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Recommended Citation

Maddani, Sagar S.; Chaudhuri, Souvik; Deepa, Hunasaghatta Chandrappa; and Amara, Vedaghosh, "A multicenter questionnaire-based study to know the awareness and medical treatment plan of physicians involved in the management of covid-19 patients" (2020). *Open Access Archive*. 1698.
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ORIGINAL ARTICLE

A Multicenter Questionnaire-Based Study to Know the Awareness and Medical Treatment Plan of Physicians Involved in the Management of COVID-19 Patients

Sagar S Maddani[1], Souvik Chaudhuri[2], Hunasaghatta Chandrappa Deepa[3], Vedaghosh Amara[4]

Abstract

Introduction: The pandemic coronavirus disease 2019 (COVID-19) is on the raise in our country and there is there is no specific treatment modality available presently. The treatment of the disease largely remains symptomatic but repurposed drugs used to treat other disease conditions are being used to treat moderate to severe form of the disease. As the clinical trials for these drugs are ongoing, we conducted this survey to know the physicians' medical treatment plan for COVID-19 patients.

Materials and methods: It was a Web-based questionnaire study. Institutional ethical committee clearance was taken before the commencement of the study. There were a total of 17 questions, the first 6 being about the demographics, place of work, and whether the clinician was involved in the care of COVID-19 patients. Subsequent 11 questions were to assess physician's awareness and plan of the medical management of the COVID-19 patients.

Results: The majority of the clinicians were aware of the various treatment modalities available for the treatment of COVID-19. Regarding the plan for use of hydroxychloroquine (HCQ), 55% of the total respondents intended to use the drug in combination with azithromycin, even as 62% agreed that there was no clear evidence yet. About 90% of all clinicians, from junior residents to consultants, were monitoring electrocardiogram (ECG) during HCQ therapy; however, there were 10% of physicians who were not practising ECG monitoring. About 68% of clinicians were aware of the various therapeutic options being tested, like convalescent plasma, lopinavir–ritonavir, and 64% knew about remdesivir. There was divergence regarding the use of steroids in a cytokine storm among the physicians, with only 39% of consultants planning to use steroids whereas about 50% of junior residents and 79% of junior consultants were planning to use the drug.

Conclusion: The majority of the clinicians involved in the management of COVID-19 were aware of the various drug modalities available for treatment. However, more emphasis on the adverse effects and possible drug interactions is required. There is disaccord regarding the use of steroids in cytokine storm in COVID-19 and further guidelines and educational programs should address these issues.

Clinical significance: Clinicians have to be made more aware of the possible adverse effects and drug interactions of the medications used for the treatment of COVID-19. The treatment of the serious, cytokine storm syndrome and the role of steroids must be elucidated as soon as it is feasible.

Keywords: Coronavirus disease 2019, Cytokine storm, Hydroxychloroquine, Medical management, Remdesivir.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23567

Introduction

The coronavirus disease-2019 (COVID-19) is a global pandemic caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] No specific therapeutic regimen has yet been recommended for patient management. Many drugs have shown antiviral activity against SARS-CoV-2 in *in vitro* studies; however, their efficacy and safety in humans have yet not been authoritatively established. As the pandemic ravages across the world, repurposed drugs like chloroquine, hydroxychloroquine (HCQ), lopinavir–ritonavir, ribavirin, and interferon-α and -β are being tested in trials.[2,3] As the management strategies for COVID-19 still evolve, we designed this questionnaire-based survey to perceive the awareness and practice among treating physicians regarding the various treatment modalities. The multicenter survey involving juniormost to the senior clinicians would enable us to know skepticism, if any, regarding the treatment approaches, and work toward these lacunae. Guidelines by critical care society or educational programs may be imperative.

Materials and Methods

This was a Web-based, multicenter, questionnaire-based, cross-sectional study, conducted over 6 weeks (May 3–June 10, 2020). Institutional ethics committee clearance was obtained before the start of the study (IEC: 295/2020). The questionnaires were sent to physicians presumed to be involved in the care of COVID-19 patients.

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How to cite this article: Maddani SS, Chaudhuri S, Deepa HC, Amara V. A Multicenter Questionnaire-Based Study to Know the Awareness and Medical Treatment Plan of Physicians Involved in the Management of COVID-19 Patients. Indian J Crit Care Med 2020;24(10):919–925.

Source of support: Nil

Conflict of interest: None

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Study Design

The study was designed by members of the intensive care unit using a Web-based platform. The questions were selected to identify the responder's demographic characters, their awareness, and the plan of medical management. The content of the questionnaire was based on the literature review and the questions were further validated by five experts who were involved in the care of COVID-19 subjects. The comments from the experts were analyzed and modification was made in the questionnaire. The questionnaire was then sent to 10 doctors to know whether they could interpret the questionnaire appropriately. Their response was examined and relevant changes were made in the questionnaire.

The drafted questionnaire was sent as an e-mail link to the physician intensivists all over India who were presumed to be involved in COVID-19 care. The physicians were allowed to take part in the survey only if they consented for the same, after reading the participant information sheet. The questionnaire had 17 questions and was segregated into two parts. Part one consisted of 6 questions about demographics data of the study participants. Part two had 11 questions about physician's awareness and plan of medical management. Answer choices were determined based on the type of question and a range of discrete options were used to assess demographics and patient management. Participants were allowed to enter their answers wherever it was appropriate. Only once a person was allowed to take the survey as repeated attempts were not allowed.

Statistical Analysis

No previous study in this subject matter and no standard treatment guidelines are available presently; hence, it was not possible to calculate the sample size. The data collected through the Web platform were entered into Microsoft Excel. The categorical variables were expressed as frequency (percentage) and a chi-square test was applied to the demographic profile of respondents to correlate it with their awareness and plan of medical management.

Results

Demographics of Respondents

The responders were junior residents, senior residents, assistant professors/junior consultants, associate professors/associate consultants, and professors/consultants (Table 1). Among the responders, 72% were male and 28% were females. The age group and distribution of the responders are described in Table 1. Total 190 responders completed the survey and opined they are involved in COVID-19 patient management.

Table 1: Demographic characteristics of responders, *n* (%)

Gender	Male	137 (72)
	Female	53 (28)
Age	20–35	140 (73)
	36–50	44 (23)
	51–65	4 (2)
	>65	2 (1)
Designation	Junior resident	51 (27)
	Senior resident	35 (18)
	Assistant professor/junior consultant	52 (28)
	Associate professor/associate consultant	13 (7)
	Professor/consultant	39 (20)

Awareness and Plan Regarding Medical Management

Regarding the use of HCQ, 55% of the total respondents intended to use the drug in combination with azithromycin (AZ), and only 17% were planning to use HCQ as the sole drug (Fig. 1). However, when responses were analyzed according to their designation, about 48% consultants were planning to use HCQ + AZ combination, against 69% of SR (Table 2). More physicians in corporate hospitals compared to medical colleges were convinced about the use of combination therapy of HCQ with AZ (63% vs 52%) (Table 3). About 94% of the physicians were aware of HCQ's propensity to cause cardiac arrhythmias; however, only 30% were aware of the other adverse effects like hepatitis (Fig. 2). The majority of the physicians from JR, SR, and junior consultants said there is some evidence for HCQ use, but still it is unclear as various study results are awaited (Fig. 3). However, most consultants (50%) opined presently there was no evidence to use HCQ for the treatment of COVID-19 (Table 2). Regarding Indian Council of Medical Research (ICMR) recommendations, about 59% of respondents were aware that HCQ has to be used with AZ in severe COVID-19 infection as an off-label treatment (Fig. 4). About 90% of all physicians, from juniormost to consultants, were monitoring electrocardiogram (ECG) during HCQ therapy; however, there were about 10% of physicians who were not practising ECG monitoring (Fig. 5). Even though 56% were monitoring liver function tests during HCQ therapy, fewer were monitoring for blood glucose levels and complete blood picture (about 36 and 47%, respectively) (Fig. 6). Regarding the use of other drugs in COVID-19 patients, more than two-thirds of the physicians were aware of the use of convalescent plasma therapy, lopinavir–ritonavir, and remdesivir (Fig. 7). About 80% of the physicians were aware that antiretroviral agent lopinavir–ritonavir is being proposed for COVID-19 patient management. Whereas only one-third were aware of its adverse effects, like exaggerated QT prolongation when used with HCQ (37%), and a common cause of discontinuation of therapy is severe gastrointestinal side effects (26%). Regarding remdesivir, 79% of physicians were aware that this drug is being used for the treatment of COVID-19 and trials are ongoing regarding its use; 39% were aware it is currently United States Food and Drug Administration (USFDA) approved (Fig. 8). There was a major variation regarding the opinion

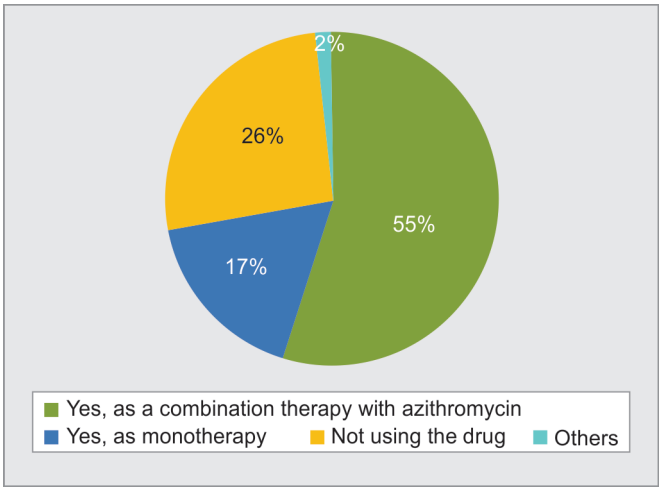

Fig. 1: Use of hydroxychloroquine in the medical management of COVID-19 patients

Table 2: The most common responses of physicians regarding medical management of COVID-19 patients according to their designation

	Junior resident (n = 51)	*Senior resident (n = 35)*	*Junior consultant/asst. professor (n = 52)*	*Professor/consultant (n = 52)*
In the medical management are you using/planning to use HCQ	Yes in combination with AZ (50%)	Yes in combination with AZ (69%)	Yes in combination with AZ (55%)	Yes in combination with AZ (48%)
Awareness regarding the adverse effect of HCQ	QT prolongation and arrhythmias (100%)	QT prolongation and arrhythmias (100%)	QT prolongation and arrhythmias (93%)	QT prolongation and arrhythmias (85%)
Evidence to use HCQ	Some evidence, but it is unclear (57%)	Some evidence, but it is unclear (81%)	Some evidence, but it is unclear (66%)	No evidence (50%)
Routinely monitoring ECG	Yes (90%)	Yes (95%)	Yes (80%)	Yes (88%)
Other medication awareness	Convalescent plasma therapy (71%)	Lopinavir–ritonavir (77%)	Lopinavir–ritonavir (76%)	Convalescent plasma therapy (67%)
Awareness regarding remdesivir	Trials are ongoing for COVID-19 treatment (68%)	Trials are ongoing for COVID-19 treatment (81%)	Trials are ongoing for COVID-19 treatment (69%)	Trials are ongoing for COVID-19 treatment (85%)
Use of steroids for suspected cytokine storm	Yes (50%)	Yes (70%)	Yes (79%)	Yes (39%)

Table 3: Comparing most common responses of the physicians in medical college and corporate hospitals

	Medical college 99 (52%)	*Corporate hospital 91 (48%)*
Use of HCQ in the medical management	Yes in combination with AZ (52%)	Yes in combination with AZ (63%)
Awareness regarding the adverse effect of HCQ	QT prolongation and arrhythmias (95%)	QT prolongation and arrhythmias (95%)
Evidence to use HCQ	Unclear evidence (58%)	Unclear evidence (64%)
ICMR guidelines	Off-label indication for severe cases (61%)	Off-label indication for severe cases (59%)
Routinely monitoring of ECG	Yes (83%)	Yes (91%)
Other medication awareness	Convalescent plasma therapy (80%)	Lopinavir–ritonavir (68%)
Awareness regarding remdesivir	Trials are ongoing for COVID-19 treatment (74%)	Trials are ongoing for COVID-19 treatment (82%)
Use of steroids for suspected cytokine storm	Yes (64%)	Yes (54%)

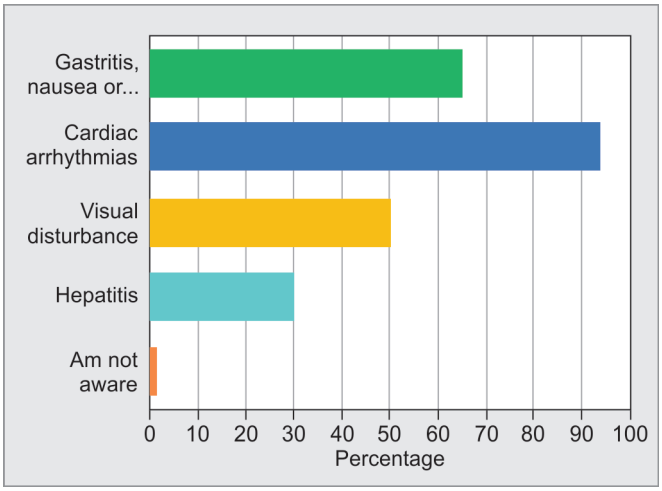

Fig. 2: Awareness regarding adverse effects of hydroxychloroquine

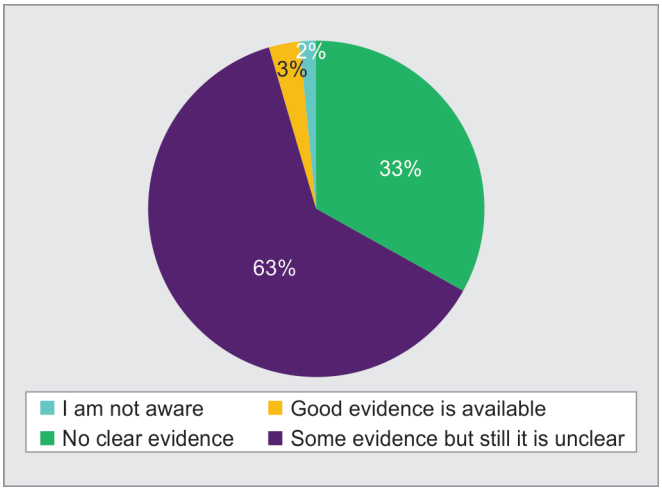

Fig. 3: Evidence for hydroxychloroquine use

of using steroids in the cytokine storm in COVID-19 (Fig. 9). About 50% of JR, 70% of SR, and 79% of junior consultants were in favor of using it, whereas only 39% of consultants were willing to use it in such a scenario; this variation was statistically significant (p value < 0.05) (Table 2). Likewise, a greater number of physicians in medical colleges favored use of steroids in cytokine storm (64%), compared to corporate hospitals (54%). Convalescent plasma being used as a potential treatment was reflected in the opinion with 71% showing awareness about it, but only 14% were conscious of the fact that the sooner during the disease course it is administered, the more beneficial it may be (Fig. 10). A greater number of physicians in medical colleges were aware of remdesivir and convalescent therapy,

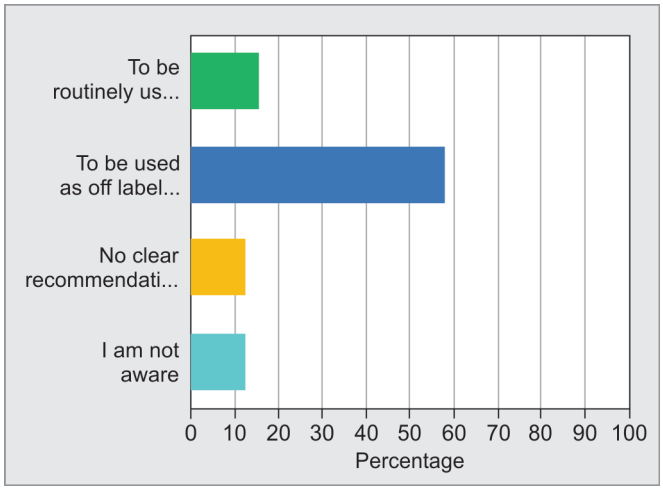

Fig. 4: Awareness of the ICMR recommendation for the use of HCQ in COVID-19 patient

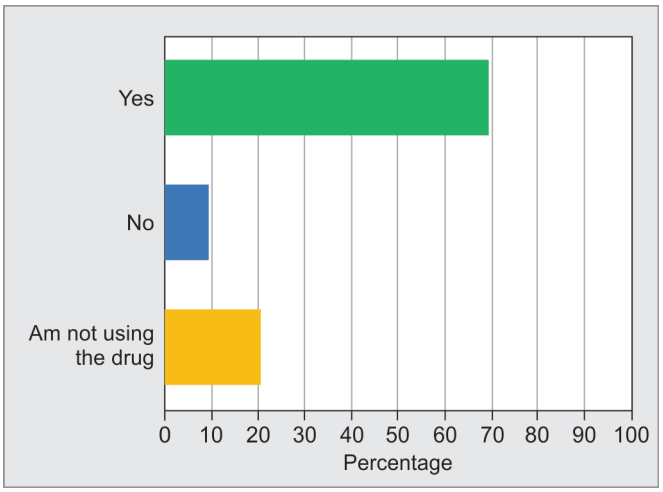

Fig. 5: Regular monitoring of ECG in patients to whom HCQ is prescribed

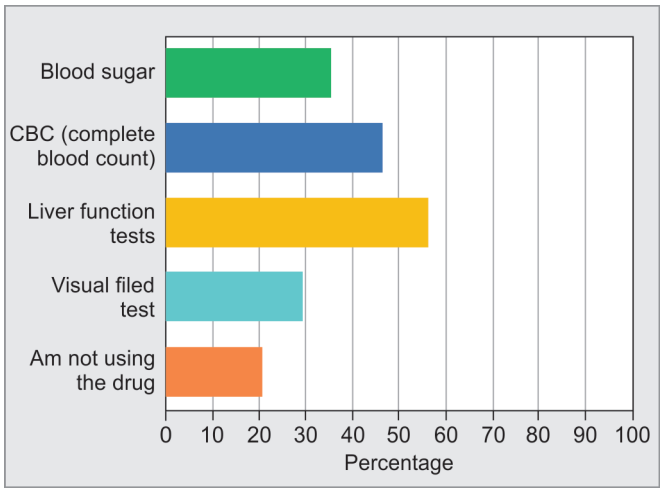

Fig. 6: Monitoring of laboratory parameters in patients when HCQ was prescribed

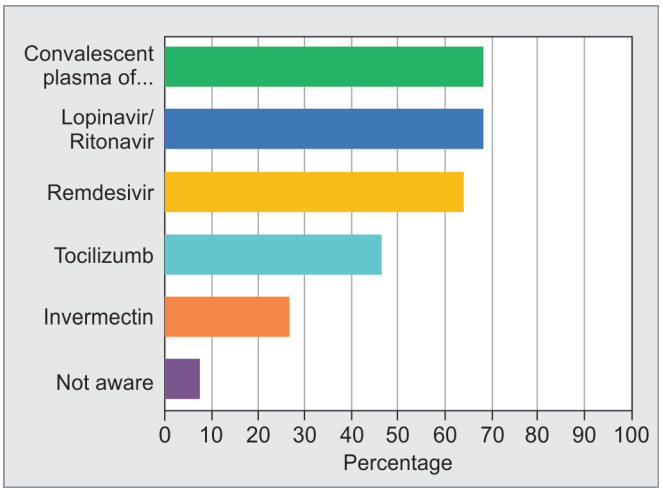

Fig. 7: Awareness regarding other medications being used to treat COVID-19 patients

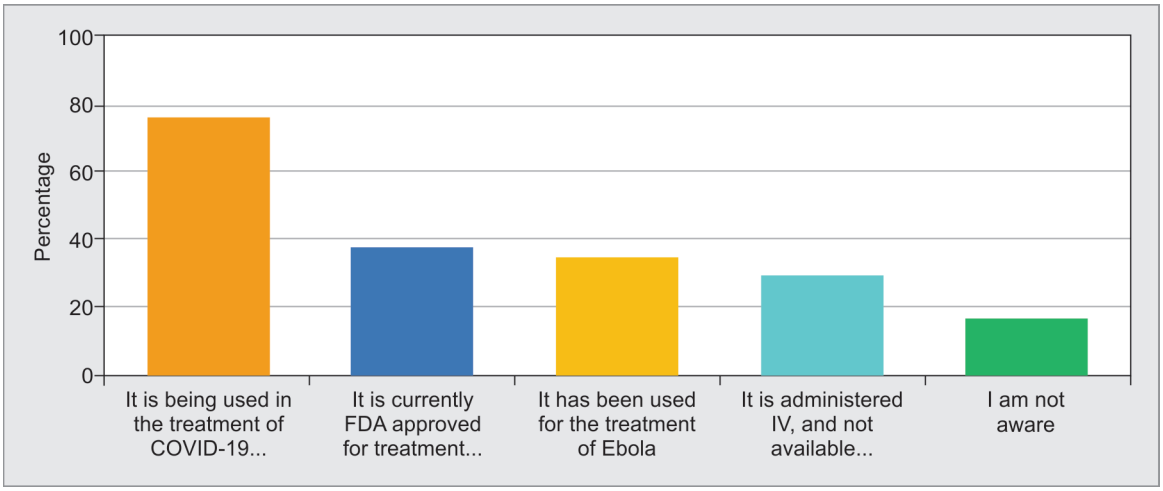

Fig. 8: Awareness regarding use of remdesivir

whereas in the corporate hospitals, more were cognizant about lopinavir–ritonavir (Table 3).

Discussion

A majority of the physicians were planning to use HCQ + AZ combination as therapy for the treatment of COVID-19 patients. However, there was a major difference in the number of SR compared to the number of consultants or professors who were willing to use HCQ. This implies consultants/professors would need further evidence to use of HCQ as it is known to cause adverse effects like QT prolongation when used with other medication. The majority favoring the use of HCQ with AZ would have been influenced by the result of the French study, where they analyzed 1,061 patients treated with HCQ and AZ combination.[1] The study concluded that the administration of the HCQ + AZ combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients.[1] However, an important aspect of the above study was that most of the patients (95%) had mild disease. Apart from inhibition of SARS-CoV-2, HCQ has been also shown to inhibit human immunodeficiency virus type I (HIV 1), dengue virus, enterovirus, Zika virus, hepatitis C virus, and influenza A H5N1.[4–6] The utility of HCQ was also corroborated by the advisory of the Indian Council of Medical Research advisory on the use of HCQ for prophylaxis among healthcare workers.[7]

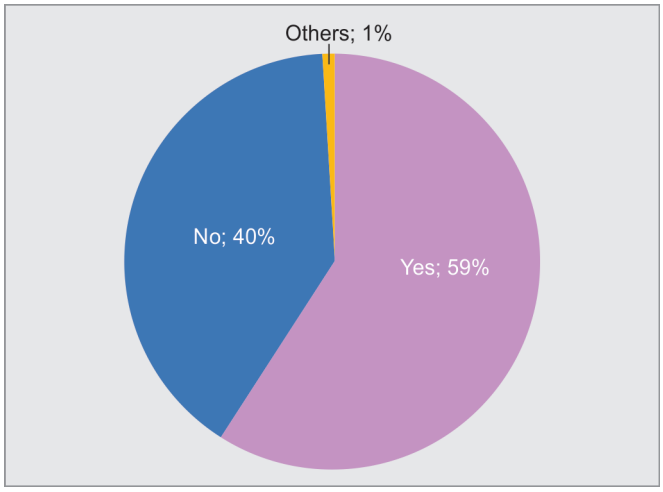

Fig. 9: Use of steroids in COVID-19 patients, suspected to have cytokine storm

Adverse effects of HCQ includes QTc prolongation, hypoglycemic episodes, hepatitis, acute pancreatitis, neutropenia, and retinopathy.[2] Baseline ECG too is essential before and following initiation of these medications especially in critically ill patients and those taking concomitant QT interval-prolonging medications such as AZ and fluoroquinolones.[3] Majority of the physicians involved in the survey were aware of the cardiac arrhythmias and were monitoring ECG, but less percentage of them were aware of other common adverse effects like hypoglycemia, leucopenia, and hepatitis. This shows physicians should use HCQ with more sagacity and they should be acquainted with all the adverse effects of HCQ.

Remdesivir is one of the potential drugs being used in the management of COVID-19 infection.[8,9] Remdesivir efficacy was proclaimed in a cohort study by Grein et al., where they showed a recovery in 68% of hospitalized patients with severe COVID-19.[10] In our study compared to senior physicians, fewer junior residents were aware of the use of remdesivir; this signifies senior physicians are updated about recent evidence compared to residents. Most of the respondents were aware that lopinavir–ritonavir combination is proposed for patient management but only a one-third knew gastrointestinal side effects of lopinavir–ritonavir like nausea, vomiting, and diarrhea are common and they frequently cause discontinuation of therapy.[11,12] Thus, there is a lacuna in the knowledge of drug adverse effects and interactions among physicians.

Cytokine storm syndrome can occur in a subset of patients with severe COVID-19.[13] It is characterized by hemophagocytic lymphohistiocytosis (HLH) and causes cytokine-related damage to the lungs and multiple organs of the body.[14] Early warning indicators include temperature >38.4°C, raised interleukin-6 (IL-6), cytopenias, hypertriglyceridemia, raised fibrinogen, ferritin, and serum aminotransferase.[13] Various therapies are being studied, including steroids, intravenous immunoglobulin, selective cytokine blockades like anakinra (interleukin 1 receptor antagonist), and tocilizumab.[13]

Tocilizumab is a monoclonal antibody and is an IL-6 receptor antagonist and is primarily approved for severe rheumatoid arthritis.[15] It also received emergency use authorization from USFDA for treatment in severe COVID-19 patients. A report of 21 patients with severe COVID-19 infection, who received tocilizumab 400 mg,

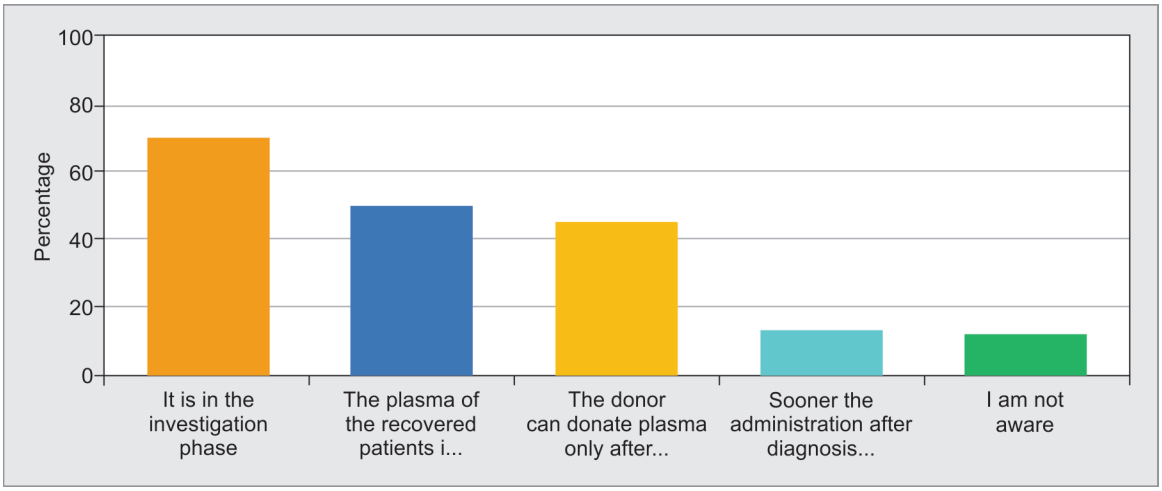

Fig. 10: Awareness regarding convalescent plasma therapy in COVID-19 patients

showed clinical improvement in 91% of patients as measured by improved respiratory function, rapid defervescence, and successful discharge, with most patients receiving only one dose.[16] In our study, only 50% of respondents were aware of tocilizumab for severe COVID-19 disease. Physicians must be more cognizant about tocilizumab as it is one of the potential treatments for cytokine storm, as more data regarding its use keep emerging.

One controversial aspect of treatment of the cytokine storm in COVID-19 is the use of corticosteroids. Predominantly consultants/professors were not in favor of its use compared to the rest of the physicians, who were convinced of using steroids. This lack of consensus is because of a lack of clear evidence. The WHO guidelines at present do not recommend steroid use in COVID-19, and increased mortality and secondary infection have also been noted in a study.[17,18] In contrary to the above, a recent article in the Lancet recommends steroids as a treatment option for cytokine storm in COVID-19.[13] Larger trials are mandated to have a comprehensive and definitive answer to this issue.

About 71% of the physicians in the questionnaire were keeping themselves abreast about the use of convalescent plasma. A systematic review of the results of treatment with convalescent plasma transfusion revealed that it is safe, effective, and reduces mortality.[19] However, a more recent study concluded that among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days.[20] This shows that we must be constantly updating our knowledge about treatment modalities of COVID-19, which is changing very rapidly.

The results of our study indicate most of the physicians were aware of the medical treatment options available to treat COVID-19 patients. However, a deeper look reveals that more educational programs are required to provide sound knowledge for COVID-19 patient management. This thought was also echoed in the questionnaire study done by Modi et al., in the Mumbai metropolitan region.[21]

To the best of our knowledge, this is the first questionnaire-based study conducted pan India to know about the awareness of medical management of COVID-19 among treating physicians.

There were few limitations of our study, which include the study could have been more informative about the therapeutic profile of commonly used drugs so that responders could have gained more knowledge by simply answering it. Aspects like cytokine storm in COVID-19, how to identify it, and early warning scores could have been incorporated in study questions. The use of corticosteroid not only in a cytokine storm but early acute respiratory distress syndrome (ARDS) due to COVID-19 also could have been addressed.

Conclusion

The awareness about HCQ use with AZ is present widely; however, ECG monitoring must be emphasized in all cases where this drug combination is used. Apart from cardiac toxicity, other adverse effects of HCQ like hypoglycemia should be looked for and also an exhaustive knowledge of the entire safety profile of HCQ should be disseminated among treating physicians. Drug interactions are another aspect where we found a knowledge deficit, which needs more emphasis. We need further evidence for the management of "cytokine storm" in COVID-19 patients so that the early recognition and management helps in a better outcome, especially with the use of tocilizumab and corticosteroids.

Clinical Significance

The results of our study indicate present awareness and medical treatment plan of physicians involved in the management of COVID-19 patients. Most of the physicians were aware of the medical treatment options; however, physicians have to be made more aware of the possible adverse effects and drug interactions of the medications used for the treatment of COVID-19. The treatment of the cytokine storm syndrome and the role of steroids must be elucidated as soon as it is feasible with more evidence.

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