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The impact of delayed anti-vascular endothelial growth factor treatment for retinal diseases during the COVID-19 lockdown

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ABSTRACT

Purpose: : To assess the clinical status of treatment-naive patients who had to delay 3-dose loading anti-VEGF (anti-vascular endothelial growth factor) injections during the COVID-19 lockdown, and to evaluate the effect of the delayed visual acuity treatment on spectral domain optical coherence tomography (SD-OCT) parameters.
Method: : A total of 55 eyes of 46 patients who were received in the study period participated in this retrospective study, including 28 patients (37 eyes) with diabetic macular edema (DME), 11 patients (11 eyes) with retinal vein occlusion (RVO), and 7 patients (7 eyes) with wet age-related macular degeneration (wet-AMD). The patients were diagnosed with DME, RVO, or wet-AMD in February 2020 and had planned 3-dose loading injections in March, April, and May 2020, but could not be injected due to the COVID-19 pandemic.
Results: : From the patients' initial examination in February 2020, the mean best corrected visual acuity (BCVA) was 0.72 ± 59 logMAR. After the patients' lockdown visit in July 2020, the mean BCVA was 0.76 ± 64 logMAR. BCVA was stable in 11 eyes, decreased in 12 eyes, and increased in 14 eyes for patients with DME. BCVA was stable in 6, decreased in 3, and increased in 2 eyes for patients with RVO, and it was stable in 4 eyes and decreased in 3 eyes for patients with wet-AMD.
Conclusion: : We concluded that 6-month delay in treatment of DME patients with non-proliferative DRP had no adverse effect on the visual acuity. However, the loading dose in wet-AMD and RVO patients should be applied as soon as possible.

Background

Since the beginning of 2020, the world has faced significant challenges due to the COVID-19 outbreak. In different parts of the world, many medical support efforts have been reduced or stopped due to SARS-CoV-2's high infectiousness and the severe respiratory failure it causes. Notably, Turkey's Health Ministry took measures in mid-March 2020 to prevent the spread of coronavirus infections. This led to significant changes in many healthcare, business, and social practices, including restrictions on access to examinations and surgeries for eye diseases.

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent injections are widely used as first-line treatment for patients with retinal diseases, including neovascular wet age-related macular degeneration (wet-AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO), which consists of macular edema related to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). [1'2'3] Patients with these diseases but without a previous injection history generally receive serial loading phase injections and may require these treatments on a regular basis. [4] Compliance with the injection algorithm is crucial, as even slight deviations may cause vision loss. [5] However, the COVID-19 outbreak in Turkey resulted in postponed intravitreal injection sessions.

Important organizations have released guidance for retina specialists on managing patients during the pandemic, including the American Academy of Ophthalmology[6], the French Society of Ophthalmology [7], the German Ophthalmological Society[8], the Royal College of Ophthalmologists[9](RCOpht) and the Japanese Ophthalmological Society. [10] According to these guidelines, we assessed the clinical status of treatment-naive patients who had to delay 3-dose loading anti-VEGF injections during the COVID-19 lockdown, as well as evaluated which patients were affected by the delayed treatment using data on visual

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acuity and spectral domain optical coherence tomography (SD-OCT) parameters.

Procedure

A total of 46 patients (55 eyes) participated who were received in the study period, including 28 patients (37 eyes) with DME, 11 patients (11 eyes) with RVO, and 7 patients (7 eyes) with wet-AMD. The patients were diagnosed with DME, RVO, or wet-AMD in February 2020 and had planned 3-dose loading injections in March, April, and May 2020, but could not be injected due to the COVID-19 pandemic.

All patients underwent comprehensive ophthalmic examination for a re-injection decision in July 2020. Accordingly, we performed best corrected visual acuity (BCVA) with a Snellen chart, intraocular pressure measurement with a Goldmann applanation, anterior segment biomicroscopy, dilated fundoscopy, and SD-OCT (Nidek-RS300). We noted HbA1c levels for patients with DME within 3 months of their last appointment after treatment delay and at the initial visit. Patients who had other retinal diseases; macular edema not associated with DME, RVO, or wet-AMD, including degenerative myopia, polypoidal choroidal vasculopathy, and angioid streaks; who had intraocular surgery for diseases such as glaucoma and vitrectomy; or who received anti-VEGF injections in this period were excluded from the study.

For the SD-OCT measurements, we evaluated central macular thickness (CMT), the presence of hyperreflective dots (HRD), and the presence of subretinal fluid (SRF) at the baseline and post-lockdown visits. We converted BCVA levels to the logMAR system for statistical analysis. For patients who had no decrease in CMT values and/or line increase in BCVA after lockdown, we considered re-injection. If the patients demonstrated improved BCVA and/or CMT, we paused injection therapy.

Statistical analyses

We analyzed the data obtained during the research using the SPSS version 22.0 software package (Statistical Program for Social Sciences, Chicago, USA). We compared continuous variables by conducting a paired sample t-test. We assessed the statistical significance of the differences between qualitative variables using Fisher's exact test. We also used Pearson's correlation to investigate the relationship between the two measured values in the patient groups. We analyzed the CMT values' capacity to predict a re-injection decision using receiver operating characteristics (ROC) curve analysis. When a significant cutoff value appeared, we also presented the sensitivity and specificity values. In all analyses, a p value less than 0.05 indicated statistical significance.

Results

In total, we assessed 55 treatment-naive eyes of 46 patients who had planned 3-dose anti-VEGF loading therapy, but who could not be injected due to the COVID-19 pandemic. The indications for anti-VEGF injections were 37 eyes of 28 patients (60.9%) with DME, 11 eyes of 11 patients (23.9%) with RVO-related macular edema, and 7 eyes of 7 patients (15.2%) with wet-AMD. The study included 24 (52%) males and 22 (48%) females at a mean age of 60.96 ± 12.5 years. All patients in the DME group had non-proliferative DRP.

At the initial examination in February 2020, the patients' mean BCVA was 0.72 ± 59 logMAR and the IOP 14.1 ± 5 mmHg. Then, at the post-lockdown visit in July 2020, the mean BCVA was 0.76 ± 64 logMAR and the mean IOP 14.2 ± 4 mmHg. There were no statistically significant differences in BCVA and IOP between the two visits ($p = 0.36$ and 0.47, respectively). In subgroup analyses according to each indication, BCVA was stable in 11 eyes, decreased in 12 eyes, and increased in 14 eyes for patients with DME. BCVA was also stable in 6, decreased in 3, and increased in 2 eyes for patients with RVO, while it was stable in 4 and decreased in 3 eyes for patients with wet-AMD. Two patients with CRVO in the RVO group had decreased vision at their final visit. Table 1 shows the comparison of each study group's BCVA values at the two visits.

After the SD-OCT examinations, mean CMT was 449.2 ± 116.0 μm at the initial visit and 415.2 ± 153.5 μm at the post-lockdown visit. The differences in CMT between the two visits was statistically significant ($p = 0.02$). (Fig. 1) In the subgroup analyses, a statistically significant decrease in CMT occurred only in the patients with DME($p = 0.04$); there was no statistically significant difference in the patients with RVO and wet-AMD ($p = 0.4$ and 0.4 respectively). Table 2 shows the comparison of each study group's CMT values at the two visits.

Of the patients, 37 eyes that were decided to receive injections at the patient's initial visit continued injections at the second visit according to their CMT values and/or BCVA levels. Of the eyes to receive injections were 24 of the 37 eyes with DME, 9 of the 11 with RVO, and 4 of the 7 with wet-AMD. Patients with a BCVA of 0.7 or less according to the Snellen chart and a CMT above 250 μm received a re-injection decision.

Hyperreflective dots were detected in 31 of the 37 eyes with DME at the initial visit. There were 17 eyes with SRF and 15 with both SRF and HRDs. The mean HbA1C level was 9.5 ± 1.2 mg/dl at the initial visit and 9.2 ± 1.4 mg/dl at last visit. We then performed a correlation analysis between age, initial BCVA, initial CMT, HbA1C level, presence of HRD, presence of SRF, and re-injection decision for the patients with DME. The univariate analysis revealed a statistically significant correlation between final injection decision and the female gender, initial CMT, and the presence of SRF.(Table 3) ROC analysis indicated that a CMT ≥ 423.5 μm predicted a re-injection decision with a sensitivity of 64% and specificity of 83.7% (AUC: 0.802, $p = 0.003$, CI 95%: 0.662–0.941).

Discussion

In this study, we evaluated the impact of a 6-month delay of a 3-dose loading anti-VEGF treatment due to COVID-19 lockdown on the anatomical and functional findings of treatment-naive patients with DME, RVO, and wet-AMD. Our findings indicated that 6-month delay in treatment of DME patients with non-proliferative DRP had no adverse effect on the visual acuity. However, the loading dose in wet-AMD and RVO patients should be applied as soonas possible.

RISE and RIDE studies are the study of Ranibizumab (Lucentis®) injection in subjects with clinically significant DME with center involvement secondary to diabetes mellitus have reported that the patients had a significant increase in visual acuity after 2 years of follow-up with anti-VEGF treatment. In addition, one study applied intravitreal ranibizumab to the sham group in the second year, and at the end of the third year, there was no difference in the group's CMT. [11'12] In the RIDE study, at the end of the third year, in the group treated with intravitreal ranibizumab for 3 years and the group that received a sham injection for the first 2 years and then intravitreal ranibizumab, the 15-letter ETDRS gain was 19.2%, 36.8%, and 40.2%, respectively. In another RISE study, the 15-letter ETDRS gain in the ranibizumab treatment group was 41–51%, while in the sham injection group, 22% of the patients achieved a 15-letter ETDRS gain. [13] As such, even if CMT

Table 1
The comparison of BCVA for each group.

	BCVA at initial visit	BCVA at after the lockdown visit	P value
All the study population	0.72±059	0.76±0.64	0.36
Patients with DME	0.60±0.47	0.58±0.43	0.66
Patients with RVO	0.85±0.52	1.02±0.79	0.19
Patients with wet-AMD	1.11±1.05	1.27±0.99	0.09

Data are presented as mean ± standard deviation. Abbreviations: wet-AMD: wet age related macular degeneration; BCVA: best corrected visual acuity; DME: diabetic macular edema; RVO: retinal vein occlusion.

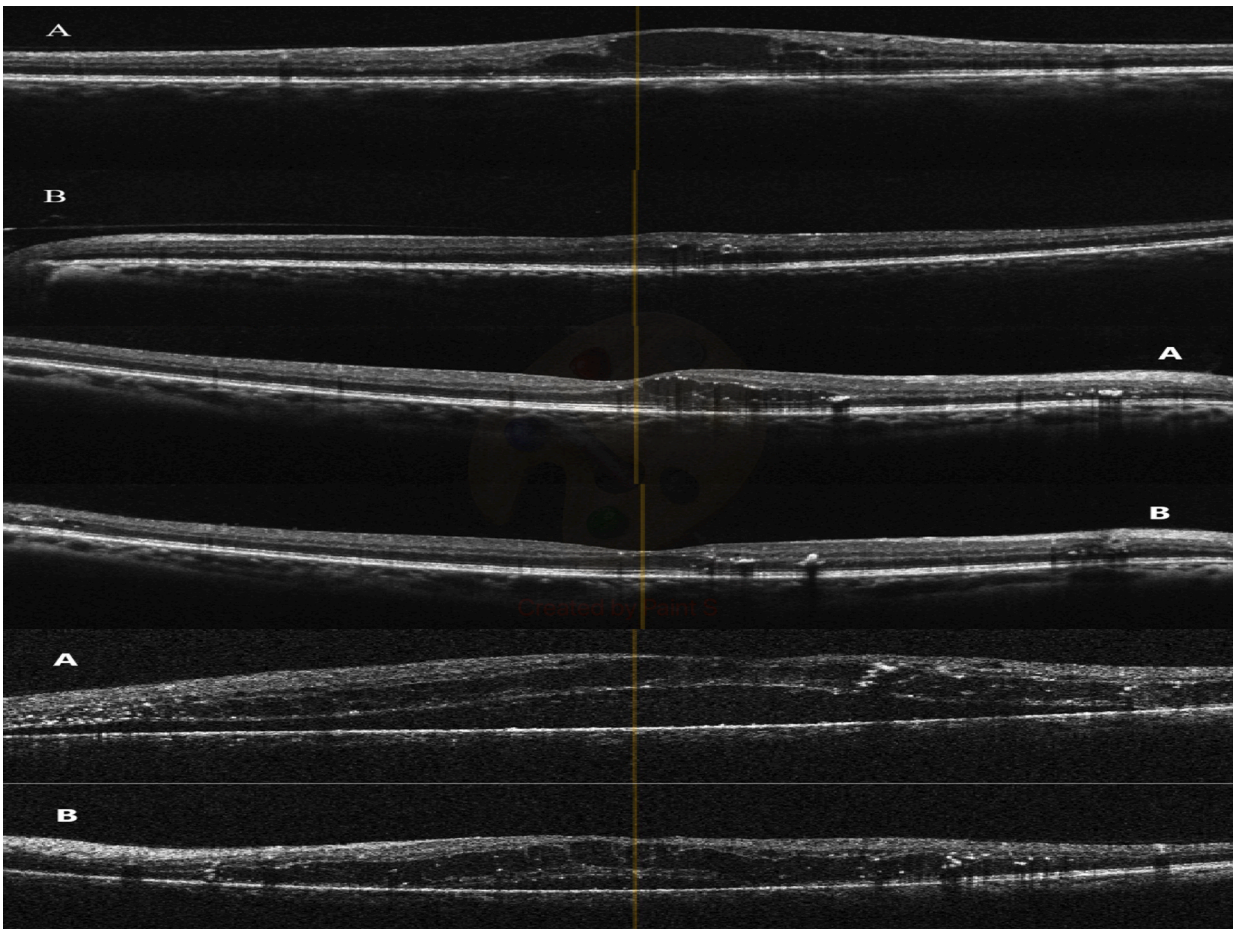

Fig. 1. OCT image of DME patients between the two visit. (A.initial visit B. Post-lockdown visit).

Table 2
The comparison of CMT values for each group.

	CMT at initial visit	CMT at after the lockdown visit	P value
All the study population	449.2 ± 116.0	415.2 ± 153.5	**0.02**
Patients with DME	458.3 ± 117.4	418.7 ± 159.8	**0.04**
Patients with RVO	494.6 ± 76.8	471.8 ± 136.6	0.4
Patients with >wet-AMD	336.1 ± 96.3	315.7 ± 98.8	0.4

Data are presented as mean ± standard deviation. Abbreviations: wet-AMD: wet age related macular degeneration; CMT: central macular thickness; DME: diabetic macular edema; RVO: retinal vein occlusion.

Table 3
The univariate correlation between repeated injection decision and clinical parameters.

	P value	OD	CI 95%
Initial CMT	**0.010**	**1.014**	**1.003–1.025**
Presence of SRF	**0.021**	**0.133**	**0.024–0.742**
Sex (Female)	**0.009**	**0.125**	**0.027–0.589**
Age	0.28	0.967	0.911–1.028
Initial BCVA	0.78	1.328	0.293–6.018
HbA1C	0.37	1.146	0.848–1.548
Presence of HRD	0.69	1.467	0.211–10.19

Data are presented as mean ± standard deviation. Abbreviations: BCVA: best corrected visual acuity; CI: confidence interval; OD: odds ratio; HbA1C: hemoglobulin A1C; HRD: hyperreflective dot; SRF: subretinal fluid.

is similar in the third year of treatment, there may be significant differences between visual gains. Yalamancılı et al. revealed no significant change in CMT and visual acuity in patients with DME after an average of 6 months of treatment delay, though they emphasized that despite the delay in treatment, they found similar results to the visual gains reported in the RISE and RIDE studies, which may be related to the initial loading dose administered to the patients. [14] In our study, we could not apply a loading dose at the beginning, and there was no significant change in CMT or visual acuity at the patients' 6-month visit. In our study, while visual acuity remained stable in 11 of the 37 eyes with DME, we observed an increase in 12 and decrease in 14 eyes. When we evaluated the patients with increased, decreased, and stable vision in terms of hyperreflective dots and subretinal fluid, hyperreflective dots at the beginning did not make a significant difference between vision groups, though we did observe that subretinal fluid occurred more frequently in those with decreased vision. This can be explained by the fact that the HRD is a stronger biomarker of early DME[15], and these patients have good visual gain. Kai Bo et al. reported a 70% reduction in anti-VEGF injections in China due to the COVID-19 pandemic. This study included 82 eyes of 72 patients and found visual acuity significantly lower when comparing the pandemic period values to those of the previous year. [16] However, while approximately 75% of the patients in Kai Bo et al.'s study had wet-AMD and CRVO, in our study, patients with wet-AMD and CRVO constituted 39.1% of the sample, thus potentially explaining our different results. In our study, vision remained stable in 4 of 7 patients with wet AMD and decreased in the remaining 3 patients as well. In light of these results, it may be necessary to consider the loading dose of patients with wetAMD more than those with DME.

A study conducted by Stone et al. with the RCOpht told that delaying DME and BRVO treatment, continuing injection therapy for wet-AMD at 8-week intervals, and treating patients with CRVO could delay treatment in 24% of the total patients in the United Kingdom. The researchers observed that this rate increased to 58% with delayed treatment of the eyes of patients with worse visual acuity, though they stated that the exact results of these delays will be shared in the future. [17] Still, the results in our study showed that RCOpht recommendations are the most optimal even if a loading dose is not administered. It would thus be wiser to prioritize the delayed treatment of DME and BRVO patients while planning treatment by reducing hospital appointments, especially during the peak periods of the pandemic.

The another recently study by Stone et al. in which they evaluated 858 patients, it was reported that when there was a delay of more than eight weeks in patients who received at least one anti-VEGF treatment, there was a significant decrease in visual acuity in wet-AMD patients, while no significant difference was observed in RVO patients. It was emphasized that there was no significant change in visual acuity in the DME Group, supporting the RCOphth guide. [18] Similarly, Mana et al. In their study, 17 wet-AMD patients and 11 DME patients who received at least one dose of anti-VEGF showed a significant decrease in visual acuity when the second and third doses were delayed, while visual acuity increased in DME patients, but this increase was not statistically significant. [19] Treatment delays and changes in visual acuity in these two studies were similar to our results. In addition, while patients in both studies received at least one dose of anti-VEGF, the dose of anti-VEGF was not administered in our study. In this case, it can be interpreted that similar visual acuity results can be achieved even if anti-VEGF treatment is not started.

It is an important question of what the long-term vision gains will be in patients whose loading doses are delayed when they receive routine anti-VEGF treatments after a 6-month delay. However, the fact that we could not administer anti-VEGF doses to any patients during this period makes it impossible for us to conduct controlled studies. There is thus a need for long-term controlled studies on this subject.

Our study has some limitations, including a small study population (especially in wet-AMD and RVO group), retrospective design, lack of a control group, no long-term results after administering delayed treatments. Also, the functional vision level was determined by BCVA only according to Snellen; contrast sensitivity, visual fields testes and other methods were not evaluated.

Conclusion

Even so, we observed that 6-month delay in treatment of DME patients with non-proliferative DRP had no adverse effect on the visual acuity. However, the loading dose in wet-AMD and RVO patients should be applied as soon as possible. We concluded that by examining disrupted treatments' effectiveness during the COVID-19 pandemic, changes may occur in treatment algorithms, especially for patients with DME, by giving patients a greater chance of metabolic recovery at the end of the pandemic. Still, studies with long-term follow-up and a more sufficient number of patients are needed on these issues.

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