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ORIGINAL PAPER

Predictive value of short-term steroid intraocular pressure elevation testing for long-term steroid intraocular pressure elevation in diabetic macular edema treatment

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Abstract

Purpose This study aims to investigate whether there is a correlation between intraocular pressure (IOP) elevation after intravitreal triamcinolone acetonide (TA) testing and IOP response following fluocinolone acetonide (FAc) implant injection in the treatment of diabetic macular edema.

Methods This study employed a real-world observational cohort retrospective design, enrolling patients who had received at least one intravitreal TA injection prior to a FAc implant injection between December 2018 and July 2022. Demographic data, medical and ophthalmic history were collected at baseline. Mean IOP was assessed before and after both treatments and steroid-response was defined as an IOP greater than 21 mmHg. Statistical analysis was performed to determine correlated IOP changes.

Results A total of 28 eyes were included in the study. Six eyes exhibited a steroid response following the initial TA injection, and none of these eyes demonstrated a steroid response following the FAc implant. The FAc implant resulted in steroid response in six additional eyes. The analysis revealed no statistically significant correlation between the occurrence of a steroid response following a TA injection and the subsequent mean IOP progression following an FAc implant injection at any time point. No correlation was observed between the variation in IOP following the two treatments.

Conclusion It is crucial to evaluate the necessity of a prior short-acting steroid challenge, which carries the risk of multiple disease relapses, given the potential for a prolonged and stable steroid to provide superior control. The predictive value of the test with TA was not evident in our sample, suggesting some usefulness in delaying treatment with the FAc implant.

Keywords Macular diabetic edema · Triamcinolone acetonide · Fluocinolone acetonide implant · Intravitreal injections · Intraocular pressure

Introduction

Diabetic retinopathy (DR) is a major microvascular complication of diabetes that can lead to severe visual impairment and is a leading cause of vision loss between the ages of 20 and 64 years-old [1, 2]. The prevalence of diabetic macular edema (DME) increases with the duration and stage of DR [3].

Inflammation contributes to the development of DR in general and DME in particular [4]. Hyperglycemia causes the activation of cytokines and growth factors that can induce vascular and neuronal dysfunction, increasing the oxidative stress and inflammation and stimulating the production of advanced glycation end

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products. This inflammatory pathway has a positive feedback enhancing the inflammatory response by itself and affecting pericytes, endothelial, Müller and microglial cells, and leading to the production of vascular endothelial growth factor (VEGF), which causes leukostasis and increased cell permeability [1, 2]. Thus, the breakdown of the blood-retinal barrier (BRB) is caused by the hyperglycemia-induced damage to the endothelial pericytes and tight junctions. Hyperglycemia also causes the activation of angiogenesis [2].

DME is the abnormal accumulation of fluid in the subretinal and/or intraretinal spaces of the macula. It is caused by several factors including hypoxia and oxidative stress, presence of VEGF, BRB dysfunction, leukostasis (adherence of blood cells to the endothelial wall), loss of pericytes (which play a critical role in maintaining the inner BRB along with glial cells processes, Müller cells and astrocytes), and vascular hyperpermeability [1]. Focal edema is generally caused by leakage from retinal capillary microaneurysms and diffuse edema is due to the breakdown of the BRB [3]. Low-grade inflammation with leukostasis causes BRB dysfunction and is an early event in the cascade of DME, preceding any clinical signs of DR. These leukocytes upregulate the expression of proinflammatory cytokines leading to the recruitment of other inflammatory cells such as neutrophils and monocytes and the deterioration and enhancement of vascular permeability and capillary nonperfusion. VEGF also triggers inflammation [2, 4].

The exact role of inflammation seems to differ between the different phenotypes of DME. Analysis of intravitreal cytokine concentrations showed that elevated levels of IL-6 were strongly associated with the presence of the subretinal detachment (SRD) type of DME. There is also greater choroidal thickness, which may indicate increased choriocapillaris permeability due to VEGF production by the dysfunctional RPE [1]. Evidence suggests that hyperreflective foci (HF) may represent the activated microglia due to the severe inflammatory response. The SRD phenotype has a higher number of HF and they are associated with poorer visual acuity improvement and poorer glycemic control in patients without significant DME. It is important to understand how the different DME subtypes respond to intravitreal injections of different drugs in order to improve patient management [1].

Steroids not only target the synthesis of proinflammatory mediators but also reduce VEGF synthesis. They block the arachidonic acid pathway by inhibiting the phospholipase A2 and downregulate the synthesis of thromboxanes, leukotrienes and prostaglandins, leading to an improvement of the BRB and endothelial tight junction and subsequently better retinal oxygenation.

Steroids are widely and increasingly used in the treatment of DME, mostly as second-line therapy, but in some cases as first-line therapy. The main complications associated with their use are cataract progression and increased of intraocular pressure (IOP) [4].

The available steroids commonly used are triamcinolone acetonide (TAc), dexamethasone (DEX) implant, both of short term duration of action, and the long duration fluocinolone acetonide (FAc) implant. Intravitreal (IV) TAc injections have been shown to be effective in the cystoid macular edema (CME) type of DME. This is due to the reduction of Müller cell swelling and the prevention of their liquefaction and necrosis. These injections have also shown efficacy in patients with SRD type [1]. Protocol I has shown that pseudophakic patients treated with TAc have similar visual and anatomical outcomes as patients treated with ranibizumab. However, due to the short clearance half-time, they require repeated injections and should be used only in cases that cannot receive other agents, as they are associated with more complications such as cataract and ocular hypertension [4].

Two sustained-steroid delivery devices have been approved for the treatment of DME with the benefit of reducing the treatment burden: a bioerodible slow-release dexamethasone (DEX) implant (Ozurdex, Allergan, Inc., Irvine, CA) and a non-bioerodible extended-release fluocinolone acetonide (FAc) implant (Iluvien, Alimera, Alpharetta, GA). Ozurdex has a high rate of dexamethasone release during the first 2 months when it reaches its maximum, followed by a decline until 6 months. It has been shown to be effective in naïve DME and in eyes that have not responded to anti-VEGF. Iluvien lasts up to 3 years and has been approved for the treatment of severe cases such as chronic DME unresponsive to other treatments in patients previously treated with

corticosteroids without clinically significant IOP elevation [4].

Due to the RCM of the fluocinolone acetonide (FAc) implant, it is common practice to test the risk of IOP elevation with steroids by first injecting a short-term steroid before the injection of fluocinolone acetonide (FAc) implant.

The main purpose of our investigation was to evaluate whether there is a correlation between IOP variation after the IV TAc testing and after the FAc implant treatment, in patients with DME.

Methods

A real-world retrospective observational study was conducted in patients with DME from the Ophthalmology Department of Unidade Local de Saúde Entre Douro e Vouga (ULSEDV), Santa Maria da Feira, Portugal. This study was conducted in accordance with the principles set forth in the Declaration of Helsinki. The clinical patient data were retrieved from the Retina database, which has been approved by the Ethics Committee of the ULSEDV for research purposes (CA-0398/18-0t_MP/AC from 16/05/2018) and for which all patients have provided written consent. The patient information was previously de-identified for the purposes of analysis.

The data were collected from patients who had undergone treatment with FAc between December 2018 and July 2022. Patients with DME were included in the study if they had received at least one intravitreal TAc injection prior to the injection of the FAc implant. Patients with other causes of macular edema, such as retinal vein occlusion, uveitis, postoperative macular edema, tractional macular edema, inherited retinal dystrophies, and drug-induced macular edema, were excluded from the study. Additionally, patients lacking IOP data were excluded.

The data collected at the baseline assessment included demographic data (age and gender), medical history (duration and type of diabetes *mellitus* (DM) and glycated hemoglobin (HbA1c) level) and ophthalmologic history (type and number of previous intravitreal injections, previous laser therapy and its type and previous history of high IOP or use of IOP-lowering medications.

The mean IOP prior to and following IV TAc injection (assessed 0.5 and 2.5 months after injection) and mean IOP before and after FAc implant injection (assessed 0.5, 2.5 and 6 months post-implant) were recorded after measurement through Goldmann applanation tonometry. The time-points for intraocular pressure (IOP) measurements were determined by following the Department's protocol, which stipulates that patients undergoing a steroid intravitreal injection, irrespective of the specific steroid, are evaluated at ± 0.5 months and subsequently at three-month intervals. The requirement for IOP-lowering medications was documented at each assessment point. The steroid response was defined as IOP exceeding 21 mmHg.

In accordance with the established protocol of the Ophthalmology Department, all patients who are to be treated with FAc must undergo a preliminary test involving at least one intravitreal injection of the short-acting steroid. An increase in IOP that is adequately managed with topical medications does not preclude the possibility of pursuing FAc treatment. Optic nerve glaucoma changes are monitored with optical coherence tomography (OCT) at each visit.

A statistical analysis was done using the program Statistical Package for the Social Sciences (SPSS) 28.0. Descriptive statistics were reported as mean $\pm$ standard deviation (SD) for continuous variables or frequency and percentage for categorical variables. The increase in IOP after TAc was correlated with the increase in IOP after FAc using the Wald Chi-Squared correlation test. The variation of IOP after TAc was correlated with the variation of IOP after FAc at different time points by Spearman's test. A p-value inferior to 0.05 was considered statistically significant in all tests executed. Most of the statistical analysis is presented though tables to provide better readability. The Kaplan–Meier analysis was employed to assess the survival curves for IOP elevation.

Results

A total of 28 eyes of 18 patients were included in the study. Ten patients received bilateral FAc injections. The mean follow-up duration after this injection was 7.2 months (ranging from 4 to 12 months).

A summary of the demographic and ocular characteristics, as well as the previous treatments received, is presented in Table 1. At baseline, the mean age of the patients was 70.5 ± 10.1 years old, with 55.6% of the cohort comprising male subjects. All patients had been diagnosed with type 2 DM for a mean duration of 15.5 ± 8.7 years, with a mean HbA1c of 7.5 ± 0.8%. With regard to prior DME treatment, 75% of patients had undergone intravitreal anti-VEGF injections, while 25% had initiated corticosteroid treatment without prior anti-VEGF intervention. All patients were transitioned to a FAc implant injection following the administration of at least one TAc injection. Prior to the TAc injection, the mean IOP was 16.2 ± 2.5 mmHg and six eyes were on IOP lowering medication. No patients had a diagnosis of glaucoma.

The following data are presented in Tables 2 and 3. With regard to IOP variation, the mean IOP increased to 18.6 ± 4.0 mmHg and 18.2 ± 3.5 mmHg, at 0.5 and 2.5 months post-TAc injection, respectively. Twelve eyes were treated with IOP-lowering drops during the study period, with an average of 1.9 ± 0.9 per eye. Of the eyes included in the study, six were receiving monotherapy with an IOP-lowering medication three months prior to TAc injection, with an IOP range of 14 to 20 mmHg. Four of these eyes had a history of prior intravitreal steroid injections. Six eyes exhibited an IOP exceeding 21 mmHg (ranging from 22 to 34 mmHg) following TAc injection, at a mean time of 1.6 ± 1.0 months. Of these, five were treated with IOP-lowering drops, as detailed in Table 3. Table 3 also includes Patient 4, who underwent cataract surgery and TAc injection. An increase in intraocular pressure (IOP) to 26 mmHg was observed on the first day following surgery. No medication was administered,

Table 1 Baseline demographics, ocular characteristics and prior treatments of the eyes included in the study

Baseline Demographics		n
Age, years (mean ± SD)	70.5 ± 10.1	18
Gender, male/female (n (%))	10 (55.6) / 8 (44.4)	18
Type of diabetes, n (%)		
Type 2	18 (100)	18
Diabetes duration (mean ± SD)	15.5 ± 8.7	18
HbA1c level, mean (% ± SD)	7.5 ± 0.8	18
Ocular Characteristics		
Laterality, n (%)		
OD	16 (57.1)	28
OS	12 (42.9)	28
NPDR, n (%)	28 (100)	28
Pseudophakic, n (%)	28 (100)	28
IOP-lowering medications, n (%)	6 (10.7)	28
IOP, mmHg (mean ± SD)	16.2 ± 2.5	28
CMT, µm (mean ± SD)	415.5 ± 81.7	28
Prior Treatments		
Anti-VEGF IV, n (%)	21 (75)	28
Corticosteroids IV, n (%)	7 (25)	28
Number of IV (mean ± SD)	8.2 ± 4.8	28
Macular laser therapy, n (%)	4 (14.3)	28
Panretinal laser therapy, n (%)	7 (25)	28
Macular and Panretinal laser therapy, n (%)	6 (21.4)	28

Table 2 Data related to IOP values and the need of IOP-lowering medication; statistical analysis of IOP progression after FAc

IOP, mmHg (mean ± SD)		n
Prior to TAc	16.2 ± 2.5	28
0.5 months after TAc	18.7 ± 4.0	27
2.5 months after TAc	18.2 ± 3.5	28
Prior to FAc	15.5 ± 4.0	27
0.5 months after FAc	16.3 ± 3.1	28
2.5 months after FAc	17.7 ± 4.3	28
6 months after FAc	17.4 ± 3.9	28
IOP-lowering medication, n (%)		
Prior to TAc	6 (21.4)	28
0.5 months after TAc	8 (29.6)	27
2.5 months after TAc	11 (39.3)	28
Prior to FAc	10 (37.0)	27
0.5 months after FAc	11 (39.3)	28
2.5 months after FAc	13 (46.4)	28
6 months after FAc	14 (50.0)	28
IOP > 21 mmHg, n (%)		
Prior to TAc	0 (0.0)	28
0.5 months after TAc	3 (11.1)	27
2.5 months after TAc	3 (10.7)	28
Prior to FAc	0 (0.0)	27
0.5 months after FAc	1 (3.6)	28
2.5 months after FAc	5 (17.9)	28
6 months after FAc	3 (10.7)	28
IOP progression after FAc		
Wald Chi-Squared	0.226	
p-value	0.634	

Table 3 IOP values at the different timepoints of the eyes with a steroid response

	IOP, mmHg							
	Prior to TAc	0.5 months after TAc	2.5 months after TAc	Prior to FAc	0.5 months after FAc	2.5 months after FAc	6 months after FAc	IOP-lowering medication
1	15	19	**30***	12**	18	20	20	*Timolol maleate + dorzolamide + brimonidine ** No medication
2	12	19	16	16	16	20	**24***	* No medication
3	20	**22***	16	16	16	18	18	*Timolol maleate
4	19	**26***	16	15	14	19	17	* No medication
5	14	21	**23***	23	21	20	16	*Timolol maleate + dorzolamide
6	16	18	16	16	18	**24***	**24***	*Timolol maleate + dorzolamide
7	14	**34***	17	20	12	12	18	*Timolol maleate + brinzolamide + brimonidine
8	20	20	17	17	20	**26***	17	*Non-compliant to medication
9	17	18	**28***	12	14	14	16	*Timolol maleate + brinrzolamide
10	14	18	18	17	16	**26***	16	*Timolol maleate + tafluprost + brimonidine
11	20	16	16	20	20	**22***	16	* No medication
12	20	20	19	19	**23***	**22***	**30****	* Brinzolamide ** + Timolol maleate + brimonidine

and intraocular pressure (IOP) returned to normal levels spontaneously. Of the six eyes that exhibited an IOP exceeding 21 mmHg following TAc injection, none demonstrated a recorded IOP exceeding 21 mmHg following FAc implant injection (four were on IOP-lowering medication). Following FAc implant injection, the mean IOP was 16.3 ± 3.1 mmHg, 17.7 ± 4.3 mmHg, and 17.4 ± 3.9 mmHg, at 0.5, 2.5 and 6 months post-injection, respectively. A total of six eyes exhibited an IOP exceeding 21 mmHg (ranging from 23 to 30 mmHg), with a mean occurrence at 7.3 ± 2.2 months. Patient 8, as indicated in Table 3, did not adhere to the prescribed IOP-lowering medication regimen. Nevertheless, IOP normalization was observed by the sixth month.

A total of 14 eyes were treated with IOP-lowering drops during the study period, with an average of 2.1 ± 0.6 drops per eye. Of these, six eyes were on IOP-lowering medication prior to the TAc injection and continued with the medication, five eyes were treated after the TAc injection due to a recorded IOP > 21 mmHg, of which only four continued the treatment after the FAc injection, and four eyes were treated after the FAc implant injection due to a recorded IOP > 21 mmHg. In the cohort of eyes with a recorded IOP > 21 mmHg following FAc implant injection ($n = 6$), no eyes had a recorded IOP > 21 mmHg following TAc injection. The analysis revealed no statistically significant correlation between an IOP value exceeding 21 mmHg following TAc injection and the mean IOP progression after FAc implant injection at any time point ($p = 0.634$). IOP elevation was effectively managed with topical medication, and no patient exhibited evidence of nerve fiber layer loss or glaucoma.

Furthermore, the correlation of IOP variation after TAc injection and after FAc injection at the different time points demonstrated no statistically significant significance. This result remained consistent when the four eyes that were initiated on IOP-lowering medication following the TAc injection were excluded (Table 4).

The survival graphs (Figs. 1 and 2) illustrate the cumulative proportion of eyes that have not yet developed an IOP elevation over time for the TAc and FAc groups.

Eyes that did not demonstrate an increase in IOP during the follow-up period were designated as censored.

For the TAc group, the survival curve indicates that approximately 35% of eyes experienced IOP elevation in the first three months following administration. A

Table 4 Correlation of the IOP variation at the different timepoints after TAc and FAc

	Correlation	IOP variation 0.5 months after TAc	IOP variation 2.5 months after TAc
IOP variation 0.5 months after FAc	Spearman's rho	-0.227	-0.306
	p-value	0.255	0.128
IOP variation 2.5 months after FAc	Spearman's rho	0.045	-0.132
	p-value	0.819	0.512
IOP variation 6 months after FAc	Spearman's rho	0.017	-0.089
	p-value	0.934	0.681
Excluding the 4 eyes which were started on IOP-lowering medication after TAc			
IOP variation 0.5 months after FAc	Spearman's rho	-0.102	-0.183
	p-value	0.642	0.416
IOP variation 2.5 months after FAc	Spearman's rho	0.251	0.071
	p-value	0.236	0.746
IOP variation 6 months after FAc	Spearman's rho	0.171	0.152
	p-value	0.447	0.511

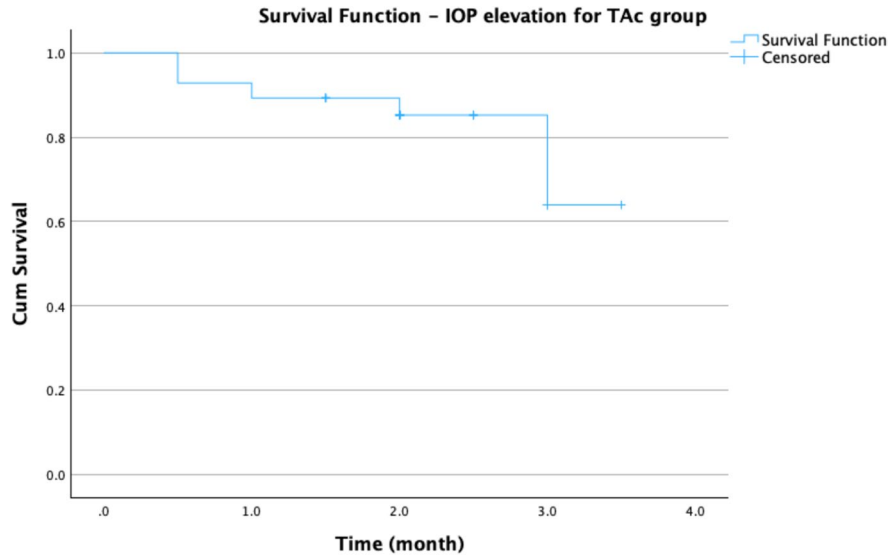

Fig. 1 Survival Graph 1 – TAc group

more pronounced decline in survival function was observed between the first and third month, indicating that IOP elevation events in this group manifest early on. The curve further demonstrates that, at the three-month mark, approximately 65% of eyes had not yet experienced an elevation in IOP.

In the FAc group, the Kaplan–Meier curve demonstrates a more gradual decline in survival over time. The majority of events occur within the initial four-month period, after which the curve stabilises, indicating a reduced frequency and prolonged time distribution of IOP elevation in this group. The study found that approximately 20–25% of eyes exhibited IOP elevation over a 12-month period of observation. The curve stabilises at approximately 4 months with a cumulative survival of around 78–80%. This indicates that 20–22% of eyes had experienced IOP elevation by 4 months. The horizontal line that delineates the subsequent period (up to 12 months) indicates a cessation of new events, suggesting a stabilisation of the risk.

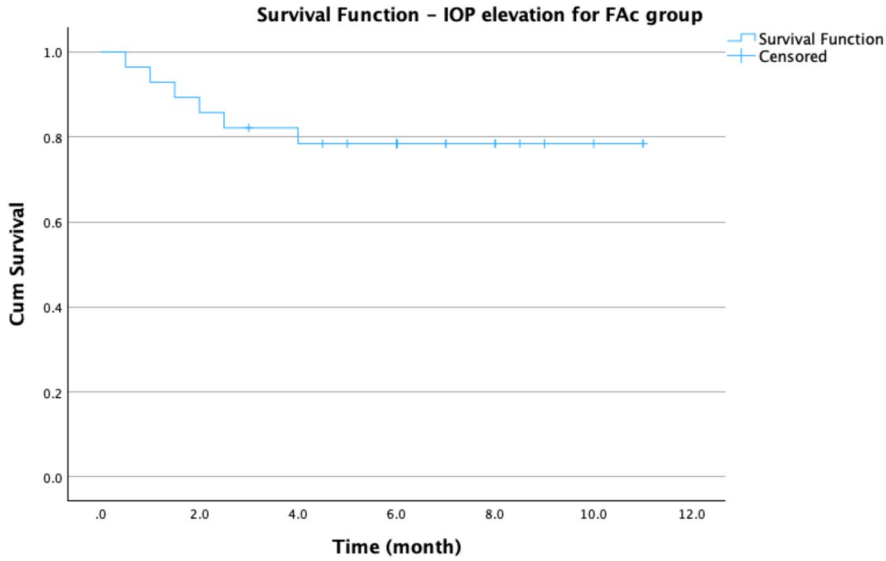

Fig. 2 Survival Graph 2 – FAc group

Discussion

Glucocorticoids (CG) can lead to ocular hypertension and secondary open-angle glaucoma, one of the most feared side effects of the intravitreal treatment with this group of drugs [5]. The FAc implant has been shown to be effective in patients with chronic DME already treated with other available therapies, with improved visual outcomes and reduced treatment burden [6, 7]. However, the main concern regarding its use is IOP elevation and related complications, although these are usually manageable [8, 9].

The fluocinolone acetate implant has been approved for the treatment of diabetic macular edema in patients who have undergone prior treatment with a course of steroids and did not experience a clinically significant increase in IOP. In accordance with the recommendations set forth by our department, patients should be treated with at least one injection of a short-acting steroid prior to FAc injection. The design of our study was based on the assumption that the primary concern in the treatment of patients with steroids is not the IOP non-responders, but rather those at risk of IOP elevation (IOP responders). In light of the aforementioned considerations, the present study was designed to assess the predictive value of TAc-related IOP elevation on IOP elevation following FAc implantation. With respect to the necessity for IOP reduction, five eyes initiated therapy during the TAc follow-up period, while three eyes commenced treatment during the FAc follow-up. In the TAc cohort, none of the eyes with an IOP exceeding 21 mmHg were receiving IOP-lowering medication prior to TAc injection. It has been demonstrated that patients who have previously undergone treatment with IOP-lowering medications are more prone to experience clinically significant IOP elevation [9]. Furthermore, a higher IOP prior to injection has been shown to correlate with a higher IOP during the follow-up period. However, of the six eyes that exhibited an IOP above 21 mmHg following TAc injection, none demonstrated a recorded IOP above 21 mmHg following FAc implantation.

The impact of an IOP exceeding 21 mmHg following TAc injection on the mean IOP progression following FAc implant was assessed. Our findings revealed no statistically significant effect at any time point, prompting the question of whether a steroid challenge with TAc prior to FAc implant injection is a mandatory procedure. Glucocorticoids (GCs) regulate distinct sets of genes in the trabecular meshwork (TM), eliciting varying chemical responses. [5, 10] This may provide insight into why the eyes that demonstrate a clinically significant elevation in IOP following TAc are not the same ones that exhibit this response after FAc.

Although some of the eyes (n = 6) were on IOP-lowering medication only before FAc which could be considered a potential source of bias, the variation on IOP at each time point (and not only the isolated IOP

value above 21 mmHg) was examined and compared between TAc and FAc. No statistically significant correlation was found, with or without these six eyes. This indicates that the fluctuation in IOP following TAc injection is not associated with the variation in IOP observed after FAc injection at any given time point. This further supports the notion that the previous steroid challenge may not be a reliable predictor of the IOP response to FAc.

In order to evaluate the proportion or risk of developing IOP elevation for both groups, Kaplan–Meier survival analysis was performed. The analysis revealed that approximately 35% of eyes in the TAc group exhibited IOP elevation during the initial three months, while in the FAc group, 20–22% of eyes demonstrated IOP elevation by 4 months, with no subsequent IOP elevations observed in the subsequent period. The results suggest that ocular pressure elevation occurs earlier and more frequently after treatment with TAc, whereas the risk is lower and more diluted over time in the FAc group. The issue of the sample size must be considered, on account of the fact that the number of subjects is limited. This may result in an estimate of the survival function that is less precise, particularly over extended periods. Furthermore, the disparity in the duration of follow-up between the groups complicates the direct comparison of accumulated long-term risk.

In the PALADIN study, the difference in IOP from baseline became insignificant by the end of the study [7]. It is estimated that at least 20–30% of treated eyes require IOP-lowering medications and 2–5% require surgery [8]. Therefore, careful IOP assessment and control is very important in patient follow-up, especially in younger patients and those with high pre-FAc IOP values [8, 9].

The most widely accepted theory attributed to IOP elevation after GC exposure is increased resistance to aqueous humor outflow due to extracellular debris accumulation in the trabecular meshwork (TM), through morphologic and biochemical changes [5, 8, 9]. GC effects on TM are caused by GC-mediated TM cell gene expression and the genes or combinations of genes that are modulated by GCs and lead to elevated IOP are still under investigation [5]. Unlike naturally occurring GCs, synthetic GCs selectively bind to the glucocorticoid receptor (GR) and have minimal mineralocorticoid activity [10]. GCs bind to GRs, which positively or negatively regulate gene expression. GR has two major variants—α and β—that result from alternative splicing, and, each one of these variants has several isoforms. GRβ is a dominant negative inhibitor of GRα and of the subsequent gene transactivation. It has been shown that the potency of this negative effect depends on the type and dose of the GC used and that the chemical structure of each GC influences the intranuclear distribution and mobility of the GR [5]. GCs have differences in their structure (Fig. 3) that lead to differences in their pharmacokinetic profiles and functions. Studies have shown that a unique set of genes is differentially regulated by DEX, FAc and TAc, meaning that they can generate both a common and unique pattern of gene expression, leading to the generation of unique cellular responses. [5, 10]

Due to the associated complications, a steroid challenge prior to FAc implant injection is considered mandatory although it is unclear which steroid is superior in determining the risk of IOP elevation. The PALADIN study has demonstrated that this challenge is predictive of the IOP response to FAc implant, independent of the steroid choice [11]. Although there is a high level of agreement among retinal specialists, consensus has not yet been reached on this issue [12]. The PALADIN study was designed to ascertain the predictive value of short-term steroid non-responders to IOP elevation with the FAc implant. The results of the study indicated that in 97% of the eyes that were subjected to a challenge using a short-acting steroid and which exhibited an IOP elevation of less

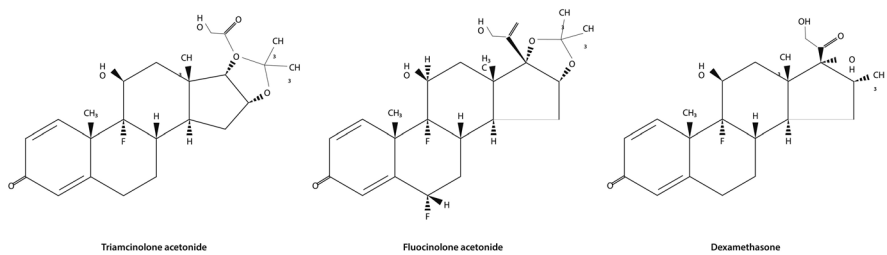

Fig. 3 Biochemical differences among different glucocorticoids

than 25 mmHg, a comparable response was observed following the injection of FAc. Moreover, an investigation was conducted to ascertain the positive predictive value of an intraocular pressure (IOP) measurement of over 25 mmHg. The investigation yielded a result of 78%, indicating that 22% of the sample exhibited an ineffective challenge. A number of studies have demonstrated that the risk of increased intraocular pressure following FAc implantation is relatively low. Nevertheless, only a limited number of studies have investigated the predictive value of non-rising eye pressure in patients who have been challenged with a short-acting steroid. To the best of our knowledge, our study is the first to examine the predictive value of the risk of increased eye pressure in this context.

> *However the results showed similar to the the Paladin study that even if you try to screeen for steroid responders before the Fac implant the results are not 100% predictive.*
> *In the paladin study the positive predictive value of having IOP over 25 was 78% whcih means 22% had IOP over 25 even with a steroid challenge in addition even with treatment 97% had IOP under 25 at last visit which mean 3% could not be controlled by medication.*

It is crucial to evaluate the necessity of a prior short-acting steroid challenge, which carries the risk of multiple DME relapses and multiple spikes of ganglion cell lesions. The use of a longer and stable steroid may offer a superior approach for disease control and damage mitigation, while ensuring proper IOP follow-up and control.

We recognize the inherent limitations of our study, including its relatively small sample size (n = 28). A larger number of participants would have enabled a more robust and powerful statistical analysis. Additionally, the retrospective nature of the study constrained data collection to what was documented in the electronic medical record. Furthermore, due to the observational nature of the study involving real-life patients, it was not feasible to adhere to a strict protocol with precise follow-up times, leading to a diverse and heterogeneous patient population.

Further research is required to gain a deeper understanding of the mechanisms underlying the increase in IOP associated with different steroids. A further evaluation is required to ascertain the effective predictive value of elevated IOP risk, as well as the cost implications, of a prior short-acting steroid challenge. The primary objective should be to provide the most efficacious and appropriate treatment for patients with diabetic macular edema.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Catarina Pestana Aguiar, João Alves Ambrósio and Lilianne Duarte. The first draft of the manuscript was written by Catarina Pestana Aguiar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This is an observational study. The clinical patient data were retrieved from the Retina database, which has been approved by the Ethics Committee of the ULSEDV for research purposes (CA-0398/18-0t_MP/AC from 16/05/2018) and for which all patients have provided written consent. The patient information was previously de-identified for the purposes of analysis.

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