Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Surgery 82 (2020) 179–181

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Correspondence

Dexamethasone to combat cytokine storm in COVID-19: Clinical trials and preliminary evidence

ARTICLE INFO

Keywords
Cytokine storm
Clinical trials
COVID-19
SARS-CoV-2
Dexamethasone
Therapeutics

COVID-19 is characterized by cytokine storm or cytokine release syndrome (CRS) that is associated with the overproduction of pro-inflammatory cytokines. Roshanravan et al. have previously analyzed the inflammatory pathways involved in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, and the methods to target the host cytokine storm in patients with coronavirus disease (COVID-19) [1]. We would like to present our analysis of the current evidence and preliminary findings regarding the use of dexamethasone to combat the SARS-CoV-2-induced cytokine storm, based on the completed and ongoing clinical trials.

The high morbidity and mortality associated with SARS-COV-2 infection can be linked to the autoimmune destruction of the lungs that is mediated by the release of a storm of pro-inflammatory cytokines [2]. In patients with COVID-19, anti-inflammatory drugs such as corticosteroids can be used to reduce the lung damage induced by the cytokine storm [3]. Dexamethasone, a synthetic corticosteroid, acts as a broad-spectrum immunosuppressor and has a greater activity and longer duration of action than cortisone [2,4]. It has a diverse mechanism of action and can therefore affect several body systems. Corticosteroids such as dexamethasone possess anti-inflammatory potential because of their ability to decrease the gene transcription of several pro-inflammatory cytokines, chemokines, and adhesion molecules [5]. Dexamethasone can be beneficial in patients with COVID-19 because of its ability to inhibit the generation of cytokines and reduce their destructive effects. Therefore, it can be useful to counter the COVID-19-associated cytokine storm [4]. It has been demonstrated that short-term dexamethasone therapy can reduce the severity of inflammation by inhibiting the severe cytokine storm or the hyperinflammatory phase in patients with COVID-19 who develop pneumonia [6].

However, as dexamethasone is a broad-spectrum immunosuppressant, it can also hinder B cell-mediated antibody production, reduce the protective function of T cells, and prevents the macrophage-mediated clearance of apoptotic cells. This can result in a higher plasma viral load and an increased risk of secondary infections [2,4]. The beneficial effect of corticosteroid therapy in viral respiratory infections depends on the dose used, the time of administration, and the type of patient. High doses of corticosteroids may be counterproductive [7]. Hence, the beneficial effects of dexamethasone therapy cannot be generalized and are limited to critically ill COVID-19 patients who have progressed to a stage necessitating respiratory support [7]. Therefore, we can assume that immunomodulatory effects of glucocorticoids are beneficial only in the later, hyperinflammatory phase of the disease. As a safer approach, a pulse dose of intravenous dexamethasone can be administered, followed by nebulized triamcinolone (another corticosteroid) to concentrate the effects in the lungs only [2]. Another strategy to reduce the side effects associated with corticosteroid treatment involves the simultaneous administration of intravenous immunoglobulins and interferon-beta [3]. A multicenter randomized controlled trial (Identifier: IRCT20120225009124N4) conducted from April 18, 2020 to June 19, 2020 evaluated the therapeutic potential of dexamethasone administered in combination with intravenous immunoglobulin and interferon-beta [3]. The results of this trial are expected to be available soon.

The Randomized Evaluation of COVID-19 therapy trial (RECOVERY) is a large-scale, randomized, controlled, open-label, and adaptive platform trial comparing the therapeutic efficacy of different drugs in patients hospitalized with COVID-19 in the United Kingdom. This trial investigated the potential of several drugs including lopinavir-ritonavir, hydroxychloroquine, azithromycin, dexamethasone, or tocilizumab to reduce the mortality rate in patients with COVID-19 (NCT04381936). A total of 2104 patients who were randomly allocated to receive dexamethasone (6 mg, once daily) for up to 10 days were compared to 4321 patients who received the usual standard of care [7]. The dexamethasone dose used in this trial was approximately half of the functional corticosteroid dose used to prevent treatment-induced acute respiratory distress syndrome in patients with *Pneumocystis* pneumonia [8]. The preliminary results from the RECOVERY trial for the comparison of dexamethasone with the usual care indicated that dexamethasone reduced the 28-day mortality in COVID-19 patients receiving invasive mechanical

DOI of original article: https://doi.org/10.1016/j.ijsu.2020.05.018.

https://doi.org/10.1016/j.ijsu.2020.08.038
Received 5 August 2020; Received in revised form 21 August 2020; Accepted 25 August 2020
Available online 4 September 2020

Table 1
Clinical trials evaluating the therapeutic efficacy of dexamethasone in COVID-19 patients (www.clinicaltrials.gov).

S. No.	NCT No.	Title	Status	Phase	Population	Country
1.	NCT04325061	Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19 (DEXA-COVID19)	Recruiting	Phase 4	200 individuals (18 years and older)	Spain
2.	NCT04395105	Dexamethasone for COVID-19 Related ARDS: a Multi-centre, Randomized Clinical Trial	Recruiting	Phase 3	284 individuals (18 years and older)	Argentina
3.	NCT04347980	Dexamethasone Treatment for Severe Acute Respiratory Distress Syndrome Induced by COVID-19 (DHYSCO)	Recruiting	Phase 3	122 individuals (18 years and 80 years)	France
4.	NCT04344730	Dexamethasone and Oxygen Support Strategies in ICU Patients With Covid-19 Pneumonia (COVIDICUS)	Recruiting	Not Applicable	550 individuals (18 years and older)	France
5.	NCT04360876	Targeted Steroids for ARDS Due to COVID-19 Pneumonia: A Pilot Randomized Clinical Trial	Not yet recruiting	Phase 2	90 individuals (18 years and older)	Not provided
6.	NCT04327401	COVID-19-associated ARDS Treated With Dexamethasone: Alliance Covid-19 Brasil III (CoDEX)	Active, not recruiting	Phase 3	350 individuals (18 years and older)	Brazil
7.	NCT04445506	Short Term Corticosteroids in SARS-CoV2 Patients	Completed	–	50 individuals (18 years and older)	United States
8.	NCT04476979	Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients With Covid-19 (TOCIDEX)	Not yet recruiting	Phase 2	120 individuals (18 years and older)	France
9.	NCT04452565	NA-831, Atazanavir and Dexamethasone Combination Therapy for the Treatment of COVID-19 Infection (NATADEX)	Recruiting	Phase 2 and Phase 3	525 individuals (18 years and 80 years)	United States
10.	NCT04381936	Randomized Evaluation of COVID-19 Therapy (RECOVERY)	Recruiting	Phase 2 and Phase 3	15,000 individuals (Child, Adult, Older Adult)	United Kingdom

ventilation or oxygen therapy without invasive mechanical ventilation, but not in patients who were not receiving any respiratory support [7]. These findings support the use of dexamethasone in COVID-19 patients with hypoxemia, and therefore, the results should not be extrapolated to patients with the milder form of the disease [7,8]. Further studies are required to determine whether dexamethasone therapy can induce harm in patients with mild to moderate COVID-19 [9].

Although the results obtained from this clinical trial have given hope to millions of people worldwide, there is a need for caution, as the findings are based on a well-designed trial conducted in a high-income country [10]. Therefore, extrapolating the findings to change guidelines elsewhere in the world with entirely different healthcare systems may not be appropriate. Hence, region-specific data must be generated based on randomized controlled trials before including dexamethasone in any global therapeutic guidelines for the treatment of patients with COVID-19. Some of the major clinical trials that have evaluated the therapeutic potential of dexamethasone in COVID-19 patients are summarized in Table 1.

Dexamethasone is a cheap and easily accessible drug that can be obtained without a prescription in some countries. Hence, there is an increased likelihood of self-medication and drug shortage following the social media reports of its beneficial effects. Therefore, extreme caution should be exercised to avoid the possibility of harm instead of benefits. Although preliminary reports suggest that low-dose dexamethasone therapy has beneficial effects in COVID-19 patients, it is important to note that dexamethasone is neither an antiviral drug nor a definitive cure for COVID-19. Improper use of such broad-spectrum immunosuppressive drugs may weaken a patient's immunity, resulting in a greater susceptibility to the virus. Therefore, further studies are required to identify the ideal dose and time window for the administration of the drug that would provide maximum benefits, before its inclusion in the treatment guidelines for COVID-19.

Ethical approval

Not applicable.

Sources of funding

None.

Author contribution

All authors equally contributed to the analysis and writing of the manuscript.

Research registration Unique Identifying number

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

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Data statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Conflicts of interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

Acknowledgements

None.

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