Evaluation of efficacy dexamethasone intravitreal implant compared to treatment with anti-VEGF in the treatment of diabetic macular edema

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Abstract

Objective: *The study compares the effectiveness of an intravitreal slow-release dexamethasone implant respect to an intravitreal injection of a anti-VEGF, ranibizumab, in the treatment of diabetic macular edema (DME).*
Design: we used a non randomized retrospective study to compare the effectiveness of two treatment approaches to DME
Subjects: 50 patients were investigated, 30 of whom underwent injections of ranibizumab and 20 of whom underwent dexamethasone implantation.
Methods: When patients were injected with the anti-VEGF ranibizumab, they were monitored every three months.
Dexamethasone implant was administered only once in 6 months, different to ranibizumab which was administered monthly .
Main Outcome Measures: these were carried out by measuring the improvements in ETDRS (visual acuity scores) and CMT (central macular thickness) after one month, three months, and six months (T1, T3, T6). intraocular pressure were performed.
Results: Data evidenced that the slow-release dexamethasone implant is more efficacious than the intravitreal injection of the anti-VEGF, ranibizumab, in terms of improvement of visual acuity and central macular thickness.
Dexamethasone implant at T3 produced an improvement of visual acuity which was significantly better respect to injections of ranibizumab, with a mean ETDRS gain of nearly 8,5 letters, compared to only 4 letters gained in the case of ranibizumab injected patients. This significance, however, is lost by T6, (p=0.516), where those treated with dexamethasone had lost 6 of the eight letters gained, while those with ranibizumab had lost 4 letters. As such, the overall gain at the T6 checkpoint was only 2.5 letters for dexamethasone implant and 2 for ranibizumab.
Conclusion: The study highlighted a better initial efficacy of the dexamethasone implant due to its superior performance at 3 and 6 month evaluation points.

Keywords: *Diabetic Macular Edema (DME), Anti-VEGF, Dexamethasone intravitreal implant.*

1.Introduction

Diabetic retinopathy (DR) represents the principal cause of blindness in the working age group of the industrialized world [1]. In particular, diabetic macular edema (DME) results from the exuding and accumulation of extracellular liquid and proteins in the macula [2] following structural changes to the

endothelium of the blood retinal vessels that leads to the rupture of the blood -retinal barrier and thus to an increase in vascular permeability [3]. The pathological neo-angiogenesis at the basis of such alterations is provoked by the increase in cytokines (like IL-6 and IL-8), prostaglandins, and Vascular Endothelial Growth Factor (VEGF) [4].

Macular Laser Photo-coagulation has represented the gold standard treatment of DR. The immediate advantages of focal coagulation were demonstrated in the ETDRS (Early Treatment Diabetic Retinopathy Study) [5].This treatment reduces moderate visual loss by possibly 50%, by inducting the proliferation of both the endothelial cells of retinal capillaries and the pigmented retinal epithelium, thus improving the filtering efficacy of the blood-retinal barrier both internally and externally [6]. Despite this, the ETDRS showed that patients only had minor visual improvements, and immediate to the intervention, and that only 3% of patients showed more than a 3-line improvement at 3 years, whilst 12% of eyes had actually worsened in that three year period, and 40% of eyes had shown a retinal thickening involving the macula, with persistent edema at 12 months [7].

For these reasons, research has shifted towards finding more effective means of treatment [8].

Anti-VEGF drugs showed good results in slowing the progressive degeneration associated with DR, and its associated macular edema (ME). Numerous studies have shown the efficacy of these drugs in the inhibition of neo-vascularization, and for producing a reduction of vascular permeability [9, 10].

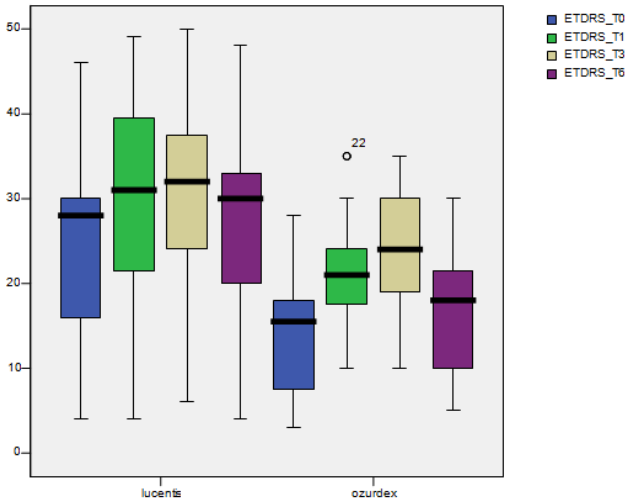

Figure 1. ETDRS levels trends in patients treated with lucentis and ozurdex.

Recently, a slow prolonged release Dexametasone intravitreal implant has been proposed as an alternative or additional treatment option for DME [11-13].

This drug has also been approved for the treatment of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). In any case, multi-centric studies have demonstrated its efficacy, as well as numerous clinical reports dealing with DME, ME in vitrectomised eyes, ME associated to uveitis or Irvine-Gass syndrome, persistent ME, non-infective vitritis, and as an adjuvant therapy for age-related macular edema [14-21]. In July 2014, considered, also in Italy, as drug efficacy nell'DME, Official Journal special series 171 of July 25, 2014.

Our study compares the effectiveness of dexamethasone implant respect to an intravitreal anti-VEGF ranibizumab injection for the treatment of ME due to DR.

Materials and Method

The parallel comparison of the effectiveness of two treatment paths was carried out by measuring the improvements in ETDRS (visual acuity scores) and CMT (central macular thickness) after one month, three months, and six months (T1, T3, T6).

The study was conducted with the consent of all patients and follow all directions.

Institutional Review Board (IRB)/Ethics Committee approval was obtained.

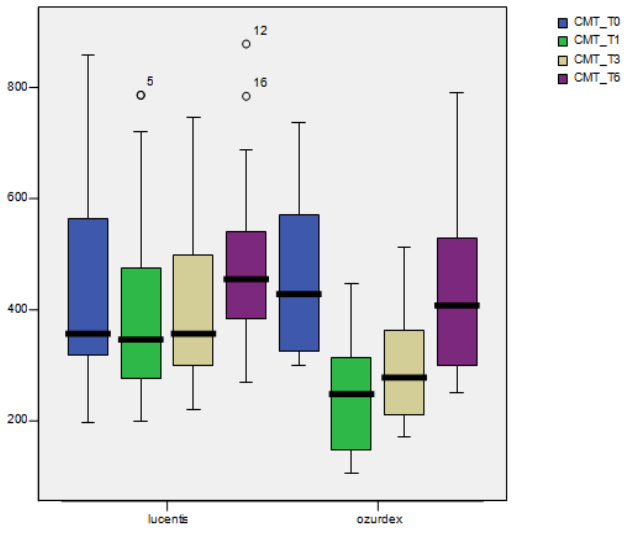

Figure 2. CMT levels trends in patients treated with lucentis and ozurdex.

Regarding ophthalmic performance, an evaluation was carried out prior to injections (at T0) and comprised of:

- Best correct visual acuity evaluation (BCVA);
- slit lamp bio microscopy;
- ocular tonometry using a Goldmann applanation tonometer;
- indirect binocular ophthalmoscopy;
- ocular coherence tomography (OCT);
- color fundus photograhy;
- retinal fluorangiography (FAG) (only carried out on enrollment).

The controls carried out the day after the injection consisted of:

- slit lamp biomicroscopy;
- tonometry;
- indirect binocular ophthalmoscopy.

In successive follow ups (at three days, and at one, three, four and six months, as required in the case of dexamethasone implant; at one and three weeks as required in the case of ranibizumab injections) the following visual exams were carried out:

- Best correct visual acuity (BCVA);
- slit lamp bio microscopy;
-ocular tonometry using Goldmann applanation tonometer;
- indirect binocular ophthalmoscopy;
- ocular coherence tomography (OCT);

The therapeutic differences between interventions lie in the fact that dexamethasone implant is administered only once in 6 months, contrary to ranibizumab which necessitates monthly administrations.

Table 1. Characteristics of the patients.

	Lucentis	Ozurdex	p
Age (median; range)	67 (57-87)	71 (55-88)	0.789
Monthe of DME	29.5 (13-68)	36 (14-65)	0.091
Years of Diabetes mellitus	19 (9-34)	18 (4-34)	0.371

Results

Our retrospective study considers 50 patients, of whom 30 underwent injections of ranibizumab and 20 underwent dexamethasone implantation. These patients did not differ in terms of age, number of months diagnosed with DME, or years diagnosed with Diabetes Mellitus, as shown in table 1. However, clinical differences between the groups were observed.

ETDRS for both treatments, between T0 (prior to treatment) and T1 (1 month) T3 (3 months) and T6 (6 months) were significantly different for both groups (injected and implanted) ($p< 0.001$), though more significant in patients implanted with dexamethasone implant ($p = 0.006$), as can be noted in Figure 1. CMT differences were only significant at T1 and T3, with an initial reduction in macular thickness which improved up to month 3 and which then worsened towards month 6, as can be noted in Figure 2.

The differences between treatments, at every time interval, were significant, both for ETDRS (all temporal points) and for CMT (at T1 and T3), as shown in table 2. If we consider data differences at T3 respect to T0, the differences between type of treatment were significant ($p< 0.001$). In fact, dexamethasone implant at T3 produced an improvement of visual acuity which was significantly better respect to injections of ranibizumab, with a mean ETDRS gain of nearly 8,5 letters, compared to only 4 letters gained in the case of ranibizumab injected patients. This significance, however, is lost by T6, ($p=0.516$), where those treated with dexamethasone implant had lost 6 of the eight letters gained, while those with ranibizumab had lost 4 letters. As such, the overall gain at the T6 checkpoint was only 2,5 letters for dexamethasone implant and 2 for ranibizumab. These results are shown in table 2.

Table 2. Trends of ETDRS levels over time of the patients treated with Lucentis and Ozurdex.

	Lucentis Median (range)	Ozurdex Median (range)	p
ETDRS T0	28 (4-49)	15.50 (3-28)	0.003
ETDRS T1	31 (4-49)	21 (10-35)	0.015
ETDRS T3	32 (5-50)	24 (10-35)	0.040
ETDRS T6	30 (4-48)	18 (5-30)	0.002
Delta T3-T0	4 (-5-29)	8.5 (4-14)	< 0.001
Delta T6-T0	2 (-4-29)	2 (1-7)	0.516

Discussion

Data suggest that the dexamethasone implant is more efficacious respect to the intravitreal anti-VEGF ranibizumab injection procedure.

Stronger clinical effectiveness is shown by dexamethasone implant at 3 months, where a gain of 8,5 letters (ETDRS) was seen, respect to a gain of just 4 in patients treated with ranibizumab, as opposed to results reported in other clinical trials [23-25].

Infact the slow-release intravitreal dexamethasone implant, shows efficacy for the treatment of DME, as both substantial improvements were registered in BCVA values, and significant reductions of CMT observed. In accordance with other literature [13,21], this significant improvement is seen from day 3 of the intravitreal implant. The peak efficacy of the implant appears to be reached at month 1 through to month 3.

In the confrontation with other pharmacological treatments, dexamethasone implant is the drug with the best benefit in relation to therapeutic efficacy, has the best tolerance of side effects and it is the preferred treatment of patients (because it involves fewer operative interventions). This study, as reported in literature [26, 27], suggests that dexamethasone implant is clinically suggests that dexamethasone implant is clinically an efficacious treatment for DME, as reflected in the substantial improvements both values that BCVA of CMT registered. It guarantees clinical outcomes and ultimately better health outcomes for the individual patient.

As regards the second objective of the study, namely the assessment of the safety profile of the system, in agreement with the studies of Haller [11] and

Kuppermann [12], there were no complications determined by the procedure of the system or by the drug [28]. The present study has some limitations, especially concerning the small sample size and for the retrospective design. However, it underlines the need to deeply study the comparison between dexamethasone implant and ranibizumab using a more appropriate experimental design [29]. Moreover, beside the effectiveness of dexamethasone implant, it will be fundamental to perform a cost- effectiveness analysis in order to acquire also value for money of this drug in the treatment of DME.

It is conceivable that the combination of this treatment with other therapeutic strategies can improve the course of this disease. Further studies on the efficacy and safety of Ozurdex are certainly needed, with a larger number of patients and a longer follow-up.

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