Original research article

EJO European Journal of Ophthalmology

Treatment of neovascular age related macular degeneration during COVID-19 pandemic: The short term consequences of unintended lapses

European Journal of Ophthalmology
2022, Vol. 32(2) 1064–1072

DOI: 10.1177/11206721211010613
journals.sagepub.com/home/ejo
SAGE

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Abstract

Aim: To investigate the short-term effects of COVID-19 pandemic related unintended treatment lapses on neovascular age related macular degeneration (nAMD) patients.

Methods: In this prospective cross-sectional study, 140 patients who had at least one anti-vascular endothelial growth factor (VEGF) injection for nAMD within 12 months before COVID-19 pandemic and who had at least 3 months of unintended lapse for control visits during pandemic were recruited and underwent a detailed opthalmological examination and optical coherence tomography imaging.

Results: Of these 140 eyes, 113 (80.7%) were active with presence of either intraretinal and/or subretinal fluid and necessitated intravitreal anti-VEGF injections; and 20 (14.3%) of them complicated with subretinal hemorrhage. The mean interval of clinical visits and intravitreal antiVEGF injections were found to be prolonged during COVID-19 pandemics, which demonstrates a statistically significant lapse for both ($p = 0.001$ and $p = 0.003$ consecutively). The decreased visual acuity due to lapse was positively correlated with number of intravitreal anti-VEGF injections at last 6 months before COVID-19 pandemic ($r = 0.217$, $p = 0.010$) and central subfoveal thickness at first post-COVID-19 visit ($r = 0.175$, $p = 0.038$); and negatively correlated with follow-up duration ($r = -0.231$, $p = 0.006$) and number of control visits ($r = -0.243$, $p = 0.004$). Fifteen (16.9%) of the 89 patients who had drusen in the fellow eye before COVID-19 pandemic evolved to nAMD with an accompanying subretinal and/or intraretinal fluid.

Conclusion: Unintended lapses during COVID-19 pandemic resulted with poor functional and structural outcomes for nAMD patients, especially for those at the beginning of the treatment period and who still have an unstable clinical course.

Keywords

Anti-VEGF agents, COVID-19 pandemic, neovascular age related macular degeneration

Date received: 7 January 2021; accepted: 27 March 2021

Introduction

Age related macular degeneration (AMD) is one of the leading causes of blindness among elderly population. Macular neovascularization infiltrates the subretinal, sub-retinal pigment epithelium and intraretinal spaces in neovascular AMD (nAMD), which is an advanced type of AMD, and may result with hemorrhage and/or exudation

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causing to a damage to the surrounding retinal structures and irreversible vision loss. Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents have become highly effective first line treatment for nAMD.[1] Early diagnosis of nAMD, timely detection of the disease activity and initiation of early and adequate number of injections are mandatory for favourable anatomical and functional outcomes.[2] Non-compliance to regular follow-up visits and anti-VEGF treatment are reported to be related to decreased visual acuity.[3] However, the provision of optimal treatment for nAMD patients is challenging in real-life because of non-compliance of patients to visits and non-adherence to treatment regimens mainly due to greater number of comorbidities among elderly population, financial problems due to economic burden of the treatment, fear of injection and high patient load of medical retina units.[4] After the World Health Organization declared the outbreak of the novel coronovirus disease 2019 (COVID-19) as a global pandemic on 11 March 2020, retina specialists faced with an additional challenge for the treatment of these elderly patients with nAMD who have the greatest risk of mortality with COVID-19.

Ophthalmic examination brings high risk for viral transmission, and an outbreak of COVID-19 at the Department of Ophthalmology of Oslo University has been reported as the ground zero for COVID-19 in Norway.[5] Therefore, many international ophthalmic societies recommended the cessation of non-emergent ophthalmological examinations and treatments in order to reduce the risk of viral transmission at the first days of pandemic and to conserve medical supplies for departments facing COVID-19.[6,7] Medical retina units within the ophthalmology departments are also high risk venues for COVID-19 due to high daily patient numbers and overcrowded waiting rooms, close proximity during examination, possible conjunctival involvement during the course of the disease and the potential contamination of instruments used for imaging. With this manner, we initially cancelled all appointments after first confirmed COVID-19 case was reported on March 10, 2020 in our country, in order to free up all staff and hospital facilities to fight against COVID-19. At that days, many international ophthalmological societies provided guidelines supporting retina specialists to continue to perform intravitreal anti-VEGF injections especially for patients with nAMD.[8] After the initial efforts to struggle with this unexpected public health emergency and see that the fight against COVID-19 will be long, we tried to re-schedule the appointments especially for those with the greatest medical need such as the ones with ongoing nAMD treatment in order to prevent lapses in the treatment of these patients.

The aim of this study was to investigate the short-term functional and structural outcomes seen in nAMD patients who were under ongoing treatment of intravitreal anti-VEGF injections and who experienced at least 3-months delay for follow-up visits and an un-intended lapse in treatment because of COVID-19 pandemic and discuss factors that affect these outcomes.

Methods

One hundred and forty subjects who were under ongoing treatment for nAMD at the medical retina unit of a single tertiary eye hospital, who had at least one anti-VEGF injection within 12 months before COVID-19 pandemic and who had at least 3 months unintended lapse for control visits during pandemic were recruited between May 2020 and August 2020 for this prospective cross-sectional study. The written informed consent was obtained from each participant and all procedures were in compliance with the tenets of the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee.

All participants underwent a detailed ophthalmological examination including best corrected visual acuity (BCVA) testing with Snellen chart, intraocular pressure measurement with non-contact tonometry, anterior segment examination with slit-lamp biomicroscopy, fundus examination and optical coherence tomography (OCT) imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany) in order to detect post-lapse central subfoveal thickness (CST), disease activity based on presence of subretinal and/or intraretinal fluid and presence of some complications such as subfoveal hemorrhage, subretinal fibrosis and vitreous hemorrhage in the study eyes. The fellow eyes were also examined in order to detect any change.

Following detailed ophthalmological examination, we also comprehensively reviewed the medical records of the patients and rendered the following data; demographic data of the patients including the age and the gender; the clinical data including the disease duration, type of nAMD (Type 1, 2 or mixed), initial treatment choice (aflibercept, ranibizumab, bevacizumab), baseline BCVA at the time of their first anti-VEGF injection, number of follow-up visits and total number of intravitreal injections, BCVA and CST at the last visit before the lapse, the length of the lapse after last visit and the time elapsed after the last intravitreal injection before COVID-19. The Snellen visual acuity was converted to ETDRS letters as described elsewhere.[9] The patients with a history or the evidence of ocular disorders other than nAMD such as diabetic retinopathy, pathologic myopia, retinal dystrophies, retinal vascular occlusion, uveitis, vitreoretinal interface disorders and glaucoma were excluded from the study. Only one eye of each patient were included in the study and the data from the right eyes were used for statistical analysis if both eyes were eligible for the study.

Statistical analyses were performed by using Statistical Package for the Social Sciences 22.0 version for Windows software (SPSS Inc., Chicago, IL, USA). Descriptive statistics

Table 1. Demographic and baseline clinical characteristics of patients ($n = 140$).

Age (years) (mean ± SD)(min–max)		72.0 ± 8.9 (55–92)
Baseline BCVA (ETDRS letters) (mean ± SD)(min–max)		42.1 ± 25.3 (5–83)
Baseline CST (μm) (mean ± SD)(min–max)		345.1 ± 33.7 (285–466)
Gender, *n*(%)	Male	62 (44.3)
	Female	78 (55.7)
Eye laterality, *n*(%)	Right	80 (57.1)
	Left	60 (42.9)
Baseline NV type, *n*(%)	Type 1	99 (70.7)
	Type 2	27 (19.3)
	Mixed	14 (10.0)
Initial treatment, *n*(%)	Aflibercept	88 (62.9)
	Ranibizumab	25 (17.8)
	Bevacizumab	27 (19.3)
Fellow eye before COVID-19 pandemic, *n*(%)	Drusen	89 (63.6)
	Disciform scar	32 (22.8)
	Macular NV	19 (13.6)

n = Number of Patients, SD = Standard Deviation, BCVA = Best Corrected Visual Acuity, CST = Central subfoveal thickness, NV = Neovascularisation.

Table 2. Comparison of BCVA and CST values at last pre-COVID-19 and first post-COVID-19 visits.

	Pre-COVID-19 last visit	Post-COVID-19 first visit	*p*
BCVA (ETDRS Letters) mean ± SD (min–max)	50.2 ± 23.6 (5–85)	38.8 ± 25.5 (5–83)	0.001*
CST (μm) mean ± SD (min–max)	283.7 ± 26.3 (218–345)	312.1 ± 42.7 (225–461)	0.001*

BCVA = Best corrected visual acuity, CST = Central subfoveal thickness.
*Paired sample t test, $p < 0.05$ accepted as statistically significant.

were expressed as frequency and percentage for categorical variables whereas quantitative data were expressed as mean ± standard error of mean for normally distributed variables and median (minimum-maximum) for non-normally distributed data. Categorical variables were analyzed by Pearson chi square test and Fischer's exact test. Normal distribution of the variables was tested using visual (histogram and probability graphs) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). For the variables that were not normally distributed, Mann-Whitney *U* test was used to compare two independent groups, Wilcoxon signed rank tests for two dependent groups and Friedman test for three dependent groups. The correlation of two quantitative data were tested by using Spearman correlation analysis. A probability level of $p < 0.05$ was considered as statistically significant.

Results

One hundred and forty eyes of 140 patients (62 males, 78 females) with a mean age of 72.0 ± 8.9 years (55–92 years) were evaluated in the study. Demographic and baseline clinical characteristics of patients are shown in Table 1. The mean follow- up duration of patients before COVID-19 pandemic was 24.2 ± 15.4 months (3–66 months) with a mean of 16.2 ± 9.9 (2–57) clinical visits and 8.5 ± 5.1 (2–27) intravitreal injections. Three loading doses of intravitreal anti-VEGF injections was completed in 125 (89.3%) and not yet completed in 15 (10.7%) of the eyes before COVID-19 pandemic in our cohort.

The mean interval of clinical visits and intravitreal anti-VEGF injections before COVID-19 pandemic were 6.0 ± 1.6 weeks (4–12 weeks) and 11.6 ± 5.2 weeks (4–28 weeks) respectively. However, mean duration between last pre-COVID-19 and first post-COVID-19 follow-up visit was 19.6 ± 5.5 weeks (12–32 weeks); and mean duration between last pre-COVID-19 and first post-COVID-19 injections was 29.4 ± 14.1 weeks (12–64 weeks), which demonstrates a statistically significant lapse for both ($p = 0.001$ and $p = 0.003$ consecutively, Wilcoxon signed ranks test). The BCVA was decreased in 90 (64.3%) and remained stable in 50 (35.7%) patients. The decrease in BCVA was less than five letters in 54 (38.6%), between 5 to 20 letters in 66 (47.1%) and more than 20 letters in 20 (14.3%) patients. The mean BCVA of the eyes were decreased and CST were increased at first post-COVID-19 visit when compared to last pre-COVID-19 visit (Table 2) ($p = 0.001$ for both, paired sample t test). The decreased BCVA due to lapse was positively correlated with number of intravitreal anti-VEGF injections at last 6 months before COVID-19 pandemic ($r = 0.217$, $p = 0.010$) and CST at first post-COVID-19 visit ($r = 0.175$, $p = 0.038$); and negatively correlated with follow-up duration ($r = -0.231$, $p = 0.006$) and number of control visits ($r = -0.243$, $p = 0.004$)

Of these 140 eyes, 67 (47.9%) were active with presence of either intraretinal and/or subretinal fluid and necessitated intravitreal anti-VEGF injections at last pre-COVID-19 visit, contrary to first post-COVID-19 visit in which 113 (80.7%) were active; and 20 (14.3%) of them complicated either with massive subretinal hemorrhage or fibrosis. The patients who had either subretinal and/or intraretinal fluid at post-COVID-19 first visit have significantly higher decline in mean BCVA when compared to the ones without any subretinal or intraretinal fluid. (14.0 ± 15.5 [0–70] and 0.9 ± 3.1 [0–15] letters consecutively, $p = 0.001$, Mann Whitney U Test). Fifteen (16.9%) of the 89 patients who had drusen in the fellow eye before COVID-19 pandemic evolved to nAMD with an accompanying subretinal and/or intraretinal fluid.

Patients who have been completed three loading doses of intravitreal injections and did not required any intravitreal injections at last 6 months before COVID-19 pandemic were found to be related to less intraretinal and/or subretinal fluid on OCT at first post-COVID-19 visit. Comparison of clinical and demographical characteristics of patients with clinically active and in-active nAMD at first post-COVID-19 visit are shown in Table 3.

Patients who have been treated with bevacizumab as the initial treatment, who did not completed three loading doses of intravitreal injections and who required any intravitreal injections at last 6 months before COVID-19 pandemic were found to be related to complications such as subfoveal hemorrhage at first post-COVID-19 visit. The comparison of clinical and demographical characteristics of patients according to presence of complications at first post-COVID-19 visit are demonstrated in Table 4.

Discussion

The experts of the Vision Academy published recommendations for anti-VEGF treatment during COVID-19 pandemic to prioritize the patients with nAMD especially those in the first 2 years of treatment.[10] After the initial panic at early days of COVID-19 pandemic and efforts to be ready for a fight with this unknown enemy, we prioritized nAMD patients and tried to re-schedule their control visits. For that purpose, we re-scheduled the control visits and invited 375 patients between May and August 2020. Of these, 255 were examined and 140 of them were recruited for the study who had at least one anti-VEGF injection within 12 months before COVID-19 pandemic and who had at least 3 months unintended lapse for control visits during pandemic. One-hundred and twenty nAMD patients rescheduled and invited but not-attended to the visit during the patient recruitment period, probably because of some reasons such as government restrictions on travel between cities and lockdown for people over the age of 65 years at early days of the pandemic, and mostly due to COVID-19 anxiety and fear of going outdoor of elderly patients which resulted with a significant non-attendance to scheduled control visits. Similarly, Stone et al. reported a 67% non-attendence to scheduled control visits of patients in the first 4 weeks after UK lockdown who are under ongoing anti-VEGF treatment at Newcastle Eye Department.[11] There were almost 1000 nAMD patients who were under ongoing follow up/treatment for nAMD in pre-COVID-19 period but could not be examined during recruitment period due to strict hygiene and hospital social distancing measures to minimize the exposure of patients and hospital staff to COVID 19. Not only scheduled regular control visits, even patients with severe ophthalmological manifestations did not admitted to ophthalmology departments in the early days of COVID-19 pandemic. Wickham et al.[12] reported the impact of COVID-19 on emergency admissions in Moorfields Eye hospital, and found the number of rhegmatogenous retinal detachment (RRD) presentation had fallen by 62% at early days after the implementation of lockdown measures. Dervenis et al.[13] similarly reported a fall of 58% in RRD cases at The St. Paul's Eye Unit, a tertiary referral centre in Liverpool and late presentations of patients with RRD due to COVID-19-related concerns.

The aim of our study was to evaluate the short-term effects of treatment lapses during early days of COVID-19 pandemic for nAMD patients receiving anti-VEGF injections. We demonstrated that the mean interval between the visits (6.0 vs 19.6 weeks) and intravitreal injections (11.6 vs 29.4 weeks) were significantly prolonged when compared to pre-COVID-19 period, which in turn caused to unfavourable structural and functional outcomes showing the collateral health damage of the COVID-19 pandemic especially for those at the beginning of the treatment period and who still have an unstable clinical course. The number of anti-VEGF injections and control visits at Pre-COVID-19 period in our study (8.5 injections and 16.2 control visits within 24.2 months) was comparable with the literature reporting real-world evidence for nAMD treatment.[14,15] However, unintended lapses for intravitreal anti-VEGF injections during COVID-19 pandemic resulted with BCVA loss which is again comparable with the real-world evidence in the literature that reports lower BCVA gains with decreased injection frequency.[16] Furthermore, in the RAINBOW study, treatment-naïve patients who received three initial loading doses of anti-VEGF treatment experienced better BCVA outcomes than patients who received no initial loading doses which is consistent with our data.[17] All of the 15 patients who did not completed the three loading doses at pre-COVID-19 period in our study were still active and 10 of these had complications such as sub-macular hemorrhage at first post-COVID-19 visit. The 92.3% of patients who had intravitreal injections at last 6 months before COVID-19 pandemic again necessitated; contrary, only 47.2 % of patients who did not have intravitreal injections at last 6 months before COVID-19 pandemic necessitated intravitreal injections at first post-COVID-19 visit.

Retreatment decisions during ongoing treatment of nAMD are mainly based on detection of either subretinal

Table 3. Comparison of clinical and demographical characteristics of patients with clinically active and in-active nAMD at first post-COVID-19 visit.

	nAMD activity at first post-COVID-19 visit		*p*
	Active	Inactive	
Gender, *n*(%)			
Male	51 (45.1)	11 (40.7)	0.680[a]
Female	62 (54.9)	16 (59.3)	
Eye laterality, *n*(%)			
Right	65 (57.5)	15 (55.6)	0.853[a]
Left	48 (42.5)	12 (44.4)	
Fellow eye, *n*(%)			
Drusen	69 (61.1)	20 (74.1)	0.225[a]
Disciform scar	26 (23.0)	6 (22.2)	
Macular NV	18 (15.9)	1 (3.7)	
Initial NV type, *n*(%)			
Type-1	79 (69.9)	20 (74.1)	0.466[a]
Type-2	21 (18.6)	6 (22.2)	
Mixt	13 (11.5)	1 (3.7)	
Initial treatment, *n*(%)			
Aflibercept	67 (59.3)	21 (77.8)	0.202[a]
Ranibizumab	22 (19.5)	3 (11.1)	
Bevacizumab	24 (21.2)	3 (11.1)	
Three intravitreal loading injections, *n*(%)			
Yes	98 (86.7)	27 (100.0)	**0.045**[b]
No	15 (13.3)	0 (0.0)	
Intravitreal injection at last 6 months, *n*(%)			
Yes	96 (85.0)	8 (29.6)	**0.001**[a]
No	17 (15.0)	19 (70.4)	
Age (years), mean ± SD (min-max)	72.0 ± 9.0 (55–92)	72.3 ± 8.2 (59–88)	0.858[c]
Follow-up duration (months), mean ± SD (min-max)	23.9 ± 15.8 (3–64)	25.4 ± 13.6 (6–66)	0.472[d]
Baseline BCVA (ETDRS letters), mean ± SD (min-max)	44.1 ± 24.3 (5–83)	33.7 ± 27.9 (5–83)	0.057[d]
BCVA at last pre-COVID-19 visit (ETDRS letters), mean ± SD (min-max)	52.6 ± 21.9 (5–85)	40.5 ± 28.0 (5–83)	**0.041**[d]
Baseline CST (μm), mean ± SD (min-max)	342.5 ± 32.5 (285–466)	356.0 ± 37.0 (295–426)	0.060[c]
CST at last pre-COVID-19 visit (μm), mean ± SD (min-max)	283.6 ± 26.5 (218–345)	284.0 ± 25.5 (230–325)	0.943[c]
Total number of control visits, mean ± SD (min-max)	16.2 ± 10.5 (2–57)	16.0 ± 6.3 (6–30)	0.663[d]
Total number of intravitreal injections, mean ± SD (min-max)	8.9 ± 5.4 (2–27)	6.6 ± 2.5 (3–13)	0.058[d]
Total number of intravitreal injections at last 6 months, mean ± SD (min-max)	2.1 ± 1.2 (0–6)	0.5 ± 0.9 (0–3)	**0.001**[d]
Pre-COVID-19 injection interval (weeks), mean ± SD (min-max)	10.7 ± 4.8 (4–24)	15.2 ± 5.4 (8–28)	**0.001**[d]
Duration between last pre-COVID-19 and first post-COVID-19 intravitreal injection (weeks), mean ± SD (min-max)	26.0 ± 12.3 (12–60)	43.4 ± 12.1 (20–64)	**0.001**[d]
Pre-COVID-19 visit interval (weeks), mean ± SD (min-max)	5.9 ± 1.5 (4–12)	6.1 ± 1.5 (4–12)	0.407[d]
Duration between last pre-COVID-19 and first post-COVID-19 follow-up visit (weeks), mean ± SD (min-max)	19.5 ± 5.8 (12–32)	19.7 ± 3.6 (12–28)	0.491[d]

n = Number of Patients, SD = Standard Deviation, BCVA = Best Corrected Visual Acuity, CST = Central subfoveal thickness, NV = Neovascularisation.
[a]Pearson Chi-Square Test, [b]Fisher's Exact Test, [c]Student-t test, [d]Mann Whitney U test.
$p<0.05$ accepted as statistically significant. (Statistically significant values denoted in bold)

and/or intraretinal fluid on OCT, which shows the requirement for prompt intravitreal antiVEGF injection to avoid further complications and irreversible vision loss. Greenlee et al. examined the anatomic changes that occur as a result of loss to follow-up for nAMD patients and the reversibility of these changes upon resumption of regular treatment.[18] They demonstrated that CST normalizes on resumption of the treatment contrary to the decline on visual acuity which does not recover and concluded that nAMD patients who have lapses during follow-up are at risk for poor outcomes. Soares et al.[19] investigated the eyes that received antiVEGF for nAMD and were loss to follow-up for more

Table 4. Comparison of clinical and demographical characteristics of patients according to presence of complications at first post-COVID-19 visit.

	Complication at first post-COVID-19 visit		*p*
	Yes	No	
Gender, *n*(%)			
Male	10 (50.0)	52 (43.3)	0.578[a]
Female	10 (50.0)	68 (56.7)	
Eye laterality, *n*(%)			
Right	11 (55.0)	69 (57.5)	0.834[a]
Left	9 (45.0)	51 (42.5)	
Fellow eye, *n*(%)			
Drusen	14 (70.0)	75 (62.5)	0.883[b]
Disciform scar	4 (20.0)	28 (23.3)	
Macular NV	2 (10.0)	17 (14.2)	
Initial nAMD type, *n*(%)			
Type-1	15(75)	84(70)	0.858[b]
Type-2	4(20)	23(19,2)	
Mixt	1(5)	13(10,8)	
Initial treatment, *n*(%)			
Aflibercept	9(45)	79(65,8)	**0.002[b]**
Ranibizumab	1(5)	24(20)	
Bevacizumab	10(50)	17(14,2)	
Intravitreal injection at last 6 months, *n*(%)			
Yes	20(100)	84(70)	**0.004[a]**
No	0(0)	36(30)	
Three intravitreal loading injections, *n*(%)			
Yes	10(50)	115(95,8)	**0.001[c]**
No	10(50)	5(4,2)	
Age (years), mean ± SD (min-max)	68.2 ± 8.7 (55–85)	72.7 ± 8.7 (55–92)	0.064[d]
Follow-up duration (months), mean ± SD (min-max)	11.9 ± 14.8 (3–60)	26.3 ± 14.5 (5–83)	**0.001[e]**
Baseline BCVA (ETDRS letters), mean ± SD (min-max)	38.2 ± 23.1 (5–70)	42.8 ± 25.7 (5–83)	0.493[e]
BCVA at last pre-COVID-19 visit (ETDRS letters), mean ± SD (min-max)	51.1 ± 22.5 (5–83)	50.1 ± 23.9 (5–85)	0.900[e]
Baseline CST (μm), mean ± SD (min-max)	345.5 ± 30.4 (289–404)	345.1 ± 34.4 (285–466)	0.956[d]
CST at last pre-COVID-19 visit (μm), mean ± SD (min-max)	294.3 ± 25.8 (246–328)	281.9 ± 26.1 (218–345)	0.051[d]
Total number of control visits, mean ± SD (min-max)	8.7 ± 10.3 (2–40)	17.4 ± 9.2 (2–57)	**0.001[e]**
Total number of intravitreal injections, mean ± SD (min-max)	5.5 ± 4.9 (2–20)	9.0 ± 4.9 (2–27)	**0.001[e]**
Total number of intravitreal injections at last 6 months, mean ± SD (min-max)	2.8 ± 1.5 (1–6)	1.6 ± 1.2 (0–5)	**0.007[e]**
Pre-COVID-19 injection interval (weeks), mean ± SD (min-max)	7.5 ± 2.8 (4–13)	12.3 ± 5.2 (5–28)	**0.001[e]**
Duration between last pre-COVID-19 and first post-COVID-19 intravitreal injection (weeks), mean ± SD (min-max)	25.2 ± 5.9 (12–32)	30.1 ± 14.9 (12–64)	0.769[e]
Pre-COVID-19 visit interval (weeks), mean ± SD (min-max)	5.1 ± 1.4 (4–8)	6.1 ± 1.6 (4–12)	**0.005[e]**
Duration between last pre-COVID-19 and first post-COVID-19 follow-up visit (weeks), mean ± SD (min-max)	23.8 ± 6.9 (12–32)	18.9 ± 4.9 (12–32)	**0.001[e]**

n = Number of Patients, SD = Standard Deviation, BCVA = Best Corrected Visual Acuity, CST = Central subfoveal thickness, NV = Neovascularisation.
[a]Pearson Chi-Square Test, [b]Fisher Freeman Halton Test, [c]Fisher's Exact Test, [d]Student-t Test, [e]Mann Whitney U Test.
$p<0.05$ accepted as statistically significant. (Statistically significant values denoted in bold)

than 6 months, and reported a decline on visual acuity at final visit after re-initiation of the treatment despite normalization of CFT. Ramakrishnan et al.[20] also concluded that visit adherence contributes to BCVA outcomes in patients with nAMD. Prolonged and multiple lapses during treatment can be complicated with sub-macular hemorrhage, leading to a sudden and irreversible vision loss.[21] Romano et al.[22] reported a significantly increased number of patients with large sub-macular hemorrhages during the early months of COVID-19 pandemic following a meaningful decrease in the attendance rate of nAMD patients to the clinic. All previously aforementioned reasons during COVID-19 pandemic caused to lapses for the treatment of nAMD patients in our cohort resulting with some severe

complications such as sub-macular hemorrhage (14.3% in our cohort); and possibly a delay in the treatment of new macular NV in the fellow formerly non-exudative eyes (16.9% in our cohort), which possibly would be detected earlier and treated more effectively if they could be examined on-time. Worse than that, we still have hundreds of nAMD patients who are anxious about attending to their appointments. When the World returns the 'old-World' again, or at least close to normality as possible, we will need extra resources and support to adjust a new model of post-COVID-19 medical retina care which may include tele-ophthalmology and artificial intelligence supports.

As of 15th of December 2020, we still have daily almost 30,000 new confirmed cases in our country, which means that social distancing measures should still be a part of daily routine, which in turn will have direct impact on both the ability and desire of patients to attend to an appointment in the retina unit. We detected almost 40% decrease for the regular follow up visits of nAMD patients and 30% decrease for the intravitreal injections of them during patient recruitment period of the study when compared to data of same period in 2019. We are trying to continue intravitreal injections in order to prevent permanent vision loss, however, medical retina units still poses a significant risk for COVID-19 transmission and elderly nAMD patients are often at increased risk for COVID-19 complications.[23] Some expert recommendations advised to check the medical files of patients prior to patient admission and skip some of the regular steps such as BCVA testing and OCT imaging to minimize time spent in the clinic. However, the presence of nAMD in one eye is a major risk factor for the development of disease in the fellow eye.[24] In our cohort, 16.9% of the patients who had drusen in the fellow eye before COVID-19 pandemic found to be evolved to nAMD with an accompanying subretinal and/or intraretinal fluid at first post-COVID-19 visit. Studies demonstrated the importance of early detection of nAMD in the fellow eye in order to make interventions before significant vision loss occurs, which can't be detected if we do not regularly examine these patients.

All above aforementioned studies point to a similar conclusion that despite the efficacy of anti-VEGF treatment for restoration of anatomical alterations, a delay in treatment most probably result with an irreversible deterioration of the BCVA possibly related to a damage at the retinal cellular level. Therefore, substantial effort should be expended to maintain alternative therapeutic strategies that reduce the visit burden without compromising BCVA outcomes during COVID-19 pandemic. An ideal therapeutic strategy for ongoing treatment of nAMD patients during the COVID-19 era should include injection of antiVEGF on the same day of the examination, preferring longer-acting antiVEGFs and same-day bilateral injections where applicable, avoiding treatment regimens that require frequent monitoring like pro-re-nata, instead preferring proactive regimens like treat-and-extend or bimonthly fixed dosing, and finally giving-up next-day follow up visits in order to minimize exposure, providing detailed information about post-injection complications and urgent re-admissions, so patients do not have to return clinic until the next scheduled injection.

Another group of patients that we frequently examine in medical retina units are the patients with diabetic macular edema (DME). In a study of Yalamanchili et al.,[25] a single and relatively short-term lapse in anti-VEGF treatment in patients with DME resulted a reversible macular thickening and reversible decline in BCVA upon resumption of regular follow-up and anti-VEGF treatment. In the light of the aforementioned study results, we can speculate that short term treatment lapses during COVID-19 pandemic in patients with DME may not lead to significant or permanent anatomic or visual deterioration contrary to the patients with nAMD. However, the answer of the long term consequences beyond 6 months of a lapse in treatment or the effect of multiple lapses on treatment are not present in their study. In a study of Weiss et al.,[26] the BCVA was found to be decreased with multiple treatment lapses in patients with DME.

The medical retina units will never be the same again after COVID-19 pandemic. The initial accelerating phase of COVID-19 appears to be controlled, however, we all fear the subsequent peaks of the disease until the use of effective antiviral treatment and vaccine to achieve herd immunity. We should focus to adjust pre-COVID-19 regular clinical practice with strict hygiene and hospital social distancing measures to minimize the exposure of both patients and ophthalmologists to COVID-19 and maintain a sustainable medical retina practice to prevent irreversible vision loss. In near future, the medical retina care will be redefined to facilitate social distancing while maintaining access to treatment, by a potential acceleration towards tele-ophthalmology after development of standardized home-based retinal imaging and novel treatment protocols.

Our data, which demonstrated a negative impact on both functional and structural outcomes especially for those at the beginning of the treatment period and who still have an unstable clinical course, may be important if ophthalmologists have to make difficult choices about prioritising treatment in future, for example if there is a disruption to treatment provision, similar to which happened with the COVID-19 pandemic. Besides many strengths of our study, there are some limitations such as relatively small sample size, short duration of follow-up and its cross-sectional nature. Lacking of the OCTA data is another limitation of the study and beyond the purpose of our study. Further larger and prolonged studies should investigate the long-term consequences of treatment lapses

after resumption of the intravitreal anti-VEGF treatment and these may further delineate the patients at risk for treatment lapses.

In conclusion, we demonstrated that the interval between the visits and intravitreal injections were significantly longer than the pre-COVID-19 period among patients with the ongoing treatment for nAMD, which in turn resulted with a negative impact on both functional and structural outcomes especially for those at the beginning of the treatment period and who still have an unstable clinical course.

Acknowledgements

The authors have no financial or proprietary interest in any of the materials mentioned in this manuscript

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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