from anti-inflammatory therapies such as steroids. In the work by Fadel et al, it is difficult to ascertain which was the time from the onset of symptoms to initiation of steroid treatment. The fact that a large proportion of patients in the standard of care group also received steroids makes it more difficult to interpret.

Based on these considerations, we suggest that in future studies evaluating the effect of immunomodulatory drugs in COVID-19, the moment of the onset of symptoms should be considered the reference time for the start of the study drug.

Note

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Reply to Fernandez Cruz, et al.

We thank Fernandez-Cruz et al for their thoughtful comments in explaining the right time to initiate corticosteroids for coronavirus 19 (COVID-19). We are eager to read their article when published and are happy that they noticed a similar survival advantage in the early use of corticosteroids for moderate to severe COVID-19.

We agree with their observation that the appropriate time to initiate corticosteroids is likely in the second week of symptom onset. This is, in fact, reflected in our article in the discussion section: “The present study findings support that timing is key. An early course of corticosteroid, specifically methylprednisolone, at the onset of dyspnea, may attenuate progression to the hyper-inflammation phase that requires escalation of care in patients with COVID-19. In this study, 3 days of early corticosteroids were administered at a median 2 days into hospitalization and eight days from symptom onset. However, the administration of a 3 day course of corticosteroids later in the disease course (median 5 days after hospitalization), as occurred in our SOC group, did not appear to confer the same benefit” [1].

We believe that our study has significant clinical implications. If patients with COVID-19 present early to the hospital with symptoms, in particular dyspnea, appropriate management with corticosteroids can be initiated to prevent escalation of care to the intensive care unit with consequent survival benefit.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Reference


Pneumocystis jirovecii

Pneumonia and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection in a Patient With Newly Diagnosed HIV-1 Infection

To the Editor—It was recently suggested that excess risk of respiratory failure due to coronavirus disease 2019 (COVID-19) may be lower than expected for people living with human immunodeficiency virus (HIV) [1]. We report the case of a 52-year-old man from our intensive care unit (ICU) who developed acute respiratory failure due to COVID-19, Pneumocystis jirovecii pneumonia (PJP), and newly diagnosed stage 3 HIV [2]. Diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disguised the presence of PJP.

On 25 April 2020, a 52-year-old man presented at the emergency unit of a nearby hospital with fever of 40°C, cough, and shortness of breath. He deteriorated soon after, requiring endotracheal intubation. SARS-CoV-2 was detected from tracheal aspirate. In addition, bronchial aspirate samples grew with Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter díjkshoorniae. Blood cultures grew vancomycin-resistant Enterococcus faecium and Staphylococcus epidermidis. Hence, a broad antibiotic regimen containing meropenem and linezolid was initiated, yet the patient continued to have daily fevers up to 40°C without responding to antipyretics or antibiotics. He deteriorated further despite escalated pressure-controlled invasive ventilation and was finally transferred to our intensive care unit on 13 May 2020, for possible initiation of extracorporeal membrane oxygenation (ECMO).
For evaluation of pulmonary COVID-19 manifestation and in preparation for possible ECMO, computed tomography (CT) was performed on 13 and 14 May. Chest CT showed bilateral ground-glass opacities, consolidations, and crazy-paving pattern typical for COVID-19 [3, 4]. As a potential sign for subacute manifestation, airway changes, pleural changes, fibrosis, and nodules were present (Figure 1). Careful changes of ventilator settings finally made ECMO unnecessary.

Differential cytology (Supplementary Data) revealed a severe depletion of CD4+ cells (12 cells/µL, equaling 2%, and CD4+/CD8+ ratio of 0.08). Lack of CD4+ cells in combination with the fact that the patient is a man who has sex with men led us to the suspicion that he might be a HIV late presenter. Reverse-transcription polymerase chain reaction for HIV type 1 (HIV-1) was indeed positive, measuring a viral load of 360,000 HIV-1 RNA copies/mL. The presence of fine reticular changes in his chest CT together with an elevated level of lactate dehydrogenase prompted us to also consider PJP as a possible additional diagnosis. Bronchoalveolar lavage fluid was positive for P. jirovecii, and the patient was treated with intravenous trimethoprim-sulfamethoxazole (20 mg of trimethoprim component per kg body weight per day 4 times daily) together with 50 mg of prednisone daily to prevent adverse immune reactions in PCP and immune reconstitution inflammatory syndrome.

After the diagnosis of AIDS, rapid antiretroviral therapy (ART) was initiated consisting of orally administered darunavir (600 mg twice daily), ritonavir (100 mg twice daily), and tenofovir/emtricitabine (450/400 mg once daily). Concomitant cytomegalovirus (CMV) infection (170,000 U/mL blood) was treated with ganciclovir at 5 mg/kg body weight. Antibacterial treatment with meropenem and linezolid was continued for 7 days.

Coinfection with hepatitis B, hepatitis C, and syphilis was ruled out. On 15, 18, and 20 May, the patient tested negative for SARS-CoV-2 in bronchial aspirates. Cerebrospinal fluid testing showed 5,600 copies/mL HIV-1 but no evidence of JC virus or bacterial meningitis or encephalitis.

Over the next 2 weeks, his state improved significantly. Noradrenaline administration could be terminated 3 days after initiation of trimethoprim-sulfamethoxazole. Antiretroviral therapy had no apparent side effects; creatinine

Figure 1. A, Chest radiograph shows diffuse ground-glass opacification (GGO) of the lung on both sides and consolidation in the left lower lobe. B, Corresponding to the chest radiograph, computed tomography (CT) in coronal view depicts diffuse GGO and consolidation in the left lower lobe. C, Chest CT in transversal view illustrates diffuse GGO in both lungs and crazy-paving pattern combined with a distinct consolidation in the right upper lobe. D, Chest CT in transversal view reveals diffuse GGO in both lungs, large consolidation in the left lower lobe, and subpleural fibrosis combined with pleural changes in the right lower lobe.
clearance and liver function remained stable over the following weeks. CMV copies declined to <450 U/mL 2 weeks after ganciclovir was started on 14 May. Under ART, the viral load declined to 2800 copies/mL (equalling 2.11 log units) on 25 May. HIV-1 genotyping revealed no relevant drug resistance. After convalescence and ability to swallow reliably, ART was switched to a single-tablet regimen to maintain the patient’s compliance and to reduce the pill burden.

The patient is continuously improving. He is free from ventilator support and was discharged from ICU with 2 L/minute of supplementary oxygen on 4 June 2020.

The case is remarkable for several reasons: (1) SARS-CoV-2 infection initially prompted physicians to neglect other causes of respiratory failure; (2) the patient was immunosuppressed by HIV, which might have caused a mild course of COVID-19; and (3) administration of ART to analgosedated patients on the ICU is challenging since most currently approved therapeutics are pills that cannot be pulverized (see Supplementary Materials for a detailed discussion of these aspects).

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, these materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors contributed to collection, review, and/or analysis of the data. “S.M. drafted the manuscript.” The manuscript does not contain statistical data. All authors have seen and approved the final version of the manuscript.

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The Raw Cycle Threshold Values From Reverse-transcription Polymerase Chain Reaction Detection Are Not Viral Load Quantitation Units

To the Editor—I read with great interest the recent publication by Yu and colleagues [1] regarding quantitative detection and viral load analysis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in infected patients. The authors asserted that the results of reverse-transcription polymerase chain reaction (RT-PCR) and droplet-digital polymerase chain reaction (ddPCR) for SARS-CoV-2 detection were consistent in 95 positive samples and the cycle threshold (Ct) values of RT-PCR were highly correlated with the copy number values of ddPCR. However, the Ct values per se cannot be directly interpreted as viral load without a standard curve, which is the most direct and precise approach for analyzing quantitative data using a reference, such as in-house plasmid controls, with known viral copy numbers [2]. The linearity of the standard curve is denoted by the R² value (Pearson correlation coefficient) and should be very close to 1.

The authors did not state whether RT-PCR experiments were performed based on the current standard, nor do they present supplementary data that could support the assumption that they performed the standard dilution series to establish adequate limits of detection required for viral load quantification. Therefore, without a standard curve, the correlation analysis between the Ct value of RT-PCR and the viral load of ddPCR cannot be established rigorously since it is being done via a qualitative (RT-PCR) vs a quantitative (ddPCR) comparison. Thus, the R² values and the virus copies/reaction or virus copies/test to which these Ct values correspond must be compared with viral load obtained by ddPCR.

Moreover, because ddPCR allows for more careful quantitation of viral RNA copy numbers throughout the disease, this highly sensitive test may also be useful to evaluate treatment progress or assess patient release after quarantine [3, 4]. However, in this study, the viral load of SARS-CoV-2 was examined in different clinical stages of COVID-19 and various tissue samples, but it was
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Abbreviations

3TC, lamivudine; CD4, cluster of differentiation 4; DTG, dolutegravir; FDA, United States Food and Drug Administration; FTC, emtricitabine; HIV, human immunodeficiency virus; ITT-E, intention-to-treat exposed; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RCT, randomised controlled trial; RNA, ribonucleic acid; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; XTC, emtricitabine.

Footnotes

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.
**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).
†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).
‡TANGO is a randomised, open-label, phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.
¶STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.† Results at week 24 of the study. The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).
§TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≤50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).
#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≤50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).

REFERENCES


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