



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

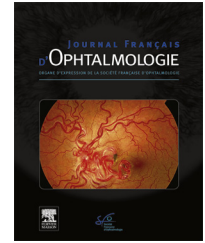


Disponible en ligne sur

**ScienceDirect**  
www.sciencedirect.com

Elsevier Masson France

**EM|consulte**  
www.em-consulte.com



ORIGINAL ARTICLE

# The importance of monitoring wet age-related macular degeneration patients during Coronavirus disease 19 pandemic: A retrospective study of assessment of functional and structural outcomes

*L'importance de la surveillance des patients atteints de dégénérescence maculaire liée à l'âge humide pendant la pandémie à coronavirus 19 : une étude rétrospective de l'évaluation des résultats fonctionnels et structurels*

G.N. Tsiropoulos<sup>a,b,c</sup>, R. Vallee<sup>a,d</sup>, D. Gallo Castro<sup>a,b</sup>,  
A. Ambresin<sup>a,b,e,\*</sup>

<sup>a</sup> Swiss Visio Montchoisi, avenue du Servan 38, 1006 Lausanne, Switzerland

<sup>b</sup> RétinElysée, Ophthalmology Center, avenue d'Ouchy 14, 1006 Lausanne, Switzerland

<sup>c</sup> Aristotle University of Thessaloniki (A.U.Th), Department of Health Sciences, Medical School, Thessaloniki, Greece

<sup>d</sup> Laboratory of Mathematics and Applications (LMA) CNRS 7348, Data Analysis and Computations Through Imaging Modeling Mathematics (DACTIM team) University of Poitiers, 15, rue de l'Hôtel-Dieu, TSA 71117, 86000 Poitiers, France

<sup>e</sup> University of Lausanne (UNIL), Faculty of Biology and Medicine, 1015 Lausanne, Switzerland

Received 27 January 2022; accepted 5 May 2022

Available online 6 July 2022

## KEYWORDS

Anti-vascular endothelial growth factor;

## Summary

**Objectives.** – Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the gold standard treatment for wet age-related macular degeneration (wet AMD). Coronavirus disease 2019 (COVID-19) has led to the cancellation of many scheduled intravitreal anti-VEGF injection visits. We compared the functional and structural visual outcomes of wet AMD patients who did not adhere to their planned intervals (group 1) with those who did (group 2).

\* Corresponding author at: Swiss Visio Montchoisi, avenue du Servan 38, 1006 Lausanne, Switzerland.  
E-mail address: [AAmbresin@swissvisio.net](mailto:AAmbresin@swissvisio.net) (A. Ambresin).

Wet age-related macular degeneration; Coronavirus disease 2019; Anti-VEGF; Wet AMD; COVID-19

**Methods.** – Wet AMD patients of Swiss Visio Montchoisi and RétinElysée were included. Best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) changes between their first visit after the end of the first national lockdown in Switzerland (27 April 2020, first post-lockdown visit) and their last visit before the beginning of the first national lockdown in Switzerland (13 March 2020, last pre-lockdown visit) were assessed. The BCVA outcome was defined as unfavorable when there was a loss of  $\geq 5$  ETDRS letters in the first post-lockdown visit compared to the BCVA at last pre-lockdown visit. The OCT outcome was defined as unfavorable when there was an increase in at least one of the parameters, intraretinal fluid (IRF), subretinal fluid (SRF), or pigment epithelial detachment (PED), at the first post-lockdown visit compared to the last pre-lockdown visit.

**Main results.** – Group 1 (89 patients, 109 eyes) had a 13.41% greater rate of unfavorable BCVA outcomes and a 38.27% greater rate of unfavorable OCT outcomes than group 2 (96 patients, 122 eyes) ( $P=0.04$ ,  $P<0.0001$ , respectively). Multivariate analysis showed that the more the patients deviated from their programmed injections and the higher the BCVA pre-lockdown, the higher the rate of unfavorable BCVA outcomes ( $P=0.03$  and  $P=0.02$ , respectively). OCT outcomes were not a predictive factor for an unfavorable BCVA outcome.

**Conclusions.** – The cancellation of many intravitreal anti-VEGF injection appointments resulted in worse functional and structural outcomes in wet AMD patients. The COVID-19 pandemic led many patients to refrain from their routine intravitreal anti-VEGF injection appointments, allowing us to analyze the role of designated intervals in the treatment of wet AMD. During any future lockdown due to COVID-19 or similar circumstances, continuity of care for wet AMD patients should be maintained.

© 2022 Elsevier Masson SAS. All rights reserved.

## MOTS CLÉS

Anti-facteur de croissance endothélial vasculaire ; Dégénérescence maculaire liée à l'âge humide ; Maladie à coronavirus 2019 ; Anti-VEGF ; DMLA ; COVID-19

## Résumé

**Objectifs.** – Les injections intravitréennes d'anti-facteur de croissance vasculaire endothélial (anti-VEGF) constituent le traitement de référence de la dégénérescence maculaire liée à l'âge (DMLA). La maladie à coronavirus 2019 (COVID-19) a entraîné l'annulation de nombreuses visites programmées. Nous avons comparé les résultats visuels et structurels des patients atteints de DMLA qui n'ont pas respecté les intervalles prévus (groupe 1) à ceux qui les ont respectés (groupe 2).

**Méthodes.** – Les patients atteints de DMLA de notre clinique ont été inclus. La meilleure acuité visuelle corrigée (BCVA) et les changements par tomographie en cohérence optique (OCT) entre leur première visite après la fin du premier confinement national en Suisse (27 avril 2020, première visite post-confinement) et leur dernière visite avant le début du premier confinement national en Suisse (13 mars 2020, dernière visite pré-confinement) ont été évalués. Le résultat de la BCVA était défavorable en cas de perte de  $\geq 5$  lettres ETDRS lors de la première visite post-confinement par rapport à la valeur de BCVA de la dernière visite pré-confinement. Le résultat de l'OCT était défavorable lorsqu'il y avait une augmentation d'au moins un des éléments suivants : liquide intrarétinien (IRF), liquide sous-rétinien (SRF) ou décollement de l'épithélium pigmentaire (PED) lors de la première visite post-confinement par rapport à la dernière visite pré-confinement.

**Résultats principaux.** – Le groupe 1 (89 patients, 109 yeux) présentait un taux d'évolution défavorable de la BCVA de 13,41 % et un taux d'évolution défavorable de l'OCT de 38,27 % supérieurs à ceux du groupe 2 (96 patients, 122 yeux) ( $p=0,04$ ,  $p<0,0001$ , respectivement). L'analyse multivariée a montré que plus les patients s'écartaient des injections programmées et plus la BCVA était élevée avant le confinement, plus le taux de résultats de BCVA défavorables était élevé ( $p=0,03$  et  $p=0,02$ , respectivement). Le résultat de l'OCT n'était pas un facteur prédictif d'un résultat défavorable de la BCVA.

**Conclusion.** – L'annulation de nombreux rendez-vous d'injections intravitréennes d'anti-VEGF a entraîné une détérioration des résultats fonctionnels et structurels chez les patients atteints de DMLA humide. Lors d'un prochain confinement dû au COVID-19, la continuité des soins pour les patients atteints de DMLA devra être maintenue.

© 2022 Elsevier Masson SAS. Tous droits réservés.

## Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in patients over the age of 65 years in Western populations [1,2]. Early or intermediate AMD, and late AMD have a prevalence of 25.3% and 2.4%, respectively, in Europeans over 60 years old, while the incidence of any late AMD in Europe is estimated to be 1.4 per 1000 individuals [3]. The most common form of AMD, dry AMD, represents 90% of AMD cases [4,5], is characterized by permanent central vision loss due to the slow apoptosis of RPE, neuroretina and choriocapillaris, and has no effective treatment [6]. The wet, or exudative, form of AMD, also known as neovascular AMD (nAMD), is characterized by photoreceptor damage due pathological neovascularisation, and represents 10% of AMD cases [4–6]. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the gold standard treatment for wet AMD [7]. Due to its chronic nature, intravitreal injections should be performed repeatedly over individually planned intervals for maintenance of visual acuity. At our institution, we use the “observe and plan” regimen [8], a modified version of the “treat and extend” regimen [9], in which the interval is planned and periodically adjusted according to disease activity based on visual acuity and anatomical parameters obtained from optical coherence tomography (OCT).

The appearance of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has changed the routine clinical practice in all medical fields [10], including ophthalmology [11,12]. Increasing evidence suggests that patients avoid scheduled intravitreal anti-VEGF injection visits for the treatment of their nAMD due to fear of COVID-19 [13]. This adds to the complexity of the management of patients with nAMD, a condition that can lead to permanent vision loss if not treated regularly with intravitreal injections [14,15]. Worldwide retinal expert committees have recommended that ophthalmologists cease providing any treatments other than urgent or emergent care [11,12]. Intravitreal injections are considered an urgent treatment modality that should be maintained [16,17]; therefore, our centre has contacted patients during confinement and urged them to attend their planned appointments for injections, which were performed in the operation room with all required measures taken to ensure protection from COVID-19. Still, some patients refused or were unable to visit. COVID-19 pandemic was a unique circumstance, which led many patients to refrain from their routine intravitreal anti-VEGF injection appointments, allowing us to evaluate the role of designated intervals in the treatment of patients with wet AMD. The main objective of this study was to compare the functional and structural visual outcomes of patients who did not adhere to their planned intravitreal anti-VEGF injection intervals (group 1) with those who did (group 2).

## Materials and methods

### Study design and ethical approval

This study was based on the reuse of data collected from patients with nAMD treated at RétinElysée and Swiss Visio

Montchoisi in Lausanne, Switzerland. The best-corrected visual acuity (BCVA) data and OCT assessments of the last pre-confinement visit and the first post-confinement visit of each patient were used in the analysis. We defined the term ‘last pre-confinement visit’ as the last visit before the beginning of the first national confinement in Switzerland (13 March 2020) when both BCVA and OCT assessments were performed. Similarly, we defined the term ‘first post-confinement visit’ as the first visit after the end of the first national confinement in Switzerland (27 April 2020), when both BCVA and OCT assessments were performed. This study adhered to the Declaration of Helsinki and its amendments and was approved by the Swiss Ethics Committee (approval number: 2020-01912) [18].

### Study participants

Patients diagnosed with nAMD of any type (I, II, or III) who received intravitreal anti-VEGF injections both before and after the period of confinement due to the COVID-19 pandemic, were included in this study after providing informed consent. We excluded patients who received intravitreal anti-VEGF injections for retinal pathologies other than nAMD (e.g., central retinal vein occlusion, branch retinal vein occlusion) or for whom BCVA measurements or OCT photographs either before or after confinement were unavailable. The BCVA measurements were reported in Early Treatment Diabetic Retinopathy Study (ETDRS) letters [19]. The participants were classified into two groups, as follows: group 1 (non-respected-interval group) included patients who missed at least one of their scheduled intravitreal anti-VEGF injections during the confinement period, and group 2 (respected-interval group) included patients who did not miss any scheduled intravitreal anti-VEGF injections during the confinement period. The primary endpoints of the study were BCVA and OCT outcomes. The BCVA outcome was a dichotomous variable with two possible values: a favourable BCVA outcome (a loss of < 5 ETDRS letters in the first post-confinement visit compared to the BCVA value of the last pre-confinement visit, same post-confinement and pre-confinement BCVA values, or an increase in the post-confinement BCVA value) or an unfavourable BCVA outcome (a loss of  $\geq$  5 ETDRS letters in the first post-confinement visit compared to the BCVA value of the last pre-confinement visit). For the OCT outcome, three factors were analysed during the evaluation of the OCT photographs: (i) change in intraretinal fluid (IRF), (ii) change in subretinal fluid (SRF), and (iii) detection of pigment epithelial detachment (PED). These factors were evaluated manually. PED modification was considered as presence of fluid under PED, which is an indicator of wet AMD activity. The machine used for the OCT was the Heidelberg Spectralis OCT and the scan pattern that was used was the following: 97 sections, 60 microns, 20° × 20°, Art 10 frames, High Speed. IRF, SRF and PED in the OCT photograph of the first post-confinement visit were compared with the IRF, SRF and PED in the OCT photograph of the last pre-confinement visit for each patient. If IRF was present in the OCT photograph of the first post-confinement visit but was absent in the OCT photograph of the last pre-confinement visit for a respective patient, then the change in IRF was unfavourable and therefore the OCT outcome was unfavourable as a whole. If IRF was absent in the OCT photo-

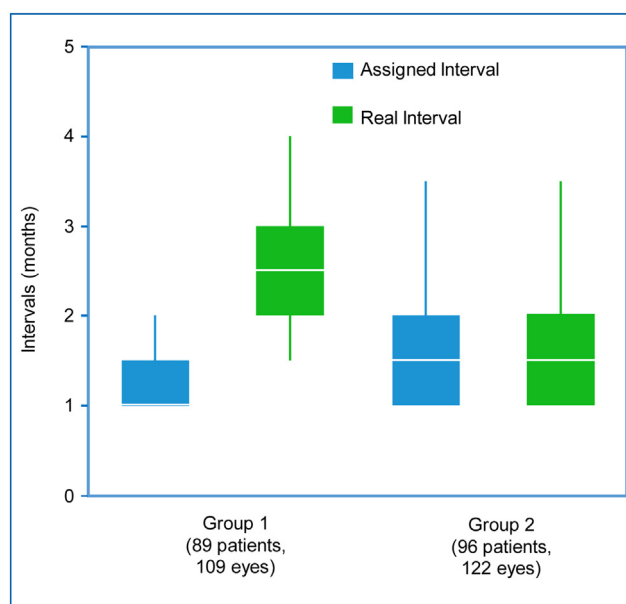
graph of the first post-confinement visit but was present in the OCT photograph of the last pre-confinement visit, then the change in IRF was favourable, and the OCT outcome would depend by the change in SRF and PED for the respective patient. If both SRF and PED were favourable, then the OCT outcome would be favourable for the respective patient. If at least one of SRF or PED was unfavourable, then the OCT outcome would be unfavourable for the respective patient. If IRF in the OCT photograph of the first post-confinement visit was in the same state (present or absent) as in the OCT photograph of the last pre-confinement visit, then the change in IRF was favourable. SRF and PED were assessed in the same manner as IRF. The OCT that was used was the Heidelberg Spectralis OCT. The OCT lecture was blinded from the favourable or unfavourable BCVA outcome. There was a double lecture of the OCT parameters. The OCT outcome also had two possible values: favourable or unfavourable. An increase in at least one of IRF, SRF, or PED at the first post-confinement visit compared to the last pre-confinement visit resulted in an unfavourable OCT outcome, while in any other case the OCT outcome was considered as favourable. We assessed the mean assigned and mean real injection intervals for each of the two groups. We defined the real injection interval as the actual injection interval that the patients followed during the confinement due to the COVID-19 outbreak, while the assigned injection interval for each patient was the interval that was assigned to them in their last pre-confinement visit.

## Data sources

BCVA and OCT data were anonymized, exported, and encoded into a dedicated Excel database at the time of analysis. Personal identifiers were removed and replaced by a code that was unique to each study participant.

## Statistical analysis

The significance level was set to  $\alpha=0.05$  (SAS software, version 9.4; SAS Institute, Carry, NC). Mean values and frequencies were expressed with their standard deviation ( $\pm$  SD) and percentages (%) respectively. Fisher's exact test and Mann–Whitney U test were performed for categorical and continuous variable comparisons between the two patient groups, respectively. Matched-pairs *t*-test was used for numeric variable comparisons between last pre- and first post-confinement visits. Power analysis for a Z-test (two proportions, two-sided) was conducted, and a sample size of  $\sim 180$  observations was chosen to detect a difference of 0.2 with an alpha set to 5% and a power of 80%. Multivariate logistic regression analyses with mixed stepwise selection (forward and backward) of variables were performed to identify potential factors that independently predict the unfavourable BCVA outcome. The maximum threshold of the *P*-value was 0.25 for an effect to be able to enter the model during a forward step, and the minimum threshold was 0.10 for an effect to be able to remove from the model during a backward step.



**Figure 1.** The difference between the assigned and real injection intervals was significant for group 1 ( $P < 0.0001$ ) but not significant for group 2 ( $P = 0.75$ ). The mean real injection interval was significantly higher than the mean assigned injection interval for group 1 ( $P < 0.0001$ ).

## Results

Group 1 consisted of 89 patients (109 eyes), and group 2 consisted of 96 patients (122 eyes). There was no significant difference in gender between group 1 and 2,  $P = 0.43$ . However, in each group, females outnumbered males [F/M ratio: 60 (67.42%)/29 (32.58%),  $P < 0.0001$  in group 1, and 70 (72.92%)/26 (27.08%),  $P < 0.0001$  in group 2] (Table 1). The mean age was not significantly different between the two groups: 81.16 ( $\pm 6.64$ ) years in group 1 and 82.12 ( $\pm 6.99$ ) years in group 2 ( $P = 0.34$ ). In group 1, 74 (67.9%) eyes were injected with aflibercept (Eylea® [BAYER, Leverkusen, Germany]), 34 (31.2%) eyes were injected with ranibizumab (Lucentis® [NOVARTIS, Basel, Switzerland]), and 1 (0.9%) eye was injected with brolocizumab (Beovu® [NOVARTIS, Basel, Switzerland]). In group 2, 78 (63.9%) eyes were injected with aflibercept (Eylea®), and the other 44 (36.1%) eyes were injected with ranibizumab (Lucentis®). In group 1, the mean assigned injection interval was 1.28 ( $\pm 0.46$ ) months, and the mean real injection interval was 2.76 ( $\pm 0.96$ ) months, while, in group 2, the aforementioned variables were 1.75 ( $\pm 0.70$ ) months and 1.77 ( $\pm 0.70$ ) months, respectively. The difference between group 1 and group 2 was significant for the mean assigned injection interval ( $P < 0.0001$ ), and for mean real injection interval ( $P < 0.0001$ ). Mean assigned injection interval was significantly shorter in group 1 than in group 2 ( $P < 0.0001$ ). Mean real injection interval was significantly longer in group 1 than in group 2 ( $P < 0.0001$ ) (Table 2). The difference between the mean assigned injection interval and the mean real injection interval was significant for group 1 ( $P < 0.001$ ) but not for group 2 ( $P = 0.75$ ) (Fig. 1). Moreover, in group 1, the mean real injection interval was significantly longer than the mean assigned injection interval ( $P < 0.001$ ) (Fig. 1).



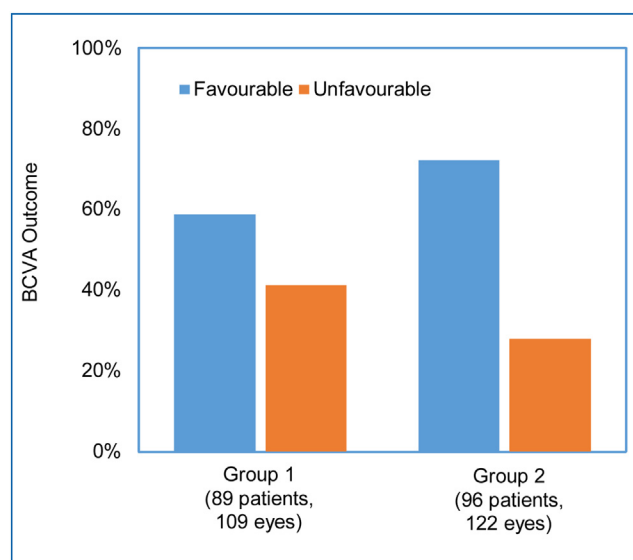
**Table 1** The statistical analysis of group 1 and group 2 by gender.

Gender, n (%)	Group 1	Group 2	P-value <sup>a</sup>
Females	60 (67.42%)	70 (72.92%)	P=0.43
Males	29 (32.58%)	26 (27.08%)	
Total	89	96	

<sup>a</sup> Fisher's exact test.**Table 2** Comparison of mean assigned and real anti-VEGF injection intervals between group 1 and group 2.

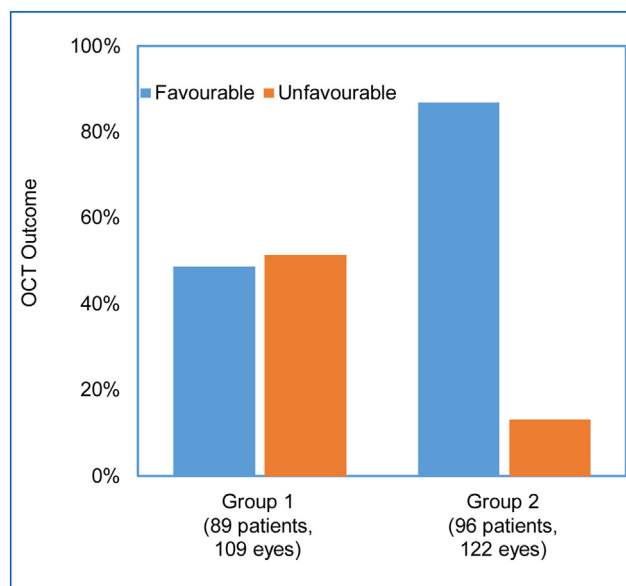
Time intervals (months)	Assigned injection interval			Real injection interval		
	Group 1	Group 2	P-value <sup>a</sup>	Group 1	Group 2	P-value
n (%)	109 (47.19%)	122 (52.81%)	P < 0.0001	106 (46.49%)	122 (53.51%)	P < 0.0001
Mean ± SD	1.28 ± 0.46	1.75 ± 0.70		2.76 ± 0.96	1.77 ± 0.70	
Median	1.0	1.5		2.50	1.5	

VEGF: vascular endothelial growth factor; SD: standard deviation.

<sup>a</sup> Mann–Whitney U test.**Figure 2.** Group 1 had 58.7% favourable and 41.3% unfavourable best-corrected visual acuity (BCVA) outcomes, while group 2 had 72.1% and 27.9% favourable and unfavourable BCVA outcomes, respectively. Group 1 had a 13.4% greater rate of unfavourable BCVA outcome than group 2 ( $P=0.04$ ).

The mean BCVA values in the last pre-confinement visit were 66.65 ( $\pm 18.04$ ) and 65.66 ( $\pm 19.03$ ) ETDRS letters for groups 1 and 2, respectively. The mean BCVA values in the first post-confinement visit were 66.38 ( $\pm 15.48$ ) and 66.38 ( $\pm 18.32$ ) ETDRS letters in groups 1 and 2, respectively. The BCVA values in the last pre-confinement visit were not significantly different between groups 1 and 2 ( $P=0.68$ ). However, group 1 had a significantly higher incidence of the unfavourable BCVA outcome (41.3%) than group 2 (27.9%) ( $P=0.04$ ) (Fig. 2).

Mean BCVA change  $\pm$  SD was  $-0.28 \pm 9.62$  (range  $[-30; 40]$ ) in group 1, and  $+0.72 \pm 9.40$  (range  $[-15; 40]$ ) in group

**Figure 3.** Group 1 had 48.6% favourable and 51.4% unfavourable optical coherence tomography (OCT) outcomes, while group 2 had 86.9% and 13.1% favourable and unfavourable OCT outcomes, respectively. Group 1 had a 38.3% greater rate of unfavourable OCT outcome than group 2 ( $P < 0.0001$ ).

2. Compared to patients with an unfavourable BCVA outcome (a loss of  $\geq 5$  ETDRS letters) in group 2, those in group 1 were more numerous but with a lesser average loss of BCVA. Compared to patients with a favourable BCVA outcome (a loss of  $< 5$  ETDRS letters) in group 2, those in group 1 were less numerous but with a greater average gain of BCVA (Table 3).

Similarly, group 1 had a significantly higher incidence of the unfavourable OCT outcome (51.4%) than group 2 (13.1%) ( $P < 0.001$ ) (Fig. 3). In addition, the rates of PED and IRF increases at the first post-confinement visit were significantly higher in group 1 than in group 2 ( $P=0.0004$  and  $P=0.04$ ,

**Table 3** BCVA values (ETDRS letters) in the last visit pre-confinement and in the first visit post-confinement according to the variable BCVA outcome [favourable (a loss of < 5 ETDRS letters) versus unfavourable (a loss of  $\geq$  5 ETDRS letters)] in the groups 1 and 2.

	BCVA values (ETDRS letters)			
	Favourable		Unfavourable	
	Group 1	Group 2	Group 1	Group 2
<i>n</i> (%)	64 (58.7%)	88 (72.1%)	45 (41.3%)	34 (27.9%)
BCVA in the last visit pre-confinement				
Mean $\pm$ SD	62.89 $\pm$ 19.80	65.28 $\pm$ 20.26	72.00 $\pm$ 13.71	66.62 $\pm$ 15.61
Range	[5; 85]	[5; 85]	[40; 90]	[20; 85]
BCVA in the first visit post-confinement				
Mean $\pm$ SD	67.89 $\pm$ 15.98	69.69 $\pm$ 17.94	64.22 $\pm$ 14.65	57.79 $\pm$ 16.61
Range	[5; 85]	[5; 90]	[35; 85]	[10; 80]
BCVA change				
Mean $\pm$ SD	5.00 $\pm$ 8.40	4.41 $\pm$ 8.16	-7.78 $\pm$ 5.28	-8.82 $\pm$ 4.27
Range	[0; 40]	[-2; 40]	[-30; -5]	[-15; -7.5]

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; SD: standard deviation.

**Table 4** The effect of IRF, SRF and PED in the OCT outcome of group 1 and group 2.

	Group 1	Group 2	Total	Relative difference of OCT Outcome between groups (OCT Outcome <sub>Group1</sub> - OCT Outcome <sub>Group2</sub> )/OCT Outcome <sub>Group2</sub>	<i>P</i> -value <sup>a</sup>
IRF, <i>n</i> = eyes (%)					
Favorable	84 (77.06)	107 (87.71)	191 (82.68)	-21.50%	0.0374
Unfavorable	25 (22.94)	15 (12.30)	40 (17.32)	+66.67%	
Total	109 (100.00)	122 (100.00)	231 (100.00)		
SRF, <i>n</i> = eyes (%)					
Favorable	93 (85.32)	113 (92.62)	206 (89.18)	-17.70%	0.0906
Unfavorable	16 (14.68)	9 (7.38)	25 (10.82)	+55.56%	
Total	109 (100.00)	122 (100.00)	231 (100.00)		
PED, <i>n</i> = eyes (%)					
Favorable	82 (75.23)	113 (92.62)	195 (84.42)	-27.43%	0.0004
Unfavorable	27 (24.77)	9 (7.38)	36 (15.58)	+200%	
Total	109 (100.00)	122 (100.00)	231 (100.00)		
OCT outcome, <i>n</i> = eyes (%)					
Favorable	53 (48.62)	106 (86.89)	159 (68.83)	-50.00%	< 0.0001
Unfavorable	56 (51.38)	16 (13.11)	72 (31.17)	+250%	
Total	109 (100.00)	122 (100.00)	231 (100.00)		

IRF: intraretinal fluid; SRF: subretinal fluid; PED: pigment epithelial detachment; OCT: optical coherence tomography.

<sup>a</sup> Fisher's exact test.

respectively), with relative increases in the unfavourable OCT outcome of 200% and 66.7%, respectively (Table 4).

To predict the unfavourable BCVA outcome, multivariate logistic regression models were used to test the effects of the following variables: OCT outcome (favourable or unfavourable), assigned injection interval, real injection interval, last anti-VEGF product used (aflibercept [Eylea®], ranibizumab [Lucentis®], or brolucizumab [Beovu®]), and the BCVA value in the last pre-confinement visit. The

real injection interval and the BCVA value in the last pre-confinement visit were determined to be independent predictive factors for the unfavourable BCVA outcome ( $P=0.03$  and  $P=0.02$ , respectively), with longer real injection intervals and higher BCVA values in the last pre-confinement visit associated with the unfavourable BCVA outcome. The OCT outcome (favourable or unfavourable) was not a predictive factor for an unfavourable BCVA outcome.

## Discussion

The objective of this study was to compare the functional and structural visual outcomes of wet AMD patients who did not adhere to their planned intravitreal anti-VEGF injection intervals (group 1) with those who did (group 2). Our study demonstrated that group 1 had significantly higher rates of unfavourable BCVA outcome (by 13.41%,  $P=0.04$ ) and unfavourable OCT outcome (by 38.27%,  $P<0.001$ ) than the patients of group 2. Multivariate logistic regression analysis showed that the unfavourable BCVA outcome was associated with the injection interval followed by the patients, as well as the BCVA value in the last pre-confinement visit. Indeed, patients who delayed their injection visits and patients who had better BCVA values in their last pre-confinement visit were the most affected groups. These results were similar to those published by Borrelli et al. in his study which was conducted during the COVID-19 pandemic in Milan, Italy, and which also reported that BCVA and OCT outcomes were assessed to be significantly worse in the patient visit during the period of confinement, than in the preceding ( $V-1$ ) visit [20]. Borrelli et al. also reported an association between unfavourable BCVA outcomes and extended intervals in patients who delayed their injection visits [20]. Furthermore, Yeter et al. [21], in his study which was organised during the COVID-19 pandemic in Turkey, reported an association between BCVA changes and injection intervals, with worse BCVA values observed when intervals were extended due to confinement and better BCVA values observed when intervals were shortened after the end of national lockdown. Furthermore, Yeter et al. also reported significantly worse functional and structural visual outcomes in the visit after the release of the national lockdown, compared to the last two visits before restrictions [21]. The difference between the aforementioned studies and our study is that the unfavourable BCVA outcome was also predicted by a good BCVA value in the last pre-confinement visit in our study [20,21]. This finding may have resulted from the larger sample size of our study (185 patients, 231 eyes versus 100 patients, 112 eyes [20], and 106 patients, 116 eyes [21]), which permitted the use of a multivariate logistic regression analysis that could reach statistical significance for more than one variable affecting the unfavourable BCVA outcome. Our study, as well as those of Borrelli et al. and Yeter et al. [20,21], showed that patient adherence to a programmed injection interval is of paramount importance for maintaining a satisfactory level of visual outcome. In a study by Saleh et al. [22], which was conducted at a tertiary university hospital in Jordan during the COVID-19 lockdown, and in which the mean period of delay from the scheduled visit due to confinement was 6 weeks, the authors reported a statistically significant decrease in BCVA and a statistically significant increase in the mean central macular thickness, which could also add to the deteriorating visual and structural effects of non-compliance with scheduled visits. However, the population in the study by Saleh et al. consisted of patients with AMD, diabetic retinopathy, and retinal vein occlusion [22], while our population of interest only included patients with wet AMD. In a study by Naravane et al. [23], which was conducted in the University of Minnesota retina clinic and the retina center in Minneapolis

during the COVID-19 pandemic, the authors reported that the group of patients who delayed their injection visits had significantly worse BCVA values than those who did not. Furthermore, Naravane et al. report that only the delayed group that consisted of patients with diabetic macular oedema had significantly worsened OCT results compared to the non-delayed group ( $P=0.03$ ), while the OCT features did not significantly worsen in the delayed group that consisted of patients with nAMD group ( $P=0.4$ ) [23]. That study included 167 eyes of 117 patients; however, it included patients with nAMD, diabetic retinopathy, and retinal vein occlusion [23]. In a study by Teo et al. [23], which obtained patient data from the FRB! Registry and included patients from Australia, New Zealand, Switzerland and Singapore, the authors concluded that there was a significant BCVA loss in patients who delayed their injection visits by more than 12 weeks. However, the effects of the visit delay on the structural visual outcomes of patients were not assessed [24]. OCT features can specify the location and type of fluid (IRF, SRF, and PED) in wet AMD patients, which is important because it has been shown that BCVA is better in eyes with no IRF (cysts or oedema) observed on OCT than in eyes with persistent IRF [25,26]. The presence of IRF negatively affects BCVA more than the presence of SRF, though both have deteriorating effects on vision [25,26]. PED is a critical biomarker for long-term vision loss in individualized anti-VEGF therapy, according to Schmidt-Erfurth and Waldstein [26]. In our study, the rates of increase in PED and IRF at the first post-confinement visit were significantly higher in group 1 than in group 2 ( $P=0.0004$  and  $P=0.04$ , respectively), with relative increases in the unfavourable OCT outcome of 200% and 66.67%, respectively. Our results are in accordance with the findings of Schmidt-Erfurth and Waldstein and further support the importance of continuing intravitreal anti-VEGF injections, despite the short duration of PED and IRF increases in our study [26]. The multivariate logistic regression analysis that we conducted did not identify an association between the unfavourable BCVA outcome and the unfavourable OCT outcome. This finding may have occurred because the patient follow-up period was not long enough for the multivariate logistic regression analysis to identify the aforementioned association, since we analysed patient data from only the last pre-confinement and the first post-confinement visits, rather than a series of visits before and after confinement.

The major weakness of our study was its retrospective design, as it was based on the reuse of data from the medical records of patients who fulfilled the eligibility criteria. Therefore, our study had an inherent vulnerability to selection bias and recall bias. Furthermore, it was prone to confounding, and, consequently, there is a chance that factors that can predict an unfavourable BCVA outcome were not identified in our multivariate logistic regression analysis. Another limitation is the short follow-up, which prevents understanding of long-term effects in patients who did not respect their intervals. Prospective studies with larger sample size and larger period of follow-up, who overcome the aforementioned limitations, need to be conducted in the future.

Finally, our study showed threatening OCT features in the group of patients that did not adhere to their



intervals (group 1), supporting the increased roles of remote OCT and home-monitoring OCT devices to help identify patients whose visual function may deteriorate in the near future.

## Conclusion

Telemedicine tools could also offer a valuable solution in similar future situations in which the number of patient visits decreases. The COVID-19 pandemic has led to treatment interruptions for a large number of patients, and this unique situation has allowed us to confirm the crucial role of maintaining continuity in intravitreal anti-VEGF injection therapy in order to ensure the best functional and structural visual outcomes for patients with wet AMD.

## Acknowledgements

None.

## Disclosure of interest

The authors declare that they have no competing interest.

## References

- [1] Pascolini D, Mariotti SP, Pokharel GP, Pararajasegaram R, Etya'ale D, Négrel AD, et al. 2002 global update of available data on visual impairment: a compilation of population-based prevalence studies. *Ophthalmic Epidemiol* 2004;11:67–115.
- [2] Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PTVM, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004;122:564–72.
- [3] Li JQ, Welchowski T, Schmid M, Mauschitz MM, Holz FG, Finger RP. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. *Br J Ophthalmol* 2020;104:1077–84.
- [4] Salmon JF. Age-related macular degeneration. In: Salmon JF, editor. *KANSKI'S clinical ophthalmology: a systematic approach*. 9th ed. United Kingdom: Elsevier; 2020. p. 572.
- [5] Al-Zamil WM, Yassin SA. Recent developments in age-related macular degeneration: a review. *Clin Interv Aging* 2017;12:1313–30.
- [6] Zajaç-Pytrus HM, Pilecka A, Turno-Kręcicka A, Adamiec-Mroczek J, Misiuk-Hojło M. The dry form of age-related macular degeneration (AMD): the current concepts of pathogenesis and prospects for treatment. *Adv Clin Exp Med* 2015;24:1099–104.
- [7] Ba J, Peng RS, Xu D, Li YH, Shi H, Wang Q, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. *Drug Des Devel Ther* 2015;9:397–405.
- [8] Giannou C, Dirani A, Ferrini W, Marchionno L, Decugis D, Deliet A. Two-year outcome of an observe-and-plan regimen for neovascular age-related macular degeneration: how to alleviate the clinical burden with maintained functional results. *Eye (Lond)* 2015;29:342–9.
- [9] Haga A, Kawaji T, Ideta R, Inomata Y, Tanihara H. Treat-and-extend versus every-other-month regimens with aflibercept in age-related macular degeneration. *Acta Ophthalmol* 2018;96:e393–8.
- [10] Dawood AA. Mutated COVID-19 may foretell a great risk for mankind in the future. *New Microbes New Infect* 2020;35:100673.
- [11] Royal College of Ophthalmologists. Management of ophthalmology services during the COVID pandemic; 2020 [Accessed 18 May 2020] <https://www.rcophth.ac.uk/wp-content/uploads/2020/03/RCOphth-Management-of-Ophthalmology-Services-during-the-Covid-pandemic-280320.pdf>.
- [12] American Academy of Ophthalmology. Recommendations for urgent and nonurgent patient care; 2020 [Accessed 18 March 2020] <https://www.aao.org/headline/new-recommendations-urgent-nonurgent-patient-care>.
- [13] Fung THM, Kuet ML, Patel MK, Puri P. Addressing COVID-19 fear to improve clinic attendance for patients with wet age-related macular degeneration. *Acta Ophthalmol* 2021;99:e285.
- [14] Colantuono D, Miere A, Semoun O, Amoroso F, Souied EH. AMD management during the COVID-19 pandemic. *Acta Ophthalmol* 2020;98:e925.
- [15] Corradetti G, Corvi F, Nguyen TV, Satta SVR. Management of neovascular age-related macular degeneration during the COVID-19 pandemic. *Ophthalmol Retina* 2020;4:757–9.
- [16] Antaki F, Dirani A. Treating neovascular age-related macular degeneration in the era of COVID-19. *Graefes Arch Clin Exp Ophthalmol* 2020;258:1567–9.
- [17] Kodjikian L. How to approach intravitreal injections during this COVID-19 pandemic? *J Fr Ophthalmol* 2020;43:539–40.
- [18] Declaration of Helsinki. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>. [Accessed 9 July 2018].
- [19] Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular oedema. *Arch Ophthalmol* 1985;103:1796–806.
- [20] Borrelli E, Grosso D, Vella G, Sacconi R, Battista M, Querques L, et al. Short-term outcomes of patients with neovascular exudative AMD: the effect of COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol* 2020;258:2621–8.
- [21] 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 Ophthalmol* 2021;44:299–306.
- [22] Saleh OA, Jammal H, Alqudah N, Alqudah A, Abu-Yaghi N. Clinical experience in the administration of intravitreal injection therapy at a tertiary university hospital in Jordan during the COVID-19 lockdown. *Clin Ophthalmol* 2020;14:2473–80.
- [23] Naravane AV, Mundae R, Zhou Y, Santilli C, van Kuijk FJGM, Nazari H, et al. Short term visual and structural outcomes of anti-vascular endothelial growth factor (anti-VEGF) treatment delay during the first COVID-19 wave: a pilot study. *PLoS One* 2021;16:e0247161.
- [24] 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 (Lond)* 2020;25:1–9.
- [25] Wickremasinghe SS, Sandhu SS, Busija L, Lim J, Chauhan DS, Guymer RH. Predictors of AMD treatment response. *Ophthalmology* 2012;119 [413–2414.e5].
- [26] Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog Retin Eye Res* 2016;50:1–24.