Treating retinal diseases by optical coherence tomography alone during COVID-19 lockdown.

Fidaa El Zhalka[1*], Dalila Abu Atta[1], Ori Segal[1,2], Elad Moisseiev[1,2]

[1]Department of Ophthalmology, Meir Medical Center, Kfar Saba, Israel

[2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Received: *09-Aug-2024, Manuscript No. AACOVS-24-145045;* **Editor assigned:** *13-Aug-2024, PreQC No. AACOVS-24-145045 (PQ);* **Reviewed:** *28-Aug-2024, QC No. AACOVS-24-145045;* **Revised:** *04-Sep-2024, Manuscript No. AACOVS-24-145045 (R);* **Published:** *11-Sep-2024, DOI: 10.35841/aacovs.8.5.476-480*

Abstract

Purpose: To investigate the effects of managing retinal diseases by OCT exam alone due to COVID-19 pandemic on the treatment course of nAMD, DME and RVO patients, and compare it with real-life data.

Methods: A comparison between patients whose treatment was based on OCT alone during COVID-19 lockdown limitations and patients who visited the retina unit one year before. Recorded parameters included demographic data, visual acuity, OCT characteristics, number of anti VEGF injections to each eye before the COVID-19 visit, referral for intravitreal injections, number of injections and anti-VEGF drugs administered.

Results: A total of 165 eyes of 133 patients were included in the study group, and 189 eyes of 145 patients in the control group. Both groups had similar baseline characteristics. Patients in the study group were referred to more anti VEGF injections than the control group (71.5% of patient's *vs* 41.8, p<0.0001) final visual acuity was better in the study group, but although this difference achieved statistical significance (p=0.037), it was a small change not likely to be clinically significant. The differences in CMT and volume changes were also not significant.

Conclusion: Treating patients with nAMD, CME due to RVO or DME with anti VEGF injections according to OCT imaging alone did not harm patients, and achieved satisfactory results. Adoption of this treatment regimen can be considered also for patients live in remote areas.

Keywords: COVID-19, Retina, AMD, RVO, DME, OCT.

Abbreviations: Age-related Macular Degeneration (AMD), Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Optical Coherence Tomography (OCT).

Introduction

The Coronavirus disease (COVID-19) caused by "Severe Acute Respiratory Syndrome Coronavirus type 2" (SARS-CoV-2) was declared on 11th March, 2020 by the World Health Organization (WHO) as a pandemic. This respiratory virus, leading to pneumonia, Severe Acute Respiratory Syndrome (SARS) and even death, has emerged in Wuhan, China and then spread worldwide at tremendous speed [1]. The coronavirus appears to be highly contagious, particularly by respiratory droplets, the major mode of diffusion besides discharges and conjunctival secretions [2].

Ophthalmologists are considered a high-risk category, for the daily close contact with a high volume of patients. The American Academy of Ophthalmology (AAO) alerted ophthalmologists, to manage their workflow, including surgeries, treatment modalities, and patient visit intervals, during the outbreak of COVID-19 to minimize the risk of infection transmission and prevent disease spreading among both patients and health workers [3]. Frequent and careful disinfection of clinics, and personal protective equipment such as face coverings were recommended [4]. Patients with retinal diseases are generally elderly and have multiple comorbid conditions, which could increase the morbidity and mortality of COVID-19 disease [5]. These retinal diseases, particularly Diabetic Macular Edema (DME), and neo vascular Age-related Macular Degeneration (nAMD), mostly need anti-Vascular Endothelial Growth Factor (VEGF) injections for treatment and can cause permanent vision loss if left untreated [6].

Treatment delay caused by lock-down or by patients fear of visiting busy clinics and hospitals during COVID-19 pandemic has been reported as a cause for deterioration of nAMD and visual impairment to reduce the chance of transmitting the virus to either patients or healthcare personnel during lock-down, our clinic triaged patients so only those who needed an ocular examination were seen by ophthalmologists [7-9]. These included mostly urgent cases, while the majority of patients routinely seen in the retina clinic underwent only OCT scans, which were later reviewed by specialists along with their previous data from the electronic medical records, and the decision was made whether anti-VEGF injections were needed. This practice was used for 6 weeks, during which these patients came to the clinic for very short visits-consisting of only OCT scans and/or intravitreal injections. In addition to the review of

OCT scans, an ophthalmologist was available by phone in order to be able to answer all the doubts or questions that patients may have had.

In this study, we aimed to investigate the effects of managing retinal diseases by OCT exam alone due to COVID-19 pandemic on the treatment course of nAMD, DME and Retinal Vein Occlusion (RVO) patients who received anti-VEGF injection therapy, and compare it with real-life data.

Methodology

A retrospective review of the electronic medical records of the ophthalmology department at the Meir Medical Center was conducted for two groups of patients:

The study group were patients visited the retina unit with previous diagnoses of AMD, DME or Cystoid Macular Edema (CME) due to RVO during the 'first wave' lock-down, between 15th March and 30th April, 2020. Due to the COVID-19 caution limitations, these patients underwent only OCT scans without visual acuity test and ophthalmological examination. A retina specialist decided according to the OCT images and the previous records whether to refer the patient to intravitreal anti-VEGF injections, as well as their interval and number.

The control group were patients visited the retina unit one year before COVID-19 pandemic (1st January to 28th February, 2019), with the same retinal diagnoses. The referral for intravitreal injections in this group was based on a visual acuity test, full ophthalmic examination as well as OCT exam. Patients with a history of ocular trauma or patients with prior vision limiting ocular conditions were excluded. All patients were 18 years or older, who were diagnosed with DME, NVAMD or CME due to RVO by a retina specialist, based on clinical examination and imaging. Recorded parameters included demographic data, Visual Acuity (VA) at the last visit before the COVID-19 visit, at the first follow up after the lock-down, number of anti VEGF injections to each eye before the COVID-19 visit, referral for intravitreal injections, number of injections the patient referred to and what anti VEGF agent was administered. OCT images were also analyzed for Central Macular Thickness (CMT) and volume. The same data was collected to the control group. The study was approved by the Institutional Review Board (IRB) of Meir Medical Center.

All VA values were converted to the logMAR scale for statistical analysis. According to the results of Holladay and the University of Freiburg studies, counting fingers was set at 0.014/1.85, hand movements at 0.005/2.3, light perception at 0.0025/2.6 and blindness at 0.00125/2.9 (decimal/logMAR) [10,11]. To analyze categorical parameters chi-square tests were used, to continuous parameters between groups T tests were used. To analyze changes in VA and CMT over time Paired t-tests were used. Correlations between the permanent variables were analyzed using Pearson's correlation coefficient. Data was analyzed using SPSS for windows version 21. A p-value of 0.05 was used to show the statistically significant difference between groups.

Results

Descriptive data

A total of 165 eyes of 133 patients were included in the study group, and 189 eyes of 145 patients in the control group. There were 85 (51.5%) males in the study group, *vs* 86 (45.5%) males in the control group. The mean age in the study group was 75 ± 11 years (range 47-95 years), AMD patients were older with a statistically significant difference (80.8 ± 8 years, p=0.00). The mean age in the control group was 77.5 ± 11.4 years (9-97 years of age).

In the study group 92 (55.7%) patients had AMD, 51 (30.9%) had DME and 22 (13.3%) had RVO. The majority of patients (98.7%) were treated previously by anti VEGF injections, and mean number of prior injections was 26 ± 17. Initial visual acuity was 0.5 ± 0.5 logMAR (equivalent to 20/63 Snellen), and initial mean CMT thickness was 321 ± 101 micron (178-729 micron) and initial volume was 8.7 ± 1.3 μm^3. These results are detailed in Table 1.

Table 1. *Descriptive table-study group by diagnosis.*

Parameter	AMD (n=92)	DME (n=51)	RVO (n=22)	p-value
Age (years)	80.8 ± 8.	65.8 ± 9.6	72.0 ± 8.8	<0.0001
Past injection number (n)	29.6 ± 19.8	21.8 ± 11.3	20.6 ± 11.3	0.009
VA initial (LogMar)	0.6 ± 0.5	0.5 ± 0.4	0.4 ± 0.5	0.247
VA final (LogMar)	0.6 ± 0.4	0.4 ± 0.4	0.5 ± 0.4	0.142
CMT initial (micron)	301.2 ± 68.6	349.3 ± 127.7	342.9 ± 127.2	0.013
CMT final (micron)	303.0 ± 72.9	318.3 ± 108.3	348.6 ± 179.6	0.171
Volume initial (μm^3)	8.3 ± 1.1	9.1 ± 1.5	8.9 ± 1.7	0.001
Volume final (μm^3)	8.3 ± 1.1	9.1 ± 1.5	8.8 ± 1.9	0.007

In the control group 99 (52.3%) patients had AMD, 67 (35.4%) had DME and 23 (12.1%) had RVO. All the patients were treated previously by anti VEGF injections, and the mean number of prior injections was 23 ± 15. Initial visual acuity was 0.6 ± 0.5 logMAR (equivalent to 20/80 Snellen), initial CMT thickness mean was 328 ± 112 micron (141-822 micron) and initial volume was 8.9 ± 1.5 μm^3. These results are detailed in Table 2.

Table 2. *Descriptive table-control group by diagnosis.*

Parameter	AMD (n=99)	DME (n=67)	RVO (n=23)	p-value
Age (years)	84.7 ± 8.0	67.8 ± 9.0	74.6 ± 7.9	<0.0001
Past injection number (n)	30.2 ± 16.6	15.8 ± 10.4	19.7 ± 11.3	0.009
VA initial (LogMar)	0.7 ± 0.5	0.5 ± 0.4	0.6 ± 0.4	0.037

VA final (LogMar)	0.7 ± 0.5	0.5 ± 0.4	0.6 ± 0.5	0.207
CMT initial (micron)	315.4 ± 104.9	336.0 ± 108.6	362.2 ± 144.4	0.155
CMT final (micron)	308.1 ± 115.9	332.1 ± 106.8	340.9 ± 121.6	0.272
Volume initial (μm^3)	8.5 ± 1.1	9.4 ± 1.7	9.4 ± 1.9	<0.0001
Volume final (μm^3)	8.4 ± 1.3	9.3 ± 1.4	9.4 ± 1.9	<0.0001

Analysis of differences between groups

Both groups had similar initial characteristics, age, number of previous injections, follow up interval, initial visual acuity and initial CMT thickness and volume.

Patients in the study group were referred to more anti VEGF injections than the control group: 118 (71.5%) patient's *vs* 79 (41.8%) patients (p<0.0001) The final visual acuity was better in the study group, but although this difference achieved statistical significance (p=0.037), it was a small change not likely to be clinically significant.

The differences in CMT and volume changes were also not significant. These results are detailed in Table 3.

Table 3. *Comparison between study and control group.*

Parameter	Study group (n=165)	Control group (n=189)	p-value
Age (years)	74.97 ± 10.97	77.47 ± 11.44	0.038
past injection number (n)	25.98 ± 17.01	23.81 ± 15.58	0.213
VA initial LogMar)	0.52 ± 0.46	0.60 ± 0.47	0.092
VA final (LogMar)	0.52 ± 0.42	0.62 ± 0.48	0.037
CMT initial (micron)	321.62 ± 100.96	328.40 ± 112.09	0.552
CMT final (micron)	313.80 ± 104.34	320.57 ± 113.65	0.562
VOLUME initial (μm^3)	8.67 ± 1.29	8.95 ± 1.51	0.063
VOLUME final (μm^3)	8.63 ± 1.37	8.79 ± 1.42	0.297
VA difference (LogMar)	0.01 ± 0.24	0.02 ± 0.34	0.583
CMT difference (micron)	-7.82 ± 107.75	-7.83 ± 101.96	0.999
Volume difference (μm^3)	-0.03 ± 0.98	-0.16 ± 1.28	0.306

None of the patients in both groups suffered endophthalmitis or any other complication related to the intravitreal injection procedures.

Discussion

Neovascular AMD, DME and CME due to retinal vein occlusion all are common retinal conditions, causing considerable visual impairment. Anti-VEGF agents are the mainstay of treatment for these diseases, capable of effectively limiting their progression and improve vision [12].

However, the application of these agents at appropriate intervals is essential to control the activation of the disease, prevent disease progression and improve vision. The optimal treatment regimen intervals in each retinal disease are variable, and may differ between patients and over time. Delay or discontinuation of treatment can lead to permanent visual loss due to progressive retinal pigment epithelium and photoreceptor atrophy.

COVID-19 pandemic lock down limitations required ophthalmologist to manage ocular diseases in unusual and different ways in order to minimize patient-physician interaction, especially with the older population. The use of telemedicine in ophthalmology, and specifically in retinal diseases, has made significant advancements in recent years especially during pandemic era. Although the use of telemedicine in AMD screening is not as well validated as in diabetic retinopathy screening. But studies examining OCT studies demonstrating the remote use of OCT in the evaluation of AMD and even potential cost-saving areas similar to diabetic retinopathy [13].

Our retina specialists managed patients' treatment based on only OCT exam without clinical exam nor visual acuity test.

Similar treatment strategies were recommended in practice protocol during COVID-19 pandemic by Safadi et al., in which visual acuity assessment and clinical examination could be postponed, and treatment decision may be based on OCT findings reviewed by a retina specialist at home with a remote connection, who decides on the interval of injections for each patient following a treat and extend protocol [14].

In our study we compared the effect of managing patients with lock down limitations to the real life data were patients underwent visual acuity test, clinical exam and OCT imaging in three common retinal disorders, nAMD, DME and retinal vein occlusion. Our results show that patients treated based on OCT exam alone had been referred to more anti VEGF injections. Similar findings shown in the CATT trial, where in the majority of cases of disagreement between the clinicians and the reading centers, their cause were small amounts of intra retinal or sub retinal fluid detected by OCT. These were either not noted on clinical examination or were tolerated because of stable vision [15]. As supported by our findings, basing treatment decisions on OCT findings alone results in a higher rate of referral for intravitreal injections. It is possible that the higher rate of referral for injections reflected the concern of the treating physician in the absence of a clinical exam, visual acuity or subjective input from the patients, as well as the insecurity and uncertainty regarding the possibility and timing of future visits.

Higher frequency of injections appears to be correlated with more successful maintenance of visual acuity gains over time. The SEVEN-UP study, a non-interventional trial which evaluated outcomes 7-8 years after initiation of ranibizumab and included 65 patients originally treated with ranibizumab in the ANCHOR, MARINA and HORIZON studies showed a mean gain in letter score since exit from HORIZON was significantly better in patients who had received ≥ 11 anti-VEGF injections, suggesting vision may be partly related to injection frequency [16-18]. On the other hand, more injections increase the number of sight-threatening complications, such as endophthalmitis, and increase the burden on patients, caregivers and health care systems.

The final change in visual acuity and OCT characteristics had no statistically significant difference which indicate that managing patients with exudative retinal diseases treated with anti VEGF injections based on OCT alone in unusual and special circumstances like pandemic can be achieve satisfactory results without harming the patient treatment. In the French IMPACT study that evaluated the impact of adherence to intravitreal injections during COVID-19 lockdown and included 3020 eyes from 18 centers, there was a small decrease in VA at 4 months in non-adherent patients, adherent patients had better visual outcomes Factors associated with non-adherence were in multivariable analysis, older age, hospital practice, low-density population areas, high viral incidence areas, longer intervals between injection and treat and extent protocol. Factors associated with visual loss at 4 months in multivariable analysis were, being in the non-adherent group, older age, treat and extend fixed regimens [19].

Conclusion

COVID-19 pandemic forced ophthalmologists, as well as other disciplines of medicine, to treat patients differently, under challenging conditions. Our study we show that treating patients with AMD, CME due to RVO or DME with anti VEGF injections according to OCT imaging alone did not harm patients, and achieved satisfactory results. Adoption of this treatment regimen can be considered also in patients live in remote areas which will be time and cost consuming.

Limitations

This study includes its retrospective nature, patients treated by multiple retina specialists and non-uniform treatment regimens. However, both groups had sufficient sample size and represent cohorts of real-life patients treated under two different general conditions, making their comparison applicable to the clinical reality.

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***Correspondence to**

Fidaa El Zhalka

Department of Ophthalmology,

Meir Medical Center,

Kfar Saba, Israel

E-mail: fidaa.asali@gmail.com