Ophthalmol Ther (2021) 10:935–945
https://doi.org/10.1007/s40123-021-00381-y

ORIGINAL RESEARCH

The Effect of Treatment Discontinuation During the COVID-19 Pandemic on Visual Acuity in Exudative Neovascular Age-Related Macular Degeneration: 1-Year Results

Martin Stattin · Daniel Ahmed · Alexandra Graf · Anna-Maria Haas · Stefan Kickinger · Michael Jacob · Katharina Krepler · Siamak Ansari-Shahrezaei

Received: July 7, 2021 / Accepted: July 23, 2021 / Published online: August 9, 2021

ABSTRACT

Introduction: To evaluate the effect of a 9-week treatment deferral due to healthcare restrictions caused by Austria's first governmental lockdown associated with the coronavirus disease 2019 (COVID-19) pandemic on visual acuity (VA) in eyes compromised by exudative neovascular age-related macular degeneration (nAMD) after 1 year.

Methods: Retrospective data collection of 98 eyes (98 patients) with a treatment discontinuation at a tertiary eye care center (Clinic Landstraße, Vienna Healthcare Group, Austria) between March 16 and May 4, 2020. Prior to the lockdown, patients received multiple intravitreal injections (IVI) of anti-vascular endothelial growth factor with a personalized treatment interval for 3 years on average and at least three IVI after the lockdown.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-021-00381-y.

M. Stattin · D. Ahmed · A.-M. Haas · S. Kickinger · M. Jacob · K. Krepler · S. Ansari-Shahrezaei
Karl Landsteiner Institute for Retinal Research and Imaging, Vienna, Austria

M. Jacob
e-mail: michael.jacob@gesundheitsverbund.at

M. Stattin · D. Ahmed · A.-M. Haas · S. Kickinger · K. Krepler · S. Ansari-Shahrezaei (✉)
Medical Retina Unit, Clinic Landstraße, Department of Ophthalmology, Vienna Healthcare Group, Juchgasse 25, 1030 Vienna, Austria
e-mail: siamak.ansarishahrezaei@gesundheitsverbund.at

M. Stattin
e-mail: martin.stattin@gesundheitsverbund.at

D. Ahmed
e-mail: daniel.ahmed@gesundheitsverbund.at

A.-M. Haas
e-mail: anna-maria.haas@gesundheitsverbund.at

S. Kickinger
e-mail: stefan.kickinger@gesundheitsverbund.at

K. Krepler
e-mail: katharina.krepler@gesundheitsverbund.at

A. Graf
Center for Medical Statistic, Informatics, and Intelligent Systems, Medical University of Vienna, Spitalgasse 23,
1090 Vienna, Austria
e-mail: alexandra.graf@meduniwien.ac.at

S. Ansari-Shahrezaei
Medical School, Sigmund Freud University Vienna, Campus Prater Freudplatz 3, 1020 Vienna, Austria

S. Ansari-Shahrezaei
Department of Ophthalmology, Medical University of Graz, Auenbruggerplatz 1, 8036 Graz, Austria

Results: When the treatment interval doubled to 117.6 ± 31.4 days in spring 2020, patients lost 2.2 ± 4.6 ETDRS letters ($p = 0.002$) on average before reinitiating therapy. In total, 4.1 ± 8.1 letters ($p < 0.0001$) were lost despite continuous individual re-treatment over the course of the next year. In a univariate analysis, the extended interval time remained statistically significant ($p < 0.0001$), indicating a larger VA reduction within intervals with increasing interval time in days.
Conclusion: The short-term treatment interruption had a persistent negative impact on the VA course of eyes under therapy after 1 year. Continuous therapy independent of the underlying treatment regimen remains of utmost importance in exudative nAMD. Our data should create awareness to regulators regarding future decisions despite the global pandemic.

PLAIN LANGUAGE SUMMARY

Age-related macular degeneration (AMD) is the leading cause of legal blindness in developed countries. Wet AMD refers to the existence of new vessel growth in the macular, the part of the retina with the highest concentration of photoreceptors and hence the best visual acuity. The gold standard therapy of wet AMD consists of repeated injections of an antibody against new vessel formation into the eye to stabilize the disease. The sudden break of a treatment regimen for an individual person has never been investigated as it is ethically not acceptable. The coronavirus disease 2019 (COVID-19) pandemic and its associated lockdown led to an emerging situation in spring, 2020. We were forced by governmental restrictions to minimize contact with the most vulnerable patient cohort—the elderly. As an initial consequence, the Medical Retina Unit of Department of Ophthalmology (Clinic Landstraße, Vienna Healthcare Group, Austria) postponed appointments of patients with only one eye afflicted by wet AMD. This study examined the effect of a short-term treatment deferral caused by the first national COVID-19 lockdown in eyes of patients with ongoing therapy of wet AMD in Austria. The break led to a persistent visual loss despite re-treatment, which was still evident after 1 year. Our findings provide further support for an adequate and permanent therapy of wet AMD and regard intravitreal injections as urgent standard of care. It should be taken into consideration by authorities in future pandemic planning.

Keywords: Age-related macular degeneration; Anti-vascular endothelial growth factor; Coronavirus disease 2019; Intravitreal injection; Lockdown; Pandemic

Key Summary Points
Why carry out this study?
The recent COVID-19 pandemic lockdown forced a treatment interruption in eyes with ongoing intravitreal anti-vascular endothelial growth factor (anti-VEGF therapy) of exudative neovascular age-related macular degeneration (nAMD).
It was unknown whether a short-term treatment discontinuation of eyes under previous therapy would have a negative impact on visual outcomes.
The negative effect—if detectable—could diminish over the course of 1 year.
The negative effect—if detectable—could depend on several factors other than the extended interval.
What was learned from the study?
The treatment deferral led to a significant visual loss after 1 year.
The extended interval was the only significant parameter related to the visual loss.
Our data provide further support of an urgent and ongoing therapy in active nAMD despite the global pandemic.
This study demonstrates the potential damage done when patients are forced to forego therapy.

INTRODUCTION

The pandemic named coronavirus disease 2019 (COVID-19) by the World Health Organization in February 2020, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became an inevitable matter of concern worldwide and affected all aspects of daily life [1, 2]. COVID-19 demanded quick adaptation and prompt decision-making in an emerging and rapidly evolving situation [3, 4]. On March 16, 2020, restrictions in public spaces were imposed as a result of the actions taken by the Austrian government to limit collateral damage. As an initial consequence, scheduled appointments of patients with unilateral exudative neovascular age-related macular degeneration (nAMD) for follow-up and treatment with intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) were postponed at the Medical Retina Unit of the Department of Ophthalmology (Clinic Landstraße, Vienna Healthcare Group, Karl Landsteiner Institute for Retinal Research and Imaging, Austria) until May 4, 2020. It was unknown whether a short-term treatment discontinuation would have an impact on the visual acuity (VA) course of eyes under previous therapy. Moreover, the VA loss—if detectable—could very well be temporary after reinitiating treatment.

The purpose of this study was to evaluate the effect caused by the governmental restrictions due to the first COVID-19 pandemic lockdown on the VA course in eyes with active nAMD after 1 year.

METHODS

This retrospective, observational case study was performed at a single center in Vienna. The study protocol adhered to the tenets of the Declaration of Helsinki. The Federal Hospitals Act §15a Abs. 3a states that approval from the Viennese ethics committee is not needed for this study design. All subjects provided informed consent to analyze their data retrospectively and hence to participate in the study at first presentation.

Patients

This study included patients with a unilateral diagnosis of macular neovascularization (MNV) including polypoidal MNV secondary to exudative nAMD under current treatment with serial IVI of two different anti-VEGF agents (aflibercept 2 mg, bevacizumab 1.25 mg) at the tertiary eye care center of the Clinic Landstraße (formerly named Rudolf Foundation Hospital, Vienna) for the past 3 years (1094.6 ± 828.3 days) on average [5]. All patients routinely underwent a comprehensive ophthalmic examination including best-corrected VA using the Early Treatment Diabetic Retinopathy Study chart at 4 m (ETDRS)—counting every correctly read letter—converted to Snellen, indirect slit-lamp biomicroscopy (Haag-Streit AG, Bern, Switzerland) with dilated pupils using 0.5% tropicamide and spectral domain-optical coherence tomography (SD-OCT; Zeiss Cirrus HD 4000, Carl Zeiss Meditec AG, Jena, Germany) imaging at each follow-up. The decision for treatment and its respective interval was made after the loading dose of three monthly IVI [6, 7]. Patients continued on a pro re nata regimen with individual visits and treatment as needed on the basis of the previously elaborated personal interval (see Fig. S1 in the electronic supplementary material for details). Only patients with a VA of 40 ETDRS letters (20/160 Snellen) or better in the affected eye at last follow-up of the pre-lockdown era were included in the study, who had an appointment within the time period of the first COVID-19-associated restrictions and who came back for a follow-up and treatment until March, 2021. The VA course of eyes with individual treatment intervals resulting in a different number of injections was surveyed over the next year. Only eyes with three IVI following the lockdown were included for evaluation. After that, eyes could be observed without injection according to the treatment protocol and still be included in the study. Exclusion criteria were eyes of patients with scheduled appointments without treatment over the past 6 months prior to the lockdown or without the necessity of ongoing treatment thereafter. Patients with a sudden onset of VA

deterioration in the affected eye and a subsequent urgent intervention (three patients with subretinal hemorrhage and straightforward surgery) were also excluded from further analysis to minimize the statistical bias in VA change. Meanwhile, additional measures were undertaken to reduce the risk of further loss to follow-up and guarantee the best safety profile for patients and staff [8–10].

Statistical Analysis

First, data were collected via charts of patients who missed an appointment between March 16 and May 4, 2020. The allocated interval between the two last consultations of each patient resulting in IVI treatment was compare to the rescheduled appointment and its delay. Then, data of all eyes receiving at least three consecutive IVI after reopening were analyzed until March, 2021. Descriptive statistics were calculated for all eyes as well as separately for the subgroups divided into different numbers of visits. Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized using absolute and percentage values. Univariate linear mixed regression models with patient as a random factor were performed to investigate factors potentially influencing the VA change such as age, sex, drug, total duration, missed interval, last interval, baseline VA, last measured VA, MNV subtype, number of visits, and number of IVI. To investigate the time course in detail, linear mixed regression models were performed for the difference in VA of each visit compared to the visit before as dependent variable and patient as a random factor. Since only one variable showed a significant result in the univariate analyses (interval time) in both analyses, no multivariate regression models were calculated. p values less than 0.05 were considered statistically significant and 95% confidence intervals (95% CI) were calculated for main findings. All analyses were performed using R, release 3.3.3.

RESULTS

For this retrospective data analysis, 98 patients were eligible for enrollment with a mean follow-up period of 1 year (376.9 ± 31.5 days) after treatment deferral and reinitiating therapy. A total of 572 IVI in 586 consultations were administered in the post-lockdown era. The number of visits corresponded to the number of IVI in 88 of 98 eyes (90%). The demographic data is listed in Table 1. The mean injection interval was extended to 117.6 ± 31.4 days from the planned interval of 56.5 ± 27.7 days because of the first COVID-19-associated lockdown and led to an immediate significant 2.2 ± 4.6 letters loss (95% CI − 3.552 to − 0.815; $p = 0.002$). The overall VA loss 1 year after the lockdown was calculated as 4.1 ± 8.1 letters (95% CI − 5.481 to − 2.744; $p < 0.0001$)

Table 1 Demographic data of all eyes compromised by exudative nAMD and affected by the COVID-19-associated lockdown with a 1-year follow-up

Total *n* (%)	**98 (100)**
MNV subtype (%)	
Type 1	77 (79)
Type 2	6 (6)
Type 3	4 (4)
Mixed type	7 (7)
Others[a]	4 (4)
Mean age, years ± standard deviation	77.7 ± 8.1
Sex	
Male	45
Female	53
Drug	
Bevacizumab	62
Aflibercept	36

nAMD neovascular age-related macular degeneration, *COVID-19* coronavirus disease 2019, *MNV* macular neovascularization

[a] Polypoidal lesion or not classified

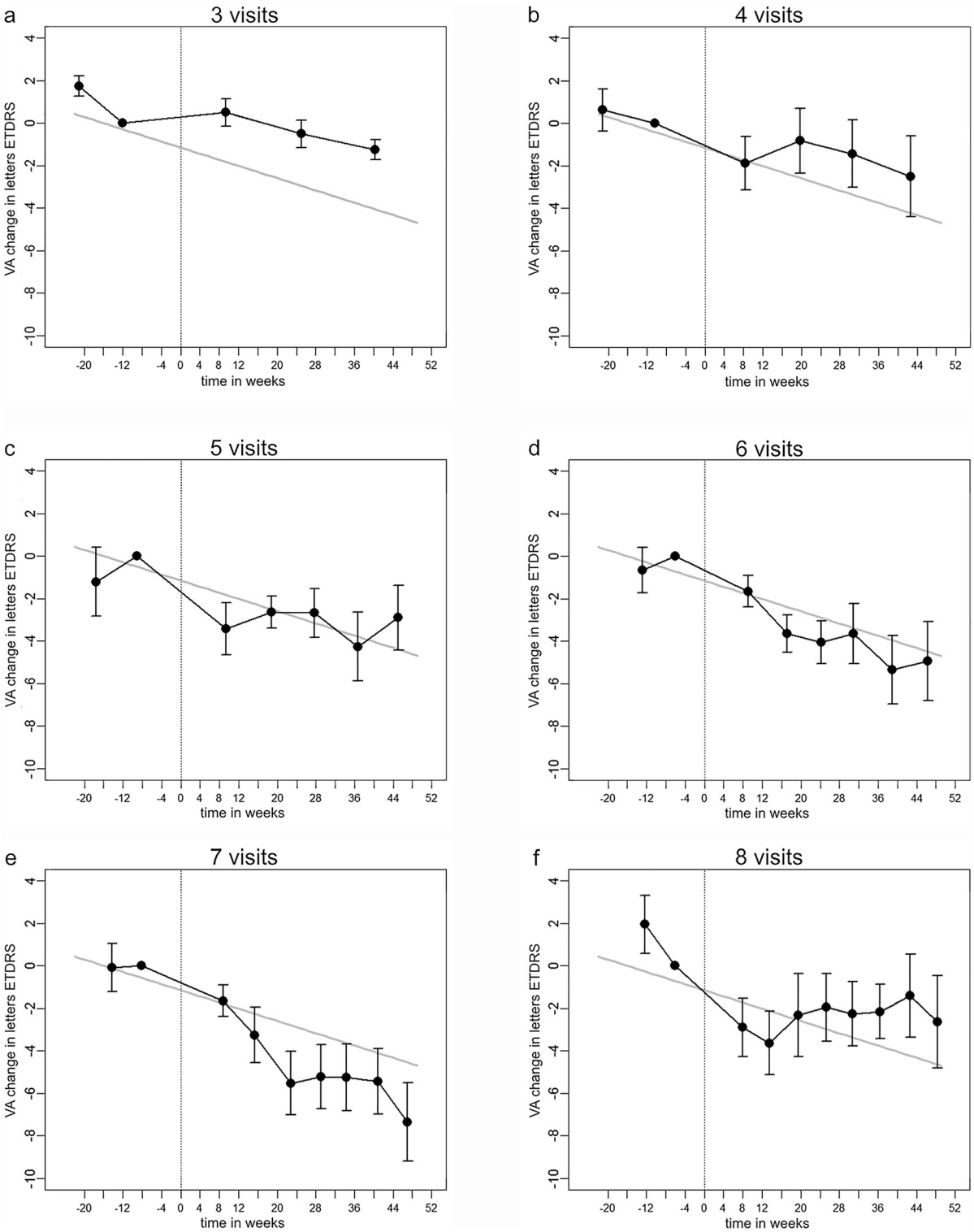
Table 2 VA development in ETDRS letters of all eyes and separated into subgroups according to the number of visits with the respective time intervals in days before and after the COVID-19-associated lockdown

	Total (n = 98)	V3 (n = 4)	V4 (n = 16)	V5 (n = 19)	V6 (n = 17)	V7 (n = 23)	V8 (n = 19)
Before COVID-19 lockdown							
First VA	70.1 ± 11.2	72.5 ± 7.5	67.7 ± 8.6	70.8 ± 10.4	67.7 ± 11.3	72.2 ± 13.1	70.6 ± 12.2
Total duration[a]	1094.6 ± 828.3	625.8 ± 322.6	1133.4 ± 959.0	1329.9 ± 868.8	981.8 ± 647.5	1053.8 ± 930.7	1075.7 ± 777.4
Penultimate VA	67.4 ± 13.4	78.0 ± 6.2	67.7 ± 13.1	67.2 ± 14.3	64.4 ± 14.5	68.3 ± 14.2	66.5 ± 11.8
Last interval	53.4 ± 23.3	63.3 ± 15.5	76.3 ± 24.1	59.7 ± 26.2	48.3 ± 17.6	42.3 ± 18.0	43.7 ± 15.4
Last VA	67.2 ± 12.9	76.3 ± 5.9	67.1 ± 11.6	68.4 ± 13.7	65.1 ± 13.7	68.4 ± 12.9	64.6 ± 13.5
Planned interval	56.5 ± 27.7	84.5 ± 55.5	72.1 ± 15.3	63.5 ± 23.6	42.1 ± 9.8	57.2 ± 37.7	42.5 ± 14.3
After COVID-19 lockdown							
Missed interval	61.1 ± 15	65.3 ± 7.9	59.0 ± 13.0	65.5 ± 22.2	63.1 ± 18.3	61.1 ± 8.4	55.6 ± 11.1
Actual interval	117.6 ± 31.4	149.8 ± 55.0	131.1 ± 16.1	129.0 ± 31.9	105.2 ± 18.4	118.3 ± 38.3	98.1 ± 20.6
First VA	65.0 ± 13.3	76.8 ± 5.9	65.2 ± 12.7	64.9 ± 14.8	63.4 ± 12.6	66.7 ± 12.9	61.7 ± 14.2
Treatment interval	56.7 ± 17.5	107.3 ± 7.2	78.6 ± 6.8	62.5 ± 7.0	52.2 ± 3.6	44.7 ± 3.4	40.4 ± 2.3
Total duration[b]	376.9 ± 31.5	367.0 ± 60.5	370.5 ± 20.5	379.0 ± 32.3	366.4 ± 17.4	386.3 ± 45.2	380.6 ± 16.4
Last VA	63.1 ± 14.7	75.0 ± 5.0	64.6 ± 15.0	65.5 ± 14.9	60.1 ± 14.9	61.0 ± 15.4	61.9 ± 14.7

VA visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *COVID-19* coronavirus disease 2019, *V3–V8* number of visits after the lockdown

[a] Time between first and last consultation before the lockdown

[b] Time between last consultation before the lockdown and last consultation after the lockdown; all values as mean ± standard deviation


a
3 visits
b
4 visits
c
5 visits
d
6 visits
e
7 visits
f
8 visits
VA change in letters ETDRS
time in weeks
4
2
0
-2
-4
-6
-8
-10
-20
-12
-4
0
4
8
12
20
28
36
44
52

◀**Fig. 1** Mean visual acuity (VA) change in Early Treatment Diabetic Retinopathy Study (ETDRS) letters of all patients (gray line) and separated into subgroups (**a**–**f**) according to the number of visits over time in weeks. The vertical dashed line illustrates the mean planned interval, which was postponed during the coronavirus disease 2019 (COVID-19) pandemic and its associated governmental lockdown. The VA change including standard error (vertical lines) of each subgroup for the penultimate and the last visit with its respective average time interval before the lockdown are compare to the VA change at each visit after restarting treatment over the course of 1 year

as compared to 2.9 ± 12.7 letters loss in 3 years (1094.6 ± 828.3 days) on average before the lockdown. A subanalysis of eyes with individual numbers of visits and their corresponding time intervals despite different numbers of IVI was performed (Table 2). A significant trend for the VA change with increasing time in days after treatment interruption was detected in the subgroup of patients with five visits (regression estimate [RE] − 0.009; 95% CI − 0.015 to − 0.003; $p = 0.005$), six visits (RE − 0.014; 95% CI − 0.020 to − 0.009; $p < 0.0001$), and seven visits (RE − 0.018; 95% CI − 0.023 to − 0.013; $p < 0.0001$) in contrast to the subgroup of patients with three visits (RE − 0.003; 95% CI − 0.006 to − 0.001; $p = 0.1171$), four visits (RE − 0.005; 95% CI − 0.011 to 0.001; $p = 0.118$), and eight visits (RE − 0.002; 95% CI − 0.008 to 0.003; $p = 0.4117$). The penultimate VA and last VA before the lockdown were plotted alongside the VA course thereafter to illustrate the VA decline in the overall cohort as well as in the subgroups (shown in Fig. 1). No significant influence of age (RE 0.047, 95% CI − 0.069 to 0.162; $p = 0.433$), sex (female vs. male RE 1.709, 95% CI − 0.119 to 3.536; $p = 0.07$), drug (aflibercept vs. bevacizumab RE 0.551; 95% CI − 1.369 to 2.469; $p = 0.576$), total duration before lockdown (RE − 0.001; 95% CI − 0.002 to 0.001; $p = 0.271$), missed interval (RE − 0.044; 95% CI − 0.105 to 0.018; $p = 0.169$), last interval (RE 0.032; 95% CI − 0.008 to 0.072; $p = 0.117$), baseline VA (RE − 0.031; 95% CI − 0.114 to 0.052; $p = 0.462$), last measured VA (RE − 0.014; 95% CI − 0.086 to 0.058; $p = 0.701$), MNV subtype ([type 2 vs. type 1 RE 1.271; 95% CI − 2.532 to 5.074; $p = 0.521$], [type 3 vs. type 1 RE 3.097; 95% CI − 1.528 to 7.722; $p = 0.199$], [mixed type vs. type 1 RE − 0.721; 95% CI − 4.267 to 2.826; $p = 0.696$], [others vs. type 1 RE 2.918; 95% CI − 1.703 to 7.538; $p = 0.226$]), number of visits (RE − 0.385; 95% CI − 1.006 to 0.235; $p = 0.227$), or number of IVI (RE − 0.396; 95% CI − 0.987 to 0.196; $p = 0.193$) on the VA loss was observed. In the univariate linear mixed regression models with VA change between visits as dependent variable, only interval time remained statistically significant (RE − 0.034; 95% CI − 0.033 to − 0.013; $p < 0.0001$) indicating a larger VA reduction within intervals with increasing interval time in days. No significant influence of the number of visits (RE − 0.034, 95% CI − 0.269 to 0.200; $p = 0.775$) or the number of IVI (RE − 0.058; 95% CI − 0.279 to 0.162; $p = 0.604$) on the VA change within the treatment intervals was detected.

DISCUSSION

This study evaluated the persistent negative effect of a governmental lockdown and its associated restrictions during the COVID-19 episode on care for patients with only one eye afflicted with exudative nAMD. The interval between two injections doubled to 117.6 days mainly as a result of reduced patient volumes and intensified safety procedures. The VA course remained at a lower level and even decreased another 1.9 letters ($p = 0.0062$) 1 year after treatment suspension. In total, the number of visits ($p = 0.227$) or IVI ($p = 0.193$) had no influence on the VA course. Subgroups with a different need for re-treatment were investigated independently. All eyes received at least three IVI after the lockdown. Most eyes required more injections over the course of 1 year but still suffered from a VA loss (Fig. 1). Our data conform with a recently published report of preliminary results for adherence to intravitreal treatment of macular diseases, rating only a long treatment interval (more than 3 months) as nonurgent [11]. Similar 6-month results were extracted from a data registry, which stated that VA remained stable if re-treatment interval was

extended by not more than 10–12 weeks [12]. Another study group associated unintended lapses over 3 months with poor functional and structural outcomes for patients with nAMD, especially in unstable clinical courses [13]. In our study cohort, four eyes with a long treatment interval before the lockdown did not experience a persistent VA loss due to the extended interval (Table 1 V3 and Fig. 1a). A Chinese study investigated the 6-month VA outcomes of a treatment suspension with intravitreal anti-VEGF due to the COVID-19 pandemic regardless of the underlying disease [14]. The most significant negative effect was detected in nAMD. Less severe adverse sequelae were attributed to macular edema secondary to diabetes and retinal vein occlusions. An Italian study group recently evaluated the effects of COVID-19 and its restrictions on short-term VA outcomes of eyes with nAMD and found proof of significant worsening [15]. In France, a comparable patient cohort (116 eyes in 106 patients) was analyzed for differences in VA and OCT findings after postponing treatment for nAMD [16]. They also related the negative short-term effect on VA to the treatment interruption. Data records of a small British patient cohort (n = 17) with a mean treatment delay of 47 days (median 26 days) showed no significant VA loss as compared to the latter year [17]. A South Korean group showed marked VA deterioration after discontinuing treatment with a follow-up of 24 months in a different setting [18]. Soares et al. [19] recently published data on eyes under anti-VEGF injections that were lost to follow-up for a mean of 12 months and concluded that the recovery would only be partially after re-treatment. As an initial consequence, a model calculation of the study cohort based on the long-term VA course of untreated eyes was performed to estimate the effect of the installed measures (unpublished results). The model was compare to the real-life outcomes before restarting treatment. The estimated VA loss was borderline significantly higher as compared to the effective VA loss, which was likely due to the preceding treatment as well as the applied model. At that time, it was unknown if the measured data was reliable as no similar model on short-term treatment discontinuation was available. The present study investigated eyes under permanent and adequate therapy for more than 3 years on average, which were hence forced to forego their treatment for more than 2 months. A significant VA loss in spite of ongoing treatment remained 12 months later. The Austrian government installed two more lockdowns starting in November, 2020 and called upon healthcare regulators to impose new restrictions to reduce numbers of patients in hospitals [3]. Our data indicated that intravitreal anti-VEGF injections should be considered as an urgent treatment for patients.

The administered drug, the total treatment duration before the lockdown, the MNV subtype, the initial VA, and the last VA before the lockdown had no significant impact on the VA course thereafter. Eyes with a low VA (< 20/160 Sn) at the onset of the restrictions were excluded in order to establish VA development in both directions—negative and positive. It was well known that eyes with very low vision could rarely lose VA because of the "floor effect" [20, 21]. On the other hand, eyes with good vision had a limited potential to gain VA and if so, the benefit would only be temporary. Many pivotal 12-month trials showed a VA gain after initiating treatment with an undulated course based on the underlying regimen and IVI interval, independent of the administered drug [22–26]. The initial VA gain could be sustained by different therapeutic approaches for a prolonged period as long as the treatment was continued [27–29]. Arguably, the therapeutic effect faded once treatment was suspended over a certain time period, but could likely recover when treatment was restarted. That said, the interval extension beyond the planned interval remained the only significant variable attributed to the VA loss of eyes in need of therapy after 1 year ($p < 0.0001$). The healthcare restrictions associated with the first Austrian COVID-19 lockdown as applied at our institution helped to understand this phenomenon as no comparable analysis on short-term treatment discontinuation in exudative nAMD with a 1-year follow-up exists to date. Our findings contribute to the current understanding that the average eye that is compromised by active

exudative nAMD requires an adequate and ongoing therapy.

Limitations of this study were attributed to its retrospective design and its bias in terms of patient selection. All included patients showed 40 ETDRS letters (20/160) or better in the affected eye when the treatment discontinuation was determined. Thus, our results may not be true for patients with less VA. Co-existing fibrosis at the time of recruitment was not investigated, nor was it an exclusion criterion in case of active disease. Mixing different therapeutic agents and switching treatment regimen were not exclusion criteria before the lockdown. The general lockdown enforced by the Austrian government and the cessation of care as executed at the Clinic Landstraße was unique and not comparable to strategies in other countries [30–33]. Patients affected by the restrictive measures may have missed one or more injections depending on their individual interval, which was not analyzed separately. Therefore, no conclusions about a prolonged treatment deferral or a series of missed IVI could be drawn. Such questions may be answered by way of a prospective trial. For example, the study did not pursue VA behavior of a comparable cohort under continuous therapy.

CONCLUSIONS

This study provides novelty as it supports further evidence for an urgent and ongoing treatment with intravitreal anti-VEGF for MNV secondary to exudative nAMD, regardless of the treatment regimen. Its findings should be taken into consideration by authorities in future pandemic planning. Amidst multiple lockdowns to come, it remains more important than ever to demonstrate the potential damage done when patients are forced to forego therapy.

ACKNOWLEDGEMENTS

Funding. This research was performed as part of the employment of the authors, namely the Clinic Landstraße and the Karl Landsteiner Institute for Retinal Research and Imaging. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The journal's Rapid Service Fees were funded by the authors.

Prior Presentation. The paper has not been published previously and is not under consideration elsewhere. The authors have not published or submitted any related papers from this study. Neither was the paper presented at a meeting. Publication is approved by all authors as well as the responsible authorities.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Martin Stattin is the lead author and guarantor: conception, design, data acquisition, writing, interpretation of data, original draft preparation; Daniel Ahmed, Anna-Maria Haas, Stefan Kickinger, Michael Jacob: data acquisition, formal analysis and interpretation of data, draft of the article; Alexandra Graf: statistical analysis and interpretation of data, draft of the article; Katharina Krepler: resources, thorough revision of the article; Siamak Ansari Shahrezaei: conception, final draft preparation, critical revision. All authors read and approved the final version of the manuscript.

Disclosures. Martin Stattin, Daniel Ahmed, Anna-Maria Haas, Stefan Kickinger, Michael Jacob, Alexandra Graf, Katharina Krepler, and Siamak Ansari Shahrezaei declare that they have no conflict of interest related to this submission.

Compliance with Ethical Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Federal

Hospitals Act §15a Abs. 3a states that approval from the Viennese ethics committee is not needed for this study design. All subjects provided informed consent to analyze their data retrospectively and hence to participate in the study at first presentation. No identifying information is included in the manuscript.

Data Availability. Martin Stattin and Siamak Ansari-Shahrezaei had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.

2. Coronavirus. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Updated 20 Apr 2021. Accessed 16 May 2020.

3. Coronavirus - Aktuelle Maßnahmen. https://www.sozialministerium.at/Informationen-zum-Coronavirus/Neuartiges-Coronavirus-(2019-nCov).html. Updated 20 Apr 2021. Accessed 19 Apr 2020.

4. Gemeinsam gegen das Coronavirus. https://www.oesterreich.gv.at/public.html. Updated 5 Feb 2021. Accessed 28 Apr 2020.

5. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data: consensus on neovascular age-related macular degeneration nomenclature study group. Ophthalmology. 2019;127(5):616–36. https://doi.org/10.1016/j.ophtha.2019.11.004.

6. Stattin M, Forster J, Graf A, Ahmed D, Krebs I, Ansari-Sharezaei S. Five-year outcomes of a personalized pro re nata treatment regimen with anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Acta Ophthalmol. 2019;97(1):e131–3. https://doi.org/10.1111/aos.13840.

7. Stattin M, Forster J, Ahmed D, et al. Seven-year visual and anatomical outcomes of intravitreal vascular endothelial growth factor inhibition for neovascular age-related macular degeneration. J Ophthalmol. 2020;2020:8345850. https://doi.org/10.1155/2020/8345850.

8. Borrelli E, Sacconi R, Querques L, et al. Taking the right measures to control COVID-19 in ophthalmology: the experience of a tertiary eye care referral center in Italy. Eye. 2020;34(7):1175–6. https://doi.org/10.1038/s41433-020-0880-6.

9. The Lancet. COVID-19: protecting health-care workers. Lancet. 2020;395(10228):922. https://doi.org/10.1016/S0140-6736(20)30644-9.

10. Seitzman GD, Doan T. No time for tears. Ophthalmology. 2020;127(7):980–1. https://doi.org/10.1016/j.ophtha.2020.03.030.

11. Viola F, Milella P, Pozzo Giuffrida F, Ganci S, Invernizzi A. Impact of coronavirus disease pandemic on intravitreal injections treatment for macular diseases. Report from a referral hospital in Milan. Retina. 2021;41(4):701–5. https://doi.org/10.1097/IAE.0000000000002941.

12. Teo KYC, Nguyen V, Barthelmes D, Arnold JJ, Gillies MC, Cheung CMG. Extended intervals for wet AMD patients with high retreatment needs: informing the risk during COVID-19, data from real-world evidence. Eye. 2020;25:1–9. https://doi.org/10.1038/s41433-020-01315-x.

13. Sekeroglu MA, Kilinc Hekimsoy H, Horozoglu Ceran T, Doguizi S. Treatment of neovascular age related macular degeneration during COVID-19 pandemic: the short term consequences of

unintended lapses. Eur J Ophthalmol. 2021. https://doi.org/10.1177/11206721211010613.

14. Yang KB, Feng H, Zhang H. Effects of the COVID-19 pandemic on anti-vascular endothelial growth factor treatment in China. Front Med (Lausanne). 2020;7: 576275. https://doi.org/10.3389/fmed.2020.576275 (eCollection 2020).

15. Borrelli E, Grosso D, Vella G, et al. Short-term outcomes of patients with neovascular exudative AMD: the effect of COVID-19 pandemic. Graefes Arch Clin Exp Ophthalmol. 2020;258(12):2621–8. https://doi.org/10.1007/s00417-020-04955-7.

16. Yeter DY, Dursun D, Bozali E, Ozec AV, Erdogan H. Effects of the COVID-19 pandemic on neovascular age-related macular degeneration and response to delayed Anti-VEGF treatment. J Fr Ophtalmol. 2021;44(3):299–306. https://doi.org/10.1016/j.jfo.2021.02.001.

17. Rahimzadeh M, Muniraju R, Izadi S. Effect of COVID-19 pandemic on anti-VEGF treatment of medical retinal conditions. Physician. 2021;3:1–10. https://doi.org/10.38192/1.6.3.10.

18. Kim JH, Chang YS, Kim JW. Natural course of patients discontinuing treatment for age-related macular degeneration and factors associated with visual prognosis. Retina. 2017;37:2254–61. https://doi.org/10.1097/IAE.0000000000001494.

19. Soares RR, Mellen P, Garrigan H, et al. Outcomes of eyes lost to follow-up with neovascular age-related macular degeneration receiving intravitreal anti-vascular endothelial growth factor. Ophthalmol Retina. 2020;4(2):134–40. https://doi.org/10.1016/j.oret.2019.07.010.

20. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology. 2014;121(5):1092–101.

21. Pedrosa AC, Reis-Silva A, Pinheiro-Costa J, et al. Treatment of neovascular age-related macular degeneration with anti-VEGF agents: retrospective analysis of 5-year outcomes. Clin Ophthalmol. 2016;10:541–6.

22. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897–908. https://doi.org/10.1056/NEJMoa1102673.

23. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology. 2011;118(4):663–71.

24. IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology. 2012;119(7):1399–411.

25. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. Retina. 2013;33(7):1351–8.

26. Danyliv A, Glanville J, McCool R, Ferreira A, Skelly A, Jacob RP. The clinical effectiveness of ranibizumab treat and extend regimen in nAMD: systematic review and network meta-analysis. Adv Ther. 2017;34(3):611–9.

27. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388–98. https://doi.org/10.1016/j.ophtha.2012.03.053.

28. Peden MC, Suñer IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. Ophthalmology. 2015;122(4):803–8.

29. Berg K, Roald AB, Navaratnam J, Bragadóttir R. An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration. Acta Ophthalmol. 2017;95(8):796–802. https://doi.org/10.1111/aos.13522.

30. Korobelnik JF, Loewenstein A, Eldem B, et al. Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic. Graefes Arch Clin Exp Ophthalmol. 2020;258:1149–56. https://doi.org/10.1016/j.ophtha.2020.03.030.

31. COVID-19: Clinical Eye Care. RANZCO. https://ranzco.edu/home/covid-19-information/clinical-eye-care/. Updated 9 Mar 2021. Accessed 19 Apr 2020.

32. IVT - Epidémie au Covid-19. SFO-online - Société Française d'Ophtalmologie. https://www.sfo-online.fr/covid-19-infos. Updated 3 Nov 2020. Accessed 7 May 2020.

33. New recommendations for urgent and nonurgent patient care. American Academy of Ophthalmology. https://www.aao.org/headline/new-recommendations-urgent-nonurgent-patient-care. Updated 17 Apr 2020. Accessed 18 Mar 2020.