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ORIGINAL PAPER

The negative impact of COVID-19 pandemic on age-related macular degeneration patients treated with intravitreal bevacizumab injections

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Abstract

Purpose COVID-19 emerged in the end of 2019 and was declared a worldwide pandemic shortly after. Social distancing and lockdowns resulted in lower compliance in intravitreal injections and office visits. We aimed to assess clinical outcomes among patients who missed these visits compared to those who arrived as planned.

Methods Patients who missed or were late to office visits or intravitreal injections were defined as non-adherent and were compared to adherent patients. Our main outcomes were the need for subsequent injections, mean change in best-corrected visual acuity (BCVA), and central macular thickness (CMT).

Results This study included 77 patients (24 adherent and 53 non-adherent). The mean BCVA remained stable during the study period for the adherent group ($p=0.159$) and worsened in the non-adherent group ($p<0.001$). Changes in CMT and maximum thickness were not significant for either group. A higher proportion of patients in the non-adherent group needed subsequent intravitreal injections (49% vs 20%, $p=0.014$).

Conclusion The findings demonstrate the negative implications of the COVID-19 pandemic and the effect of deferring bevacizumab injections among individuals with age-related macular degeneration. This emphasizes the importance of a scheduled follow-up, also during a pandemic.

Keywords AMD · COVID-19 · Bevacizumab · Injection · Loss of follow-up

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Introduction

The emergence of the coronavirus disease 2019 (COVID-19) pandemic in the beginning of 2020 has led to high morbidity and mortality rates. Daily activities have been severely impacted, and many limitations and restrictions imposed. The new reality forced

hospitals to limit their ambulatory activities, and ophthalmic clinics were no exception.

During the pandemic, the vision academy (an international group of retinal experts) published recommendations regarding managing ophthalmological disorders, to ensure patients' and physicians' safety, while preventing vision loss as much as possible [1]. Despite these measures, patient adherence to treatment and follow-up declined. Various reasons for such are fear of personal health, concerns about leaving home during the pandemic and arriving at a hospital, lack of clear guidelines, unavailability of a chaperone, and quarantine [2, 3].

Anti-vascular endothelial growth factor (VEGF) injections are routinely used for various causes of macular edema and macular neovascularization [4]. While intravitreal injections are a non-emergent activity, skipping or extending the interval between injections or follow-up visits can lead to severe vision loss, as commonly seen among individuals with age-related macular degeneration (AMD) [5, 6]. Large-scale studies, including HORIZON, PIER, EXCITE, CATT, and SEVEN-UP, demonstrated vision loss as a natural course of disease activity when the injection interval was extended beyond 1 month [7–10].

We aimed in this study to assess the ramifications of delayed AMD treatment and management. We compared visual acuity (VA) and macular anatomy between patients who missed intravitreal injections and follow-up visits and those who arrived as planned. After the lockdown was lifted, our patients eventually presented at the clinic at a full and standard capacity, and we were able to reassess their clinical status and present outcomes in the post-lockdown period.

Materials and methods

This was a single-center, retrospective, observational cohort study. Institutional review board (IRB) approval was obtained from Assuta-Samson Medical Center IRB Office of Human Protection. The study was conducted in compliance with the Health Insurance Portability and Accountability Act of 1996 and the Declaration of Helsinki.

Patients

Our study population was comprised of patients with neovascular-AMD who were scheduled to be treated or to visit our clinic during the COVID-19 lockdown. One eye was arbitrarily selected from each patient to follow.

Data were collected from patients' charts. The study population comprised patients who arrived at our retina clinic in the immediate six-week period after the lockdown (from May 10, 2020, to June 30, 2020) was lifted. Exclusion criteria were first-time presentation in our clinic, regardless of ophthalmological history; the absence of any scheduled visits for injection or follow-up during the lockdown; a history of ocular surgery; the use of intravitreal agents other than bevacizumab; and a known reason for vision loss other than AMD disease.

History taking included the reason for the delay in follow-up visits or injections. Best-corrected visual acuity (BCVA) using the logMAR scale [11], and central macular thickness (CMT) according to spectral-domain optical coherence tomography (SD-OCT) were analyzed. For both these measures, the data collected included current and previous follow-up, the last follow-up, the last type of injection, the date of injection, and whether a follow-up or treatment session was delayed due to a patient's cancellation during the lockdown period. Patients who arrived at all office visits and injections were categorized as adherent. Patients who missed or arrived late for an injection and those who came later than 10 days to follow-up visits were classified as non-adherent. We compared outcomes between the adherent and non-adherent groups. For each patient, we calculated differences in BCVA, CMT, and maximal retinal thickness between the first follow-up visit after the lockdown and the last follow-up visit before the lockdown.

Injection and OCT protocol

During the lockdown period, we continued to perform injections in the regular in-office setting, as has been standardized for eye care treatments. Every patient was assessed by the triage stand in the hospital entrance, for COVID-19 suspicion. After clearance, the patients proceeded to the waiting room before receiving an injection. The injections were scheduled at wide intervals between patients to limit

human-to-human contact and to maintain a 2-m distance between persons [1, 12].

Our team of ophthalmologists performed all the injections in the same designated room that was used before the pandemic. All the patients were treated with bevacizumab injections. Our method of injection is capped pro-re-nata (capped PRN) [13]. Office visits are routinely scheduled one month after injections. At each office visit, every patient was assessed clinically by the same retina specialist and was analyzed by SD-OCT (OCT-HS100, Canon Inc., Tokyo, Japan).

Outcome evaluation

We compared the adherent and non-adherent groups. Our primary outcomes were the need for subsequent intravitreal injections, the mean change from baseline in BCVA, and the mean change from baseline in CMT. For statistical purposes, BCVA measurements were converted from the Snellen chart to LogMAR. Only patients with a vision of at least counting fingers were included in the analyses related to VA. Secondary outcomes were the mean number of days from the last injection, the mean number of days late for follow-up visits, the mean number of previous injections, the presence of subretinal fluid (SRF), and baseline BCVA; and the predictive value of these parameters for deterioration of vision.

Deterioration of vision was defined as 0.1 logMAR drops of BCVA; an OCT thickness increase by 50 μm; evidence of new intraretinal fluid (IRF) or SRF; and clinical evidence of macular hemorrhage [14, 15]. The treatment was decided in the office for each patient individually by a retina specialist.

Statistical analysis

The statistical software SPSS version 25.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Statistical significance was set at $p<0.05$. The Mann–Whitney U test and Pearson's Chi-square test were applied for comparison of continuous and categorical data, respectively. Univariate and multivariate regression analysis was used to detect significant risk factors for deterioration of vision. Based on the univariate analysis, a stepwise multivariate linear regression model was employed to identify the factors that correlated significantly with BCVA at the most recent visit. The model comprised demographic parameters (i.e., age and sex) and clinical parameters that were expected to affect changes in BCVA. These parameters included BCVA at baseline, retinal fluid type, the number of injections prior to the study period, baseline OCT measurements (i.e., CMT and maximum thickness), delay from the scheduled visit, and the time elapsed since the last injection.

Results

A total of 77 eyes were included, of 77 patients, whose mean age was 79.33 years. Forty-five (58%) were females. The left eye was included in 56%. The mean follow-up was 159.16 ± 56.30 days.

At baseline, BCVA (logMAR) was 0.73 ± 0.6, CMT was 299.43 ± 113.7 microns, maximal retinal thickness was 368.73 ± 100.89 microns, and the mean previous number of injections was 7.9. Forty percent of the patients presented with combined IRF + SRF at baseline, 25% presented with no retinal fluid at baseline, 17% presented with only IRF, and 18% presented with only SRF.

Baseline characteristics regarding age, gender, the presence of retinal fluid or type, BCVA, OCT parameters, and a number of injections prior to the study period were similar between the groups (all $p>0.15$) (Table 1).

The adherent group included 24 patients, and the non-adherent group, 53. At baseline, 71% of the adherent patients and 77% of the non-adherent patients had retinal fluid. The most common type of retinal fluid was combined SRF + IRF: 42% in the adherent group and 40% in the non-adherent group ($p=0.863$). Mean baseline BCVA (logMAR) was 0.883 ± 0.700 and 0.728 ± 0.602 in the respective groups ($p=0.205$). The respective mean values for baseline CMT were 273.5 ± 69.74 and 318.79 ± 131.35 microns ($p=0.405$).

The mean gap from the scheduled visit was 6.38 ± 5.9 days in the adherent group and 71.62 ± 40.34 in the non-adherent group ($p<0.001$). Among the non-adherent group, 80% (42 patients) missed follow-up visits and 21% (11 patients) missed follow-up visits and intravitreal bevacizumab injections. Overall, 14 injections were missed; 82% (nine) patients missed one injection, 9% (one) missed two injections, and 9% (one) missed three injections.

Table 1 Baseline characteristics

	Adherent	Non-adherent	*p* value
Age (years) (Mean ± SD)	79.83 ± 7.01	79.34 ± 7.38	0.601
Female %	50%	62.2%	0.33
Baseline presence of retinal fluid, %	70.8	77.4	0.576
Baseline RF type			0.863
None (*n*, %)	7, 29.2	12, 22.6	
SRF (*n*, %)	3, 12.5	10, 18.8	
IRF (*n*, %)	4, 16.6	10, 18.8	
Combined—SRF + IRF (*n*, %)	10, 41.6	21, 39.6	
Baseline BCVA, logMAR (Mean ± SD)	0.883 ± 0.7	0.728 ± 0.602	0.205
Baseline CMT, microns (Mean ± SD)	273.50 ± 69.73	304.76 ± 117.19	0.405
Baseline max thickness, microns (Mean ± SD)	354.9 ± 101.041	372.83 ± 102.49	0.152
No. of previous injections	8.33 ± 5.723	7.94 ± 5.76	0.628

Table 2 Mean BCVA, CMT, and max retinal thickness change between the first visit after the lockdown and the last visit before the lockdown

	BCVA change, logMAR (Mean ± SD)	*p* value	CMT change, microns (Mean + SD)	*p* value	Max thickness change, microns (Mean + SD)	*p* value
Adherent	0.072 ± 0.24	0.159	22.58 ± 110.15	0.445	29.50 ± 122.04	0.110
Non-adherent	0.26 ± 0.49	< 0.001	0.74 ± 137.29	0.289	35.60 ± 167.48	0.347

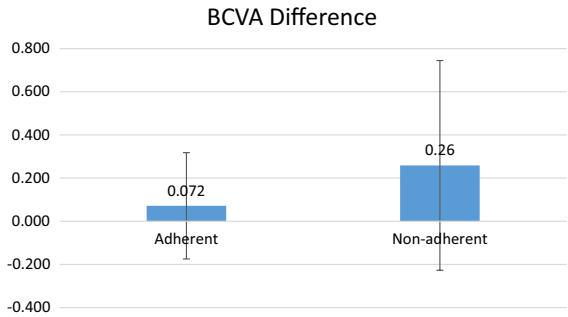

Fig. 1 BCVA change (logMAR, mean ± SD) between the first visit after the lockdown and the last visit before the lockdown

The mean BCVA remained stable during the study period for the adherent group (0.072 ± 0.24 logMAR change, $p = 0.159$) and worsened in the non-adherent group (0.26 ± 0.49 logMAR change, $p < 0.001$). Mean changes in CMT and maximum thickness were not significant for either group (Table 2, Fig. 1). A higher proportion of patients in the non-adherent group needed subsequent intravitreal injections (49% vs 20%, $p = 0.014$). The proportion of patients whose VA decreased by at least logMAR 0.1 was greater in the non-adherent than in the adherent group: 26 (49%) vs 6 (25%) ($p = 0.049$). In a stepwise multivariate linear regression model analysis, BCVA at baseline was the sole statistically significant predictive factor ($p < 0.001$). A logistic regression model found that delay from a scheduled visit significantly associated with deterioration of vision during the study period ($p < 0.001$). Other factors, including age, gender, the presence of retinal fluid at baseline, the number of previous injections, and baseline OCT parameters, were not significantly associated with deterioration of vision ($p > 0.14$). The type of retinal fluid at baseline also did not have a significant association with the risk of deterioration of vision.

Discussion

This study reviewed the impact of the COVID-19 pandemic on the anti-VEGF injection routine of individuals with AMD. The population who are at greater risk to develop more severe disease from COVID-19 infection share some characteristics with the

population with AMD, such as older age, diabetes, and other cardiovascular comorbidities. [5, 16].

Various barriers prevent adequate treatment adherence [17, 18]. The COVID-19 pandemic added more barriers; this resulted in further decline in treatments and follow-up visits [19].

We report that the COVID-19 pandemic resulted in reduced patient adherence to injections and office visits. Our findings support reports of loss of compliance during the COVID-19 period, concerning medical ophthalmological care and intraocular injections. Initial guidelines were established in the early period of the pandemic for managing intravitreal injection regimes during the pandemic, and recommendations were issued for ensuring the safety of the medical staff (Supplement Table 1). However, compliance remains a significant factor, which depends on patient characteristics [1, 3, 20, 21]. Wasser et al. demonstrated a 50% decline in intravitreal injections and loss of follow-up during the pandemic and specifically during a lockdown period [2]. Carnevali et al. showed a reduction of 91% in intravitreal injections compared to the same period in 2019 [22]. Campos et al. witnessed a 70% decline in patients' general adherence, to both treatment and follow-up visits. [3]

Neovascular AMD is known to be associated with significant visual loss and anatomical distortion [23]. When untreated, neovascular AMD is highly associated with poor prognosis; a mean visual loss of 1–3 lines was reported at three months from diagnosis and 3–4 lines by one year from diagnosis [5]. Cessation of treatment can lead to poor visual prognosis after 24 months, [24] thus mandating routine follow-up and immediate care for each scheduled visit and injection [4].

This study showed the negative impact of the decline in adherence. Among the non-adherent patients, the rate of deterioration of vision was 59.2% higher in the non-adherent than in the adherent group. The mean decline in BCVA was significant in the non-adherent group (0.26 ± 0.49 logMAR, $p < 0.001$) but not significant in the adherent group (0.072 ± 0.24 logMAR change, $p = 0.159$). The change in CMT, however, did not differ significantly between the groups. This discrepancy, of VA decline simultaneous with stable CMT, was previously reported in patients with AMD. Wickremasinghe et al. reported a similar finding for their cohort of 103 patients treated solely with ranibizumab for 12 months. [25] They found a poor correlation between VA decline and the presence of fluid; visible fluid on OCT was not found to be associated with episodes of VA loss. Anatomical findings are not always found to be in correlation with functional visual loss. The complexity of the pathophysiology of neovascular AMD and the limitation of OCT devices has been suggested as causes of the minor effect of SRF thickness and neurosensory retinal volume on VA [26]. Other charts for VA assessment were reported as more sensitive than Snellen charts and may result in different correlations with the anatomic findings [27]. Atrophy of the outer neurosensory retina was also reported to cause VA decline [28], without necessarily affecting central macular thickness. However, a specific explanation has yet to be found for such.

Considering the total cohort, the multivariate analysis showed BCVA at baseline as the only predictive factor for final BCVA; a positive correlation was shown between BCVA at the two points of time. Other variables at baseline (gender, baseline retinal fluid, the number of previous injections, baseline CMT, missed injections, and type of retinal fluid) did not predict BCVA decline. A 5-year follow-up of the CATT study found comparable results; worse baseline BCVA was a predictor of worse final BCVA [29]. In contrast, in a post hoc analysis of the HARBOR study, lower BCVA at baseline predicted greater BCVA gain after 12 months [30]. In a series by Chae et al., a correlation was not found between BCVA at the two points of time [31]. Similar to previous studies, we did not find gender to be a predictor of VA loss [30, 32]. The associations of a higher number of injections with the development of geographic atrophy and subsequent vision loss were previously reported [33]. In our cohort, however, these associations were not found.

Baseline retinal fluid, SRF, and IRF were also assessed as final BCVA predictors. Regillo et al. reported the presence of SRF at baseline as a predictor for higher VA gain after 12 months [30]. This finding, however, was not observed in our series. In addition, although a limited amount of SRF seems to be tolerable [34], the presence of IRF seems to be much more devastating [35]. Although 18% of our patients presented with only SRF, and 40% with combined SRF and IRF, declines in BCVA were witnessed with either type of retinal fluid or their combination.

Nonetheless, the type of retinal fluid was not found to be a predictable factor of final BCVA ($p=0.120$).

The period of non-adherence provided an opportunity to understand the consequences of patients not showing up for follow-up visits and intravitreal injections. Even before the pandemic, non-adherence was a major concern in all retinal diseases [17, 36]. Studies conducted prior to the pandemic demonstrated poor outcomes following even short delays in treatment. Borelli et al. reported the impact of treatment delay in AMD due to the COVID-19 pandemic. They showed negative impact on both anatomic and BCVA measures among all the patients who were treated with anti-VEGF agents [37–39]. Other studies also demonstrated the negative impact of declined compliance on several retinal diseases. Nonetheless, none described exclusively, the impact of the loss of bevacizumab injections in AMD (Supplement Table 2).

Our findings corroborate recent studies that demonstrated negative effects of non-adherence to treatment, including VA decline, new or increased retinal fluid, and retinal hemorrhages [39]. We found that delays in scheduled visits during the COVID lockdown were significantly associated with deterioration of vision during the study period (49% vs. 25%, $p=0.049$).

Our study is the first to show VA loss due to delay in follow-up visits. This corroborates the findings of studies that showed VA loss due to treatment delay or cancellation. Together, these data are important for clinicians, in that they elaborate the ramifications of non-adherence to treatment.

The short period of the lockdown facilitated assessing outcomes of missing injections and follow-up visits. Prior large-scale studies demonstrated visual loss (2.2–8 letters) as part of the natural course of AMD and following lower frequencies of injections [7–9, 40, 41]. The current study demonstrated the impact of a global pandemic on the treatment course of bevacizumab as monotherapy, for patients with AMD. In addition, this study enabled comparing outcomes between patients who received intravitreal injections as scheduled, to patients who missed follow-up visits and intravitreal injections. Moreover, previous studies compared outcomes of treatment with ranibizumab and aflibercept and did not compare monthly bevacizumab injections to an extended and irregular injection regimen during the COVID-19 pandemic. [9, 40, 42].

Our results demonstrated the importance of treatment adherence, as was noted in a recent meta-analysis. Compliance may be increased in various ways. One study showed that performing follow-up visits via telemedicine increased compliance of both follow-up visits and intravitreal injections [43]. Other studies demonstrated increased compliance to intravitreal injections and maintaining BCVA when the injection was considered together with an office visit [44]. To adjust to this new reality, ophthalmologists may need to find additional strategies to increase compliance. Remote follow-up visits and home treatments may provide some solution. Nowadays, the Amsler grid test can be done independently at home for self-follow-up. M-charts (Inami Co., Tokyo, Japan) may also be used to detect and follow metamorphopsia [45]. OCT can be done at home or at a nearby clinic, and the results can be sent to an ophthalmologist in a remote location. Recent evidence shows comparable image quality of home OCT and commercial devices [46], and injections may also be done at home, when the conditions are suitable [1].

Our study is limited by its retrospective design and the relatively small number of patients. In addition, it presents a relatively short follow-up period according to the lockdown period imposed in our country. However, a strength of the study is the focus on patients with similar characteristics, whose sole eye disease was AMD, and who were treated with bevacizumab.

In conclusion, the new reality enforcing social distancing and limiting personal contact, to mitigate the spread of COVID-19 disease, has led to reduced compliance in treatment and follow-up appointments. The COVID-19 pandemic may continue more than previously expected, consequent to the emerging virus variants. This study demonstrated the negative implications of the COVID-19 pandemic and the rapid effect of early delay in bevacizumab injections, in individuals with AMD. We were able to show a decline in VA during the COVID-19 pandemic within a relatively short period among patients who missed their treatment. Thereby, we hope our results will emphasize and increase awareness to the importance of scheduled follow-up visits, even during pandemics.

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Author contributions RA helped in designing, data collection, writing, editing; JP performed examination of patients, concept and design, editing; TY and NS contributed to data collection and editing; KW collected the data; AL helped in statistical analysis; AA was involved in concept and design, editing; AH helped in concept and design, editing, supervision.

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Data availability Data are available on the secured servers of Assuta-Samson Hospital.

Code availability Not applicable.

Declarations

Conflict of interest The authors have no conflicts of interest.

Ethical approval This study protocol was reviewed and approved by Assuta-Samson Hospital IRB, Approval Number 0117-20-AAA. The study has been granted an exemption from requiring written informed consent.

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