Letter to the Editor

Overcoming the therapeutic nihilism of out-of-hospital management of COVID-19 patients

Simone Meini

Internal Medicine Unit. Felice Lotti Hospital, Pontedera; Azienda USL Toscana Nord-Ovest, Pisa, Italy

simonemeini2@gmail.com

Sir,

I read with great interest the Risch's paper [1] on the urgent need to discuss COVID-19 outpatient treatment. Many strategies have been tested since the pandemic began, but all that has emerged regarding non-hospitalized patients is a sort of therapeutic nihilism.

As I write (November 17, 2020), in Italy (60,244,639 inhabitants) there are 33,074 persons hospitalized for COVID-19, 3,612 requiring intensive-care, and many more (697,124) are in home isolation: our health-care system is on the verge of a new unsustainable burden. Most infected people are asymptomatic, but many will worsen and require hospitalization. It is therefore crucial to interrupt as early as possible disease progression. Outpatients do not receive regular laboratory monitoring, so the global disease impact on them remains unknown: any consideration on appropriate treatments must take into account this missing data.

I agree that hydroxychloroquine plus azithromycin (or doxycycline) could still be considered a suitable home-option, deserving further studies. Hydroxychloroquine 200mg twice-daily could optimize the efficacy/safety balance, doxycycline could be its ideal partner, inexpensive, safe and displaying antiviral, anti-inflammatory and lung-protective effects [2].

Other options for outpatients must be considered.

Antivirals are crucial when viral replication prevails over host response, but intravenous remdesivir is suitable only for hospitalized patients [3,4]. Oral lopinavir/ritonavir should be reconsidered [5]: loss of interest in this option began following Cao's trial [6] where no significant difference was observed in time to clinical improvement in 99 patients with severe COVID-19 treated with 400/100mg twice-daily for 14 days; excluding three patients who died within 24 h, the difference was significant. Patients on lopinavir/ritonavir, compared to 100 on standard-care, showed lower rate of 28-day mortality (19.2% vs 25.0%), intensive-care-stay (-5 days), Acute-Respiratory-Distress-Syndrome (-14.7%), secondary infections, mechanical ventilation; more patients clinically improved at 14-day (+15.5%). Lopinavir/ritonavir was started late, after a median of 13 days after symptom onset. The difference in mortality was greater among patients treated within 12 days. Overall mortality was 22.1%: the severity of patients enrolled could have contributed to the poor efficacy observed. Cao et al. [7] concluded that lopinavir/ritonavir may still be a potential treatment, recommending that clinicians review all trial's data. Gastrointestinal adverse events represent a concern [5,6], but Baldelli et al. [8] showed that COVID-19 patients co-treated with hydroxychloroquine have lopinavir/ritonavir trough concentrations three-fold higher compared with HIV-patients, due to SARS-CoV-2-induced liver damage or to interaction with hydroxychloroquine. Further investigation is warranted for a reduced dose, for early home-treatment.

Heparins counteract SARS-CoV-2 cell-entry and modulate immunothrombosis and cytokine storm [9,10]. The beneficial anti-thrombotic effects of enoxaparin 4000IU once-daily extend to a wide range of acutely ill medical patients (including acute respiratory failure and infectious disease), with

adverse effects comparable to placebo [11]. Low-molecular-weight-heparins in prophylactic doses, for a short time, could be a safe option for early home-treatment, especially for patients at higher risk of venous thromboembolism. Trials are ongoing (NCT04400799).

Finally, a dysregulated host response is crucial in causing organ failure: patients with clinical/laboratory evidence of inflammatory hyperactivation could benefit from anti-inflammatory interventions. Corticosteroids are associated with lower 28-day all-cause mortality in critical patients [12], and are recommended for all hospitalized patients with severe disease (dexamethasone 6mg=methylprednisolone 32mg=prednisone 40mg, daily) [13,14]. Although for now reserved to hospitalized patients, a wise use of low-dose corticosteroids, after the viral replication phase, might represent a suitable option also at home.

A pragmatic early home-based approach, possibly consisting of an association of HCQ 200mg twice-daily, doxycycline 100mg twice-daily, lopinavir/ritonavir 200/50mg twice-daily, enoxaparin 4000IU once-daily, for a relatively short time (5-10 days), and low-dose corticosteroids, could represent a standard approach for most symptomatic high-risk outpatients, deserving to be studied in registered clinical trials.

Funding: None.

Conflict of interest: None

References

1) Risch HA. Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis. Am J Epidemiol. 2020;189(11):1218-1226

2) Malek AE, Granwehr BP, Kontoyiannis DP. Doxycycline as a potential partner of COVID-19 therapies. IDCases. 2020;21:e00864

3) Beigel JH, Tomashek KM, Dodd LE et al; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020; NEJMoa2007764. doi: 10.1056/NEJMoa2007764.

4) Repurposed antiviral drugs for COVID-19-interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium. medRxiv preprint doi:https://doi.org/10.1101/2020.10.15.20209817

5) Meini S, Pagotto A, Longo B et al. Role of Lopinavir/Ritonavir in the Treatment of Covid-19: A Review of Current Evidence, Guideline Recommendations, and Perspectives. J Clin Med. 2020;9(7):2050.

6) Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-1799

7) Cao B, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Covid-19. Reply. N. Engl. J. Med. 2020; 382: e68

8) Baldelli S, Corbellino M, Clementi E et al. Lopinavir/ritonavir in COVID-19 patients: maybe yes, but at what dose? J Antimicrob Chemother. 2020;75(9):2704-2706

9) Meini S, Zanichelli A, Sbrojavacca R et al. Understanding the Pathophysiology of COVID-19: Could the Contact System Be the Key? Front Immunol. 2020; 11:2014

10) Drago F, Gozzo L, Li L et al. Use of Enoxaparin to Counteract COVID-19 Infection and Reduce Thromboembolic Venous Complications: A Review of the Current Evidence. Front Pharmacol. 2020; 11:579886.

11) Samama MM, Cohen AT, Darmon JY et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341(11):793-800

12) WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-1341.

13) Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5. Accessed on November, 17, 2020

14) Salton F, Confalonieri P, Meduri GU et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. Open Forum Infect Dis. 2020;7(10):ofaa421.