Outcomes of Planed Intravitreal Therapy Interruption due to COVID-19 in Patients with Diabetic Macular Edema

Impacto da Interrupção da Terapêutica Intravítrea em Doentes com Edema Macular Diabético devido à COVID-19

Catarina Castro[1], João Coelho[1], Nuno Correia[1], Miguel Lume[1], Pedro Menéres[1,2], Bernardete Pessoa[1,2,3]

[1] Department of Ophthalmology, Centro Hospitalar Universitário do Porto, Porto, Portugal.
[2] Department of Ophthalmology - Institute for the Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal.
[3] Unit for Multidisciplinary Research in Biomedicine - Institute for the Biomedical Sciences Abel Salazar, University of Porto (UMIB - ICBAS - UP), Porto, Portugal.

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ABSTRACT

INTRODUCTION: Our aim was to evaluate the outcomes of planed intravitreal injection (IVI) interruption in eyes with diabetic macular edema (DME) and the overall impact of COVID-19 in IVI.

METHODS: Retrospective analysis of clinical data of eyes with DME undergoing treatment with IVI, that missed an IVI by their doctor's decision (based on an implemented treatment guideline) due to COVID-19 pandemic, between 19 March 2020 and 2 May 2020. Primary outcomes were the best corrected visual acuity (BCVA) and the central foveal thickness (CFT) in the first appointment after the missed IVI and after 6 months. Secondary outcomes were the evolution of BCVA and CFT in eyes that missed IVI by patient's decision and the comparison of the overall number of IVI performed, missed by doctor's decision, and missed by patient's decision during the study period and the same period in 2019.

RESULTS: Between 19 March and 2 May 2020, 132 eyes with DME missed an IVI by doctor's decision. Before the missed IVI, BCVA was 65 [5-85] ETDRS letters and CFT was 338 [192-1277] µm. In the first appointment after the missed IVI, BCVA and CFT were 65 [5-85] ETDRS letters and 320 [204-1154] µm, respectively. After 6 months of the missed IVI, BCVA was 70 [5-85] ETDRS letters and CFT was 291 [185-868] µm. In the same period, 41 eyes missed IVI by patient's decision. Before the missed IVI, BCVA was 60 [5-85] ETDRS letters and CFT was 336 [178-622] µm. In the first appointment after the missed IVI, BCVA was 60 [5-80] ETDRS letters and CFT was 333 [202-1041] µm. After 6 months of the missed IVI, BCVA was 60 [5-85] ETDRS letters and CFT was 285 [205-647] µm. Between 19 March and 2 May 2019, a total of 693 IVI were performed in medical retina patients in our center. During the same period in 2020, 272 IVI were administered, 391 were missed by doctor's decision and 80 IVI were missed by patient's decision.

CONCLUSION: With the implementation of treatment guidelines, it was possible to keep an overall good control of CFT, without deterioration of BCVA.

KEYWORDS: COVID-19; Diabetes Mellitus; Intravitreal Injections; Macular Edema/drug therapy.

RESUMO

INTRODUÇÃO: O nosso objetivo foi valiar o impacto da interrupção de tratamento com injeções intravítreas (IVI) em olhos com edema macular diabético (EMD) e o impacto geral da COVID-19 nas IVI.

MÉTODOS: Análise retrospetiva da informação clínica de olhos com EMD a realizar tratamento com IVI, em que uma injeção não foi realizada por decisão médica (baseada numa diretriz de tratamento implementada), entre 19 de março de 2020 e 2 de maio de 2020. O outcome primário foi a melhor acuidade visual corrigida (MAVC) e espessura foveal central (EFC) na primeira consulta após a IVI não realizada e após 6 meses. Os *outcomes* secundários foram a evolução da MAVC e da EFC em olhos que perderam IVI por decisão do doente e a comparação do número total de IVI realizadas, canceladas por decisão do médico e canceladas por decisão do doente durante o período de estudo e no mesmo período em 2019.

RESULTADOS: Entre 19 de Março e 2 de Maio de 2020, 132 olhos com EMD perderam uma IVI por decisão do médico. Antes da IVI cancelada, a MAVC era de 65 [5-85] letras ETDRS e a EFC era de 338 [192-1277] µm. Após a IVI cancelada, a MAVC e a EFC eram 65 [5-85] letras ETDRS e 320 [204-1154] µm, respetivamente. Depois de 6 meses, a MAVC era 70 [5-85] letras ETDRS e a CFT era 291 [185-868] µm. No mesmo período, 41 olhos perderam IVI por decisão do doente. Antes da IVI perdida, a MAVC era 60 [5-85] letras ETDRS e a EFC era 336 [178-622] µm. Na primeira consulta após, a MAVC era 60 [5-80] letras ETDRS e a EFC era 333 [202-1041] µm. Após 6 meses da IVI falhada, a MAVC era 60 [5-85] letras ETDRS e a EFC era 285 [205-647] µm. Entre 19 de Março e 2 de Maio de 2019, um total de 693 IVI foram realizadas em doentes com patologia retiniana no nosso centro. Durante o mesmo período em 2020, 272 IVI foram administradas, 391 foram canceladas por decisão do médico e 80 IVI foram canceladas por decisão do doente.

CONCLUSÃO: Com a implementação das diretrizes de tratamento, foi possível manter um bom controle geral da EFC, sem deterioração da MAVC.

PALAVRAS-CHAVE: COVID-19; Edema Macular/tratamento farmacológico; Diabetes Mellitus; Injeções Intravítreas.

INTRODUCTION

Intravitreal injections (IVI) with anti-vascular endothelial growth factor (anti-VEGF) have been the first line treatment for many ophthalmological diseases, such as diabetic macular edema (DME), age-related macular degeneration (AMD) and retinal vein occlusion (RVO).[1–3]

On 2 March 2020 the first case of COVID-19 was diagnosed in Portugal. Following the quick spread of the virus and the increasing number of affected people, the need to reduce the number of patients coming to the hospital for elective, non-urgent procedures was felt, in order to better allocate the medical resources. On 18 March, the American Academy of Ophthalmology issued the recommendation that ophthalmologists should provide care only to cases considered urgent or emergent.[4] Despite this, some studies showed a negative impact of missed treatments in medical retina patients, especially in patients with DME. A study that evaluated the impact of non-adherence to treatment in patients with AMD, DME and RVO concluded that more non-adherent DME patients had a clinically significant loss of visual acuity, when compared to adherent patients.[5] Another study also showed that for DME patients, therapy break-offs (unintended absence of more than 100 days of therapy) correlated with decreased visual acuity.[6] Song *et al* analyzed the impact of delay in care among medical retina patients receiving IVI during the lockdown period between 14 March 2020 and 4 May 2020 and concluded that patients with DME and RVO lost more vision than those with AMD and may be more susceptible to fluctuations in vision with short interruptions in care.[7] Thereby, taking in consideration the public health issue lived in our country but also the possible negative impact of delaying treatments, our center decided to postpone non-urgent treatments, creating a treatment guideline to decide which patients could safely miss their scheduled IVI and which needed to keep their appointments.

The aim of this study was to evaluate the visual and functional outcomes in eyes with DME in which an IVI was missed by doctor's decision, due to the COVID-19 pandemic in CHUPorto and the overall impact of COVID-19 in IVI.

MATERIAL AND METHODS

STUDY DESIGN

Retrospective analysis of medical records. This study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto and conducted according to the Declaration of Helsinki (2013 amendment).

Due to the retrospective nature, informed consent was not requested. Patient confidentiality was assured.

POPULATION AND CLINICAL DATA

Clinical data of eyes with DME in which an IVI was missed by doctor's or patient's decision in CHUPorto, a tertiary center, between 19 March 2020 and 2 May 2020 was retrospectively analyzed. Phakic status and time interval between treatments before the missed IVI were recorded. The time interval between the appointment before and the missed IVI and between the missed IVI and the first appointment after was recorded. Best corrected visual acuity (BCVA) and central foveal thickness (CFT) were recorded in the appointment before the missed IVI, in the first appointment after and after 6 months. Patients with DME that missed all their follow-up appointments were excluded.

The total number of IVI performed between 19 March and 2 May of 2020 in CHUPorto was compared with the same period in 2019. The number of missed IVI by doctor's decision and the number of missed IVI by patient's own decision were recorded.

BCVA was recorded in Early Treatment Diabetic Retinopathy Study (ETDRS) letters. CFT was measured using macular optic coherence tomography (SD-OCT, Spectralis HRA+OCT, version 1.10.2.0, Heidelberg Engineering, Heidelberg, Germany). Worsening of macular edema was considered if CFT increased by 10% compared to last visit before the missed IVI, and an improvement was considered if CFT decrease by 10%. All other cases were considered stable.

TREATMENT GUIDELINE

Medical charts of every patient scheduled for an IVI were reviewed, with particular focus on type of disease, severity, age and other comorbidities, in order to establish priorities. If DME was present and:

- CFT<400 µm plus not in loading dose phase or in naïve patients: skip treatment or wait for treatment to start for up to 3 months, respectively.
- CFT>400 µm plus a positive response to anti-VEGF, with a long-established pattern: maintain or increase the injection interval.
- No response to anti-VEGF and already tested for efficacy and safety with short-term steroids: consider injecting fluocinolone acetonide implant with IOP assessment one month later and then quarterly.
- No response to anti-VEGF but not tested with short-term steroids: wait up to 3 months for this therapeutic test.

In patients undergoing bilateral IVI, the decision was made individually for each eye. Delay of IVI was not considered in monocular patients, if neovascular glaucoma or proliferative diabetic retinopathy was present, if CFT<400 µm in loading dose phase and in young patients (<65 years old) with good health general status and good ocular functional potential. Treatment guideline is schematized in Fig. 1.

All patients in which the decision to change the date of the next IVI was taken had a telephonic appointment to discuss the situation and to check for possible complaints or sense of subjective worsening in vision. All cases had patient's consent.

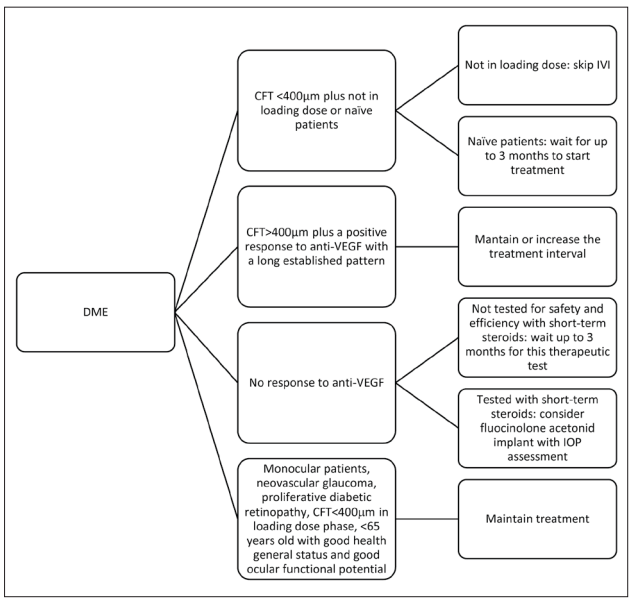

Figure 1. Treatment guideline for diabetic macular edema.

DME – diabetic macular edema; IVI – intravitreal injection; CFT – central foveal thickness; VEGF – vascular endothelial growth factor.

OUTCOMES

Primary outcomes were the BCVA and the CFT in the first appointment after missed IVI by doctor's decision and after 6 months. Secondary outcomes were the evaluation of patients that missed IVI in the same period by their own decision and the comparison of the overall number of IVI performed, missed by doctor's decision, and missed by patient's decision between 19 March 2020 and 2 May 2020 and the same period in 2019.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPP Statistics 26. Continuous variables are summarized with median [range] and categorical variables with frequency. Comparison between CFT and BCVA before and after the missed IVI were made using non-parametric tests in paired samples, after normal distribution of variables was excluded. Categorical variables were analyzed with a Chi-squared test. Significance was defined as a p value less than 0.05.

RESULTS

CHANGES IN BCVA AND CFT

Between 19 March and 2 May of 2020, IVIs were canceled in 132 eyes (111 patients, mean age 70.3±9.7 years old, 44% female) with DME by doctor's decision. Of these, 67.2% were being treated with IVI for a long period of time (more than one year), 13.0% were treatment naïve, 11.4% were re-starting after a period without IVI and in 8.4% the missed IVI was the last one scheduled. A total of 56.0% of eyes were phakic and 44.0% were pseudophakic. The median time between treatments before the missed IVI was 4 [4-12] weeks (80% had 4 to 6 weeks of interval). The time between the missed IVI and the appointment before was 10 [2-25] weeks. Before the missed IVI, median BCVA was 65 [5-85] ETDRS letters and median CFT was 338 [192-1277] μm. In the first appointment after the missed IVI (median time 8 [1-20] weeks), median BCVA and CFT were 65 [5-85] ETDRS letters and 320 [204-1154] μm, respectively. Changes on CFT (p=0.06) and BCVA (p=0.704) were not statistically significant. Regarding CFT, 52.4% of eyes were stable, 27.9% improved and 19.7% had worse CFT compared to baseline. Of those who had worsening of CFT, 33.3% had an increase between 10% and 15%, 16.7% between 15% and 20% and in 50.0% the increase was superior to 20%. Original shorter intervals between IVI were not associated with more eyes with worsening of CFT after the missed IVI when compared to original longer intervals (p=0.358). After the missed IVI patients returned to their previously scheduled treatment plan. In the first appointment after the missed IVI, treatment plans were adjusted according to the patient's evolution and the standard of care. Panretinal photocoagulation was performed in 2.3% of eyes and 4.5% of eyes were submitted to phacoemulsification after this appointment. After the first appointment, 20.5% of eyes missed 1 IVI, 3.0% missed 2 and 0.8% missed 4 IVI, by patient's decision. After 6 months, median BCVA was 70 [5-85] ETDRS letters and median CFT was 291 [185-868] μm. There was a statistically significant improvement in CFT (p=0.010) when compared to baseline, and no difference in BCVA (p=0.151). Evolution of BCVA and CFT are summarized in Figs. 2 and 3, respectively.

Considering eyes that had a worse CFT in the first appointment after the missed IVI, after 6 months, 50.0% maintained a worse CFT compared to baseline, 18.2% improved and 31.8% were stable, when comparing to values before the missed IVI. Of the eyes who had a worse CFT compared to baseline, 72.4% were undergoing treatment for a long period of time, 13.8% were treatment naïve, 10.3% were re-starting IVI after a period without treatment and 3.5% missed the last IVI scheduled. Overall, after 6 months, of the 132 eyes, 52.4% were stable when comparing to baseline CFT, 33.6% improved and 14.0% had worse CFT. Of the eyes that had worse CFT after 6 months of the missed IVI, 73.3% were undergoing treatment for a long period of time, 13.3% were re-starting IVI after a period without treatment, 6.7% were treatment naïve and 6.7% missed the last IVI scheduled. None of these patients were previous non-responders.

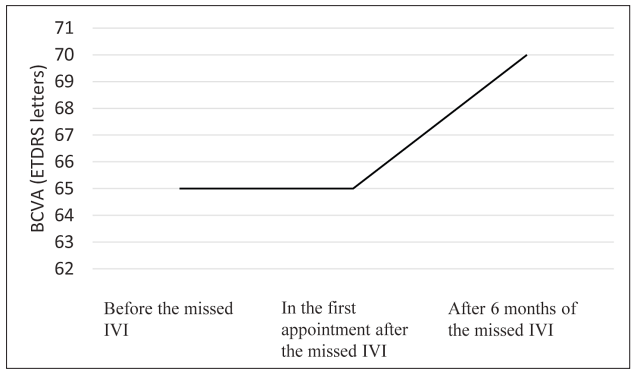

Figure 2. Evolution of best corrected visual acuity.

IVI – intravitreal injection; BCVA – best corrected visual acuity.

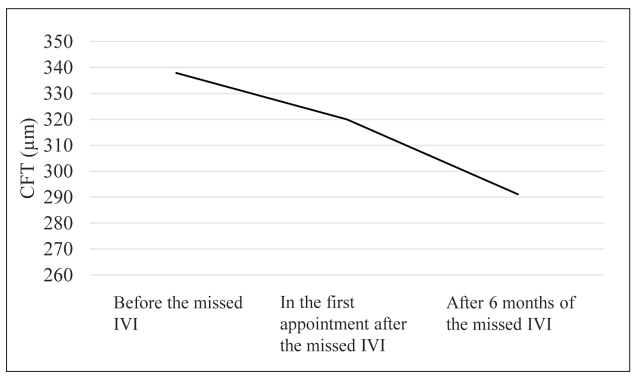

Figure 3. Evolution of central foveal thickness.

IVI – intravitreal injection; CFT – central foveal thickness.

During this study period, in two eyes treatment was switched from anti-VEGF to a steroid, according to the treatment guideline.

A total of 41 eyes of 38 patients with DME (mean age 68.2±9.4 years old, 50% female) missed IVI, by their own decision, between 19 March and 2 May of 2020. Of these, 87.8% missed 1 IVI and the remaining missed 2 IVI in this period. Following the first appointment after the missed IVI, 22.5% of eyes missed 1 additional IVI, 7.5% missed 2 IVI and 2.5% missed 4 IVI by patient's decision. The median time interval between IVIs before the missed IVI was 4 [4-20] weeks and 85.4% of patients were phakic. In the appointment before, median BCVA was 60 [5-85] ETDRS letters and median CFT was 336 [178-622] μm. In the first appointment after the missed IVI, median BCVA was 60 [5-80] ETDRS letters and CFT was 333 [202-1041] μm. Changes in BCVA (p= 0.170) and CFT (p=0.368) were not statistically significant. Regarding CFT, 44.4% of eyes remained stable, 27.8% improved and 27.8% had worse CFT. Of those with worsening of CFT, in 50% the increase was between 10% and 15%, in 10% the increase was between 15% and 20% and in 40% the increase was superior to 20%. After 6 months of the missed IVI, median BCVA was 60 [5-85] ET-

DRS letters and median CFT was 285 [205-647] μm. Both remained stable, when comparing to the appointment before the missed IVI (p=0.266 and p=0.064, respectively) and the first appointment after (p=0.708 and p=0.098, respectively). Of those with worsening of CFT in the first appointment after the missed IVI, after 6 months, 57.1% remained worse and 42.9% were stable, compared to baseline. Overall, after 6 months, 45.8% had an improvement in CFT, 29.2% were stable and 25.0% had worse CFT compared to baseline.

COVID-19 IMPACT IN IVI

Between March 19 and 2 May of 2019, 693 IVI for medical retina patients were performed in CHUPorto. During the same period in 2020, 272 IVI were administered, 391 were missed by doctor's decision and 80 IVI were missed by patient's own decision. Regarding cases where the IVI was missed by patient's decision, DME represented 57.5% of cases, 27.5% had AMD, 11.2% had RVO and 3.8% had other pathologies. Mean age was 72.5 ± 11.0 years old, 52.2% were female gender and most (69.6%) lived outside of Oporto City.

DISCUSSION

The COVID-19 pandemic led to the need to create a treatment guideline to decide which patients with DME could safely miss an IVI and which needed to keep their IVI as scheduled. There were no differences in BCVA and CFT before and in the first appointment after the missed IVI and, after 6 months, there was an improvement in CFT when compared to the last appointment before the missed IVI. Furthermore, after 6 months, there were no differences in BCVA, when compared to baseline values. This stability of CFT and BCVA shows that the implemented guideline was efficient in selecting cases that could safely have their treatment delayed.

DME is one of the diseases that most frequently requires IVI treatment. Despite this, the literature concerning the impact of delayed anti-VEGF treatment on visual and anatomical outcomes in eyes with DME is limited.

Carnevali *et al*, prioritized their patients in high, medium and low level of priority and DME patients belonged to the low priority group with indication to be treated within 30 to 40 days from the scheduled date. In contrast to our guideline, they did not differentiate priority levels within each pathology, but, similarly to our guideline, switching from anti-VEGF to corticosteroid therapy was advisable to increase time between IVI.[8]

Korobelnik *et al* considered that patients with DME are less likely to suffer from irreversible vision loss in the short term and so postponement for non-monocular patients could be considered, except for patients with significant vision loss from recent DME. However, the authors consider that postponements of more than 4 to 6 month should be avoided.[9]

Moussa *et al* treatment guideline consisted in deferring IVI in new DME patients with good visual acuity (equal or superior to 6/12 in the Snellen chart) and administration of a loading dose of 3 to 6 IVI with 4 to 6 weeks interval in new DME patients with bad BCVA. For returning DME patients, those in a treat and extend regimen with an established extension period continued this interval, those in a pro re nata treatment for more than 1 year with stable DME were deferred by 4 to 6 months and patients that just finished their loading dose or on a recent pro re nata regimen were deferred by 3 to 4 months.[10]

Despite not analyzing by pathology, Yang *et al* and Saleh *et al* showed in their studies that the interruption of IVI can be harmful to medical retina patients, as indicated by the decrease in BCVA and increase in CFT after treatment interruption.[11,12]

Naravane *et al* compared BCVA and CFT before and in the first appointment after an injection delayed or rescheduled by the patient more than two weeks after the recommended treatment interval, and their study showed a trend to decrease in BCVA and a statistically significant increase in CFT in DME patients. In comparison, DME patients without a delayed IVI did not have the same trend. In the delayed IVI group, there was an increase of more than 10.0% of CFT in 35.0% of cases, compared to 19.7% in our center.[13] These values are difficult to compare to those of our center due to differences in the definitions of delayed IVI and patient characteristics, but these results reinforce the need to implement treatment guidelines, with careful selection of patients.

Yalamanchili *et al* compared the functional and anatomical outcomes between DME patients with and without delayed IVIs (single unintended IVI delay for at least 3 months) and concluded that there were no differences in CFT or visual acuity after 6 months. Even though mixed model regression analyses showed that 3 to 24 months treatment lapses result in increased CFT, following a single anti-VEGF injection this significance was no longer present. In this study single treatment lapses did not adversely affect visual acuity at any timepoint or in mixed model regression analysis.[14]

A Jordanian center stopped all IVI procedures between 18 March and 28 April 2020. When comparing data before and after the lockdown period in DME patients, the authors found a significant improvement in BCVA and no difference in CFT.[15]

Many studies show a decrease in the total number of IVI performed during COVID-19 first wave. Our center had a decrease of 60.8% in the number of performed IVIs in a 6-week period. Similarly, Wasser *et al* reported a decrease of 58.0% in a 4-week period and Borreli *et al*, noticed a 53.6% reduction from 9 March to 3 May 2020.[16,17]

Despite missing IVI by doctor's decision, our patients maintained an overall good control of CFT, without deterioration of BCVA. Furthermore, half of the eyes that had worsening of the CFT in the first appointment after the missed IVI improved to values similar or better than those at baseline after returning to treatment following the standard of care, which demonstrates that many patients that were negatively affected by the missed IVI in the short term did not suffer long term repercussions. We believe that the potential negative effect of the missed IVI was minorized by a prompt re-

turn to treatment according to the standard of care. Despite this, it is important to notice that only 28% of patients had an improvement of CFT in the first appointment after the missed IVI. Therefore, in this unexpected setting, our treatment guideline was effective in preventing anatomical or functional worsening of the majority of our patients but as expected, did not allow significant improvement of the CFT. Therefore, we believe that DME treatment should follow the standard of care as DME damage is cumulative and leads to neurodegeneration, and that missing IVI should be carefully planed only in very specific circumstances.

We analyzed both eyes that missed the IVI by doctor's and by patient's decision, and the only statistically significant change observed was an improvement of the median CFT after 6 months of the missed IVI in the group that missed IVI by doctor's decision. Furthermore, the proportion of eyes that had worsening of CFT was superior in the group that missed IVI by patient's decision. After 6 months, despite having a superior percentage of eyes with improvement of CFT, the group of eyes that missed IVI by patient's decision also had a superior rate of worsening of CFT. Hence, this results reinforce the importance of carefully choosing patients that can safely have their IVI delayed. Nevertheless, the two groups were heterogeneous, and comparisons must be made carefully, as patients were submitted do different treatments and follow-ups.

In our study the majority of missed IVI by patient's own decision happened in DME patients. Hence, when deciding which patients to delay it is important to consider that if patients miss more IVI besides the ones decided by their doctor the interval between treatments will increase, which can lead to destabilization of the disease and subsequent increased treatment burden in the following months. Thereby, it is important to reinforce that the decision to delay treatments must follow treatment guidelines, but also consider the profile of the patient. Also, it is of utmost importance that the patient takes part in the decision process and is conscious of the motives and implications of the decision and the importance of adhering to the treatments scheduled. Even after a careful selection of eyes to skip an IVI and after discussing the plan with the patient, some of them still missed other IVI afterwards, which reinforces the need for careful selection, particularly in DME sub-group of patients, more prompt for non-adherence as previously mentioned.

Our study has some limitations, such as its retrospective design, a small number of patients, the evaluation of patients by multiple doctors and the fact that some patients had cataract, which influences their BCVA. Furthermore, some eyes were submitted to other procedures, such as phacoemulsification or panretinal photocoagulation, in the study period. Despite this, all procedures were performed after the first evaluation, and they are part of the normal follow-up of diabetic patients, so we believe excluding these patients would not give an accurate perspective of the clinical evolution of our sample. Another limitation of our study is the heterogeneity of our sample, with patients being submitted to different treatment schemes. Additionally, the time between the missed IVI and the first appointment after varied between patients. However, our treatment guideline was developed in the setting of an unexpected scenery and our purpose was to evaluate the outcomes of its implementation in this real-life setting, in order to help clinicians to make decisions should a likely situation appear in the future. It is also important to take into consideration that besides the injection missed by doctor's decision some patients failed to come to some of the other schedule injections. We included these patients, as excluding them would represent a selection bias. Despite this limitations, this is one of the few studies that evaluates the outcomes of an implemented treatment guideline for DME in an unpredictable scenery. Another positive point of this study is the evaluation of the short- and long-term outcomes of the missed IVI.

CONCLUSION

These data show that during the first weeks of the COVID-19 pandemic the majority of all our IVI appointments were delayed. Despite this, with the implementation of a treatment guideline and a careful selection of patients after an evaluation of their medical and ophthalmological history, it was possible to keep an overall good control of CFT, without deterioration of patient's visual acuity. Additionally, the implementation of a priority scale was also fundamental to reduce the number of patients coming to our center, helping to protect vulnerable patients from COVID-19 infection and allowing to better allocate scarce medical resources in the early days of the COVID-19 pandemic in Portugal.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

CC and BP: Study conception and design, and approval of the final version.

BP: Guideline design and approval of the final version.

CC: Writing of the first draft, data collection and approval of the final version.

All authors: Reviewing the manuscript; data analysis and approval of the final version.

RESPONSABILIDADES ÉTICAS

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a

Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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Corresponding Author/
Autor Correspondente:

Catarina Castro
Centro Hospitalar Universitário do Porto
Largo Prof. Abel Salazar
4099-001 Porto, Portugal
catarinamscastro@gmail.com

ORCID: 0000-0002-7707-7861