | 48.2%            | 57.1%          | 57.5              | 364.5          |
| MEAD-Treated | DME-Treated | 36              | 247 | 55.2               | 478               | 93.5%           | 25%              | 23.5%          | 58.4              | 352            |
| CHAMPLAIN | Boyer DS et al., 2011 | 6 | 55 | 54.5 | 403.4 | 69.6% | 48.2% | 57.1% | 57.5 | 364.5 |
| BEVORDEX | Gillies MC et al., 2014 | 24 | 88 | 55.5 | 474.3 | – | – | – | 62.4 | 287.3 (*) |
| Escobar-Barranco et al., 2015 | DME-Naive | 6 | 40 | 59.6 | 568 | 0% | – | – | 71.1 | 323 |
| Dutra et al., 2014 | DME-Treated | 6 | 36 | 51.3 | 600 | 100% | – | – | 59.0 | 281 |
| Totan et al., 2016 | DME-Treated | 6 | 30 | 57* | 517 | 56.7% | 100% | – | 64* | 411 |
| Bansal et al., 2016 | DME | 14.53 | 52 | 44* | 514.2 | 100% | 67.2% | – | 51* | 419.9 (6 months) |
| Bonnin et al., 2015 | DME | 4 | 39 | 51.5* | 559 | 44% | 49% | 36% | 81.5* | 477 |
| Guigou et al., 2015 | DME treated and naive | 6 | 78 | 53.9 | 537.6 | 42.3% | 52.6% | 17.9% | 60.1 | 384.6 |
| CHROME | DME (subgroup analysis) | 36 | 34 | 55* | 450.4 | 55.9% | 55.9 | 38.2 | 53 (6 months) | 259.5 |
| RELDEX | DME naive and treated | 36 | 128 | 50.5 | 450 | 16.4% | 70.3% | 15.6% | 60.6 | 280 |
| IRGREL-DEX Iglicki et al., 2019 | DME naive and treated | 24 | 130 | 55* | 575 | 15% | 7.4% | – | 65.5* | 294.4** |
| This study: Zarranz-Ventura et al. 2020 | DME-All | 24 | 203 | 39 | 498.7 | 75.8% | 53.6% | 25.6% | 45 | 402.6 |
| Naive | 24 | 67 | 42.5 | 482.1 | 56.7% | 0% | 0% | 47 | 340.5 |
| Previously treated | 24 | 136 | 37.5 | 506.5*** | 85.2% | 80.1% | 38.2% | 44 | 427.4*** |

DME Diabetic macular edema, VA Visual acuity, CRT Central retinal thickness, VEGF Vascular endothelial growth factor, IVTA Intravitreal triamcinolone acetonide.

*Logarithm of the minimum angle of resolution values converted into ETDRS letters.** Calculated from publication data. *** CRT measurements obtained with 2 different OCT machines, unadjusted for inter-device differences.
different characteristics at baseline (Table 4). This is complicated by the fact that they involve cohorts with vastly different design, the study data or the study conclusions. This work was partially supported by a research grant from Allergan. The company or associated companies did not have any access to the study design, the study data or the study conclusions.

Acknowledgements
The authors would like to thank the patients that attended the visits described in this series, as well as the help provided by the administrative and support staff in the daily work at the Retinal services of both study centers. The authors would like to thank the patients that attended the visits described in this series, as well as the help provided by the administrative and support staff in the daily work at the Retinal services of both study centers. The authors would like to thank the patients that attended the visits described in this series, as well as the help provided by the administrative and support staff in the daily work at the Retinal services of both study centers.

Abbreviations
CF: Counting fingers; CRT: Central retinal thickness; DME: Diabetic macular edema; ETDRS: Early treatment diabetic retinopathy study; HVM: Hand movement; IDI: Intravitreal dexamethasone implant; IOP: Intraocular pressure; IQR: Interquartile range; IRB: Institutional review board; IVTA: Intravitreal triamcinolone; KM: Kaplan-Meier; LogMAR: logarithm of the minimum angle of resolution; OCT: Optical coherence tomography; PRP: Panretinal photocoagulation; PT: Previously treated; SD: Standard deviation; VEGF: Vascular endothelial growth factor; VA: Visual acuity

Authors’ contributions
Conceptualization: JZV; Data curation: JZV, BRN, CBM, DVV, ASP, SC, LD, AB; Formal analysis: JZV, BRN, CBM; Investigation: JZV, BRN, CBM; Methodology: JZV; Project administration: JZV, BRN, CBM; Supervision: JZV; Validation: JZV; Visualization: JZV, Writing-original draft: JZV, BRN, CBM; Writing-review & editing: JZV, BRN, CBM, DVV, ASP, SC, LD, AB, JGA, AA. All authors have read and approved the manuscript.

Funding
This work was supported by a research grant from Allergan.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board at the Hospital Clinic of Barcelona (HCB/2016/0905) and it was conducted in accordance with the Tenets set forth in the Declaration of Helsinki. No written informed consent was required as data was retrospectively collected from routine clinical care, as approved by the reference Institutional Review Board.
Consent for publication
Not applicable.

Competing interests
IJV has been in advisory boards and is a consultant, lecturer, grant recipient and has received travel grants from Alcon, Alimera Sciences, Allergan, Bausch and Lomb, Bayer, Brill Pharma, DORC, Novartis, Roche, Topcon and Zeiss; BRN, none; CBM, none; DWV, none: ASP has given lectures for Allergan and Bayer and is a member of the Allergan International Retina Panel; MFR has given lectures for Allergan; SC, none; LD, none; AB has given lectures for Allergan, Bayer, and Novartis; JGA has been in advisory boards and has received grants from Alcon, Allergan, Bayer, Novartis; AA has been in advisory boards and is a consultant for Abbvie, Alcon, Alimera Sciences, Allergan, Bayer and Novartis, and has given lectures for Topcon and Zeiss.

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Received: 31 August 2020 Accepted: 2 November 2020
Published online: 11 November 2020

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