

Update in SARS-CoV-2 pneumonia

Antoni Torres
Catia Cilloniz

Steroid therapy and antiviral treatment in SARS-CoV-2 pneumonia: clinical contexts and indications

Pulmonology Department, Hospital Clinic of Barcelona, Spain. Spanish Society of Pneumology and Thoracic Surgery (SEPAR)

Revista Española de Quimioterapia
doi:10.37201/req/s01.13.2022

ABSTRACT

Critically ill patients with COVID-19 face a higher risk of disease progression and complications. The current standard of care includes supportive care measures and fluid management. The Recovery trial observed a reduction in all-cause, 28-day mortality ($p < 0.001$) when patients with COVID-19 requiring oxygen therapy received 6 mg of dexamethasone per day for 10 days. In contrast, in patients not requiring oxygen, no benefit was observed: 28-day mortality rates for the dexamethasone and routine care groups were 17.8% and 14%, respectively. To corroborate these results, the World Health Organization (WHO) performed a meta-analysis. The study showed that the use of systemic corticosteroids compared with routine care placebo was associated with a decrease in all-cause, 28-day mortality. With respect to the effectiveness of remdesivir, the ACTT-1 trial found that the drug conferred a benefit on time to clinical improvement. The subgroup analysis in the clinical trial also showed a benefit per mortality in patients requiring supplemental oxygen, albeit not those in need of mechanical ventilation.

Keywords: corticosteroids, antivirals, COVID-19, severe diseases

INTRODUCTION

The COVID-19 pandemic continues to cause substantial impact globally. By January 25th, 2022, more than 349 million confirmed cases had been reported and more than 5.5 million people had died. People with pre-existing comorbidities and elderly individuals comprise the most vulnerable populations of the respiratory disease. Indeed, COVID-19 is complex, with

critically ill patients facing a higher risk of progression to severe disease and multisystem complications. In the former, the cause is viral replication; in the latter, the systemic effects result from the host immune response to the virus.

Currently, for hospitalized patients with COVID-19, the standard of care includes supportive care measures for the most frequent complications, i.e., pneumonia, acute respiratory distress syndrome, sepsis and septic shock. These complications have been related to higher rates of mortality.

At the beginning of the pandemic, there was no substantial evidence to support a specific treatment strategy for COVID-19, especially in severe cases. The lack of strong evidence, therefore, resulted in the use of several medications, including antivirals and antimalarials. More specifically, clinicians began administering corticosteroids as adjunct treatment in patients with severe COVID-19. Clinical experience acquired from corticosteroid use in severe community-acquired pneumonia (CAP) suggested that lower doses of corticosteroids for a short duration appeared to decrease mortality in severe CAP and in moderate-severe acute respiratory distress syndrome (ARDS) [1]. However, given past reports of corticosteroid use in cases of severe influenza pneumonia and Middle East Respiratory Syndrome (MERS), administration of such drugs were not recommended to treat COVID-19 at the beginning of the pandemic [2].

There is still a debate about both the effectiveness of antivirals such as remdesivir and indications for systemic corticosteroids in critically ill patients with COVID-19.

COVID-19 SPECTRUM: SEVERITY, DISEASE PATHOGENESIS AND POSSIBLE TREATMENT

We can distinguish five stages of severity in COVID-19: **Asymptomatic**, in which a patient tests positive for SARS-CoV-2 but does not present any symptoms; **Mild illness**, in which mild symptoms such as fever, cough and changes in

Correspondence:
Dr. Antoni Torres
Pulmonology Department, Hospital Clinic of Barcelona
C/ Villarroel 170, 08036 Barcelona, Spain
Tel: (+34) 93-227-5549
Email: atorres@clinic.cat

Table 1 Experience with corticosteroids

Study	Relevant outcomes
RECOVERY trial 4,321 Hospitalized patients [12]	The use of 6 mg of dexamethasone per day for 10 days in patients with COVID-19 requiring oxygen therapy resulted in a reduction in all-cause, 28-day mortality ($p < 0.001$). In patients not requiring oxygen, no benefit was observed: 28-day mortality rates were 17.8% and 14% for the dexamethasone and routine care groups, respectively.
WHO prospective meta-analysis of clinical trials 1,703 Critically ill patients [13]	The administration of corticosteroids was associated with lower all-cause, 28-day mortality, compared with routine care or placebo,
Propensity score matching analysis including 409 with severe COVID-19 related to ARDS [14]	Corticosteroid use was associated with a higher 28-day mortality rate and a delay in SARS-CoV-2 RNA clearance.
A systemic review and meta-analysis 20,197 patients with COVID-19 requiring either oxygen therapy or mechanical ventilation [23]	A beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation were reported.
A single pretest, single posttest quasi-experiment study 213 moderate to severe COVID-19 [24]	An early short course of methylprednisolone in moderate to severe COVID-19 showed a reduction in escalation of care and improved clinical outcomes.
A prospective, multicenter and observational cohort study in critically ill adult patients with COVID-19 691 patients [25]	Early use of corticosteroids in critically ill patients with COVID-19 was associated with lower mortality than delayed use.

taste/smell appear, albeit not dyspnea; **Moderate illness, in which** a patient presents an oxygen saturation level $\geq 94\%$ and lower respiratory tract disease; **Severe illness, in which** a patient presents an oxygen saturation level $< 94\%$, respiratory rate $> 30/\text{min}$, and lung infiltrates $> 50\%$; and, **Critical illness**, in which a patient presents respiratory failure, shock, and multi-organ dysfunction or failure [3].

Viral replication is higher within the initial stages of COVID-19 yet lower in the more severe forms. Inflammation is, however, prominent in moderate to severe COVID-19, persisting into the critical phase of the disease. Similarly, hypercoagulability is related to severe and critical stages of COVID-19. Given such understandings, recommendations for COVID-19 therapy include antivirals during early stages of COVID-19—being the most effective when viral replication is higher—and anti-inflammatory agents for those patients with severe and critical forms of COVID-19 [4].

EXPERIENCE OF CORTICOSTEROID USE IN SEVERE LUNG INFECTIONS AND COVID-19

Severe lung infections may result in illnesses capable of causing pneumonia and acute respiratory failure. In the latter case, it could progress rapidly to ARDS, which is related to worse outcomes. This association is partly due to inflammation that can increase the risk of sepsis and septic shock, especially in individuals with a higher likelihood of infection, like the elderly or those with comorbidities, e.g., diabetes mellitus or chronic respiratory or cardiovascular diseases [5]. It is important to remark that co-infection, especially in the case of viral pneumonia with bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, are also related to worse

outcomes. In severe CAP, the use of adjunct therapy with corticosteroids—a potent inhibitor of the immune response—has shown to reduce the incidence of treatment failure and shorten the time to clinical stability [1]. However, no reduction in mortality has been demonstrated to date. Instead, there are studies that report an increase in hospital readmission and complications such as hyperglycemia [6]. Current IDSA/ATS CAP guidelines do not recommend the use of corticosteroids in routine clinical care [7]. Yet, its use is suggested in patients with CAP who either present septic shock or require mechanical ventilation due to respiratory failure primarily caused by pneumonia.

Regarding the use of corticosteroids as adjunct therapy for influenza pneumonia, strong evidence from several systematic reviews and meta-analyses show a relationship between the administration of such drugs and higher mortality rates [8]. A meta-analysis that evaluated 10 trials (6,548 patients with influenza pneumonia) reported that the mortality risk ratio was 1.75 for patients who received corticosteroids [9]. There was a reporting of similar results when only patients with influenza virus H1N1 were analyzed (RR 1.61). The authors also described that patients who received corticosteroids had longer intensive care unit (ICU) length of stay (median difference 2.14 days) compared to those patients who did not. Another systematic review and meta-analysis that included 15 studies (6,427 patients) showed that corticosteroids were associated with both higher mortality (OR 1.53) and incidence of nosocomial infections (OR 3.15) in patients with severe pneumonia and ARDS [10]. Current ATS/IDSA guidelines recommend not to use corticosteroids routinely in adults with severe influenza pneumonia (this is a conditional recommendation with low-quality evidence)[7]. Furthermore, current guidelines

Table 2 Experience with remdesivir	
Study	Relevant outcomes
ACTT-1 trial: 1,062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo) [26]	Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), while those who received placebo had a median recovery time of 15 days (95% CI, 13 to 18) Mortality rates were 6.7% (remdesivir) and 11.9% (placebo) by day 15 and 11.4% (remdesivir) and 15.2% (placebo) by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of 532 patients receiving remdesivir (24.6%) and in 163 of 516 patients receiving placebo (31.6%).
SOLIDARITY trial: 11,330 adults underwent randomization: 2,750 were assigned to receive remdesivir; 954, hydroxychloroquine; 1,411, lopinavir (without interferon); 2,063, interferon (including 651, interferon plus lopinavir); and 4,088, no trial drug [20]	Death occurred in 301 of 2,743 patients receiving remdesivir and in 303 of 2,708 receiving the control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P = 0.50). Ventilation was initiated after randomization in 295 patients receiving remdesivir and in 284 receiving the control. A small effect of remdesivir on time to recovery was observed. No mortality benefit was reported.
Prospective, controlled and non-randomized study: 151 patients with COVID-19 requiring supplemental oxygen therapy were enrolled (76 in the remdesivir/dexamethasone group, and 76 in the dexamethasone group) [21]	Faster viral clearance occurred in the remdesivir/dexamethasone group compared to the dexamethasone group (median 6 vs 16 days; p<0.001). 30-day mortality in the remdesivir/dexamethasone group was 1.3%; however, the rate was 16% in the dexamethasone group (p<0.005). There was a reduction in hospitalization days in the remdesivir/dexamethasone group, compared to the dexamethasone group (p<0.0001)

discourage the systematic use of systemic corticosteroids in cases of influenza infection.

Excessive inflammatory responses were observed in patients with severe COVID-19. Fatal ARDS—as a result of such inflammation—was related to excessive mortality. The inflammatory cytokine storm observed in severe cases were associated with an increased production of pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6 and tumor necrosis factor alpha (TNF- α) [11]. Using corticosteroids was a good option to modulate the immune response to the viral infection. However, without the necessary clinical evidence about their use, the debate on the topic remains active. The RECOVERY trial [12] that included 4,321 hospitalized patients with COVID-19 found that the use of 6 mg of dexamethasone per day for 10 days in patients with COVID-19 requiring oxygen therapy resulted in a reduction in all-cause, 28-day mortality (p<0.001). In contrast, in patients not requiring oxygen, no benefit was observed: 28-day mortality rates for the dexamethasone and routine care groups were 17.8% and 14%, respectively. These results demonstrated that the use of dexamethasone decreased mortality in patients with COVID-19 requiring oxygen therapy, irrespective of the mode of ventilation (invasive or non-invasive). After the RECOVERY trial, the World Health Organization (WHO) carried out a prospective meta-analysis of clinical trials including critically ill patients with COVID-19. The study confirmed the results obtained during the RECOVERY tri-

al, showing that the use of systemic corticosteroids compared with routine care placebo was associated with a reduction in all-cause, 28-day mortality [13] (Table 1). Interestingly, in a propensity score matching analysis that evaluated corticosteroid use in patients with severe COVID-19-related ARDS, the authors reported that the use of corticosteroids was associated with increased mortality and delayed viral clearance [14]. A subsequent editorial to the previous article proposed that treatment timing, dosage and severity of COVID-19 could determine the immune response and viral clearance. The authors stated that the use of corticosteroids in an early stage of the infection could be harmful for the patient: it could suppress the host antiviral activity and would allow for viral replication, causing cytopathic damage to the alveolar epithelial cells. On the contrary, though, the use of corticosteroids in patients after their immune system has controlled viral replication could prove beneficial. Such drug administration could contribute to reducing pro-inflammatory cytokines, enhancing anti-inflammatory cytokines, decreasing lung vascular permeability, improving epithelial barrier integrity and promoting alveolar edema fluid clearance [15].

Administering an early short course of methylprednisolone in moderate to severe COVID-19 showed a reduction in escalation of care and improved clinical outcomes. Also, when compared to delayed use, the early use of corticosteroids in critically ill patients with COVID-19 was associated with low-

er mortality. Finally, a beneficial effect of corticosteroids on short-term mortality and a decreased need for mechanical ventilation was reported (Table 1). The European Respiratory Society living guidelines recommended the use of corticosteroids only for patients with hypoxemic respiratory failure requiring oxygen administration [16]. The current National Institutes of Health (NIH) guidelines for COVID-19 therapy recommended the use of systemic corticosteroids in patients requiring supplemental oxygen. Disease severity of patients determined the use of dexamethasone alone or in combination with either remdesivir or a secondary immunomodulator such as tocilizumab or baricitinib [17]. The RECOVERY trial found that adding tocilizumab to dexamethasone had a beneficial impact on mortality in hospitalized patients with COVID-19, hypoxia and systemic inflammation, compared to routine care alone [18].

All of these data supported the recommendation for the use of corticosteroids, especially in critically ill patients with COVID-19 requiring oxygen therapy, and highlighted the beneficial effect of the association between such use and tocilizumab. However, there are some questions that warrant further investigation, including defining the required dosage and early use of corticosteroids; and understanding the effect of corticosteroid use on viral clearance and the possible long-term benefits in pulmonary sequelae.

HOW DOES REMDESIVIR CONTRIBUTE TO COVID-19 MANAGEMENT?

Remdesivir is a broad-spectrum antiviral capable of inhibiting the RNA polymerase and disrupting various stages of viral growth. Remdesivir received emergency approval after data had demonstrated its efficacy in reducing disease progression and severity, thereby resulting in shorter hospitalization time. However, there is controversy regarding the antiviral's beneficial effects. The effectiveness of remdesivir was evaluated in large randomized controlled trials (RCT). The ACTT-1 trial [19] showed a reduction in time to clinical improvement, while the subgroup analysis demonstrated a mortality benefit in patients requiring supplemental oxygen, albeit not those patients in need of mechanical ventilation. However, the SOLIDARITY trial [20] showed no mortality benefit with the use of remdesivir. In a separate prospective, controlled and non-randomized study [21] investigators evaluated the effectiveness of remdesivir with dexamethasone against dexamethasone alone in patients with COVID-19 requiring supplemental oxygen therapy. The study included 151 patients (76 patients in the remdesivir/dexamethasone group and 75 in the group receiving only dexamethasone). The authors showed that there was a significant reduction in mortality and length of hospitalization clearance in the group of patients who received remdesivir with dexamethasone compared with the group who received dexamethasone alone (Table 2). Furthermore, SARS-CoV-2 clearance was faster in the former group compared to the latter.

The latest WHO living guidelines [22] do not recommend the use of remdesivir in patients with COVID-19, irrespective

of disease severity. Also, the ERS living guidelines do not recommend the use of remdesivir in patients who require invasive mechanical ventilation. The NIH therapeutic guidelines recommend the use of this antiviral in hospitalized patients requiring oxygen supplementation yet not for those in need of mechanical ventilation.

CONCLUSIONS

Despite the rapid increase in scientific evidence on several different molecules related to treatment and COVID-19 disease stages, more data and findings are necessary to improve the overall clinical management. This statement holds especially true for those patients in critical condition. The general recommendation to treat patients with COVID-19 must depend on disease severity and the host's immune response to the viral infection. Antiviral therapy has been demonstrated to confer a beneficial effect if administered during the early stages of the disease when viral replication is higher. Corticosteroids has a great beneficial impact in severe and critical cases of COVID-19 given the excessive inflammation.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

REFERENCES

1. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; 313: 677–686.
2. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020; ciaa478.
3. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med* 2020; 383: 1757–1766.
4. Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC-C, Edwards KM, et al. Lessons learned from COVID-19 therapies: Critical perspectives from the IDSA COVID-19 treatment guideline panel. *Clin Infect Dis* 2021; ciab882.
5. Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, van der Poll T. Pneumonia. *Nat Rev Dis Primers* 2021; 7: 25.
6. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Miñambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. *J Diabetes* 2014; 6: 9–20.
7. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* American Thoracic Society - AJRCCM; 2019; 200: e45–e67.

8. Cillóniz C, Torres A, Niederman MS. Management of pneumonia in critically ill patients. *BMJ* 2021; 375: e065871.
9. Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; 23: 99.
10. Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, Wu J, Lan L, Yang S. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci Rep* 2020; 10: 3044.
11. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; 9: 622–642.
12. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; 384: 693–704.
13. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; 324: 1330–1341.
14. Liu J, Zhang S, Dong X, Li Z, Xu Q, Feng H, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. *J Clin Invest* 2020; 130: 6417–6428.
15. Matthay MA, Wick KD. Corticosteroids, COVID-19 pneumonia, and acute respiratory distress syndrome. *J Clin Invest* 2020; 130: 6218–6221.
16. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J* 2021; 57: 2100048.
17. Information on COVID-19 Treatment, Prevention and Research [Internet]. COVID-19 Treatment Guidelines [cited 2020 Dec 28]. Available from: <https://www.covid19treatmentguidelines.nih.gov/>.
18. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; 181: 32–40.
19. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; 383: 1813–1826.
20. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo A-M, Preziosi M-P, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med* 2021; 384: 497–511.
21. Marrone A, Nevola R, Sellitto A, Cozzolino D, Romano C, Cuomo G, et al. Remdesivir plus dexamethasone versus dexamethasone alone for the treatment of COVID-19 patients requiring supplemental O2 therapy: a prospective controlled non-randomized study. *Clin Infect Dis* 2022; ciac014.
22. Agarwal A, Rochweg B, Lamontagne F, Siemieniuk RA, Agoritsas T, Askie L, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020; 370: m3379.
23. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care*. 2020;24(1):696.
24. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al; Henry Ford COVID-19 Management Task Force. Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19. *Clin Infect Dis*. 2020;71(16):2114–2120
25. Monedero P, Gea A, Castro P, Candela-Toha AM, Hernández-Sanz ML, Arruti E, Villar J, Ferrando C; COVID-19 Spanish ICU Network. Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study. *Crit Care*. 2021;25(1):2.
26. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; 383: 1813–1826.