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THE EFFECTS OF LOW DOSE HYDROXYCHLOROQUINE AND AZITHROMYCIN COMBINATION THERAPY ON COVID-19 PROGNOSIS

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ABSTRACT

Background and Objective: The global pandemic of COVID-19 has challenged medical and scientific communities to produce effective therapy options for this new highly contagious virus. At present there are no effective treatment thus utilizing existing medication to counter COVID-19 is vital. This report outlines the safety, tolerability and effectiveness of combination of hydroxychloroquine and azithromycin in COVID-19 prognosis. **Methods:** From 18th March to 30th September 2020, fifteen COVID-19 patients from different parts of Iran were treated at their home following the diagnosis of COVID-19 infection. Diagnosis was confirmed by chest CT scan examination between 18th March 2020 till 10th July 2020 and by PCR testing from 11th July 2020 till 30th September 2020. **Results:** All 15 patients fully recovered from their symptoms following administration a of low dose hydroxychloroquine (200 mg mane for 10 days) and azithromycin (500 mg nocte for 7 days). There were no adverse events due to therapy and the combination therapy was well tolerated. **Conclusion:** At the time that there are no bespoke therapy options available for COVID-19, high mortality rate could be reduced by low dose hydroxychloroquine and azithromycin combination therapy.

KEYWORDS: COVID-19, Hydroxychloroquine, Azithromycin, Combination therapy, CT-diagnosis.

INTRODUCTION

Emergence and rapid spread of a novel viral infection commonly known as COVID-19 from Wuhan, China not only posed a serious health issue globally, but it also challenged medical science in providing a swift response when a communicable disease becomes pandemic. The speed of COVID-19 spread did not allow medical science the luxury of routine bespoke therapeutic drug development thus re-directing existing medications to manage COVID-19 patients were significant to healthcare providers. At present the best option to counter COVID-19 infection is prevention; not to be infected.[1] However, there are several reports of using existing drugs in treating COVID-19 infection. The treatment options used include several antiviral (hydroxychloroquine) alone or in combination with azithromycin (an antibiotic) or a cocktail of antiviral drugs sponsored as a mega trail (SOLIDARITY) by the World Health Organisation (WHO).[2] The SOLIDARITY trial used a combination of HIV drugs (Ritonavir/loinavir) plus a malaria drugs (chloroquine and hydroxychloroquine) and an Ebola drug (Remdesivir) with an extra arm with combination of ritonavir/lopinavir and interferon beta.

In this study we report effective management of COVID-19 patients with mild to moderate signs and symptoms using a combination of an antiviral (hydroxychloroquine) and an antibacterial (Azithromycin) in 15 patients in Iran.

METHODS

From 18th March 2020 to 30th September 2020, fifteen adult COVID-19 patients (11 men and 4 women) from different parts of Iran are included in this report. Patient distribution were: four from Mazandaran region, six from Tehran and five from West Azerbaijan region of Iran. They were all complaining of flu like symptoms which included headache, joint pains, general malaise, loss of appetite, swinging temperature, shivering and dry cough for at least 7 days before seeking medical help. To ascertain the likelihood of or otherwise COVID-19 infection, CT scan of lungs were performed in seven patients (seen between 18th March 2020 till 10th July 2020) whilst PCR testing was performed to confirm COVID-19 infection in the remaining eight patients (seen from 11th July 2020 till 30th September 2020). During COVID-19 treatment, paracetamol 1 g every 6

hours was used to manage temperature and a combination of hydroxychloroquine (200 mg mane) and azithromycin (500 mg nocte) were administered to all patients.

RESULTS

None of the patients reported known close contact with COVID-19 infected patients, but all were regularly attending their normal work or social pattern prior to developing signs and symptoms of COVID-19 infection. One patient (32 years old) had pemphigoid which was treated with prednisolone 40 mg daily for one month followed by a course of rituximab 200 mg 10 days prior to COVID-19 infection. One patient (67 years old) has history of hypertension for which losartan 50 mg twice daily were used. Another patient (88 years old) had history of benign prostate hypertrophy treated with 400 microgram tamsulosin once daily. All patients who had a CT scan examination showed ground-glass opacities which were bilateral in five patients (62.5%) and unilateral in the remaining three patients (37.5%) (Fig.1).

Generalised malaise and loss of appetite were the most common features seen in all patients followed by swinging temperature (up to 39.2 ^{0}C) lasting up to eight days in majority of the patients (11 out of 15), shivering and dry cough and muscle/joint pains. Three patients also complained severe nausea and vomiting which persisted up to the third day of combination therapy. Two patients' temperature climbed up to 40.3 ^{0}C and remained above 39.1 ^{0}C for three consecutive days. The average highest temperature for the remaining patients were 38.2 ^{0}C for three consecutive days. Paracetamol 1 g every 4-6 hours (no more than 4 grams at every 24 hours) together with frequent washing of upper and lower limbs with cold water were used to lower body temperature in all patients. The patient with the history of pemphigoid had the most severe respiratory problems compared with the other 14 patients. Respiratory rate range was 18-26 in all patients with >94% oxygen saturation in 12 of the patients whereas the patient with pemphigoid had oxygen saturation as low as 88% at times which required three days of oxygen therapy in a local hospital. Another patient, a 36 years old male, had oxygen saturations as low as 90% for at least two days during the treatment period which required oxygen support. All other patients were at home and had no access to supportive oxygen.

A combination therapy of hydroxychloroquine (200 mg mane for 10 days) and azithromycin (500 mg nocte for 7 days) was used to treat COVID-19 in this report. All patient responded well to this treatment regimen and their conditions were significantly improved by the end of treatment period and fully recovered after further 10 days of recuperation and rest at home. None of the patients in this report required long-term hospital admission nor any other interventions (expect the two cases of supportive oxygen therapy). No patient complained of gastrointestinal, cardiovascular or neurological side effects. All patients are now either returned to their work (12/15 patients) or enjoying their social interactions (retired patient 3/15).

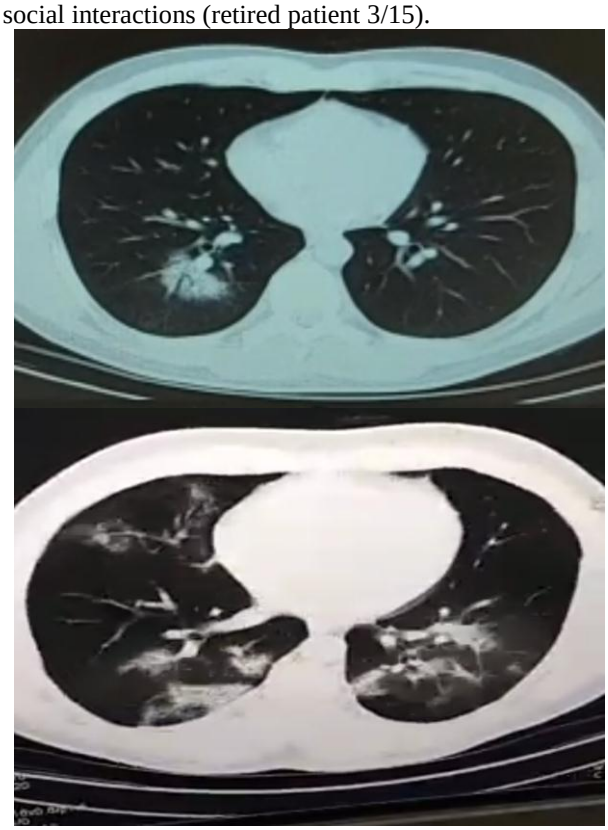

Figure 1: Chest scan showing unilateral (upper panel) and bilateral (lower panel) lung manifestation of COVID-19. The upper panel is from the patinet with no background diseases and the lower panel is from the patient with history of pemphigoid.

DISCUSSION

COVID-19 virus is highly contagious, affecting all population with poorer outcome in males and the elderly compared to female or the younger population, respectively.[1,3] Following an initial steep rise in COVID-19 infection rate, there seemed to be an apparent end to the first wave of COVID-19 infection rate and mortality,[1,4,5] however, rapid rise of infection rate globally once again is suggestive of a difficult times ahead which could pose a serious challenge on health care system in coming months. In the absence of an effective vaccine so far or being produced soon, it is more likely that COVID-19 infection will re-emerge several times until such a date that an effective vaccine is globally available. Nonetheless, the likelihood of COVID-19 vaccine being commercially available in 2020 is very slim.[6,7] therefore, it is imperative to be alert for the next COVID-19 assault and utilize existing pharmacological tools to manage its detrimental impacts. The importance of reusing/redirecting exiting medication to COVID-19 therapy has gained significant attention around the globe but have reported mixed outcomes.

Here we report the safety and effectiveness of hydroxychloroquine and azithromycin combination therapy in the management of COVID-19 infected

patients. Administration of low dose hydroxychloroquine (200 mg) for 10 days together with azithromycin (500 mg) for 7 days not only prevented deterioration of patients' conditions but also successfully improved all their COVID-19 symptoms, suggesting efficacy of this combination therapy in management of COVID-19 infection. However, it is important to note that both hydroxychloroquine.[8] and azithromycin[9] could cause QTc prolongation ultimately increasing risk of a cardiac event. To mitigate risk of QTc prolongation, we not only used low dose hydroxychloroquine (200 mg) but also ensured hydroxychloroquine and azithromycin (500 mg) dosing are at least 12 hours apart. Hydroxychloroquine was administered in the morning to allow the patient or their family members noticing potential cardiovascular symptoms and to seek medical advice via accident and emergency hospital if required. In this report, no patient complained of any cardiac symptoms and none had to attend emergency hospital for cardiac related issues. This suggests safety and tolerability of low dose hydroxychloroquine and azithromycin in this patient population.

The use of hydroxychloroquine alone or in combination with other antiviral and/or azithromycin for treatment of COVID19 patients have also been reported from different countries. A French study treating 1061 adult COVID-19 patients with a combination of hydroxychloroquine and azithromycin reported a good clinical outcome and virological cure in 91.7% (973 patients) patients within 10 days.[10] In our report we were not able to assess virological cure, but recovery was like that reported by the French team. Similarly, a Chinese study reported 67% of patients had shortened time to clinical recovery from COVID-19 induced pneumonia.[11] Nonetheless, there is controversy on the safety and effectiveness of hydroxychloroquine alone or in combination with azithromycin.[12] potentially due to their QTc prolongations.[8,9] adverse effects. Furthermore, the interim report of the WHO sponsored study (SOLIDARITY) enrolling approximately 12,000 patients in 500 hospitals over 30 countries including Iran, found that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients, whilst corticosteroids proved to be effective in severe cases of COVID-19 infection. The contrasting finding between our report and that of SOLIDARITY could be explained in term of the stage of COVID-19 infection. It is plausible to suggest that early intervention in relatively mild to moderate cases in our report but not severe cases, could benefit from combination therapy reported here. Similar finding has also been reported by Arshad etal (2020) in 2,541 COVID-19 patients followed up for over 28 days treatment where hydroxychloroquine + azithromycin provided 71% hazard reduction compared to no treatment.[14] In Arshad et al, (2020) study, hydroxychloroquine was dosed as 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5. Azithromycin was dosed as 500 mg once daily on day 1 followed by 250 mg once daily for the next 4 days. The combination of hydroxychloroquine + azithromycin was reserved for selected patients with severe COVID-19 and with minimal cardiac risk factors. In our report, we used low dose hydroxychloroquine + azithromycin in all patients with no history of cardiac risk factors thus reducing risk of potential QTc elongation. Therefore, it appears that patient focused tailored redirected use of currently available medications might provide an opportunity to manage COVID-19 infection until an effective vaccine is globally available.

In summary, our report clearly indicates safety, tolerability and efficacy of low dose hydroxychloroquine and azithromycin combination therapy in patients with mild to moderate COVID-19 infection. We acknowledge that sample in this study is very small and has no matched placebo, but at the time that there is no definitive cure for COVID-19, use of exiting potentially life-saving drugs is plausible.

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