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Preliminary Results of Tocilizumab and Interferon α-2β Treatment of SARS-CoV-2

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1. Abstract

Seven patients receiving Hydroxychloroquine (HCQ) and Zinc (Zn) for CoVid-19 with PCR positive results were admitted to hospital after failing to improve. Following NCT04349410 protocol and failure to improve with elevated interleukin-6 and ferritin levels, patient's treatment was changed following measurement of Corona Virus Pneumonia (CVP). Follow up measurements of CVP confirmed improvement with combined intravenous Tocilizumab, Interferon α-2β, nebulizer, Atrovent nebulizer and SQ heparin treatments.

2. Introduction

Currently there are no clear treatment protocols for individuals infected with SARS-2 (CoVid-19). Multiple investigations are currently underway and social media is replete with commentary on the appropriate treatment regimen from anecdotal reports. Unfortunately, clear evidence of treatment responses has focused only on survival data and discharge times. In this first of several papers resulting from international investigation of CoVid-19 patients, we look at outcomes following failure of HCQ and Zn.

3. Methods

Recruitment of CoVid-19 patients began in April 2020 and completed five months later. All patients were recruited from outside the United States. In addition to the original IRB approval of the protocol, each participating institution approved the study in accordance with the rules and regulations of their institution and country.

Entry into the study required a confirmed test for CoVid-19 defined as a positive PCR and symptoms consisting of fatigue, dyspnea, myalgias and/or elevated temperature of 38^0 C.

On day-1 of entry into the study subjects underwent initial FMTVDM [1] measurement of corona virus pneumonia (CVP) and blood tests including ferritin and interleukin-6 levels. Following measurement patients were assigned one of 11-treatment arms shown in (Figure 1). Individuals in this subset all had elevated interleukin-6 (IL-6) and ferritin levels and were defined as having an InflammoThrombotic response (ITR) to CoVid-19. According per protocol they were placed on treatment arms 7 and 9.

In this subset of patients, we looked at 7-patients who had initially received HCQ and Zn as outpatients and became symptomatically worse. They were admitted for further evaluation and treatment per protocol as defined below.

4. Treatment

Treatment with intravenous Tocilizumab 8mg/kg (not to exceed 800 mg) was infused over 60-minutes. If clinical improvement was not noted, an additional three doses were provided at 8-hour intervals for a total of 4-doses maximum.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6	Treatment 7	Treatment 8	Treatment 9	Treatment 10	Treatment 11	Treatment 12
Immune Support: Folate 3 mg qD, Magnesium 400 mg qD, Calcium Carbonate 400 mg qD, Vitamin B12 - 3 mg qD, Vitamin B6 - 30 mg qD, DHEA 50 mg BID, Vitamin C 2000 mg qD, Zinc 10 mg po or 4 mg IV, and Vitamin D3 1500 IU qD.	X	X	X	X	X	X	X	X	X	X	X	X
Respiratory Support: Atrovent (β2 bronchodilator) nebulizer treatments q 4-hours.	X	X	X	X	X	X	X	X	X	X	X	X
❖ CoVid-19 Targeted Treatments												
Hydroxychloroquine 200 mg po q 8 hrs (600 mg qD) for a total of 10-days	X	X	X	X								
Azithromycin 500 mg IV on day 1, followed by 250 mg IV on days 2-5	X											
Doxycycline 100mg IV q 12 hrs with each dose given over 1 to 4-hours		X										
Clindamycin 150-450 mg po q6 hours x 10 days OR 4800 mg IV daily – beginning with 150 mg initial rapid infusion, followed by continuous infusion q 24-hours for 7-days			X	X	X							
Primaquine 200 mg po on day # 1.				X	X							
Hydroxychloroquine Day # 1: 800 mg po initially followed by 400 mg 8 hours later. Days 2 and 3: 400 mg po qD.					X							
Remdesivir 200 mg IV on day 1, followed by 100 mg IV qD for a total of 10-days.						X						
Tocilizumab 8mg/kg IV (not to exceed 800 mg) over 60-minutes. If clinical improvement is not noted, three additional doses may be administered at q 8-hour intervals from the initial infusion for a total of 4-doses maximum.							X					
Methylprednisolone 80 mg IV over 30-minutes, BID x 7-days. Then taper off.								X				
Interferon alpha-2b 5 million units per nebulizer BID.									X			
Losartan 25 mg po qD.										X		
Plasma transfusions from CoVid-19 survivors.											X	

Figure 1: Treatment arm

Legend. Each participant received the same immune and respiratory support. Patients were randomly assigned one of 11 treatment arms unless there was evidence of InflammoThrombotic response (ITR). Patients with ITR were automatically assigned treatment including a combination of treatment arms 7 and 9.

Interferon α-2β 5 milllion units were provided by nebulizer every 12-hours in addition to Atrovent nebulizer treatments every 4-hours. Finally, heparin 5000 units subcutaneous (SC) were provided every 12-hours.

5. Evaluation of Treatment Response

Following 3-days of treatment these patients underwent a second FMTVDM measurement of CVP to determine treatment response. An increase in FMTVDM denotes deterioration and progress of CVP while a decrease in FMTVDM denoted improvement. An absence of change in FMTVDM indicates either a failed treatment response or stabilization of CVP [2].

6. Results

As shown in (Table 1), the study subset included 6 men and 1 woman ranging from 49 to 91 years of age (73 +/- 13 years) with weights ranging from 79 to 95 kg (84.8 +/- 5 kg). Two of the patients had known coronary artery disease (CVD) and five had documented diabetes mellitus.

An example of FMTVDM measurements is shown in (Figure 2). Where more than one region of CVP was present, the greatest measurement was used denoting the greatest level of disease present in the individual on that date. Results from the first set of measurements revealed an average FMTVDM of 182.86 +/- 21.74. Following 3-days of treatment repeat FMTVDM measurements was 124.14 +/- 8.82. The results were statistically significantly different with a p-value of 0.0002 [4].

The resulting levels of improvement by FMTVDM ranged from 21 to 77 (58.7 +/- 18.1).

7. Discussion

CoVid-19 has been responsible for the deaths of hundreds of thousands of people worldwide. These deaths are the result of InflammoThrombotic responses [3] resulting from immune activation following infection and replication of the virus.

In the absence of clinical trials and measurement of CVP many clinicians have been promoting and using anecdotal information to treat CoVid-19 patients. One popular treatment approach has been the use of HCQ and Zn in the outpatient setting. Participation in this clinical trial required confirmation of CoVid-19 by PCR testing; concurring signs and symptoms, and admission to a health care facility.

Table 1: Demographic information and FMTVDM measurements.

Site & Pt #	Age	Sex	Kg	CVD	DM	FMTVDM 1	FMTVDM 2	Change in FMTVDM
1 & 1	69	M	79	Yes	Yes	197	120	77
1 & 2	91	M	88	No	No	140	119	21
1 & 3	80	F	82	Yes	Yes	172	118	54
2 & 1	73	M	95	No	No	180	128	52
2 & 2	87	M	85	No	Yes	200	125	75
2 & 3	64	M	85	No	Yes	201	142	59
2 & 4	49	M	80	No	Yes	190	117	73

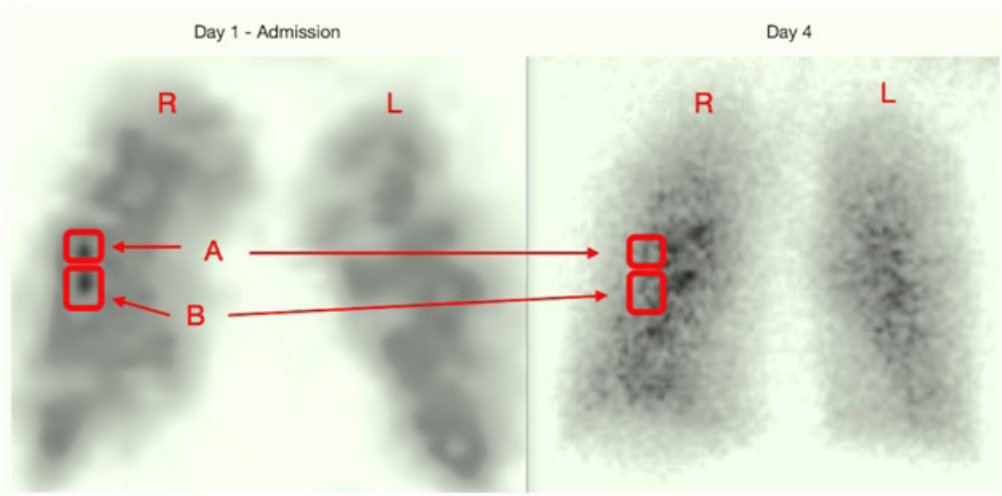

Figure 2: FMTVDM results from site 2, patient 1.
Legend: Initial CVP in the right lung measured 170 in region A and 180 in region B. After 72-hours of treatment, improvement was seen with measurements of 125 for region A and 128 in region B. The right (R) and left (L) lung fields are marked accordingly.

The hypothesis behind the proposed HCQ and Zn treatment is that (1) HCQ works by interfering with S-protein binding, inhibition of glycoprotein IIb/IIIA, inhibition of the toll 7-receptor, interference with cytosol removal of viral envelope for viral replication, and enhancement of the Zn ionophore channel; and (2) Zn interference with viral replication and the p53 protein morphologic folding.

CVP is the result of both the attachment and replication of the virus and the immune response to the viral infection – both of which result in increased metabolic and regional blood flow changes that can be measured using FMTVDM – allowing for measurement of the severity of CVP and treatment responses. In these 7-individuals, each improved as shown by the reduction in FMTVDM numbers. We also note an appreciable variability in response to treatment as shown by the change in FMTVDM.

This small subset of patients represents the first known reporting of individuals treated with HCQ and Zn as outpatients who subsequently required hospitalization for further treatment. Inclusion into the combined treatment arms required both the requirements to be entered into the study as well as elevated IL-6 and ferritin levels indicating ITR.

Since these patients had no prior outpatient FMTVDM, IL-6 or ferritin levels for comparison, treatment failure was determined by their lack of improvement and the reporting of symptoms worsening resulting in admission. We therefore cannot quantitatively state that they failed treatment with HCQ and Zn, only that they required admission and with worsening of symptoms were clinically determined to have failed HCQ and Zn treatment.

The combination of treatments including immune support, bronchodilator therapy, Tocilizumab and interferon α-2β makes it impossible to state whether the improvement seen was the result of one or a combination of these treatments.

8. Conclusion

To the best of our knowledge this is the first reported study looking at patients anecdotally treated with HCQ and Zn who required hospitalization. It does not provide information about the numbers

of patients that receive this treatment and were not admitted. It does demonstrate a potential treatment for patients with CVP who require hospitalization after failing outpatient treatment. In this instance each of the patients demonstrated improvement following treatment with Tocilizumab, Interferon α-2β Atrovent and SQ heparin – all focusing on the reduction of viral replication and ITR. Further work is needed to determine the benefit of this treatment regimen.

9. Acknowledgement: FMTVDM is IP patented to the first author and was made available following training to participating sites without cost. The figures are reproduced with the expressed consent of the first author. These patients are part of a larger NCT04349410 study to be published elsewhere in its entirety.

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