

The impact of coronavirus disease (COVID-19) pandemic on intravitreal injections treatment for macular diseases: report from a referral hospital in Milan

Francesco Viola, MD¹; Paolo Milella, MD¹; Francesco Pozzo Giuffrida, MD¹; Simone Ganci¹; Alessandro Invernizzi, MD^{2,3}

- ¹. Ophthalmological Unit, Department of Clinical Sciences and Community Health, Ca' Granda Foundation- Maggiore Policlinico Hospital, University of Milan, Milan, Italy.
- ². Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco", Luigi Sacco Hospital, University of Milan, Milan, Italy
- ³. The University of Sydney, Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, Sydney, New South Wales, Australia

Reprint requests: Francesco Viola, Eye Unit, IRCCS Foundation, Cà Granda Maggiore Policlinico Hospital, Department of Clinical Science and Community Health, University of Milan, Italy. Via F. Sforza 35, Milan 20100, Italy; e-mail: francesco.viola@unimi.it

Running head: The impact of COVID-19 pandemic on IVT

Financial support: none

Disclosures: None of the authors have any financial/conflicting interests to disclose.

Summary statement

The adherence to treatment with intravitreal injections was 0.37 during the COVID outbreak, significantly lower compared to that registered in the previous trimester (0.92) and in the same weeks in 2019 (0.90). The adherence rate in “Emergent” patients during the lockdown weeks was 0.60 regardless our managing strategy.

Abstract

Purpose

To describe our managing strategy for COVID-19 emergency, to evaluate the adherence to intravitreal treatment (AtT) rate during the outbreak in a referral hospital in Milan and to correlate it with patients clinical features.

Methods

AtT rate of patients with scheduled intravitreal injections (IVT) during the COVID-19 outbreak from 23/02/20 to 31/03/20 was compared to the previous trimester and with March 2019. The impact of age, sex, visual function and diagnosis on the AtT rate during unlocked/locked weeks (from March 8th) was evaluated.

Results

Of 650 consecutive patients with scheduled IVT, AtT rate during the COVID-19 outbreak was 0.37. This was significantly lower compared to AtT registered in the previous trimester (0.92) and in the same weeks in 2019 (0.90) (both $p < 0.001$). Patients adherent to treatment were significantly younger ($p < 0.001$) and had a lower best-corrected visual acuity in the fellow eye ($p = 0.046$).

During the lockdown weeks AtT rate was significantly lower than in the two unlocked weeks (0.19 vs 0.73, $p < 0.001$). In addition, the AtT rate in patients classified as “Emergent” during the lockdown weeks was 0.60.

Conclusions

These preliminary results can help the retina specialist community to foresee this unique scenario and to develop successful management strategies.

Keywords: COVID-19, Intravitreal injections, Macular diseases, Adherence to treatment rate, macular edema, Age-related macular degeneration, Choroidal neovascularization

Introduction

Coronavirus disease 2019 (COVID-19) is a novel highly contagious, potentially deadly, infectious disease that was firstly identified in China on December 2019.^{1,2} Since then the disease spread across the entire planet reaching the size of a pandemic within a couple of months and forcing the governments of many countries to impose highly restrictive measures to contain the contagion.

On February the 21th, the first Italian patient was tested positive for the virus in Codogno, a small town 60 kilometers far from Milan. Lombardy became the epicenter of the European outbreak and 11 towns (Red zone) near Milan were locked down. On March the 8th when 7375 people had tested positive for coronavirus and 366 had died in Italy, the government locked down the entire country.

Since March the 8th Italian public health authorities recommend to indefinitely postpone all elective visits and surgeries and to visit only patients with emergent or urgent conditions. Starting from the end of March many medical societies worldwide released guidance documents for ophthalmologists consistent with these basic principles containing recommendations about specific sub-speciality

activities, including the American Academy of Ophthalmology, the French Society of Ophthalmology, the German Ophthalmological Society, the Royal College of Ophthalmologists, the Japanese Ophthalmological Society and others.³⁻¹¹ Moreover, collective recommendations were developed by Vision Academy Steering Committee, a group of experts in retinal diseases during a virtual meeting in March 2020, who reviewed available guidance documents and debated the key challenges of managing patients receiving intravitreal injections of anti-VEGF agents during the COVID-19 pandemic.¹²

A significant percentage of patients attending ophthalmic clinics need to receive repeated intravitreal injection treatment (IVT) for macular diseases including neovascular age-related macular degeneration (nAMD), macular edema (ME) secondary to retinal vascular diseases, choroidal neovascularizations from other causes (CNV). Postponing or skipping IVT in these patients, even if just for a single injection, may result in permanent vision drop.

Often, patients who need IVT are also those with a great risk for morbidity and mortality from the COVID-19 infection as most of them are old or suffer from comorbidities like diabetes.¹³ Thus, particular strategies that allow these patients to access IVT with minimum exposure to COVID-19 infectious risk are mandatory. Despite this, many factors such as fear, movement limitations, illnesses, can reduce the number of patients attending the scheduled appointment. We present the managing processes of patients scheduled for IVT during the COVID-19 pandemic and the adherence to treatment (AtT) rate in one of the major public hospitals in Lombardy, at epicenter of the European outbreak, in order to report the profound impact COVID-19 emergency on a intravitreal injection activity of referral medical retina clinic without predefined guidelines.

Materials and Methods

From February 23rd to March 31st the AtT (ratio between all scheduled IVT and provided IVT) of patients scheduled for IVT at IRCCS Cà Granda Foundation, Policlinico Hospital, Milan was

recorded. Since March the 8th (beginning of total lockdown), retina specialists had to evaluate each single planned case to establish the IVT level of emergency and then phoned to discuss all scheduled patients about the different options including maintaining, postponing or rescheduling IVT. New patients with emergent or urgent conditions could be accepted for a visit including imaging studies such as Optical Coherence Tomography but they were excluded from the present analysis since they were treated on the same day of the visit if needed.

Several factors including diagnosis, disease activity, number of previous IVT, last interval between IVT, vision stabilization and fellow eye condition were taken into account in order to rearranged patients. Rescheduled IVT was classified as:

- “Emergent” for: (1) nAMD receiving the loading dose, (2) nAMD that had shorted the retreatment interval according to the Treat and Extend (T&E) regimen in the Altair study,¹⁴ (3) ME patients “worsened” according to the criteria of Protocol T study criteria³, (4) eyes with active CNV (5) fellow eye best corrected visual acuity (BCVA) \leq 20/200 Snellen.
- “Urgent” for: (1) nAMD in the maintenance phase with stable BCVA and disease activity in the last three consecutive visits with on a T&E regimen, (2) ME patients with BCVA and macular thickness stable after 2 consecutive IVT according the “defer injections” criteria of Protocol T.¹⁵
- “Non-urgent” for: (1) nAMD on T&E regimen maintaining an IVT interval \geq 3 months in the last three consecutive visits, (2) ME patients with stable BCVA after 2 consecutive visits and macular thickness $<400\mu\text{m}$

For “Emergent” cases, the risk of permanent vision loss without early intervention was considered high and access to IVT was highly suggested. For “Urgent” cases, the risk without immediate IVT was less and treatment could be deferred by 2-4 weeks. Since we rescheduled “Urgent” cases, we classified them by definition “Emergent”. For the “Non-urgent” indications, IVT might be

postponed by more than 1 month in consideration of the low risk of significant or permanent vision loss.

We compared the number of patients attending scheduled appointments during the COVID-19 outbreak with the previous trimester (December 2019 to February 2020) and with March 2019 to evaluate the impact of the epidemic on AtT. The impact of age, sex, BCVA and diagnosis on the AtT was analyzed. The study protocol was approved by our institutional review board. This research is conformed to the tenets of the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics for continuous variables included the mean and standard deviation (SD) where appropriate. Qualitative variables are reported in percentages. Continuous variables were compared using t-test. Pearson's test was used to assess the correlation between continuous variables. P values <0.05 were considered statistically significant.

Results

Six-hundred-fifty consecutive patients had a scheduled IVT during COVID-19 outbreak and were included. Among these 76.6% had nAMD, 14% suffered from ME and 9.6% had other CNVs.

The overall AtT rate during the COVID outbreak was 0.37. This was significantly lower compared to that registered in the previous trimester (0.92) and in the same weeks in 2019 (0.90) (both $p < 0.001$). Patients who regularly attended the scheduled treatment were significantly younger than those that did not (mean[SD] age 76.5[9.7] vs 79.7[8.6], $p < 0.001$). Patients adherent to treatment had a lower BCVA in the fellow eye ($p = 0.046$). No correlation was found between AtT and BCVA in the eye to be injected ($p = 0.93$), sex ($p = 0.69$), diagnosis ($p = 0.26$).

The AtT decreased as containment rules became more strict and during weeks with lockdown it was significantly lower than in unlocked weeks (0.19 vs 0.73, $p < 0.001$) (Figure 1). Adherent patients during the lockdown were significantly younger ($p < 0.001$) and had a significantly lower BCVA ($p = 0.024$) in the fellow eye. The number of patients with BCVA $\leq 20/200$ in the fellow eye was also significantly higher among those who attended injection during the lockdown ($p = 0.038$). No correlation was found between AtT and BCVA in the eye to be injected, sex or diagnosis. (Table 1). After charts reevaluation for IVT urgency ranking during the lockdown, 137 out of 431 planned IVT (32%) were graded as “Emergent,” among these AtT rate was 0.60. Among patients not attending “Emergent” IVT, 78% referred they were concerned about COVID-19 infection, avoiding in particular public transport and hospitals, 12% reported movement limitations and 10% illness. Patients graded as “urgent” were 43% and “non-urgent” 25%.

Discussion

Regular IVT retreatment is important to retain the vision in patients with macular diseases and even skipping a single injection can have a negative effect.¹⁶ Our clinic continued to administer IVT during the COVID-19 pandemic and we adopted special strategies to guarantee treatment appropriateness while maintaining proper social distancing. Despite this, we noted a significant reduction in the AtT, with an average decrease of about 60% compared to the previous trimester considering the entire epidemic period, with a dramatic rate drop to 0.19 during the national lockdown.

We reviewed medical charts and imaging studies of all patients to prioritize urgent treatments and properly counsel the patients. Despite this effort the AtT rate in “Emergent” patients was only 0.60 with high risk for significant or irreversible vision loss in those that did not attend the appointment.

In addition, we found that older patients were less adherent to treatment. This suggests that more

fragile individuals with higher mortality risk from the COVID-19 may also be those that suffer more from the indirect negative effects of the pandemic. We discussed with the patients by phone the possible drawbacks of postponing IVT and the special precautions adopted by the hospital to limit contagion risk, but this strategy seemed only partially effective. As many of our patients are old, they often feel uncomfortable in taking decisions by themselves and prefer to involve their younger relative when dealing with unusual situations. A written communication would have probably given the patients the possibility to evaluate the situation more serenely. A customizable template letter to explain the situation and reassure and guide patients throughout this crisis has been developed by Vision Academy and could improve the adherence to treatment of Emergent patients.¹⁷ Patients with lower BCVA in the fellow eye or with a fellow eyes with $BCVA \leq 20/200$, seem to be more motivated in attending IVT scheduled appointments. This is likely explained by the fact that the fear of becoming legally blind in both eyes overcomes the worries related to a possible contagion. It is mandatory to allow this patients to have access to treatment both prioritizing them as we did by ranking treatment urgency and guaranteeing proper safety measurements during their hospital attendance.

This study has several limitations. First there were not guidelines, national guidance or recommendations by experts for IVT urgency ranking at the time we had to face this challenging outbreak on March the 8th, the beginning of total lockdown in Lombardy. Thus, we had to decide internal guidelines to prioritize treatment for managing patients planned for IVT since public health authorities imposed physicians without notice to visit and treat only patients with emergent or urgent conditions. We decided to evaluate each single case to establish the IVT level of emergency according to criteria used in recent clinical trials in AMD or ME, and balancing the risk of exposure of often elderly and vulnerable patients to COVID-19 with the potential visual implications of treatment postponement. It is possible that using different recommendations or guidance for prioritizing IVT, a different number of patients would be graded as “Emergent”. Moreover, a strict

ranking rule was not applicable to all patients, thus the final decision was determined by a senior retinal specialist on a case-by-case basis. Finally, reasons for low adherence should be better investigated and could also differ among healthcare system and country-specific factors. A questionnaire exploring detailed reasons for not attending IVT, like fear (overall fear, fear of attending IVT in a “COVID hospital”, fear of public transportation, fear of meeting caregivers transporting to hospital), movement limitations and illnesses, will be submitted in the ongoing protocol with the aim of implementing special strategies to provide reassurance to patients to ensure that those requiring “emergent” or “urgent “ treatment attend their appointments. Of note, the purpose of this study was to evaluate the AtT rate in the early weeks of COVID-19 pandemic reporting our managing strategy. A more clinically appropriate comparison following AtT rate of the two cohorts out of 6 months with the main purpose of evaluating the impact of COVID-19 on visual outcome is ongoing.

When the crisis will end, we will face a huge backlog of IVT which will have to be properly managed. These preliminary results can help colleagues working in area with high transmission rate of COVID-19 to foresee this unique scenario in order to develop successful strategies for IVT during and after the pandemic period, weighing the risk of infection exposure against the negative effects of a skipped/delayed IVT. Adjustment to regular clinical practice (i.e.: fixed treatment regimen without frequent monitoring) and new strategies for prioritizing patients should be planned in case of a second wave of COVID-19 pandemic.

References:

- 1) World Health Organization. Pneumonia of unknown cause- China. Disease outbreak news.
URL:<https://www.who.int/csr/05-January-2020-pneumonia-of-unknown-cause-China>. [Accessed on January 5, 2020]. WHO 2020.
- 2) Guan W, Ni Z, Hu Yu, Liang W, et al. Clinical Characteristics of Coronavirus Disease 2019 in Chin. *New Engl J Med*. 2020 Feb 28. [Epub ahead of print]
- 3) American Academy of Ophthalmology. Important coronavirus updates for ophthalmologists.
URL:<https://www.aao.org/headline/alert-important-coronavirus-context>. Accessed March 31, 2020
- 4) Société Française d'Ophtalmologie. Quelle conduite à tenir adopter vis à vis des injections intravitréennes (IVT) dans cette période d'épidémie au Covid-19 - SARS-CoV-2 ?
URL:https://www.sfo.asso.fr/files/files/FPHUNG/epidemie_au_covid-19_-_ivt.pdf. Accessed March 31, 2020
- 5) Deutsche Ophthalmologische Gesellschaft. Coronavirus COVID-19.
URL:<https://www.dog.org/?cat=288>. Accessed March 31, 2020
- 6) The Royal College of Ophthalmologists. COVID-19 clinical guidance for ophthalmologists.
URL:<https://www.rcophth.ac.uk/2020/03/covid-19-update-and-resources-for-ophthalmologists/>.
Accessed March 31, 2020

- 7) The Royal College of Ophthalmologists. Medical retinal management plans during COVID-19. URL:<https://www.rcophth.ac.uk/wp-content/uploads/2020/03/Medical-Retinal-Management-Plan-during-COVID-19-UPDATED-300320-1-2.pdf>. Accessed April 2, 2020
- 8) Japanese Ophthalmological Society. Guidance for ophthalmology-related healthcare workers regarding COVID-19. URL:<http://www.nichigan.or.jp/news/065.pdf>. Accessed March 31, 2020
- 9) American Society of Retina Specialists. COVID-19: updates and resources. URL:<https://www.asrs.org/practice/asrs-member-alert-regarding-covid-19-pandemic>. Accessed March 31, 2020
- 10) The Royal Australian and New Zealand College of Ophthalmologists. Corona virus (COVID-19) guideline. URL:https://ranzco.edu/wp-content/uploads/2020/03/RANZCO-Coronavirus-COVID-19-Guideline_01042020.pdf. Accessed March 31, 2020
- 11) Canadian Ophthalmological Society. Canadian Retina Society (CRS) position statement on intravitreal injections and the management of retinal diseases during the COVID-19 crisis. URL:<https://www.crssrc.ca/files/CRS-Position-Statement-on-Intravitreal-Injection-Treatments-Mar-19-2020.pdf>. Accessed April 6, 2020
- 12) Korobelnik JF, Loewenstein A, Eldem B, et al. Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol* 2020. [Epub ahead of print]
- 13) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. 2020 Mar 28;395(10229):1038]. *Lancet*.

- 14) Ohji M, Takahashi K, Okada AA, et al. Efficacy and Safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR: a randomized controlled trial. *Adv Ther.* 2020 Mar;37(3):1173-1187.
- 15) Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med.* 2015; 372(13): 1193–1203.
- 16) Real-world outcomes in patients with age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. Mehta H, Tufail A, Daien V, et al. *Prog Retin Eye Res.* 2018; 65(7):127-146.
- 17) Korobelnik JF, Lowenstein A, The Vision Academy. Guidance for patients with nAMD and their families during the COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol* 2020. [Epub ahead of print]

Figure Legends

Figure 1. Solid line representing the adherence to treatment rate and colored bars showing weekly number of intravitreal injections before and after the COVID-19 outbreak.

Table 1. Characteristics of adherent and non-adherent patients						
	COVID period overall (N=650)			Lockdown weeks (N=432)		
	Adherent patients	Non-adherent patients	<i>p-value</i>	Adherent patients	Non-adherent patients	<i>p-value</i>
No. (%)	242 (37.2)	408 (62.8)		82 (19)	350 (81)	
Age (sd) - y	76.5 (9.7)	79.7 (8.6)	<0.001 [§]	75.6 (9.1)	79.9 (8.4)	<0.001 [§]
Sex No. (%)						
Male	104 (43)	169 (41.4)	0.69*	33 (40.2)	143 (40.9)	0.91*
Female	138 (57)	239 (58.6)		49 (59.8)	207 (59.1)	
Diagnosis (%)						
nAMD	178 (73.5)	320 (78.4)	0.26*	57 (69.5)	276 (78.8)	0.12*
Macular edema	36 (14.9)	55 (13.5)		12 (14.6)	43 (12.3)	
Other CNV	28 (11.6)	33 (8.1)		13 (15.9)	31 (8.9)	
BCVA (sd) - LogMAR						
Examined eye	60.6 (18.6)	60.4 (16.7)	0.93 [§]	59 (17)	60.4 (16.9)	0.52 [§]
Fellow eye	54.6 (31.4)	59.5 (28.3)	0.046 [§]	50.9 (30.3)	59.4 (28.2)	0.024*
Fellow eye with BCVA ≤ 20/200						
Yes	72 (29.7)	95 (23.3)	0.068*	28 (34.1)	81 (23.2)	0.038 [§]
No	170 (70.3)	313 (76.7)		54 (65.9)	269 (76.8)	

Table 1 * = chi-square test - § = t-test - BCVA = best corrected visual acuity - FE= fellow eye-nAMD = neovascular age-related macular degeneration

