The rationale for Low-Molecular Weight Heparin (LMWH) use in SARS-CoV-2 infection

Giovanni Di Perri

Clinica di Malattie Infettive, Università degli Studi di Torino, Torino, Italy

SUMMARY

In spite of many ongoing attempts to repurpose existing antivirals, no drugs have emerged yet with the desirable activity against SARS-CoV-2. Hydroxychloroquine, lopinavir/ritonavir, remdesivir, umifenovir, favipiravir, ribavirin and β-interferon-1 gave rise to variable but still inconsistent proof of clinical efficacy in the treatment of COVID-19. Pathogenetic studies have shown significant differences between commonly defined viral pneumonia and COVID-19 pulmonary disease. In severe forms, immune/inflammatory alterations reminiscent of disease forms like Macrophage Activation Syndrome (MAS) have been described, and therapeutic options other than anti-infective have been proposed and implemented, such as anti-inflammatory and anticoagulative agents. The thrombotic phenomena described in the pulmonary vascular bed of patients with severe COVID-19 suggest the administration of low-molecular weight heparin (LMWH) as standard measure in hospitalized patients with COVID-19.

Keywords: SARS-CoV-2 infection

Following the appearance and worldwide circulation of SARS-CoV-2, the etiologic agent of COVID-19, a number of existing drugs with some putative antiviral effects were administered to patients in spite of the lack of any significant evidence of a possible therapeutic effect [1]. With no existing drugs of proven efficacy, in a sort of emergency experimental scenario, a series of drugs like hydroxychloroquine, lopinavir/ritonavir, azithromycin, umifenovir, faviparivir and remdesivir have been used both in a compassionate manner and in comparative clinical trials [2]. The intention to repurpose existing drugs is not new in viral diseases, as testified by the successful use of lamivudine and tenofovir (both TDF and TAF) in both HIV and HBV infection [3, 4]. However, unlike the case of bacteria, the target specificity of antiviral drugs is mostly species-specific and the results gathered in these months are so far rather disappointing.

Hydroxychloroquine use in COVID-19 patients was described in observational studies including thousands of patients, with hard endpoints like intubation and death [5]. No benefit was associated to hydroxychloroquine use but instead a higher risk of death was found to be associated to the intake of both hydroxychloroquine alone and in combination with a macrolide. While much criticism was expressed around these observational studies [6], especially concerning some apparent inconsistency of data analyzed, no data from randomized controlled trials on hydroxychloroquine are yet available.

Lopinavir/ritonavir, still a second line antiretroviral drug, was tested in a small-sized open randomized trial in COVID-19 patients with minor degrees of respiratory failure, but the non-significant limited benefit recorded in lopinavir/ritonavir recipients has discouraged its further use in COVID-19 patients [7].

Corresponding author
Giovanni Di Perri
Email: giovanni.diperri@unito.it

Umifenovir and favipiravir were compared in a randomized study with no control arm. Although an overall better outcome was recorded in favipiravir recipients (7 day recovery rate), the lack of a control arm made it impossible to draw any meaningful conclusion about the possible role of these anti-influenza drugs in COVID-19 patients [8].

In a randomized double-blind comparative trial the use of remdesivir was not found to be associated to a significant improvement when compared to placebo [9]. In the same study, the use of remdesivir did not even provide a faster viral clearance from upper airways, thus casting doubts about its real antiviral effect against SARS-CoV-2. In a further numerically larger (538 *vs* 521 patients) double-blind comparative trial vs placebo remdesivir was instead found to be significantly associated to a shorter time to recovery and with a reduction in mortality, although not statistically significant (7.1% with remdesivir and 11.9% with placebo) [10]. These findings suggest that a very early administration of remdesivir might (mildly) impact on the clinical course of SARS-CoV-2 infection, although more insights into its real antiviral action are required.

More recently, the findings of a small-sized open randomized trial comparing β-interferon 1b in association with ribavirin and lopinavir/ritonavir vs lopinavir/ritonavir alone disclosed an advantage for the β-interferon 1b group in terms of a shorter time to viral clearance as established by nasopharyngeal swab [11].

Albeit some recognizable effects did actually emerge from few of such studies, this multifaceted drug-repurposing initiative is far from providing the desired results. This challenge is made methodologically more difficult by the relatively low mortality rate attributable to COVID-19, which makes mandatory the implementation of very large clinical trials with careful patients recruitment and stratification.

Newer findings concerning the pathogenesis of COVID-19 do suggest that pneumonitis developing in SARS-CoV-2-infected patients behaves differently as compared to viral pneumonia due to other respiratory pathogens [12]. A number of findings look atypical when compared to what is commonly known about conventional viral pneumonia, and two are particularly striking. The first concerns the rather short duration of fever in spite of developing pneumonitis. Patients requiring hospitalization are often admitted with fever, which often spontaneously subsides in spite of multiple still expanding infiltrations in the lungs. A second surprising point is the fast-developing pulmonary fibrosis, which is the pathologic landmark associated to respiratory failure and need for assisted ventilation [13]. A reappraisal of the pulmonary pathogenesis of COVID-19 has shed some light on a possible multistep mechanism taking place in the wide anatomic interface involving type II pneumocytes, interstitial space, microcirculation and macrophages [14]. SARS-CoV-2 was found to be able to infect type II pneumocytes through binding to ACE2 receptors, which are abundantly expressed in these resident pulmonary cells [15]. Infection of type II pneumocytes occurs in close anatomical connection with both the pulmonary microvascular network and lung stromal cells, including lymphocytes undergoing activation. This leads to macrophage recruitment and activation with associated release of proinflammatory and procoagulant molecules. In such a low blood pressure setting with thin vessel walls, immunothrombosis follows due to high local cytokines levels, tissue factor synthesis and eventual vessel injury [16]. Despite intensive fibrinolytic reaction microthrombi formation takes place, with ensuing pulmonary infarction, hemorrhages and pulmonary hypertension. The widespread hemorrhagic phenomena taking place in the lungs are then followed by extensive fibrotic reaction, which challenges to various extent the full recovery of respiratory function. Such a pathogenetic hypothesis well matches with the higher risk of severe disease forms in patients with pre-existing risk factors for cardiovascular diseases. This severe inflammatory response is reminiscent of the cytokine storm associated to the Macrophage Activation Syndrome (MAS), also termed secondary haemophagocytic lymphoblastocytosis (sHLH) [17], and these similarities prompted the promising experimental clinical use of anti-cytokine therapy in the treatment of severe forms of COVID-19 [18]. It is thus apparent, according to this pathogenetic hypothesis, that COVID-19 actually begins as a viral respiratory disease, but its major pathologic findings are the result of a so far incompletely disclosed delayed inflammatory/immune reaction [12]. As a consequence, while an early antiviral therapy (once available) might actually reduce the chance of a

subsequent severe progression (by possibly reducing viral replication in the airways), the treatment approach to COVID-19 should also be oriented to drugs avoiding thrombotic phenomena and mitigating the phlogistic processes.

Following both clinical experience and according to autopsy studies, coagulopathy is being perceived as increasingly important in the pathogenesis of severe COVID-19 disease [19]. In a Chinese case series in-hospital mortality was associated to D-dimer blood levels >1 μg/mL and coagulopathy was much commoner in patients who died (27/54, 50%) than in survivors (10/137, 7%, p<0.0001) [20]. However, the local (pulmonary) rather than systemic nature of coagulation abnormalities was apparent in these patients as, unlike disseminated intravascular coagulation (DIC), both platelets level and prothrombin time were found to be both in the normal range [14, 20]. D-dimer seems to actually play the role of a key parameter in estimating the severity of COVID-19 associated pulmonary disease. Although still debated, the administration of prophylactic heparin has gradually gained consent as standard measure to be applied to hospitalized COVID-19 patients, unless contraindicated [21]. In a retrospective investigation of 449 patients the mortality rate at 28 days was lower in heparin intakers when D-dimer levels were six times upper the normal limit of normality, and the same applied to those with sepsis-induced coagulopathy scores > 4 [22]. It must also be noted that heparin action in case of COVID-19 patients might not be limited to its anticoagulative effects, as interference with viral spike protein (binding to ACE2 receptors) and down-regulation of >IL-6, which

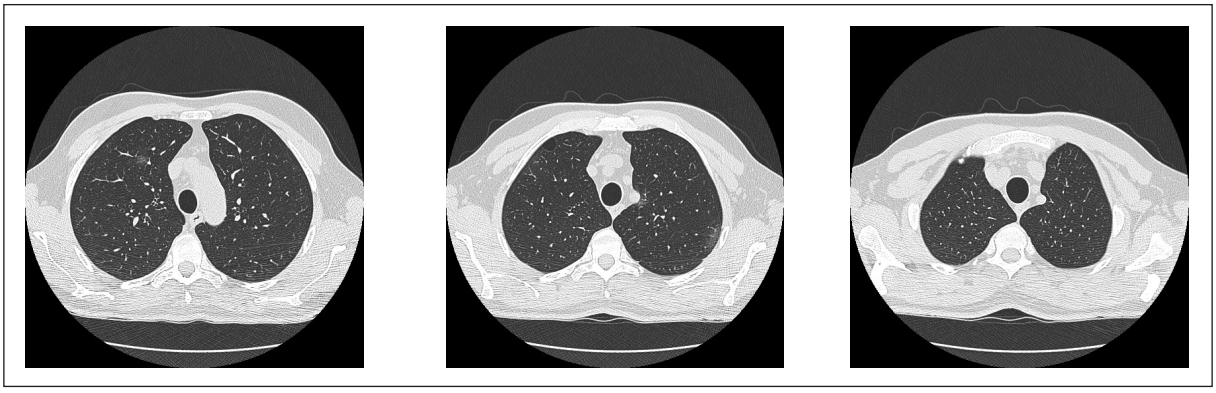

Figure 1a - Ct-Scan picture of a 52-male admitted for mild COVID-19 made on admission.

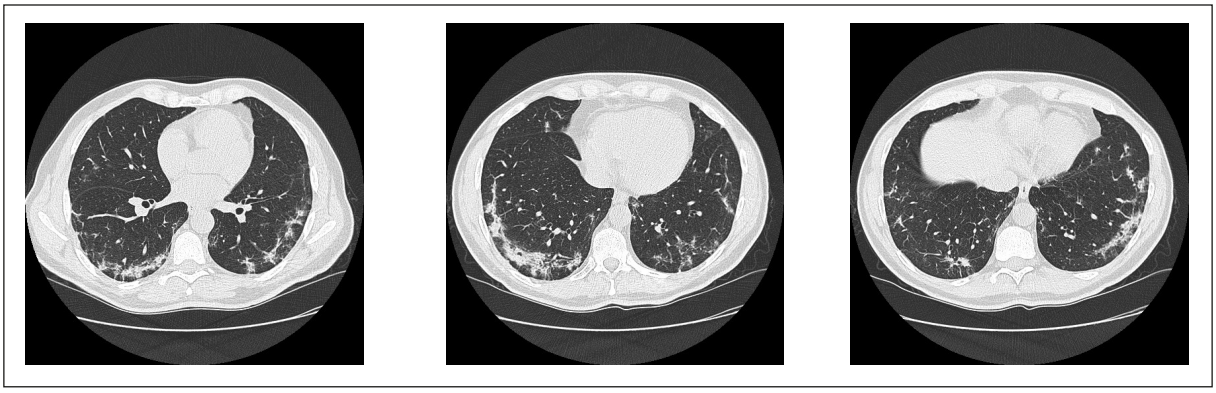

Figure 1b - Control CT-Scan picture made 15 days after hospital discharge in the same patient (who cleared his PCR signal for SARS-CoV-2 infection) showing nely appeared fibrotic lesions in the posterobasla lateral portions of the lungs. A further CT-Scan made a month later showed unaltered findings.

is part of the cytokine storm, have been both described [21, 23]. Timing and doses of heparin are still being discussed, and a randomized clinical trial with high-dose of the low-molecular weight heparin (LMWH) enoxaparin is ongoing in order to verify whether early LMWH treatment might impact on COVID-19 outcome [24]. The role of LMWH prophylaxis deserves attention also in clinical cases with limited evolution, as persistent pulmonary lesions with possible long-term impact on respiratory function have been described in patients who eventually recovered from COVID-19 [25].

The example here shown (see Figure 1) concerns a 52-year old male subjects who experienced mild respiratory failure during a 12-day hospitalization for COVID-19 in Italy. The patient was one of the first COVID-19 cases hospitalized in Torino, Italy, and no prophylactic LMWH was administered. He was admitted to the hospital following three days of cough, high fever, diffuse muscular aches and general malaise. Fever subsided after two days and an uneventful recovery took place, with first negative PCT test for SARS-CoV-2 infection at hospital discharge. Saturation was 91% on admission but rose to 97% four days afterwards. The patient had a mild disease, as also testified by his first CT-scan picture taken on admission. Once discharged he underwent a control visit after 15 days to confirm negativity of PCR testing for SARS-CoV-2 infection and for CT-Scan control. Testing for SARS-CoV-2 infection was confirmed as negative, but surprisingly, the CT-Scan disclosed new fibrotic pulmonary lesions in posterolateral-basal portions of the lung. These lesions remained unaltered at a further control made 20 days later, with saturation persistently above 97% and no additional signs or symptoms. LMWH prophylaxis was not given as such practice was standardized later in the course of the Italian COVID-19 epidemic, and the question here is whether its administration would have reduced the development or the size of these lately appearing pulmonary fibrotic lesions [26]. Whatever the answer, since residual fibrotic pulmonary lesion might impact on pulmonary function in recovered patients, these findings actually deserve attention, as such kind of post-recovery fibrotic morbidity might be less rare than otherwise expected. The analysis of a 70-patient series in China revealed that as much as 94% of patients (66/70) had residual disease on their final CT-Scans, with ground-glass opacities as the prevalent pattern [25].

While the final position of LMWH in the management of COVID-19 has still to be defined, the prophylactic use of LMWH, also considering its favorable risk/benefit ratio, seems warranted in patients requiring hospitalization.

Funding
None

Conflict of interest
None

REFERENCES

[1] Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. *Science* 2020; 367 (6485), 1412-3.
[2] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020; 14 (1), 58-60.
[3] Sokal E. Lamivudine for the treatment of chronic hepatitis B. *Expert Opin Pharmacother*. 2002; 3 (3), 329-339.
[4] Childs-Kean LM, Egelund EF, Jourjy J. Tenofovir Alafenamide for the Treatment of Chronic Hepatitis B Monoinfection. *Pharmacotherapy*. 2018; 38 (10), 1051-7.
[5] Mehra MR, Desai SS, Ruschitzka F, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020; (published online May 22.)
[6] Watson J, Adler A, Amaravadi A, et al. Open letter to MR Mehra SS, Desai, F Ruschitzka, and AN Patel, authors of "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis." *Lancet* 2020; Epub ahead of print.
[7] 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, 1787-99
[8] Chen C, Zhang Yi, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv* 2020.03.17.20037432; doi: https://doi.org/10.1101/2020.03.17.20037432
[9] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395, 1569-78.
[10] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of COVID-19 - Preliminary Report. *New Engl J Med*. 2020; May 22. Doi: 10.1056/NEJMoa2007764.
[11] Hung IFN, Lung KC, Tso EYK, et al. Triple com-

bination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* May 8, 2020; https://doi.org/10.1016/S0140-6736(20)31042-4.
[12] Cron RQ. Coronavirus is the trigger, but the immune response is deadly. *Lancet Rheumatology* 2020; May 29, 2020; Doi: https://doi.org/10.1016/S2665-9913(20)30165-X.
[13] Sivakorn C, Luvira V, Muangnoicharoen S, et al. Case Report: Walking Pneumonia in Novel Coronavirus Disease (COVID-19): Mild Symptoms with Marked Abnormalities on Chest Imaging. *Am J Trop Med Hyg*. 2020; 102 (5), 940-2.
[14] McGonagle D, O'Donnel J, Sharif K, et al. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatology.* May 7, 2020; https://doi.org/10.1016/ S2665-9913(20)30121-1.
[15] Rivellese F, Prediletto E. ACE2 at the centre of COVID-19 from paucisymptomatic infections to severe pneumonia. *Autoimmun Rev.* 2020; published April 3. Doi: 10.1016/j.autrev.2020.102536.
[16] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev.* 2020; published online April 3. Doi: 10.1016/j. autrev.2020.102537.
[17] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020; 395, 1033-34.
[18] Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020; 38 (3), 529-32.
[19] COVID-19 coagulopathy: an evolving story. Editorial. *The Lancet Hematology.* June 2020; e425.
[20] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395, 1054-62.
[21] Bassam Atallah B, Saad I. Mallah SI, Al Mahmeed W. Anticoagulation in COVID-19. *Eur Heart J Cardiovasc Pharmacother*. 2020; Doi: 10.1093/ehjcvp/pvaa036.
[22] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020; Doi: 10.1111/jth.14817.
[23] Mummery RS, Rider CC. Characterization of the heparin-binding properties of IL-6. *J Immunol* 2000; 165, 5671-9.
[24] Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-COVID 19). *ClinicalTrials.gov* Identifier: NCT04366960.
[25] Y. Wang, Chengjun Dong C, Hu Y, et al. Temporal changes of CT findings in 90 Patients with COVID-19 pneumonia: A longitudinal study. *Radiology*. Published online March 19, 2020; doi: 10.1148/radiol.2020200843.
[26] Thachil J. The versatile heparin in COVID-19. *J Thromb Haemost*. 2020; 18(5), 1020-2.