TREATMENT DEFERRAL DURING COVID-19 LOCKDOWN

Functional and Anatomical Impact on Patients With Neovascular Age-Related Macular Degeneration

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Purpose: To investigate the visual and anatomical impact of intravitreal injection treatment deferral because of the COVID-19 lockdown on patients affected by neovascular age-related macular degeneration.

Methods: We retrospectively reviewed 314 patients (394 eyes) who were scheduled to receive the impact of intravitreal injections during the Swiss lockdown. We compared patients who continued to receive scheduled impact of intravitreal treatment without clinical consultation (Group Continue "C"; n = 215) and patients for whom the impact of intravitreal treatment was completely deferred (Group Stop, "S"; n = 179). Functional and anatomical parameters were collected at four time points before and after the lockdown.

Results: In Group C, the visual acuity at baseline and after the lockdown did not differ significantly. In Group S, the visual acuity deteriorated significantly compared with baseline and then improved slightly after the resumption of treatment, but it did not recover to baseline values. The mean central subfield thickness remained stable in Group C, whereas it increased in Group S and then returned to prelockdown values after the resumption of treatment.

Conclusion: An "injection-only" approach was effective in managing patients with neovascular age-related macular degeneration during the pandemic lockdown, whereas patients who deferred their scheduled treatment showed partially irreversible deterioration of visual function. We recommend treatment continuation in patients with neovascular age-related macular degeneration during a lockdown.

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Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries,[1] and its neovascular form (nAMD) is observed in approximately 25% of advanced cases.[2] Intravitreal (IVT) injections of antivascular endothelial growth factor (VEGF) agents are the first-line treatment for nAMD.[3] Good compliance to the treatment regimen is essential to maximize the benefits of anti-VEGF treatment, and it has been shown that delays in treatment delivery have a negative impact on visual outcomes.[4]

Current treatment algorithms for nAMD include 1) fixed monthly treatment; 2) as-needed protocol (pro re nata), where injections are administered only in the presence of signs of disease reactivation; and 3) Treat and Extend, where the interval between injections is kept at a slightly shorter duration than the maximum recurrence-free interval to minimize the recurrence of the exudative activity.[5] In our center, we routinely follow an individually tailored "Observe-and-Plan" regimen, as previously described.[6,7] This regimen evaluates the individual need for retreatment in an observation phase after the initial loading doses and then applies a series of injections with fixed intervals, with the major advantage being the reduction of the number of clinic visits with ophthalmic examinations, but at the same time preserving good functional outcomes.[8,9]

The new coronavirus disease 19 (COVID-19) pandemic resulted in a drastic change in practice during its outbreaks. During the first wave of COVID-19 in Switzerland and other European countries, several national health authorities advocated the deferral of

nonurgent consultations and medical procedures to reduce the risk of disease exposure and ensure the health and safety of both patients and medical personnel. As a consequence, many patients with nAMD deferred or suspended their scheduled treatment protocol, which was gradually resumed after the lockdown. In our investigation, we aimed to determine the effects of delaying IVT anti-VEGF treatment for visual and anatomical outcomes in our retina patients.

Methods

Study Population and Lockdown Management

In Switzerland, the Federal Council issued an order legally forbidding nonurgent interventions during the first Swiss lockdown, which was declared on the 17th of March 2020 and ended on the 27th of April 2020.[10] At the Jules Gonin Eye Hospital in Lausanne, which is a tertiary referral center with a dedicated AMD clinic, all the routine outpatient consultations were completely suspended. The treatment of patients with macular edema of any origin was hence postponed to facilitate there being fewer patients in the clinics. In addition, the shortened presence in the hospital without monitoring visits (by applying the same treatment interval as before lockdown) and strict distancing between patients facilitated minimization of contamination risks.

Patients with nAMD requiring IVT treatment were thus advised to continue their scheduled treatment without attending consultations and/or undergoing optical coherence tomography (OCT), using a previously described "injection-only" approach,[11] in accordance with the French Society of Ophthalmology guidelines for the management of patients receiving IVT injections during the COVID-19 pandemic.[12] In summary, these guidelines considered the presence of subfoveal macular neovascular

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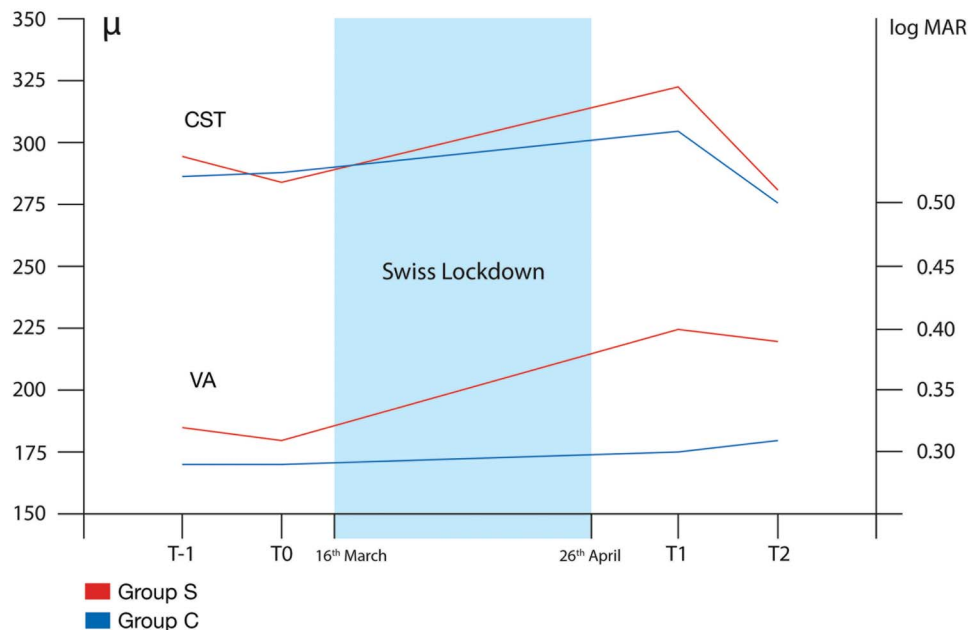
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membranes as urgent, needing timely retreatment. Moreover, patients who presented a fluid-free (intraretinal and/or subretinal) macula on the OCT scan in the past two consecutive visits were defined as "low-risk nAMD," and their IVT treatment was deferred. In addition, a considerable proportion of patients preferred to postpone their proposed treatment because of the fear of COVID-19 contamination when attending the hospital for IVT injection, because of transport limitations, or because of illnesses, and this interrupted the treatment.

This resulted in the definition of the following two groups of patients: patients who continued to follow their previously scheduled plan of IVT injections (Group Continue, "C") and patients who completely stopped the IVT injections until the resumption of clinical activity after the lockdown (Group Stop, "S").

Data Collection

We retrospectively investigated all patients who were scheduled to receive IVT treatment for nAMD at our medical retina department between January and November 2020. Four time points were chosen for the study, two before the Swiss lockdown (T-1 and T0) and two after the lockdown (T1 and T2). T0 (baseline) was defined as the last examination before the lockdown, and T-1 was defined as the preceding examination at least 3 months before T0. T1 was set as the first examination after the lockdown, and T2 was set as the following examination at least 3 months after T1 (Figure 1). Patients were required to have records of all the four time points to be included in this investigation, and the exclusion criterion was the presence of maculopathy that was secondary to causes other than AMD.

At baseline, the patient demographics, the number of previous IVT injections during the preceding 3 months, and the last interval between IVTs were recorded. For Group S, the main reason for cessation of treatment was also collected. The best-corrected visual acuity measured routinely with patient's refraction on an Early Treatment Diabetic Retinopathy Study chart and expressed as a logarithm of the minimum angle of resolution (logMAR) for analysis, and OCT parameters were collected for each time point. Optical coherence tomography parameters included central subfield thicknesses (CSTs) on OCT volumes in the 1-mm central subfield of an Early Treatment Diabetic Retinopathy Study grid centered on the fovea. Optical coherence tomography scans were also graded by two independent and experienced readers (A.M and A.G.) for qualitative features suggestive of exudative disease activity following the previously published guidelines,[13,14] including the presence of intraretinal fluid, subretinal fluid, pigment epithelium detachment,

Fig. 1. Evolution of mean visual acuity and mean CST at each study time point.

and subretinal hyperreflective material. In cases where the graders did not agree on a single consensus result, the disagreement was resolved by consultation with a third experienced retinal specialist (C.M.E.).

The research methods and analysis plan adhered to the tenets of the Declaration of Helsinki. The local institutional review board approved the study (CER-VD n. 2017-00493), and informed consent was obtained from all subjects.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 25.0, SPSS Inc, Chicago, IL). The normality of all data samples was assessed with the Kolmogorov–Smirnov test. Because the use of parametric statistics was not possible, the Mann–Whitney U test and Wilcoxon signed-ranked tests were used for independent and dependent quantitative variables, respectively. A chi-square test was used to compare categorical variables, where appropriate. In all analyses, P values <0.05 were considered statistically significant.

Results

During the study period, 352 patients (438 eyes) were scheduled to receive IVT injections for nAMD. A total of 215 eyes of 167 patients met the inclusion

Table 1. Characteristics of the Study Population

	Group C	Group S	P
No. of eyes	215 eyes of 167 patients	179 eyes of 147 patients	0.713
Eyes	95 right 120 left	97 right 82 left	0.047*
Sex (N)	38% male (63) and 62% female (104)	36% male (52) and 64% female (95)	0.666
Mean age ± SD (range)	80.9 ± 7.1 years (58–97)	84.2 ± 7.2 years (65–98)	0.396
Mean No. of previous IVT injections (past 6 months) ± SD (range)	4.1 ± 1.4 (1–6)	4.1 ± 1.3 (1–6)	0.901
Mean IVT time interval ± SD (range)	6.2 ± 2.4 weeks (4–12)	6.4 ± 2.4 weeks (4–12)	0.069
Drug (%, No. of eyes)	45% ranibizumab (96) 55% aflibercept (119)	52% ranibizumab (94) 48% aflibercept (85)	0.119
T0–T1 time (cessation of treatment)*	6.9 ± 2.6 weeks (4–16)	17.4 weeks ± 5.3 (8–32) 151 eyes; 28 eyes did not resume IVT injections	<0.001†
T1–T2 time	15.8 ± 4.6 weeks (12–28)	14.2 ± 4.2 weeks (12–29)	0.327

*Time between last IVT before lockdown and subsequent treatment.
†Statistically significant.

criteria for Group C, 179 eyes of 147 patients met the inclusion criteria for Group S, whereas 41 eyes of 35 patients were excluded because of incomplete clinical data and/or loss to follow-up. Baseline demographic characteristics of the study population are presented in Table 1.

The study groups were balanced in the number of eyes included ($P = 0.7136$), age ($P = 0.396$), sex ($P = 0.666$), the number of previous injections performed in the past 6 months ($P = 0.901$), time interval between IVTs ($P = 0.698$), and the distribution of the different treatment drugs ($P = 0.119$) (Table 1).

In Group S, the main reason for treatment interruption was the presence of systemic risk factors for COVID-19 disease (47.0%, n = 70), followed by low-risk nAMD (30.9%, n = 46), and fear of contracting COVID-19 (8.7%, n = 13) (Table 2). Group C maintained the same interval between IVTs before and during the lockdown (6.2 ± 2.4 weeks vs. 6.9 ± 26, $P = 0.303$), whereas Group S experienced a delay in treatment from 6.4 ± 2.4 weeks before the lockdown to 17.4 ± 5.3 weeks at T1 ($P < 0.001$). The treatment interval after T1 was set according to the disease activity observed during the visit. Moreover, for Group S, 28 eyes did not resume IVT treatment after the lockdown, 13 because of the absence of exudation, 10 because the patient was unwilling to pursue the treatment, and five because an irreversible late stage of nAMD had been reached.

Visual Acuity

In Group C, the mean baseline visual acuity was 0.29 ± 0.32 logMAR (20/40 Snellen equivalent), and it did not change significantly after the lockdown, being 0.30 ± 0.36 logMAR (20/40) at T1 ($P = 0.083$); however, it became slightly worse at T2 (0.31 ± 0.39 logMAR, 20/40, $P = 0.030$). Comparing T-1 with T2 values, the variation did not reach statistical significance (0.31 ± 0.39 vs. 0.29 ± 0.33 logMAR, $P = 0.366$) (Table 3).

In Group S, the mean baseline visual acuity was 0.35 ± 0.45 logMAR (20/40), and it was significantly

Table 2. Reasons for Treatment Interruption in Group S

Reason	Patients, % (n)
COVID-19 systemic risk factors	47.0 (70)
Low-risk nAMD	30.9 (46)
Patient's fear of COVID-19 exposure	8.7 (13)
Patient unwilling to undergo treatment	6.7 (10)
Patient's illness	1.3 (2)
Traveling restrictions	1.3 (2)
Others	2.7 (4)
Total	100 (147)

Table 3. Visual Acuity

	T-1	T0	T1	T2	P^{*} T_{-1}/T_0	P^{*} T_{-1}/T_1	P^{*} T_{-1}/T_2	P^{*} T_0/T_1	P^{*} T_0/T_2	P^{*} T_1/T_2
Group C	0.29 ± 0.33 (−0.1 to 2.0)	0.29 ± 0.32 (−0.1 to 2.0)	0.30 ± 0.36 (−0.1 to 2.0)	0.31 ± 0.39 (−0.1 to 2.0)	0.540	0.419	0.366	0.083	0.030†	0.304
Group S	0.35 ± 0.45 (−0.1 to 2.0)	0.32 ± 0.41 (−0.1 to 2.0)	0.42 ± 0.46 (−0.1 to 2.0)	0.40 ± 0.51 (−0.1 to 3.0)	0.574	<0.001†	0.006†	<0.001†	<0.001†	0.049†
P‡	0.415	0.882	0.002†	0.126						

Data are presented as mean VA logMAR ± SD (range).
*Wilcoxon signed-rank test.
†Statistically significant.
‡Mann–Whitney U test.

worse at T1 (0.42 ± 0.46 logMAR, 20/50, $P < 0.001$). The visual acuity improved slightly from T1 to T2 (0.42 ± 0.46 logMAR to 0.40 ± 0.51 logMAR, $P = 0.049$), but it did not recover to the values before the lockdown. The mean baseline visual acuity was significantly worse at T1 and T2 compared with both T0 and T-1 ($P < 0.001$ and $P = 0.006$, respectively).

Comparing the two study groups, the difference in visual acuity was not statistically significant before the lockdown ($P = 0.415$ and $P = 0.882$ at T-1 and T0, respectively); however, it was significantly different at T1 ($P = 0.002$). There was no significant difference between T1 and T2 ($P = 0.126$).

Optical coherence tomography Parameters

In Group C, the mean CST was 288 ± 89 μm at baseline, and it did not change significantly after the lockdown, being 294 ± 88 μm at T1 ($P = 0.449$). At T2, CST was significantly lower than the other three time points (276 ± 68 μm) ($P = 0.031$, $P = 0.028$, and $P = 0.040$ in comparison with T-1, T0, and T1, respectively) (Table 4).

In Group S, the baseline CST was 278 ± 65 μm, and it increased significantly after the lockdown (322 ± 106 μm, $P < 0.001$), but it then decreased at T2 (281 ± 78 μm), but this was not a statistically significant change in comparison with prelockdown values ($P = 0.122$ and $P = 0.365$, respectively, compared with T-1 and T0).

Comparing the two groups, the difference in CST values was not statistically significant before the lockdown ($P = 0.395$ and $P = 0.934$, respectively, at T-1 and T0), but it was significant at T1 ($P = 0.003$) and not statistically significant at T2 ($P = 0.763$, Table 4).

Disease Activity

The features suggestive of disease activity are listed in Table 5. In Group C, 50% (n = 105) of nAMD eyes showed evidence of macular neovascularization exudation at baseline, and this percentage remained stable, even after the lockdown (55% [n = 115], $P = 0.576$ at T1 and 44% [n = 92], $P = 0.444$ at T2).

In Group S, the same analysis revealed that 38% of the eyes (n = 68) showed evidence of macular neovascularization exudation at baseline, and this proportion increased substantially to 80% (n = 143, $P < 0.001$) after the lockdown and then returned to the prelockdown rate at T2 (42% [n = 75], $P = 0.639$ compared with T0).

Groups C and S were not significantly different in macular neovascularization exudation parameters before the lockdown ($P = 0.589$ and $P = 0.179$ at T-1 and T0, respectively); however, they reached a significant difference at T1 ($P = 0.026$); however, this did not persist at T2 ($P = 0.775$) (Figures 2–4).

Duration of Treatment Interruption and Anti-VEFG Agent

Additional analyses were performed in patients in Group S regarding the duration of the treatment interruption and the different anti-VEGF agents. Since the duration of the treatment interruption ranged between 8 and 32 weeks, we compared the outcomes of the patients that stopped their treatment for 8 to 16 weeks (n = 60) and the ones that did it for 17 to 32 weeks (n = 119). No statistically significant difference was reported in both anatomical and visual outcomes after the lockdown (see **Table 1**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B581). Similarly, a comparison between eyes being injected with ranibizumab, and the ones injected with aflibercept showed no statistically significant difference in both visual acuity and CST at the four time points (see **Table 2**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B581).

Discussion

The impact that the COVID-19 pandemic had on ophthalmology practice has already been reported, and

Table 4. Central Subfield Thickness

	T-1	T0	T1	T2	P^* T_{-1}/T_0	P^* T_{-1}/T_1	P^* T_{-1}/T_2	P^* T_0/T_1	P^* T_0/T_2	P^* T_1/T_2
Group C	286 ± 79 (129–785)	288 ± 89 (133–904)	294 ± 88 (143–855)	276 ± 68 (140–630)	0.663	0.667	0.031†	0.449	0.028†	0.040†
Group S	294 ± 93 (134–752)	278 ± 65 (166–701)	322 ± 106 (137–757)	281 ± 78 (140–778)	0.001†	<0.001†	0.122	<0.001†	0.365	<0.001†
P‡	0.395	0.934	0.003†	0.763						

Data are presented as mean μm ± SD (range).
*Wilcoxon signed-rank test.
†Statistically significant.
‡Mann–Whitney U test.

Table 5. Evidence of nAMD Activity

	T-1	T0	T1	T2	$P*$ T_{-1}/T_0	$P*$ T_{-1}/T_1	$P*$ T_{-1}/T_2	$P*$ T_0/T_1	$P*$ T_0/T_2	$P*$ T_1/T_2
Group C	48%, n = 100	50%, n = 105	55%, n = 115	44%, n = 92	0.865	0.445	0.606	0.576	0.444	0.189
Group S	53%, n = 95	38%, n = 68	80%, n = 143	42%, n = 75	0.097	0.016†	0.217	<0.001†	0.639	<0.001†
P‡	0.589	0.179	0.026†	0.775						

*Wilcoxon signed-rank test.
†Mann–Whitney U test.
‡Statistically significant.

worldwide many ophthalmology providers were advised to defer nonurgent or elective appointments during the lockdowns, about the government orders for stay at home concerning the entire population.[15,16] Patients affected by nAMD, who are often elderly with comorbid diseases, were particularly affected by these health care access limitations.[17] Patients requiring anti-VEGF treatments were the most affected because of the need for a normative, adequate treatment course.[18] Despite efforts to delineate the proper guidelines to reduce the burden of COVID-19 in patients with nAMD,[19] a significant drop (up to 60% in comparison with the nonpandemic period) in the provision of IVT therapies has been reported in high endemic areas, such as Italy and China.[20–22]

In accordance with previous reports,[23,24] we showed that unintentionally delayed care during the COVID-19 pandemic led to a remarkable deterioration of visual function in patients with nAMD. The cessation of the IVT treatment determined the progression of the natural course of the nAMD disease, and visual function could only be partly recovered after this short-term deferral. In fact, the resumption of IVT treatment after the lockdown improved visual acuity, but not back to baseline levels. This is probably attributable to irreversible anatomical changes. These data suggest that visual benefits of IVT therapy may be lost if regular dosing is not maintained, showing no difference in relation to the type of anti-VEGF agent in use.

Our results are in line with other real-world studies where patients with nAMD prescribed anti-VEGF injections delayed or interrupted their treatment.[4,25] Soares et al[26] in a study conducted
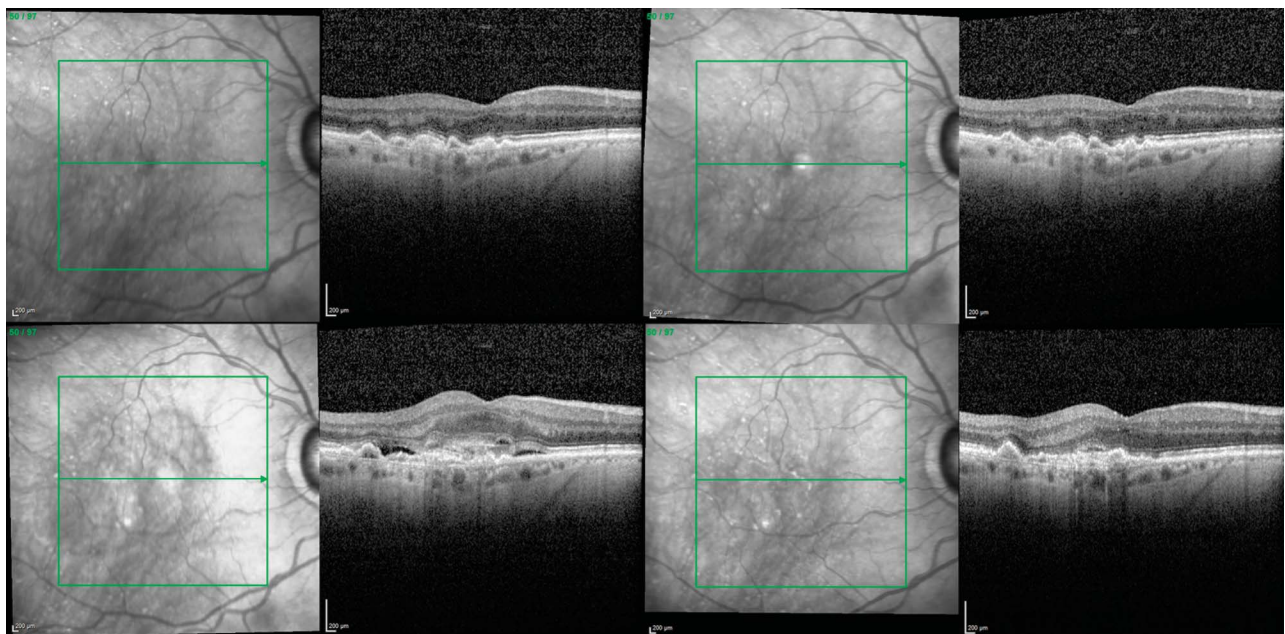

Fig. 2. Optical coherence tomography structural changes at each study time point. Macular OCT scans of the right eye of a patient from Group S. Image shows the scans before the lockdown, at T-1 and T0 (upper left and upper right panels, respectively), during which time the patient is receiving injections of ranibizumab at a 6-week interval. The visual acuity is 20/32 at both time points. Scan at T1 (lower left panel), after a treatment cessation of 24 weeks. Areas of pigment epithelium detachment (PED), subretinal fluid (SRF), and subretinal hyperreflective material (SHRM) are observed, and the visual acuity drops to 20/63. Three months after the resumption of IVT treatment with a 4-week interval (T2, lower right panel), the visual acuity partially recovers to 20/50. The central CST is 304 μm, 305 μm, 424 μm, and 323 μm at T-1, T0, T1, and T2, respectively.
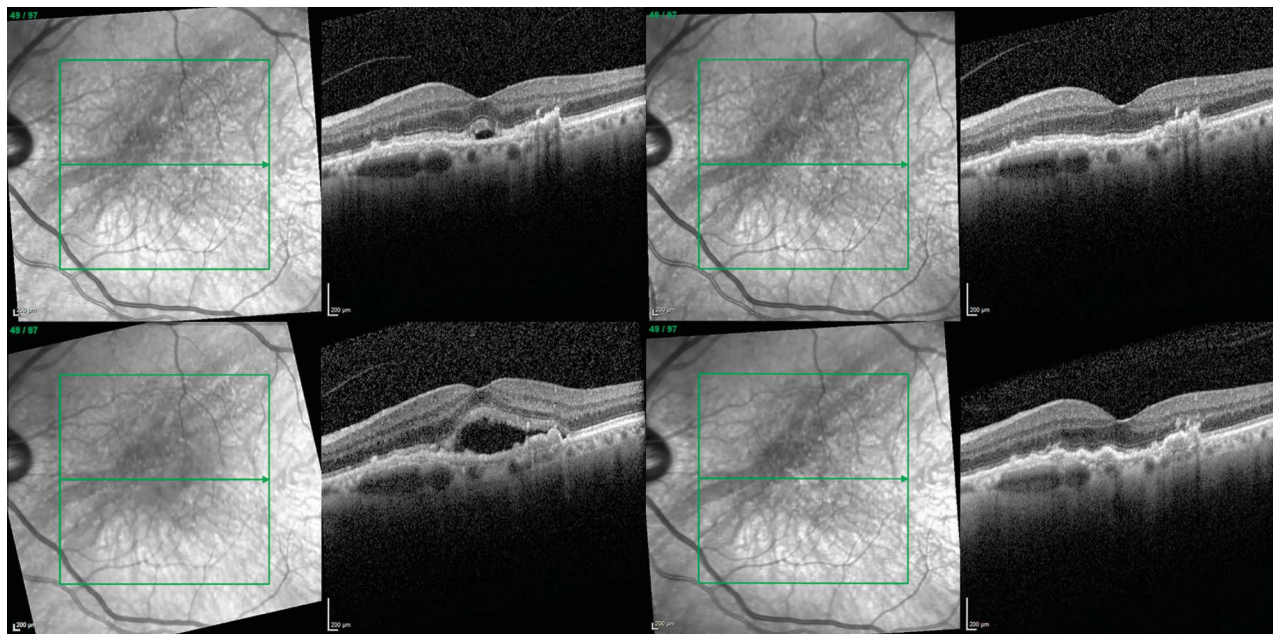
Fig. 3. Optical coherence tomography structural changes at each study time point. Macular OCT scans of the left eye of a patient from Group S. Scans before the lockdown, at T-1 and T0 (upper left and upper right panels, respectively), during which time the patient is receiving IVT of aflibercept at a 4-week interval. The visual acuity is 20/20 at both time points. Scans at T1 (lower left panel), after a treatment stop of 16 weeks. Recurrence of intraretinal fluid (IRF) and subretinal fluid (SRF) are observed, and the visual acuity drops to 20/40. Three months after the resumption of IVT treatment with a 4-week interval (T2, lower right panel), the visual acuity partially recovers to 20/25. The CST is 323 μm, 294 μm, 476 μm, and 300 μm at T-1, T0, T1, and T2, respectively.

prepandemic, reported that patients who were lost to follow-up for a mean period of 346 ± 122 days experienced an irreversible decrease in visual acuity, which did not recover after additional treatment despite the fact that anatomical changes associated with the loss to follow-up did improve back to previous levels.

In addition, in our Group S, we reported full recovery of anatomical markers, which was not followed by full recovery of visual function, regardless of the duration of the treatment interruption. Similar findings were recently reported by Yeter et al[27] in a cohort of patients with nAMD whose treatment was interrupted because of COVID-19 restrictions. These data indicate that once the visual loss is set, it is unlikely to be completely recovered. However, the correlation between OCT findings and visual acuity is still poorly understood.[28]

An additional objective of this study was to evaluate if an emergency plan for IVT administration without clinical evaluation, "injection-only," could be effective for managing treatment during pandemic periods. In our study, the cohort of patients treated with this approach (Group C) showed better anatomical and visual outcomes than Group S, with significant differences in all the parameters analyzed at the first visit after the lockdown (T1). Although Group C showed a slight decrease in visual acuity at T1 compared with

baseline, the visual acuity at the last follow-up was again comparable with T-1 ($P = 0.366$).

Intravitreal treatment because of a lockdown was a never seen unique scenario that could reoccur in the future. Our experience denotes the feasibility of an "injection-only" management plan for implementation in future pandemics, especially in a cohort of patients following an Observe-and-Plan regimen. The injection-only model, where the patients bypass visual acuity measurement, ophthalmology consultation, and OCT scan has been previously proposed to decrease the treatment burden of patients with nAMD, but it is only possible once the fixed treatment interval has been established for each individual patient.[11] In our setting, this individual fixed treatment interval was already determined because of the adherence to the Observe-and-Plan regimen; hence, we were able to achieve such favorable results in our cohort of patients. The possibility of relying on individual treatment needs to be determined in the past to plan a future treatment schedule is based on the relative stability of treatment need over time for a given individual. However, some changes may occur over time, requiring occasional adjustment of the individual treatment plan.[7,8,29]

Such knowledge is valuable if we are to experience future outbreaks leading to similar practice restrictions. The management of patients with retinal disease
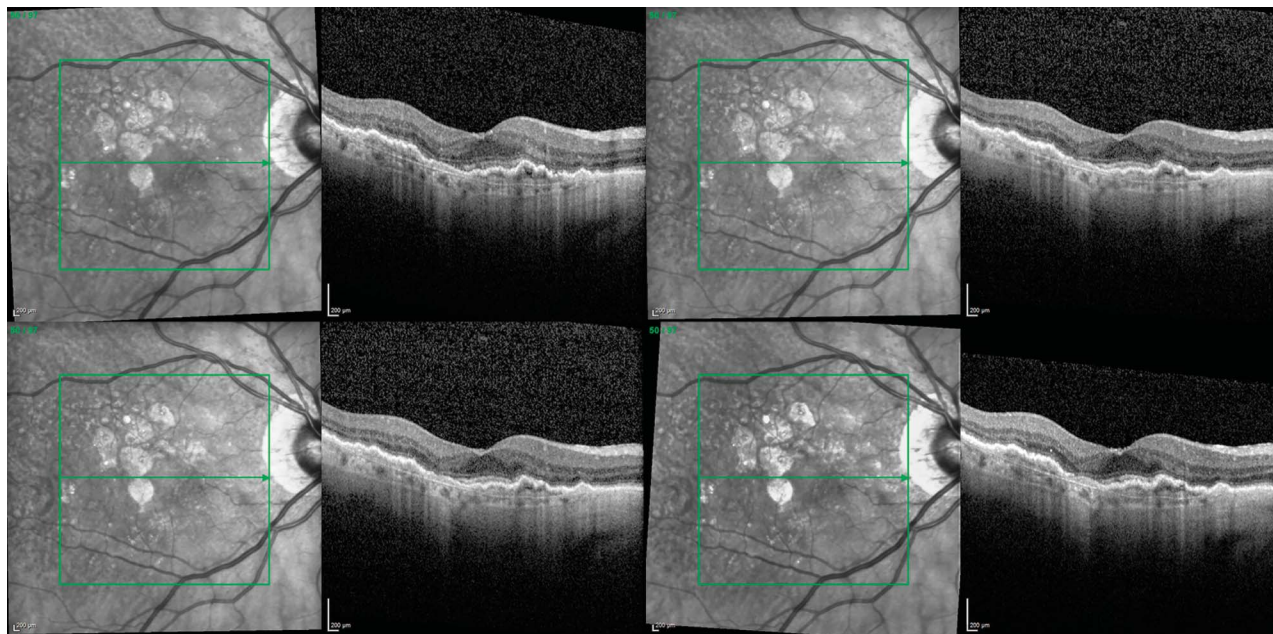
Fig. 4. Optical coherence tomography structural changes during study time point. Macular OCT scans of the right eye from a subject from Group C. Scans before the lockdown, at T-1 and T0 (upper left and upper right panels, respectively), during which time the patient is receiving IVT injections of aflibercept at a 4-week interval. The visual acuity is 20/25 at both time points. Scans at T1 (lower left panel) and T2 (lower right panel). The patients continue IVT injections at a 4-week interval during the lockdown, and no signs of disease progression were noticed. The visual acuity remains stable at 20/25. The CST is 322 μm, 298 μm, 312 μm, and 311 μm at T-1, T0, T1, and T2, respectively.

during pandemic times requires careful evaluation to minimize the risk of exposure to COVID-19 for both the patient and health care staff and should prioritize treatment for those at the greatest risk of irreversible vision loss.[19]

Limitations and Strengths

The main limitation of our investigation is its retrospective nature. In addition, we acknowledge that the decision to stop or continue the treatment plan was influenced by subjective patient-related factors that are not reproducible, representing a potential bias in the study cohort. Nevertheless, the robust size of the sample and the similar baseline demographic characteristics of the two groups represent strengths of our study, and we believe that it reflects the treatment outcomes of real-world clinical practice. Because data regarding the burden of treatment deferral during the COVID-19 pandemic on retinal patients are limited, we believed that our study could be a valuable resource for the ophthalmic community.

Conclusion

Our short-term results about the management of IVT injections in patients with nAMD during the first COVID-19 pandemic wave showed that continuing to treat patients under an Observe-and-Plan regimen with an "injection-only approach" was effective, whereas patients who delayed their scheduled treatment suffered irreversible deterioration of their visual function. These results could help retina specialists to manage future pandemic scenarios by developing successful management strategies.

Key words: SARS-CoV-2, COVID-19, lockdown, retina, intravitreal injections, anti-VEGF, neovascular age-related macular degeneration.

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