Clinical Experience and Safety Profile of Intravitreal Injections in a Tertiary Hospital

Experiência Clínica e Perfil de Segurança das Injeções Intravítreas num Hospital Terciário

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ABSTRACT

INTRODUCTION: Our aim was to evaluate the real-life experience and safety profile of intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) and/or corticosteroids for different ophthalmological conditions.

METHODS: Retrospective and observational study including all eyes submitted to IVI during the first semester of 2022. Clinical indications, the class of drug administered and the rate of therapeutic compliance were revised. Safety issues and surgical complications were also analyzed during a follow-up period between January to December 2022.

RESULTS: Three thousand four hundred and ninety-one IVI performed in 1281 eyes (of 1024 patients) were evaluated. The most common indications were macular neovascularization (MNV) (35.1%, n=450) and diabetic macular edema (DME) (34.6%, n=433), followed by retinal vein occlusion (RVO) (16.4%, n=208), proliferative diabetic retinopathy (7.3%, n=94) and inflammatory edema (4.8%, n=62). An overall therapeutic compliance rate of 90.7% (n=3491 IVI performed) was obtained: considering the missed appointments, patients with DME contributed to 43.1% of the missed appointments, followed by MNV (30.5%) and RVO (16.1%). The most common injected anti-VEGF medications were aflibercept (39.1%, n=501), followed by bevacizumab (25.8%, n=330), ranibizumab (21.8%, n=279) and brolucizumab (5.4%, n=69). Among corticosteroids, dexamethasone implant (5.9%, n=76) was the most commonly used followed by triamcinolone acetonide (1.6%, n=21) and fluocinolone implant (0.4%, n=5). Overall, the frequency of switching was 9.8%. In 40.5% cases of switch, brolucizumab was the choice for subsequent treatment, followed by aflibercept (31.7%) and ranibizumab (10.3%). During follow-up, complications occurred in 100 eyes (global rate of 2.86%): n=89 (rate of 2.53%) ocular hypertension requiring additional therapy or surgery; n=2 (rate of 0.06%) uveitis after aflibercept; n=2 (rate of 0.06%) retinal detachment, n=2 (rate of 0.06%) vasculitis after brolucizumab and n=2 (rate of 0.06%) cataract after IVI; n=1 (rate of 0.03%) endophthalmitis, n=1 (rate of 0.03%) vitreous hemorrhage and n=1 (rate of 0.03%) dexamethasone implant in the anterior chamber.

CONCLUSION: Ocular adverse events associated with IVI are relatively low and reflect the safety of these treatments. When scheduling IVI, some factors must be taken into consideration to ensure the best possible outcomes and high therapeutic compliance rates.

KEYWORDS: Intravitreal Injections; Eye Infections.

RESUMO

INTRODUÇÃO: O nosso objetivo foi avaliar a experiência real e o perfil de segurança das injeções intravítreas (IVI) de *anti-vascular endothelial growth factor* (anti-VEGF) e/ou corticosteroides para diferentes condições oftalmológicas.

MÉTODOS: Estudo retrospetivo e observacional, que incluiu os olhos submetidos a IVI durante o primeiro semestre de 2022. As indicações clínicas, a classe de medicamento administrado e a taxa de adesão terapêutica foram avaliadas. Questões de segurança e complicações cirúrgicas foram analisadas durante o follow-up de janeiro a dezembro de 2022.

RESULTADOS: Foram avaliadas 3491 IVI realizadas em 1281 olhos (de 1024 pacientes). As indicações mais comuns foram neovascularização macular (NVM) (35,1%, n=450) e edema macular diabético (EMD) (34,6%, n=433), seguidos de oclusão venosa retiniana (OVR) (16,4%, n=208), retinopatia diabética proliferativa (7,3%, n=94) e edema inflamatório (4,8%, n=62). Obteve-se uma taxa de adesão terapêutica de 90,7% (n=3491 IVI realizadas): considerando as consultas perdidas, os pacientes com EMD contribuíram com 43,1% das consultas perdidas, seguidos de MNV (30,5%) e RVO (16,1%). O medicamento anti-VEGF mais frequentemente injetado foi aflibercept (39,1%, n=501), seguido de bevacizumab (25,8%, n=330), ranibizumab (21,8%, n=279) e brolucizumab (5,4%, n=69). Entre os corticosteroides, o implante de dexametasona (5,9%, n=76) foi o mais utilizado, seguido do acetonido de triancinolona (1,6%, n=21) e do implante de fluocinolona (0,4%, n=5). A frequência de *switch* foi de 9,8%. Em 40,5% dos casos de troca, o brolucizumab foi a escolha para tratamento subsequente, seguido pelo aflibercept (31,7%) e ranibizumab (10,3%). Durante o *follow-up*, ocorreram complicações em 100 olhos (taxa global de 2,86%): n=89 (taxa de 2,53%) hipertensão ocular necessitando de terapia adicional ou cirurgia; n=2 (taxa de 0,06%) uveíte após aflibercept; n=2 (taxa de 0,06%) descolamento de retina, n=2 (taxa de 0,06%) vasculite após brolucizumab e n=2 (taxa de 0,06%) catarata após IVI; n=1 (taxa de 0,03%) endoftalmite, n=1 (taxa de 0,03%) hemorragia vítrea e n=1 (taxa de 0,03%) implante de dexametasona na câmara anterior.

CONCLUSÃO: Os eventos adversos oculares associados às IVI foram relativamente baixos e refletem a segurança destes tratamentos. No agendamento da IVI, alguns fatores devem ser levados em consideração para garantir os melhores resultados possíveis e altas taxas de adesão terapêutica.

PALAVRAS-CHAVE: Infeções Oculares; Injeções Intravítreas .

INTRODUCTION

Intravitreal injections (IVI) are the most common intraocular surgical procedures worldwide and it is expected that these numbers will increase in future year[1] as a result of the positive impact that these treatments have shown in various chorioretinal pathologies.[2] Intravitreal administration of a drug maximizes intraocular levels but also minimizes the risk of toxicity associated with systemic administration.[3] Its first application was in 1911 as a way to repair retinal detachment by injecting air into the eye.[1] However, in recent years, the use of IVI has reached an exponential growth, being currently considered the preferred treatment option for various retinal and choroidal disorders as exudative age-related macular degeneration (AMD), macular neovascularization of other causes (MNV), diabetic macular edema (DME) and macular edema secondary to retinal vein occlusion (RVO) or uveitis.[4,5]

Some studies have shown that anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection (IV) prevent vision loss in the majority of patients and lead to rapid spreading of anti-VEGF treatments in many countries.[6] However, most IVI drugs, especially anti-VEGF, have a short half-life, requiring multiple treatments to control the pathology.[1,2,7,8] The need for a large number of IVI increases the cumulative risk of complications, especially those

common to the different agents (anti-VEGF and/or corticosteroids), as endophthalmitis, intraocular inflammation, vitreous hemorrhage, rhegmatogenous retinal detachment (RRD) and intraocular pressure (IOP) elevation.[9,10]

Therefore, the high costs of medicines as well as the need of multiple treatments are considered some of the main obstacles to IVI treatment.[6] A recent study in Norway pointed other relevant barriers such as geographic variations in treatment episodes.[11] Furthermore, the growth of the aging population and diabetes worldwide also enhance the burden related to medical resources and healthcare costs.[5] The unequal and sometimes difficult access to certain treatments such as the USA and some Asian countries, where medicines are not reimbursed by healthcare systems, is a different reality and contrast to what is observed in Portugal.[6] A Portuguese study assessing the number of anti-VEGF IV concluded that there was an average annual increase of 32% between 2001 and 2012, but unequal geographical distribution in treatment rates across the country.[12]

The aim of this study was to evaluate the real-world experience and safety profile of IVIs with anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids for the treatment of different retinal disorders in Centro Hospitalar Universitário de Santo António (CHUdSA), a tertiary center, The economic impact of the different treatment choices and disease specificities was also analyzed.

METHODS

This is a retrospective, observational, single center study, conducted at the Department of Ophthalmology of CHUdSA, a tertiary center in Portugal, which included all eyes undergoing IVI treatment between January to June 2022. Demographics, laterality, comprehensive ophthalmic examination details including best corrected visual acuity (measured through Snellen's chart and converted into logMAR scale), lens status and IOP (at baseline and at the last follow-up) were recorded.

The number of patients receiving unilateral injections, clinical indications for IVI treatment, the type of drug administered, and the rate of therapeutic compliance among patients were analyzed. Primary medication was considered the one used in the first injection of each eye in the study interval, regardless the patient was previously naïve or not. Switch of medication was analyzed for the following injections performed in the specified period. Combination of therapy was considered when the injection of corticosteroid (dexamethasone and fluocinolone acetonide implant) was followed by an anti-VEGF injection. Eyes of patients who did not complete scheduled treatments due to death or hospitalization were excluded from analysis. Occurrence of side effects like RRD, endophthalmitis, IOP elevation (eyes with ocular hypertension or glaucoma requiring additional therapy or surgery) and intraocular inflammation were analyzed during a maximum follow-up period of 12 months (January to December 2022).

Injections drugs included in this study were anti-VEGF: ranibizumab (Lucentis®, Novartis), bevacizumab (Avastin®, Roche), aflibercept (Eylea®, Bayer) and brolucizumab (Beovu®, Novartis); and corticosteroids: triamcinolone acetonide (TA) (dose of 2 mg), dexamethasone implant (Ozurdex®, Allergan) and fluocinolone acetonide implant (Iluvien®, Alimera).

In this article, MNV was considered as a set of pathologies that includes exudative age-related macular degeneration, polypoidal choroidal vasculopathy, myopic choroidal neovascularization, among others. Likewise, retinal vein occlusion was considered as a set of pathologies that includes central retinal vein occlusion, branch retinal vein occlusion and hemiretinal vein occlusion. Patients with PDR and concomitant macular edema were included in the DME group.

For the evaluation of the economic impact of the different treatment choices and some disease specificities, the price of each medication was retrieved from the electronic catalog of Shared Services of the Ministry of Health, publicly available at https://www.catalogo.min-saude.pt/CEC/Publico/Default2.aspx. Thus, the price of vial is as follow: 237€ for Avastin®, 532€ for Lucentis®, 567€ for Eylea®, 532€ for Beovu®, 3€ for TA, 816€ for Ozurdex® and 5794€ for Iluvien®. Costs were calculated assuming the use of one vial per procedure to all medication but Avastin®. Avastin® is prepared for intravitreal injection by the hospital pharmacy with 1 vial yielding 50 doses, each costing 4.74€.

IVI PROCEDURE

All injections are performed in an operating room following this exact procedure: in the waiting room of the operating room, signed informed consent is confirmed, the eye to treat is identified and vital parameters are assessed; topical anesthesia is performed with oxybuprocaine hydrochloride 4 mg/mL (action repeated three times) and 10% povidone-iodine is applied on the surrounding eyelashes, caruncle and upper and lower eyelids of the eye to be treated.

In the operating room, the doctor who performs the IV uses sterile protection and gloves, disinfection is repeated with 10% povidone-iodine on the surrounding eyelashes, caruncle, upper and lower eyelids. Then sterile surgical drape and eyelid speculum are placed over the eye, a drop of 5% povidone-iodine solution is positioned at the site to be injected, (mostly the superotemporal quadrant) and in the cul-de-sac, avoiding the cornea, for at least 30 seconds.

The patient receives a fixation target inferonasal with the finger or auxiliary hand and the needle is applied, using a sterile caliper: 3,5 or 4-mm posterior to the limbus (in pseudophakic/aphakic patients versus phakic eyes, respectively) and towards the center of the vitreous cavity until a depth of 4 mm.

After immediately removing the needle, the surgeon ensures that each patient can see the light and count their fingers and complete cleaning is done with saline solution. A phone call is made by the nursing team to the patient on the day after the surgical procedure to assess the postoperative status.

STATISTICAL ANALYSIS

Categorical variables were described through absolute and relative frequencies and continuous variables through means and standard deviations, or medians and interquartile range for variables with a skewed distribution. Parametric and non-parametric tests were used according to the distribution of the data. A multivariable analysis was performed using a logistic regression model through a stepwise approach to fit the model and find independent clinical predictors for missed appointments. The area under the curve of a receiving operating characteristic curve was used to test the predictive value of the model. The Hosmer-Lemeshow test was used to test the goodness of fit of the model. A *p*-value of <0.05 was considered as statistically significant. All analyses were performed with Stata software (version 14.2).

RESULTS

The study analyses included three thousand four hundred and ninety-one intravitreal procedures performed in 1281 eyes (of 1024 patients). The mean±SD age was 71.65±12.23 years and 535 (52.2%) were females. Table 1 presents the demographics of the study population. Half of the population (50.6%) was phakic and almost one-fifth (18.2%) had glaucoma or ocular hypertension.

The most common indications for intravitreal injection were MNV (mostly in the setting of exudative) AMD (35.1%) and DME (34.6%). Among the 24 diseases grouped as "others", there were 11 (45.8%) eyes with neovascular glaucoma, 3 (12.5%) vasoproliferative tumors, 2 (8.3%) with peripheral exudative hemorrhagic chorioretinopathy and 1 (4.2%) eye for each one of the following diseases: Coats' disease, central retinal artery occlusion, macular edema secondary to endophthalmitis, retinal capillary hemangioblastoma, choroidal hemangioma, radiation retinopathy, infectious posterior uveitis complicated with retinal neovascularization, rickettsiosis and retinal vasculitis. Anti-VEGF medication comprised 92.1% of the primary medication and Eylea® was the most frequently injected drug. Among corticosteroids, Ozurdex® was the most used as primary therapy.

Table 1. Population characteristics.

Variable	
Patients / Eyes	1024 / 1281
Age, y	71.65±12.23
Female sex	535 (52.2%)
BCVA, logMAR	0.57±0.51
IOP, mmHg	14.9±4.3
Phakic	648 (50.6%)
Glaucoma/OHT	233 (18.2%)
Anti-glaucoma medication	
0	1048 (81.8%)
1	86 (6.7%)
2	84 (6.6%)
3	40 (3.1%)
4	23 (1.8%)
Diseases	
MNV	450 (35.1%)
DME	433 (34.6%)
RVO	208 (16.4%
PDR	94 (7.3%)
Inflammatory edema	62 (4.8%)
Others	24 (1.9%)
Medication	
Avastin®	330 (25.8%)
Lucentis®	279 (21.8%)
Eylea®	501 (39.1%)
Beovu®	69 (5.4%)
TA	21 (1.6%)
Ozurdex®	76 (5.9%)
Iluvien®	5 (0.4%)

DME, diabetic macular edema; MNV, macular neovascularization; RVO, retinal vein occlusion; PDR, proliferative diabetic retinopathy; TA, triamcinolone acetonide.

Table 2 presents the data concerning the switch and

Table 2. Switch and combination of intravitreal medications.

		Switch/combined medication							TOTAL
		Avastin®	**Lucentis®**	**Eylea®**	**Beovu®**	**TA**	**Ozurdex®**	**Iluvien®**	
1st medication	**Avastin®**		8	23	5	2	1	0	**39**
	Lucentis®	0		7	30	2	3	0	**42**
	Eylea®	2	5		12	1	10	0	**30**
	Beovu®	0	0	0		0	0	0	**0**
	TA	0	0	0	1		0	0	**1**
	Ozurdex®	0	0	8	3	0		1	**12**
	Iluvien®	0	0	2	0	0	0		**2**
TOTAL		**2**	**13**	**40**	**51**	**5**	**14**	**1**	**126**

TA, triamcinolone acetonide.

combination of medications. Overall, the frequency of switching was 9.8%. During the period of analysis, Lucentis® (33.3%), Avastin® (30.9%) and Eylea® (23.8%) were the most switched medications. In 40.5% cases of switch, Beovu® was the choice for the next treatment, followed by Eylea® (31.7%) and Lucentis® (10.3%). Most eyes that underwent switch were treated for DME (40.5%).

Table 3 presents the numbers of the planned and performed IVI (Fig. 1), as well as the difference of costs. Overall, the calculated cost associated of the performed IIV was 1 545 672.54€. During these 6 months it was found that patients with MNV, DME, RVO, PDR, inflammatory edema and other causes were submitted, on average, to 2.9, 2.7, 3.0, 2.6, 1.6 and 2.5 IVI during these 6 months, respectively. In this way, a treatment cost per eye during these 6 months was calculated for patients with MNV, DME, RVO, PDR, inflammatory edema and other causes in the amount of 418.2€, 502.0€, 370.4€, 393.8€, 688.9€ and 383.8€, respectively. By descending order, the diseases with higher associated costs were DME (582 361.54€), MNV (544 088.76€) and RVO (232 988.72€). Considering the missed appointments, the total potential value in losses was of 146 268.30€. DME, MNV and RVO contributed to 43.1%, 30.5% and 16.1% of the missed appointments, and to 46.1%, 31.7% and 15.1% of the total burden respectively (67 409.42€, 46 386.24€, 22 071.06€, respectively). Of note, no Iluvien® injection was missed. Fig. 2 shows the geographic distribution of patients who received IVI in our hospital, based on postal code address and the rate of missing at least one treatment per patient.

In the multivariable analysis (Table 4), male gender, MNV and inflammatory edema (*vs* DME) and Ozurdex® injection (*vs* Avastin®) were associated with lower odds of missing appointments (p=0.576 for Hosmer-Lemeshow test). Area under the curve [95% confidence interval] of the receiving operating characteristic curve for the model was 0.60 [0.56-0.64].

Table 3. Total number of injections for each group of diseases.

	Primary medication														Difference	
	Avastin®		Lucentis®		Eylea®		Beovu®		TA		Ozurdex®		Iluvien®			
	P	R	P	R	P	R	P	R	P	R	P	R	P	R	Total	Costs, €
MNV	350	324	250	223	702	657	104	92	2	2	3	3	0	0	110	-46,386.24
DME	204	171	362	323	527	461	163	149	9	8	44	42	6	6	155	-67,409.42
RVO	247	228	138	120	264	245	4	4	5	5	28	26	1	1	58	-22,071.06
PDR	76	67	110	101	55	50	26	25	0	0	0	0	0	0	24	-8,197.66
Infl. edema	14	14	11	10	26	25	2	2	15	14	29	29	4	4	3	-1,102.00
Others	25	17	31	29	9	9	3	3	1	1	1	1	0	0	10	-1,101.92
Total	**916**	**821**	**902**	**806**	**1583**	**1447**	**302**	**275**	**32**	**30**	**105**	**101**	**11**	**11**	**360**	**-146,268.30**

DME, diabetic macular edema; MNV, macular neovascularization; RVO, retinal vein occlusion; PDR, proliferative diabetic retinopathy; TA, triamcinolone acetonide; P, planned, R, real.

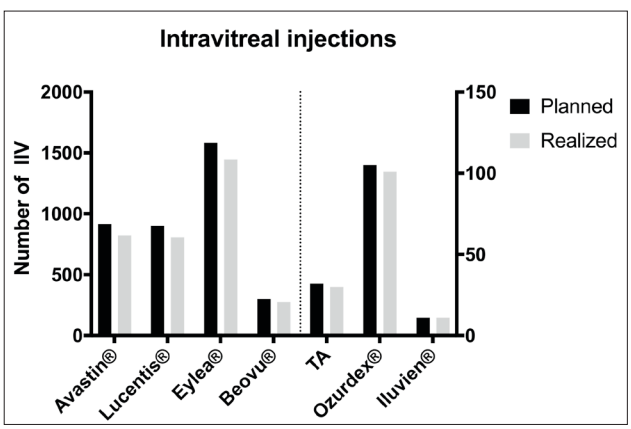

Figure 1. Planned and performed intravitreal injections.

During follow-up, complications occurred in 100 eyes (with a global rate of 2.86%): ocular hypertension requiring additional therapy or surgery needed presented in 89 eyes (rate of 2.53%); uveitis after Eylea® was detected in 2 eyes (rate of 0.06%) (one anterior uveitis and one panuveitis); in

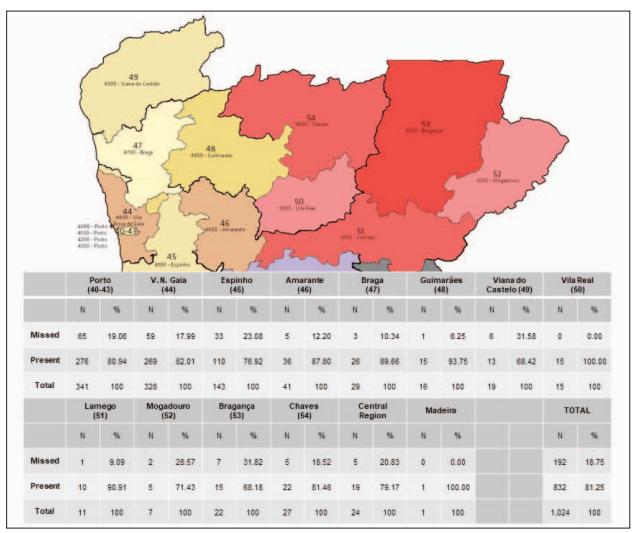

Figure 2. Postal code organization and therapeutic compliance. Image edited and adapted from the page https://liguem.com/curiosidades-sobre-os-codigos-postais-portugueses/, viewing date 09/18/2023 at 11:15 pm.

2 eyes (rate of 0.06%) was observed RRD (in one case af-

Table 4. Logistic regression for missed appointments.

	Univariable		Multivariable	
	OR [95%CI]	*p*-value	OR [95%CI]	*p*-value
Age (years)	1.00 [0.99-1.01]	0.944		
Female gender	1.05 [1.15-2.02]	0.003	1.59 [1.19-2.11]	0.002
Clinical presentation				
Visual acuity	0.76 [0.45-1.28]	0.302		
Phakic	1.04 [0.79-1.37]	0.777		
OHT/Glaucoma	1.10 [0.78-1.56]	0.588		
Disease				
DME	Reference		Reference	
MNV	0.70 [0.50-0.97]	0.035	0.62 [0.44-0.87]	0.006
RVO	0.90 [0.60-1.34]	0.594	0.85 [0.56-1.29]	0.444
PDR	0.90 [0.52-1.55]	0.713	0.87 [0.50-1.50]	0.613
Infl. edema	0.17 [0.05-0.55]	0.003	0.22 [0.06-0.80]	0.021
Others	1.11 [0.43-2.88]	0.823	1.01 [0.38-2.65]	0.984
IIV medication				
Avastin®	Reference		Reference	
Lucentis®	1.10 [0.75-1.62]	0.618	1.03 [0.69-1.53]	0.885
Eylea®	0.92 [0.65-1.30]	0.635	0.91 [0.64-1.30]	0.608
Beovu®	1.05 [0.56-1.97]	0.878	1.08 [0.57-2.07]	0.809
TA	0.40 [0.09-1.75]	0.223	0.72 [0.14-3.59]	0.688
Ozurdex®	0.32 [0.13-0.78]	0.012	0.37 [0.15-0.93]	0.034
Iluvien®	1	-	1	-

ter Ozurdex® and in another case after Lucentis®), in 2 eyes (rate of 0.06%) was objectified posterior uveitis with occlusive retinal vasculitis after Beovu® and traumatic cataract after IVI had been documented in 2 eyes (rate of 0.06%); 1 eye (rate of 0.03%) with endophthalmitis (after Ozurdex®), 1 eye (rate of 0.03%) with vitreous hemorrhage and 1 eye (rate of 0.03%) dexamethasone implant in the anterior chamber were also observed.

The proportion of patient that needed additional medical or surgical antiglaucoma therapy was higher for those injected with a corticosteroid when compared with anti-VEGF (16.7% *vs* 6.2%, $p<0.001$). The need for surgery to control IOP occurred in 5 eyes (0.14% rate) in eyes previously treated for neovascular glaucoma (in 2 eyes), retinal vein occlusion (in 2 eyes) and DME (in 1 eye). The surgical procedures to control IOP were peripheral retinal cryoablation (in 2 eyes), EX-PRESS Glaucoma Filtration Device (in 1 eye) and EX-PRESS Glaucoma Filtration Device combined with phacoemulsification of the lens (in 2 eyes).

DISCUSSION

The results obtained from the analysis of 3491 IVIs support the observation of a high number of IVIs performed at our hospital, a finding that is line with the recent growth of intravitreal procedures in Portugal and other countries.[6,13]

In international hospitals like Moorfields Eye Hospital, the primary indications for IVI were neovascular age-related macular degeneration (nAMD), with the second most common indication being diabetic macular edema.[13] Similarly, in Portugal, a multicenter study concluded that anti-VEGF drugs were first used to treat nAMD, followed by DME.[6]

Although the mentioned Portuguese study analyzed data from 2013 to 2018, the findings from our 2022 study align with the previously described trends, showing a higher prevalence of treatments for MNV and DME (together they correspond to more of half of IVI - 69.7%).[6] These values can be justified by variation in demographics such as age, ethnicity, and social determinants of health, which are known to be risk factors for retinal diseases.[14] The incidence of late AMD is expected to increase due to population growth and lengthening life expectancy.[15] Similarly, diabetes was estimated to affect a total of 463 million people in 2019 and it will grow to around 700 million by 2045.[16] This theoretically estimated high number of diabetic patients is in line with what was observed in our study, since the prevalence of diabetic patients treated for DME or PDR exceeds 40% of our sample.

Many pathologies described were difficult to manage before the appearance of IVI, more specifically anti-VEGF.

Currently, the available anti-VEGF therapies are Lucentis®, Eylea®, Avastin® and, recently, Beovu®. It should be noted that despite having been initially approved for the treatment of metastatic colorectal cancer, Avastin® has been widely used for the treatment of various ophthalmological pathologies as an off-label alternative.[12] In turn, Beovu® was only recently approved in 2019 for nAMD and in 2022 for EMD,[17] hence it is still low percentage of use, being mostly associated with switch treatments in our study. In 2 eyes, medication was changed from Eylea® to Avastin®, probably due to lack of approval by the institution Committee of Pharmacy and Therapeutics. On the other hand, corticosteroids are mainly indicated in the treatment of pathologies such as chronic DME that is insufficiently responsive to available therapies or in pathologies with an inflammatory component, which is why these treatments represent a percentage of less than 8% in our study.[18-20] By multivariable analysis, patients medicated with corticosteroids implants tend to need less IVI and consequently have better compliance.

A study performed in Portugal concluded that the cost of IVI is approximately €1913 per episode, a value similar to that in the USA.[12] Considering the cost of treatment per eye, this value was higher in patients with inflammatory edema (due to the greater need for treatment with corticosteroid implants), followed by patients with DME. Therefore, given the cost per pathology and also the high number of patients, it is not surprising that patients with DME have those that involved a higher cost.

Patients with DME were also those who showed lower therapeutic adherence. On average, 18.75% of patients missed IVI at least once. This value is higher for patients who live more distant from the hospital (which is probably justified by travel distances, which could be a barrier to attending treatments[12]) but, contrary to what would be expected, it is not lower for patients in the metropolitan area of Porto.

Our study presents an overall complication rate of 2.92%. It is a relative rate because not all studies evaluated the same proportion of complications. The incidence rate of complications varies greatly according to the literature. Regarding the incidence of endophthalmitis, the VISION Study Year 1 had a 1.3% incidence and the PIER Phase IIIb study had no cases[3]; a multicenter clinical trial reported a per-patient incidence of endophthalmitis after anti-VEGF that ranged from 0.019% to 1.6%[9]; another study reports that the incidence varies from roughly one case in 1000 to one in 5000 IVI[21]; finally, Rajesh et al reported an endophthalmitis rate of 0.07% in patients who underwent intravitreal dexamethasone implants.[10] Studies vary regarding the relationship between the rate of endophthalmitis and the drug injected: one study reports, for example, that the rate appears to be the same between different anti-VEGF agents[9]; on the other hand, another study reports that this rate is higher after bevacizumab.[21] Baudin *et al* concluded that there is a low incidence rate of acute endophthalmitis after IVI of corticosteroids or anti-VEGF agents, and this risk of endophthalmitis after IVI appeared to be greater for corticosteroids compared to anti-VEGF agents.[22] Our study showed an endophthalmitis rate of 0.03%, below the incidence values presented by some studies (previously presented),[3,9,21] with the only case in this study occurring after an Ozurdex® IVI. This may be due to the fact that IVI administered in the US is predominantly administered in the office using substerile techniques, as opposed to the practice in most European countries, where these injections are administered in an operating room.[21]

About RRD, the etiology may be the result of an induction of posterior vitreous detachment or an incorrect technique for intravitreal injection.[9] Our study presented an RRD rate of 0.06% (in one case after Ozurdex® and in another case after Lucentis®), which are in line with the incidence values presented by some studies: the EYETECH Phase II study had a 4.8% incidence, the PIER Phase IIIb study had no cases[3] and other studies report that the overall incidence of retinal detachment is low (0% to 0.67%).[9,10]

About IOP elevation, the volume expansion associated with IVI can cause an immediate rise in IOP, with IOP values over 30 mmHg. This typically resolves spontaneously and returns to safe levels within 30 minutes after IVI, as the sclera expands to accommodate the change in volume.[1] Elevated IOP results from both the added volume and the properties of the injected medication. For example, in steroid therapy, IOP elevation rates typically range from 30% to 60%, while anti-VEGF medications have been linked to elevated IOP in up to 12% of cases. The data obtained by our study were in line with the literature, since the proportion of patients who required additional medical or surgical antiglaucoma therapy tends to be higher for those who received corticosteroid injection when compared to anti-VEGF. Clinical trials, such as ZERO and MEAD, reported IOP increases ranging from 20% to 32%.[10] In another study, IOP elevation was observed in 26.5% of eyes, with 72.2% of those requiring anti-glaucoma medications for IOP control. The high IOP values in these studies are higher than the values obtained in our study, with a rate of 2.53%.

Intraocular inflammation is one of the main ocular adverse events, specially associated with intraocular anti-VEGF pharmacologic agents. Some studies had shown ocular inflammation rates of 1.4%–2.9% for ranibizumab, 0.09%–0.4% for bevacizumab and an approximate rate of 0.05% for aflibercept.[9] Another study reports that in an early evaluation after IVI (within the first 48 hours after injection), patients treated with aflibercept and ranibizumab presented anterior chamber inflammation in 19% and 2% incidence, respectively.[23]

In our study, posterior uveitis with occlusive retinal vasculitis after Beovu® was observed in 2 eyes (0.06% rate) with no cases of vasculitis after aflibercept (in line with the KESTREL study).[24] These cases occur in patients diagnosed with MNV who were treated on average with 3 IVI of Beovu® and who clinically presented with occlusive panuveitis (diagnosis 7 days after IV) or posterior uveitis (diagnosis 56 days after IV). Uveitis after Eylea® was observed in 2 eyes (rate 0.06%), with no record of uveitis after Beovu®. These cases occurred in patients diagnosed with MNV and

RVO treated on average with 14 IVI of Eylea® and which clinically presented in the form of panuveitis (diagnosis 20 days after IV) or anterior uveitis (diagnosis 2 days after IV). Our percentages are not in line with the literature, which reports higher values of uveitis with brolucizumab.[24]

This low recording value of intraocular inflammation may be a secondary limiting factor, on the one hand, due to the fact that in the vast majority of cases this inflammation is self-limited, but also due to the temporal gap between the injection period (and the subsequent phone call) and the next visit. In addition to the above, our study is retrospective in nature, which incorporates heterogeneous groups and small cohorts, which can introduce biases.

The strength of our study is the large number of IVI (3491) performed in 1024 patients from real clinical practice in a 6 months period.

CONCLUSION

Ocular complications associated with intravitreal injections in a tertiary eye center are relatively low and reflect the safety of these treatments. When scheduling IVI, some factors must be taken into consideration to ensure the best possible results and achieve high therapeutic compliance rates.

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JL: Drafting the manuscript; critical review and final approval.

AF, BCV, MJF, ML, PM and BP: Critical revision and final approval.

JL: Elaboração do manuscrito; revisão crítica e aprovação final.

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