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Analysis of intravitreal injections at the State Public Servant Hospital of São Paulo

Análise das injeções intravítreas do Hospital do Servidor Público Estadual de São Paulo

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ABSTRACT

Objective: *The objective of this work was to generate information about the profile of the patients submitted to Intravitreal Injections (IVIs) and also to evaluate the indications and costs of the procedure. Methods: The study was carried out with own protocols, applied through the analysis of medical records of patients submitted to IVIs at the State Public Servant Hospital of São Paulo from January 2017 to June 2018. Data were analyzed in the form of descriptive study. Results: The results showed that 3181 injections were performed in 1421 eyes in the study period; the main drug injected was Bevacizumab; the main pathology treated was Diabetic Maculopathy; and the cost with these procedures was at least R$ 776,257.56. Most diabetic patients did not have adequate glycemic control. Many patients with AMD had no documented improvement in Visual Acuity. Conclusion: It was concluded that deep analyzes about the indications of IVIs should be performed for the benefit of public servants of São Paulo. The information generated by this study can be used to improve the service through the development of therapeutic protocols, as well as serving as a starting point for new research and actions related to the topic.*

Keywords: *Retina; Intravitreal injection; Anti-VEGF*

RESUMO

Objetivo: Analizar o perfil dos pacientes submetidos a Injeções Intravítreas (IVTs), as indicações e os custos do tratamento. **Métodos:** O estudo foi realizado através de protocolos próprios, aplicados por meio de análise de prontuários dos pacientes submetidos a IVTs no Hospital do Servidor Público Estadual de São Paulo no período de janeiro de 2017 a junho de 2018. Os dados obtidos foram submetidos a análise descritiva. **Resultados:** Os resultados encontrados demonstraram que 3181 injeções foram realizadas em 1421 olhos no período do estudo; não foi evidenciada nenhuma complicação durante os procedimentos; nenhum paciente evoluiu com endoftalmite durante o seguimento; a principal droga injetada foi o Bevacizumabe; a principal patologia tratada foi a Maculopatia Diabética; e o custo com estes procedimentos foi de pelo menos R$ 776.257,56. Somente 10% dos pacientes diabéticos possuíam a Hemoglobina Glicada inferior a 7%. Apenas 25% dos pacientes com Doença macular Relacionada a Idade tiveram melhora documentada de Acuidade Visual. **Conclusão:** Concluiu-se que as indicações de IVTs devem ser avaliadas quanto ao prognóstico visual para benefício dos servidores públicos do estado de São Paulo. Filas de espera de acordo com o prognóstico visual são uma opção a ser aventada. As informações geradas por este estudo poderão ser utilizadas para aprimorar o serviço através do desenvolvimento de protocolos terapêuticos, como também como ponto de partida para novas pesquisas e ações ligadas ao tema.

Descritores: Retina; Injeção intravítrea; Anti-VEGF

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INTRODUCTION

Intravitreal injection (IVT) is the invasive eye procedure most often performed in the world. More than 4 million injections were performed in the United States in 2013 and, according to estimates, approximately 6 million injections were performed in 2016. (1,2)

Anti-vascular endothelial growth factor (Anti-VEGF) therapy is the first-line treatment for many retinal diseases, such as neovascular age-related macular degeneration (ARMD), diabetic macular edema (ME), ME due to retinal vein occlusion (RVO) and myopic choroidal neovascularization. Intravitreal steroid injections, either alone or in combination with anti--VEGF injections, have also been incorporated to the clinical practice. (3)

The Brazilian Retina and Vitreous Society has recently conducted a survey to assess the pathologies most often treated with IVTs by its members. ARMD was the most treated disease (57%), and it was followed by diabetic ME (27%), RVO (14%) and other pathologies (2%). With respect to the most used anti-VEGF drugs, Ranibizumab ranked first (55%), and it was followed by Bevacizumab (35%) and Aflibercept (10%), which ranked the last position. (4)

Subretinal neovascularization and pathological ocular angiogenesis are common causes of progressive and irreversible central vision loss; besides, they significantly affect patients' quality of life. Medicinal products have been developed to treat this condition; they target an extracellular signaling protein associated with vascular growth - known as vascular endothelial growth factor (VEGF) -, which stimulates the growth of abnormal blood vessels. Anti-VEGF therapy has improved the quality of life of many patients with ARMD, diabetic retinopathy (RD) and other eye diseases associated with neovascularization and edema. (5,6)

Triamcinolone Acetonide (TA) is a synthetic water-insoluble corticosteroid with anti-inflammatory action. Intravitreal Triamcinolone Acetonide injection has been used to treat a wide variety of conditions such as uveitis, diabetic ME, proliferative DR, RVO, pseudophakic ME (Irvine-Gass) and exudative ARMD. (7)

The injection of intravitreal corticosteroids and anti-VEGF drugs are therapeutic options for diabetic retinopathy. The use of such drugs has been suggested, above all, to treat diabetic ME, since laser treatments rarely improve patients' vision in this case. (8)

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after DR - it is a significant cause of visual loss. Based on a meta-analysis comprising six randomized controlled trials conducted with 937 participants, repeated IVTs of anti-VEGF agents in eyes with ME resulting from RVO have improved patients' visual outcomes in comparison to those of patients who were not subjected to any treatment. (9)

Recent reports have suggested that anti-VEGF IVTs present low complication rates. However, IVTs of any substance can lead to endophthalmitis, retinal detachment, cataracts and increased intraocular pressure. (10)

Therefore, given the need of conducting studies focused on evaluating services providing IVT-based treatments for retinal diseases, and by taking into account their resolving potential, as well as their association with improvements in patients' quality of life after these procedures, the aim of present study was to evaluate IVTs performed at São Paulo State Public Servant Hospital (HSPE - Hospital do Servidor Público Estadual de São Paulo) from January 2017 to June 2018 in order to gather information about patients' profile, as well as to evaluate treatment indications and costs.

METHODS

The study was carried out in compliance with the Declaration of Helsinki and with the Nuremberg Code; it respected Human Research Standards (CNS Res. 466/12) set by the National Health Council. It was conducted after the preliminary project was approved by the Research Ethics Committee of the Institute for Medical Assistance to São Paulo State Public Servants - under Certificate of Presentation for Ethical Appreciation (CAAE): 83617318.8.0000.5463 – as well as by the professor advisor and by the director of São Paulo State Public Servant Hospital.

The current research is a cross-sectional study based on the analysis of medical records of patients subjected to IVTs to treat retinal diseases at HSPE ophthalmology outpatient clinic from January 2017 to June 2018. All patients subjected to IVTs from January 2017 to June 2018 were included in the study after they signed the Free and Informed Consent Form. Patients younger than 18 or who were legally unable to make their own decisions were also included in the study upon acceptance by their legal representatives, who signed the Free and Informed Consent Form. Only patients who did not accept to participate in the study were excluded from it.

The current study used specific protocols (APPENDIX 1) to record personal and clinical data collected from patients' medical records, such as age, sex, number of injections performed throughout the year, injected substance, interval between injections, missing the date set for the procedure, and underlying disease.

Collected data were transcribed to a database developed in Excel spreadsheet and subjected to descriptive analysis, which was based on the elaboration of abstracts about the sample (in percentages) to enable correlating the independent variable - i.e., treatment application with intravitreal injections in patients with retinal diseases - to a set of dependent variables such as patients' age, sex, underlying disease, injected substance, number of injections performed throughout the year, among others.

RESULTS

Table 1.
Total number of administered intravitreal injections.

Substance	N. of injections
Bevacizumab	2,731
Ranibizumab	151
Aflibercept	5
Triamcinolone	294
Total	**3,181**

Table 2
Sex of patients per injected eyes

Sex	N. of patients	%
Male	644	45,0
Female	777	55,0
Total	**1,421**	**100.0**

Table 3
Age group of patients per injected eyes

Age group	Injected eyes	%
< 40 years	9	1.0
40 - 49 years	38	3.0
50 – 59 years	220	15.0
60 – 69 years	529	37.0
70 – 79 years	416	29.0
80 – 89 years	185	13.0
≥ 90 years	24	2.0
Total	**1,421**	**100.0**

Table 4
Number of intravitreal Anti-VEGF injections per disease

Disease	N of IVTs	%
Diabetic maculopathy	734	55.0
ARMD	308	23.0
No record	93	7.0
BRVO	72	5.0
RCVO	51	4.0
SRNVM of high myopic eye	23	2.0
Polypoidal vasculopathy	22	2.0
Others	36	3.0
Total	**1,339**	**100.0**

Table 5
Number of intravitreal triamcinolone injections per injected eyes

Triamcinolone IVTs	Injected eyes
1	183
2	48
3	5
Total	236

Table 6
Number of intravitreal triamcinolone injections per disease

Disease	N of IVTs	%
Diabetic Maculopathy	163	69.0
Irvine-Gass Syndrome	19	8.0
ARMD	12	5.0
CRVO	11	5.0
No record	11	5.0
BRVO	10	4.0
Others	10	4.0
Total	**236**	**100.0**

Tabela 7
Número de injeções intravítreas de Anti-VEGF em olhos com DMRI

IVTs Anti-VEGF	N° olhos DMRI
9	1
7	8
6	12
5	21
4	38
3	89
2	64
1	75
Total	**308**

Table 8
Number of intravitreal Anti-VEGF injections in eyes with diabetic maculopathy

Anti-VEGF IVTs	N. of Patients
7	3
6	4
5	11
4	49
3	138
2	181
1	348
Total	**734**

Table 9
Glycated hemoglobin per eye with diabetic maculopathy injected 4, or more, times with Anti-VEGF

Initial VA	N. of eyes	%
< 7%	7	10.0
7– 7,9%	19	26.0
8 – 8,9%	8	11.0
9 – 9,9%	9	12.0
≥ 10%	1	1.0
No record	29	40.0
Total	**73**	**100.0**

Table 10
Visual acuity of eyes with ARMD before treatment with 4, or more, Anti-VEGF injections

Initial VA	N. of eyes	%
≥ 20/70	10	13.0
20/100	6	8.0
20/200	5	6.0
20/400	5	6.0
< 20/400	31	39.0
No record	23	29.0
Total	**80**	**100.0**

Table 11
Evolution of the visual acuity in eyes with ARMD after treatment with 4, or more, Anti-VEGF injections

Reduction	N. of patients	%
Improved	20	25.0
Worsened	19	24.0
Unchanged	12	15.0
Inconclusive	29	36.0
Total	**80**	**100.0**

Table 12
Cost with Anti-VEGF IVTs at São Paulo State Public Servant Hospital

Drug	Amount spent
Bevacizumab	R$ 587.165,00
Ranibizumab	R$ 189.092,56
Total	**R$ 776.257,56**

DISCUSSION

In total, 3,181 IVTs were carried out at HSPE from January 2017 to June 2018 (Table 1). Anti-VEGFs corresponded to 2,887 IVTs. There were not complications during the procedures. No patient presented endophthalmitis during follow-up.

Fifty-five percent (55%) of the 1,421 eyes subjected to IVT belonged to female patients (Table 2). As most IVTs were performed in elderly individuals, it is possible saying that patients' sex is in compliance with the Brazilian reality since most of the elderly population is composed of women. (11)

Eighty-one percent (81%) of the eyes subjected to IVT belonged to individuals older than 60 years (Table 3). Diabetic Maculopathy and ARMD were the main causes of IVT application; thus, the ophthalmological involvement of older individuals ended up being the rule, since the prevalence of Type 2 Diabetes Mellitus often increases as individuals age due to increased insulin resistance. In addition, aging is associated with significantly increased ARMD incidence, prevalence and progression. (12,13)

Bevacizumab, which is a monoclonal antibody used against all VEGF isoforms, was the drug most widely used as IVT at HSPE throughout the investigated period. It was approved by the FDA to intravenously treat colorectal, breast and lung cancer. As the preliminary reports seemed favorable, ophthalmologists started using intravitreal injections off-label to treat neovascularization. Several studies have reported improved visual acuity and decreased retinal thickness after treatment with intravitreal Bevacizumab. (14-16)

Ranibizumab is a Bevacizumab molecule fragment capable of binding to protein VEGF in order to stop it from binding to its receptor and, therefore, to inhibit angiogenic activity. Intravitreal Ranibizumab use was approved by FDA to treat neovascular ARMD, based on results of randomized clinical trials such as MARINA and ANCHOR. (17,18)

A survey conducted in 2015 has analyzed how 352 members of the Brazilian Retina and Vitreous Society performed IVTs. (4) The mean number of weekly procedures performed by study participants was described as follows: 1-10 injections (76.10%), 11-20 injections (16.40%), 21-30 injections (4.20%), 31-40 injections (1.70%) and more than 40 injections (1.40%). The HSPE performs 37 Anti-VEGF IVTs per week, on average, which highlights the key role played by the institution in promoting eye health in Brazil. As for the international context, a study has shown that Canadian retinologists perform 43 anti-angiogenic IVTs per week, on average; this outcome is close to the one recorded for HSPE (37), thus corroborating to the institution's respectable role in promoting eye health. (19)

In total, 1,421 eyes were injected during the investigated period to treat a wide range of retinal diseases such as DR, ARMD, RVO, Irvine-Gass Syndrome, among others. Diabetic Maculopathy ranked first among the diseases mostly treated with Anti-VEGF IVTs (55%; n = 734) and it was followed by ARMD (23%; n = 308), as shown in Table 4. Unfortunately, 93 IVTs did not have record of indication in patients' medical record, which may indicate a certain negligence by health professionals in the correct record of the care provided by them to patients' medical record. It is also worth emphasizing other conditions such as BRVO (5%), CRVO (4%), Neovascular membrane of high myopic eye (2%), polypoidal vasculopathy (2%) and other conditions (3%).

These data partly disagree with the aforementioned Brazilian study (4), according to which ARMD was the most treated disease (57%); it was followed by diabetic ME (27%). It may have happened due to different features of the samples analyzed in the two studies. Thirty-eight percent (38%) of participants in the study conducted by the Brazilian Retina and Vitreous Society were patients who attended private consultations and often have better financial and schooling levels. It is likely that participants in the aforementioned study have better understanding about their pathologies and better glycemic control than São Paulo State public servants.

Two hundred and thirty-six (236) TA IVTs were performed in the herein investigated hospital (Table 5). Most of the injected eyes received only 1 IVT; this finding can indicate that it was used as casual or adjuvant treatment. Diabetic Maculopathy ranked first among the main causes of Triamcinolone Acetonide injection (69%); it was followed by Retinal Venous Occlusions (9%) and Irvine-Gass Syndrome (8%), as shown in Table 6.

A randomized study with 3 years of follow-up did not find long-term benefit from intravitreal triamcinolone injections in patients with Diabetic Macular Edema in comparison to focal/grid photocoagulation treatment. On the contrary, visual acuity results have slightly favored the laser group in comparison to the triamcinolone group. It was suggested that most eyes receiving 4 mg of triamcinolone would require cataract surgery. In addition, some patients may develop glaucoma and require surgical approach. (20) Thus, it is necessary evaluating TA use in the ophthalmologic service and perhaps using it only in patients who are not responsive to Anti-VEGF or who present contraindications to Laser use.

Although Pseudophakic Cystoid Macular Edema (Irvine-Gass Syndrome) presents spontaneous improvement in more than 80% of cases, the therapeutic treatment remains unclear. It is worth emphasizing that, so far, most treatments applied to this syndrome are off-label. The first line of treatment is based on the use of non-steroidal anti-inflammatory drugs in association with Acetazolamide (Carbonic Anhydrase Inhibitor). The second line of treatment comprises corticosteroids; first subtenonian and, later, intravitreal injections. Off-label triamcinolone IVTs were effective in treating diabetic, uveitic and post-surgical macular edema. However, it is common seeing relapses from 6 weeks to 3 months after treatment and the efficiency of reinjections can vary. In addition, the incidence of severe complications, such as hypertonia or pseudo-endophthalmitis, can limit TA indication. (21)

Based on this information, HSPE professionals must assess the real need of indicating TA IVTS to treat post-surgical ME and only use it when more conservative solutions cannot be found.

The SCORE study developed in 2009 has investigated the use of corticosteroids in patients with ME resulting from RVO. Results have shown corticosteroids' efficacy in the short term, although there was some fear about the incidence of complications. Patients in this study were divided into two group: the ones subjected to repeated Triamcinolone IVTs for four months and the observation group. Triamcinolone use was associated with improved visual acuity after 12 months of treatment. However, many patients required treatment to reduce intraocular pressure, as well as presented crystalline opacity progression, or new opacity, in comparison to the observation group. (22)

Multiple studies have shown the effectiveness of anti-VEGF agents in treating ME associated with Branch Retinal Vein Occlusion (BRVO). The BRAVO clinical trial has shown the efficacy of monthly Ranibizumab applications in comparison to a simulated injection in 397 eyes followed-up for 6 months. (23) The HORIZON study included all patients who completed the BRAVO study in a multicenter study. Patients were followed-up every 3 months for 12 months; they received repeated Ranibizumab injections, which were applied at the investigator's discretion. (24) Approximately 50% of the eyes investigated in the HORIZON study showed improved edema and 80% of them presented visual acuity higher than, or equal to, 20/40. Based on the systematic review by Ylmaz and Cordero-Coma (2012), Bevacizumab was effective in treating ME in patients with BRVO. (25) The VIBRANT trial has shown Aflibercept effectiveness in treating macular edema in patients with BRVO in comparison to laser treatment. (26)

Several clinical trials have also shown the effectiveness of anti-VEGF agents in treating macular edema in patients with Central Retinal Vein Occlusion (CRVO). The CRUISE trial has shown that patients subjected to Ranibizumab IVTs were able to read twice the number of letters than the ones subjected to simulated injections. (27) The COPERNICUS study has compared the effectiveness of Aflibercept to that of simulated injections; results have shown that patients treated with Aflibercept were able to read more letters than the ones subjected to simulated injections. (28) Similar findings were recorded in the GALILEO study. (29) Bevacizumab IVT was compared to simulated injections in a randomized study conducted in 2012; patients treated with Bevacizumab presented better visual acuity than the ones subjected to simulated IVTs. (30)

With respect to Anti-VEGF injections only applied to patients with ARMD, most of the 308 injected eyes received 3, or more, anti-VEGF IVTs (54%) during the investigated period (Table 7). It can be a positive fact, since if all these patients were starting the treatment, most of them would receive the attack dose for exudative ARMD (3 IVTs). PRO RE NATA (PRN) is the treatment regimen adopted for ARMD at HSPE; it comprises an attack dose with monthly IVT applications for 3 months and extra doses depending on the need of reinjection.

CATT was a multicenter clinical trial focused on comparing the safety and effectiveness of Bevacizumab to those of Ranibizumab, as well as on comparing the PRN dosage regimen to that of monthly Anti-VEGF injections. Based on a 2-year follow-up, it was evident that the two drugs remained compatible in effectiveness and safety, although in comparison to the monthly arms, the PRN arms did not perform well in terms of maintaining visual gains at the end of the first year, mainly in the Bevacizumab PRN group.(31) Such information suggests that HSPE patients may have better prognosis if the frequency of anti-VEGF IVTs increases. However, structural and financial issues would have to be discussed between the clinical staff and public administrators to enable a change of this magnitude.

With respect to Anti-VEGF injections only applied to patients with Diabetic Maculopathy, most of the 734 injected eyes received less than 3 anti-VEGF IVTs (72%) during the investigated period (Table 8). Since this is a cross-sectional study, it is not possible saying whether these patients were undertreated or properly treated. The treatment regimen adopted for moderate-to--severe diabetic ME at HSPE lies on performing the anti-VEGF IVT and on evaluating its effectiveness 1 month later. The decision about whether it is necessary performing a new IVT is made when patients return for the following consultation.

The Diabetic Retinopathy Clinical Research Network Writing Committee (DRCRNWC) has observed - in a study conducted in 2016 - that all 3 anti-VEGF groups (Bevacizumab, Ranibizumab and Aflibercept) showed improved VA in patients with diabetic ME, from the beginning of the treatment to 2 years of follow-up. All 3 treatments were effective and relatively safe. Eyes presenting the best initial VA have shown similar VA results after treatment. Aflibercept has shown better results than Bevacizumab in eyes presenting the worst initial VA, after 2 years of treatment; however, Aflibercept's superiority over Ranibizumab was not identified. (32)

According to the Guidelines of the International Council of Ophthalmology (2018), the first step in the treatment of Diabetic Retinopathy lies on optimizing the medical treatment by maintaining the glycated hemoglobin (HbA1c) below 7.0%, as well as on treating systemic hypertension and dyslipidemia. (33)

The present study has analyzed the HbA1c of all patients subjected to four, or more, IVTs for 18 months (Table 9) and found the following results: 40% of patients had no record of HbA1c in their medical record; 50% of them recorded HbA1c higher than, or equal to, 7%; and 10% recorded HbA1c lower than 7%. Lack of HbA1c data in patients' medical record is worrisome, since it may suggest that most HSPE ophthalmologists are only carrying out specific treatment, without taking into account the systemic aspect of the underlying disease. Thus, inadequate glycemic control can lead many patients to present diabetic ME recrudescence, a fact that requires new injections and, therefore, burdens state public-health systems. However, a study conducted by DRCRNWC in 2015 can put this hypothesis to the test. The research group has concluded that the addition of personalized education and risk assessment during ophthalmic retinal consultations did not lead to improved HbA1c in comparison to the usual care provided to patients for 1 year. These data suggest that glycemic control optimization remains a substantial challenge that requires interventional paradigms. (20)

Several recent studies have shown that better initial VA is associated with better visual prognosis in exudative ARMD treatment. (34-36) One limitation of the current study lies on the fact that it did not differentiate first-treatment patients from the ones who had been previously treated. Corrected Visual acuity was assessed in all patients before the first anti-VEGF IVT throughout the investigated period. As for the VA of patients with ARMD who were subjected to 4, or more, Anti-VEGF IVTs at the beginning of the treatment (Table 10), 29% of patients had no record of it, 39% presented VA lower than 20/400, and 33% recorded VA higher than, or equal to, 20/400. Again, inadequate filling of patients' medical records has limited a more accurate assessment in the current study. However, it is noteworthy that most of the evaluated patients presented VA lower than 20/400 during the investigated period, a fact that may indicate that most patients subjected to IVT treatment at HSPE presented poor visual prognosis.

Patients' corrected VA was evaluated after the last IVT application. The VA of patients subjected to 4, or more, IVTs for 18 months presented the following outcomes (Table 11): 36% of patients presented inconclusive outcomes due to lack of data about initial and final VA in the medical record; 39% of them presented unchanged or worsened VA, after at least 4 IVTs; and 25% of them have shown improved VA. The record of improved VA value in patients' medical record was set as VA improvement criterion, whereas the record on worsened VA value was set as worsening criterion. These data corroborate the hypothesis that most patients with exudative ARMD who were treated at HSPE had poor prognosis. Another hypothesis to be taken into consideration is that this number may be higher than 39%, since 36% of the analyzed medical records were inconclusive for VA improvement.

Another issue that should be addressed concerns the time that these patients must wait to receive the IVT treatment. The current study did not evaluate the time individuals affected by ARMD waited in line to receive treatment. This period without treatment may have been a decisive factor for the final VA, since the neovascularization of this pathology progressively damages the photoreceptor layer of the retina.

It is worth conducting an analysis from a population perspective. If most vacancies for IVTs in the service are filled with patients with poor visual prognosis, it is possible assuming that patients with better visual prognosis do not have easy access to IVT treatments. Patients with initial exudative ARMD, who have delayed access to treatment, present worse prognosis at the time they receive IVT, due to chronical damages caused by the neovascular membrane to photoreceptors. Therefore, this process may be creating a vicious cycle where patients with poor prognosis who have subretinal fluid, but already have advanced photoreceptor damage, will continue receiving injections and taking vacancies from patients with good initial prognosis, who will present poor final prognosis due to delayed access to treatment.

Finding solutions to anti-VEGF indications for patients with ARMD in a high-volume service such as HSPE is not an easy task. However, it is necessary better analyzing the indication of IVTs for patients who did not show VA improvement after several procedures in order to remove the ones without any prognosis of positive evolution from the IVT waiting line.

Creating waiting lines based on patients' visual prognosis is an interesting alternative to help mitigating the aforementioned issue. In this scenario, patients with poor prognosis would continue to receive their treatment, whereas patients with better prognosis would have access to anti-VEGF treatment sooner rather than later.

The HSPE has spent R$ 776,257.56 reais with anti-VEGF IVT-based therapy (Table 12) during the 18 months of study. Bevacizumab IVTs (n = 2,731) accounted for R$ 587,165.00 reais, whereas Ranibizumab accounted for R$ 189.092.56 reais of the state expenses (32% of expenses with anti-VEGF IVTs), despite the lower number of IVTs (n = 151). (37) Despite the difference in costs between these drugs, several studies - such as CATT, IVAN and LUCAS - have already shown equivalent therapeutic effect, as well as to be safe when it comes to adverse effects. (31,38,39) It is important emphasizing that Ranibizumab was developed based on the Bevacizumab molecule for intraocular use, which was authorized by FDA. Despite the widespread use of Bevacizumab, it is an off-label drug used in retinal pathology treatments. Patients who used Aflibercept have beared the costs.

Although HSPE does not provide Aflibercept to treat retinal disorders, there is evidence that this drug is more cost-effective than long-term Bevacizumab for exudative ARMD treatment. (40)

A systematic review focused on investigating the cost-effectiveness of DR treatments has shown that intravitreal Ranibizumab or Bevacizumab use is within the acceptable limits of cost-effectiveness for the population with ME. Thus, it is possible assuming that HSPE's expenses with Ranibizumab are not advantageous to the service. (41)

CONCLUSION

It was concluded that IVT indications should be evaluated based on patients' visual prognosis for the benefit of São Paulo State public servants. Waiting lines based on patients' visual prognosis are an alternative to be taken into consideration. The information gathered in this study can be used to help improving the service through the development of therapeutic protocols, as well as used as starting point for the implementation of further research and actions associated with the topic.

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APPENDIX 1 – RESEARCH PROTOCOL

1) Medical record: ___________________

2)Age: __________

3) Sex:
( ) Female ( ) Male

4) Injected Eye:
( ) Right Eye ( ) Left Eye

5) Number of injections performed: _________________

6) Date and Injected Substance:
_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept
_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept
_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept
_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept
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_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept
_____/_____/_____ ( ) Triamcinolone ( ) Bevacizumab ( ) Ranibizumab ( ) Aflibercept

7) Underlying disease:
( ) Age-Related Macular Disease
( ) Diabetes
( ) Other:____

8) Missed the date set for injection: ( ) Yes ( ) No
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____

9) Injection Cancellation: ( )Yes ( )No
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____
_____/_____/_____ Reason:____

10) BCVA before the 1st IVT was inserted in the medical record:________________

11) BCVA after the last IVT was inserted in the medical record:_________________

12) HbA1c at the date of the last injection:__________________