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Dexamethasone's Connection to COVID-19

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SUMMARY

Dexamethasone has been used for many years to treat a variety of ailments, and it illustrated positive results. Dexamethasone is well-known for its usage as an immunosuppressant, and an anti-inflammatory medication. Healthcare specialists worldwide searched for an existing or developing medication that may aid patients with the virus, especially as COVID-19 instances increased internationally. The Recovery Trial sought to identify a pharmacotherapeutic medication that would aid in the treatment of COVID-19 patients who were hospitalized. Dexamethasone's capacity to shorten hospital stays, and lower patient fatalities was observed throughout this experiment. These findings sparked more interest in Dexamethasone's potential as a treatment option for COVID -19. Investigating Dexamethasone's mechanisms of action, and how it affects various populations, will aid us in developing a standardized COVID-19 treatment plan by revealing how effective it is.

ABSTRACT

Dexamethasone is known for its use as an anti-inflammatory and immunosuppressant medication. This medication has been present for many years, and its benefits have been observed in the treatment of various conditions. With the rise of COVID-19 cases on an international scale, healthcare professionals globally searched for a therapeutic medication, either existing or under development that could help those who were ill with the virus. The Recovery Trial aims to find a pharmacotherapeutic medication that would assist in treating hospitalized individuals who were diagnosed with COVID-19. In this trial, Dexamethasone's ability to reduce hospitalization durations, and patient fatality was observed. These results increased curiosity about Dexamethasone's potential in the fight against COVID-19. As we work towards a standardized treatment plan for COVID-19, investigate Dexamethasone's mechanisms of action, and how it impacts different populations; together, these findings may help to determine this medication's effectiveness as a COVID-19 treatment option.

Keywords: COVID-19, Dexamethasone, corticosteroid, glucocorticoid, Recovery Trial

1.0 INTRODUCTION

Dexamethasone has many limitations and advantages as a pharmacotherapeutic medication.[1] Dexamethasone was approved in 1958 under the brand name, Decadron.[2] It is classified as a glucocorticoid, which is a unique class of drugs that can alleviate inflammation caused by a variety of diseases such as cancer, lupus, and rheumatoid arthritis.[3] Dexamethasone can be administered in tablet form or intravenously.[4] In 2021, results from the Recovery Trial – a trial which investigated many drug classes in the struggle to establish an effective treatment plan for those diagnosed with COVID-19. Dexamethasone illustrates promising results as a potential treatment for hospitalized patients with COVID-19.[5] This essay will analyze Dexamethasone's two mechanisms, along with an overview of the Recovery Trial.

2.0 MECHANISM OF ACTION

Dexamethasone is a corticosteroid medication that works as an immunosuppressant, and an anti-inflammatory agent.[5] Dexamethasone can facilitate different routes in the inflammatory pathway, which are dependent on the dose, and duration of administration.[6,7] Dexamethasone's mechanism of action is dependent on disease severity.[8] In terms of COVID-19, trials have defined a low dose as 6mg once daily for 10 days (the Recovery Trial), while a high dose is 20mg once daily for 5 days, followed by 10mg once daily for 5 days (the HIGHLOWDEX trial).[9] Specifically, higher

doses facilitate their effect through a non-genomic mechanism, while low doses use a genomic mechanism.[10] Dexamethasone has the most impact through genomic mechanisms that require a longer duration, while the non-genomic mechanism is fast-acting but increases the risk of side effects.[10]

2.1 GENOMIC MECHANISM

Through the genomic mechanism, Dexamethasone passes through the cell membrane of the target cells via simple diffusion.[6] These target cells have glucocorticoid receptors (GR) in the cytoplasm. Once Dexamethasone binds to GRs, this receptor-glucocorticoid complex results in the translocation of the glucocorticoid into the cell .[6] In the cell, it can enter the nucleus to forms a dimer with another complex to reversibly bind to many DNA sites, which suppresses or stimulates the transcriptions of several genes (Figure 1).[11] In the case of COVID-19, this causes a reduction in the generation of pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, IFN-γ, and TNF-α.[6,12] Simultaneously, Dexamethasone also initiates the synthesis of anti-inflammatory cytokines, such as lipocortin-1.[6]

2.2 NON-GENOMIC MECHANISM

The non-genomic mechanism of Dexamethasone, however, involves its binding to GRs on the membranes of T-lymphocytes. This causes a T-lymphocyte immune response, and inhibition of receptor signaling from GR (Figure 1).[6] This high dose of Dexamethasone facilitates the cross-membrane movement of sodium and calcium ions, contributing to a large decrease in inflammation.[6] Dexamethasone plays a role in the expression of the transient reception potential cation channel subcomponent V member 6 (TRPV6), plasma membrane calcium ATPase 1 (PMCA1), and sodium-calcium exchanger 1 (NCX1), and the level of intracellular calcium levels.[13] Jeon et al. (2020) found that following administration of Dexamethasone, the level of intracellular calcium increases – this led to a decline in inflammation.[13] Further, they observed a decline in the expression of PMCA1, and NCX1 genes which control calcium outflow, and an increase in TRPV6 expression which controls calcium influx. It is noted that the use of Dexamethasone helps to limit the host's inflammatory response although suppression of the inflammatory response can sometimes be detrimental.[5]

3.0 THE RECOVERY TRIAL

The 'recovery trial' is a randomized trial which began on March 19th, 2020 to investigate multiple pharmacotherapeutics, and their interactions with COVID-19.[14] The outcomes that were investigated included patients with mild to severe COVID-19 symptoms that led to hospitalizations, in addition to the lasting effects on the individual's physical state such as a persistent cough, fever, chills, and mucus.[14] Examples of drugs included in this trial are Dexamethasone, Aspirin, Empagliflozin, and Hydroxychloroquine. Patients enrolled in this trial were all hospitalized with confirmed cases of COVID-19, and randomized to either 6mg Dexamethasone or placebo administered in tablet form or intravenously.[14] Placebo was administered in tablet form or intravenously since this method of administration is simple, accessible, and efficient. From a pharmaceutical standpoint, the intravenous form can be easily dispensed, and can distribute the drug within the body at a fast, and efficient rate.

The RECOVERY trial illustrated that the use of Dexamethasone for ten days compared to standard treatment without the use of corticosteroids in hospitalized patients reduced mortality at 28 days (22.9% with Dexamethasone vs 25.7% without Dexamethasone).[9] The trial results were inconclusive, referring to the recommended timeline for using Dexamethasone for patients with COVID-19, and respiratory failure. For the primary outcome of 28-day mortality, the hazard ratio from Cox regression was used to estimate the mortality rate ratio. Kaplan–Meier survival curves were constructed to show cumulative mortality over 28 days.[14]

A preliminary analysis of the data indicates results supporting the efficacy of Dexamethasone against COVID-19. In this analysis, 2,104 patients were treated with Dexamethasone, and 4,321 patients received standard care.[14] Analyzing death within 28 days of the baseline: 482 of those treated with Dexamethasone had passed away in comparison to 1,110 standard care participants (22.9% vs. 25.7%; rate ratio, 0.83; 95% confidence interval, 0.75 to 0.93; P<0.001) (Figure 2).[14] These results indicate that Dexamethasone has a modest yet significant impact on reducing all-cause mortality within 28 days from the baseline.

4.0 CONCLUSION

Dexamethasone's impact on alleviating inflammation, and the significance it has in reducing mortality have motivated many more research trials to investigate its impacts further. Understanding multiple treatment options is essential to creating a diverse range of treatment options available to those who are diagnosed with COVID-19.

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AUTHOR CONTRIBUTIONS

BM is affiliated with the School of Interdisciplinary Science, and the Department of Biology at McMaster University. SD is affiliated with the Faculty of Science at York University.

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APPENDIX

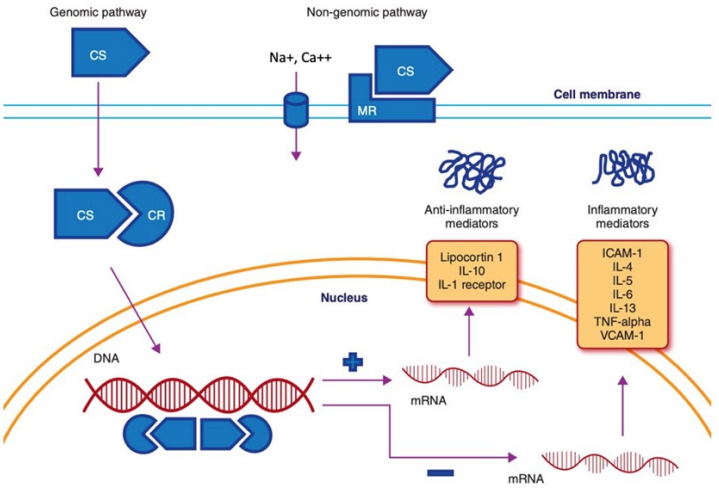

Figure 1. Shows both the genomic and non-genomic mechanisms of Dexamethasone. CS is a corticosteroid, CR is a corticosteroid receptor and MR is a membrane receptor.[15] In the genomic mechanism, the corticosteroid (Dexamethasone) passes through the membrane via simple diffusion and it binds to receptors found in the cytoplasm.[6] In relation to COVID-19, these target cells are known as macrophages situated in the alveoli. Upon binding, the corticosteroid-receptor complex will move towards the nuclear membrane where it enters through simple diffusion. In the nucleus, the receptor-corticosteroid complex will then dimerize to reversibly bind to DNA. These elements can be either negative (transcription-suppressing, inflammatory agents) or positive (transcription-stimulating, anti-inflammatory agents) genes resulting in alteration of protein and mRNA synthesis.[11] In the non-genomic mechanism, Dexamethasone will bind to the membrane receptor of the T-lymphocytes to facilitate an influx of calcium and sodium ions which work to limit inflammation.[15] Figure adapted from Sibila et al. (2015).

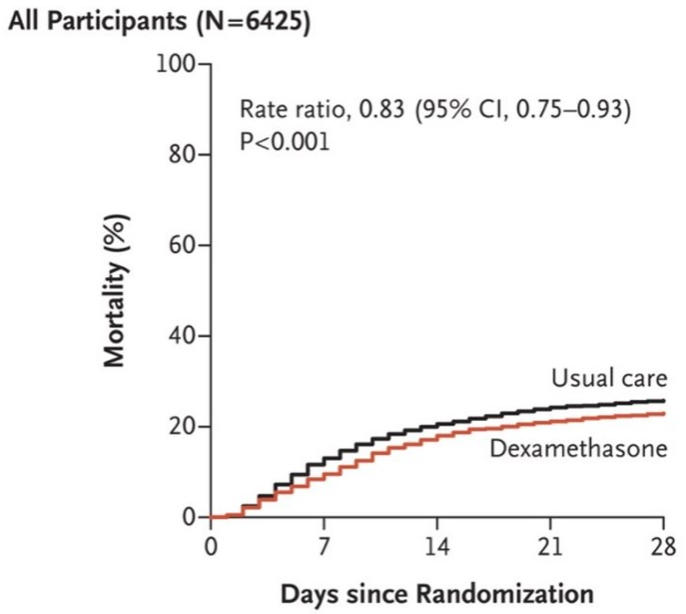

Figure 2: A graphical representation of the RECOVERY trial's preliminary results of the RECOVERY trial. In this preliminary analysis, data from 6425 patients were analyzed; 2,104 patients received Dexamethasone while 4,321 patients received usual care.[14] This relationship displays the days since randomization, versus percent mortality in patients who received usual care represented (outlined in black) and patients prescribed Dexamethasone outlined in orange. Results Illustrated a significant difference in the 28-day mortality of those for whom Dexamethasone was prescribed, in comparison to those who received usual care (22.9% vs. 25.7%; rate ratio, 0.83; 95% confidence interval, 0.75 to 0.93; P<0.001).[14] Figure adapted from The RECOVERY Collaborative Group (2021).