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Increased Number of Submacular Hemorrhages as a Consequence of Coronavirus Disease 2019 Lockdown



Neovascular age-related macular degeneration (nAMD) is a leading cause of visual impairment in the elderly population.¹ Although intravitreal anti-vascular endothelial growth factor (VEGF) treatment can delay the degenerative process, the occurrence of submacular hemorrhages (SMHs) can complicate the clinical picture, leading to sudden and irreversible vision loss.²

Coronavirus Disease 2019 (COVID-19) has rapidly spread as a pandemic, with Northern Italy being one of the most affected regions in the world.³ The implementation of national lockdown (starting March 8, 2020) and social containment measures have undoubtedly generated anxiety in the local population, resulting in significant nonattendance to scheduled office visits.⁴ After the initial efforts to cope with this unexpected public health emergency, our clinicians are starting to weigh in on the impact of this pandemic on clinical practice.

This study aims to report the attendance rates to the service of Medical Retina and the incidence of large SMHs in an Italian tertiary center for nAMD during the early months of the COVID-19 pandemic.

The admissions, clinical records, and imaging studies of patients with nAMD accessing the Eye Clinic of Luigi Sacco Hospital (Milan, Italy) from March 1 to April 30, 2020, were retrospectively reviewed. Ethics approval was obtained from the local institutional review board, and the procedures adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

The occurrence of SMHs secondary to choroidal neovascular membrane was collected from clinical records and confirmed using multimodal imaging, including color fundus photography, OCT, and fundus autofluorescence. Only patients with nAMD already undergoing pro re nata anti-VEGF treatment with SMHs of at least 1 disc diameter within the macular region were included.² Patients with a history of large SMHs were excluded from the study. Patients affected by bilateral nAMD are routinely treated with an interval of at least 14 days because of Italian Health Authorities' regulations.

The attendance rate to the clinic and the incidence rate of SMHs from the same months of the previous year (March to April 2019) were analyzed as controls. Because the majority of our patients were switched to bevacizumab from September 2019 for economic reasons, an additional control bimester (October 1 to November 30, 2019) was considered to avoid biases related to drug selection.

The attendance rates were calculated in relation to the scheduled office visits and intravitreal treatments. Student *t* test was used to explore the differences among the weekly attendances in distinct time periods. The incidence rate of SMHs was instead obtained measuring the number of SMH cases occurring per month among scheduled patients with nAMD. Poisson regression analysis was used to assess the ratio between the incidence rate ratios of large SMHs among the different study periods. All the analyses were performed with IBM SPSS Statistics for Macintosh version 26.0 (IBM Corp., Armonk, NY). Statistical significance was set at

$P < 0.05$. Overall, 6568 consecutive patients with nAMD attended our clinic for office visits in the 3 analyzed periods (mean age, 76.2 ± 6.3 years; 2071 male patients, 43.9%).

During the 8 weeks after the national lockdown, a mean of 95 ± 30 patients attended office visits every week (attendance rate: 37%; range, 23%–51%). This resulted in a 68% and 71% decrease of office visits compared with the 2 control periods (297 ± 91 and 324 ± 37 per week, respectively; both $P < 0.001$).

The attendance rate for intravitreal anti-VEGF treatments was 58% (range, 48%–68%). A significant decrease (39%) was observed when compared with control periods (122 ± 29 vs. 200 ± 40 injections per week; $P < 0.001$).

A total of 41 patients presented with large SMHs during the 3 analyzed periods (mean age, 82.2 ± 5.4 years; 16 male patients, 39%). With respect to the prior examination, visual acuity significantly decreased from 0.57 ± 0.16 logarithm of the minimum angle of resolution (logMAR) ($\sim 20/70$ Snellen equivalents, range, 0.15–1.0 logMAR) to 1.66 logMAR ($\sim 20/900$, range, 1.20–2.30 logMAR; $P < 0.001$). The occurrence of SMHs peaked in April 2020, with an incidence rate of 1 SMH case per 79 scheduled patient-months (1.3%). This rate was significantly higher than the rates collected from all the other studied months (incidence rate ratio range, 3.21–4.92; *P* value range, 0.005–0.015) (Fig S1, available at www.ophtalmologyretina.org).

Although only 2 patients with SMHs (8.7%) had missed the scheduled appointments during the control periods, 6 patients (40%) presenting with large SMHs in April 2020 did not attend office visits or anti-VEGF treatments in the previous month ($P = 0.035$). In April 2020, the interval between the appearance of large SMHs and the last intravitreal anti-VEGF injection was significantly longer than the usual interval between 2 intravitreal anti-VEGF injections for this subset of patients (3.6 ± 0.8 vs. 1.9 ± 0.5 months; $P = 0.01$).

Complete demographic data and rates are reported in Table 1. Figure S2 (available at www.ophtalmologyretina.org) shows the weekly attendance to scheduled appointments and SMH incidence during the 3 analyzed periods.

This report reveals that a meaningful decrease in the attendance rate to our clinic was followed by an ominous increment of large SMHs during the early months of the COVID-19 pandemic. Several real-world studies have reported that poor adherence to treatment or strict follow-up can be responsible for worse visual outcomes in nAMD.^{5,6}

We hypothesize that nonattendance to scheduled appointments after the implementation of national lockdown might have partially contributed to the significant increase in the occurrence of large SMHs. Although this might be a plausible explanation, we acknowledge that a selection bias may exist because patients with SMHs are more prone to present because of the sudden worsening of central vision. However, the higher number of total hemorrhages in April 2020 and the elevated rate of nonattendance to office visits among SMH cases seem to support our hypothesis.

Our findings confirm that the COVID-19 pandemic is leaving the medical community with indirect consequences to address. This seems particularly true for nAMD, for which regular follow-

Table 1. Comparison of Weekly Visits, Weekly Intravitreal Treatments, and Submacular Hemorrhages between 2 Months during the Coronavirus Disease 2019 Outbreak and 4 Control Months

	Age (Mean ± SD)	Study Period		Control Periods			
		April 2020	March 2020	November 2019	October 2019	April 2019	March 2019
Weekly Visits	76.2 ± 6.3						
Scheduled, n (mean ± SD)		263.8 ± 29.4	259.3 ± 26.0	338.7 ± 30.9	375.3 ± 13.3	289.1 ± 54.2	357.1 ± 19.3
Attended, n (mean ± SD)		109.5 ± 28.13	98.3 ± 64.0	324.8 ± 27.5	356.5 ± 16.9	268.3 ± 64.9	327.1 ± 27.7
Attendance rate, %		41.5%	37.9%	95.9%	95.0%	92.8%	91.6%
Weekly Intravitreal Treatments	78.4 ± 7.2						
Scheduled, n (mean ± SD)		216.1 ± 41.8	197.1 ± 11.1	239.3 ± 13.4	231.2 ± 6.9	213.0 ± 35.3	222.0 ± 8.0
Attended, n (mean ± SD)		134.4 ± 31.0	108.4 ± 16.5	224.5 ± 9.5	219.4 ± 6.8	194.5 ± 28.7	206 ± 9.1
Attendance rate, %		62.2%	55.0%	93.8%	94.9%	91.3%	92.8%
SMHs	82.2 ± 5.4						
No. per month, n		15	3	6	6	5	6
Incidence rate (per scheduled visits)		1 per 79.1	1 per 389.0	1 per 254.0	1 per 281.5	1 per 260.2	1 per 267.8

SD = standard deviation; SMH = submacular hemorrhage.

up visits and intravitreal treatments are essential to maintain good vision and prevent serious complications. Ophthalmologists in the future will likely need to manage a higher number of complications, reorganize their clinical practice in observance of social containment measures, and possibly implement telemedicine programs introducing home-monitoring equipment.⁷

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Abbreviations and Acronyms:

COVID-19 = Coronavirus Disease 2019; **logMAR** = logarithm of the minimum angle of resolution; **nAMD** = neovascular age-related macular degeneration; **SMH** = submacular hemorrhage; **VEGF** = vascular endothelial growth factor.

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