Alaska Pharmacists Association

Continuing Education Home Study Series

Program 0139-0000-20-204-H04-P/T
Quarterly AKPhA Newsletter
Release Date 8/14/2020
Expiration Date 8/14/2023
CPE Hours: 1.0 (0.1 CEU)

This lesson is a knowledge-based CPE activity and is targeted to pharmacists and technicians in all practice settings.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. State two positive changes you can make to your practice following participation in this series.
2. Summarize three practice updates or changes you acquired while participating in this series.

Disclosure

The author(s) and other individuals responsible for planning AKPhA continuing pharmacy education activities have no relevant financial relationships to disclose.

Fees

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Role of Corticosteroids in the Treatment of COVID-19

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As the spread of the SARS-CoV-2 virus persists worldwide, a variety of treatment options have been theorized and included in observational studies and in some cases randomized trials. These treatments have included antivirals, supportive agents involving a variety of monoclonal antibodies, and other agents with potential activity against the complications of infection related to inflammatory processes and hypercoagulability. One such class, corticosteroids, has recently received particularly heightened attention due to the reported efficacy of dexamethasone in the multi-centered, open-label, randomized trial, also known as the RECOVERY trial.

One important aspect understood about the immunopathology of infection with the SARS-CoV-2 virus is the maladaptive response of excessive cytokine release, otherwise known as a cytokine storm. In addition to viral load, inflammatory cytokine and chemokine responses influence the morbidity and mortality of human coronavirus evidenced by severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) infections that show improved prognosis with immunomodulation.[1] The inflammatory response presents specifically with increased levels of interleukin 2 and 7, granulocyte-colony stimulating factor, interferon-γ, attractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. This cytokine profile highly resembles that of a hyperinflammatory syndrome known as Secondary hemophagocytic lymphohistiocytosis (sHLH), which is commonly triggered by viral infection and will often precipitate acute respiratory distress syndrome (ARDS).[2] This pathology is also likened to the coalescence of deficient lymphocyte cytolytic activity with increased macrophage activity and downstream immune system activation, known as macrophage

activation syndrome (MAS), which similarly results in a cytokine storm leading to ARDS and organ failure. Due to these complicating processes resulting from infection, addressing the immunopathology has been determined to be an essential part of the management of coronavirus disease of 2019 (COVID-19), the disease caused by SARS-COV-2.[3]

Corticosteroids have been considered as a mode of immunomodulation for use in human coronaviruses; however, the true clinical benefit of dosage and timing has been disputed. During the SARS epidemic in 2003 one retrospective study in severe SARS patients showed a significant benefit in mortality and hospital stay while another study showed that early treatment might contribute to exacerbation of the disease in non-critical patients evidenced by increased viral load.[4, 5] Recent data from corticosteroid use in COVID-19 have helped to further define optimal intervention in reference to dosage, severity, and progression of the disease. Corticosteroids have been determined to provide the greatest benefit in patients who are in a more severe or critical clinical presentation at the early onset of cytokine storming. Prompt administration at the onset of this exaggerated immune response can prevent excessive inflammatory processes and eventual ARDS. Intervention with corticosteroids of large doses (>2mg/kg methylprednisolone daily) or too early in the disease progression can have inappropriate and unwanted immunosuppressive effects exacerbating the viral infection.[1] Due to the limited data available for COVID-19 patients, use in this population should be considered based on the individual risks and benefits of each individual.

General recommendations regarding the use of corticosteroids in COVID-19 patients per the World Health Organization (WHO), Center for Disease Control (CDC), National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) have been against routine implementation. Most of the data regarding any recommendations for the use of corticosteroids are based on trials focused on efficacy in the setting of patients with ARDS. Results from studies on use in COVID-19 patients specifically are mixed and based on observational studies. The NIH specifically recommends against corticosteroid use in hospitalized patients without ARDS. Regarding supposed cytokine storming, there is suggestion for the use of higher dosed corticosteroids (intravenous methylprednisolone 60-125 mg every 6 hours) tapered based on inflammatory biomarker trends.[6] The Surviving Sepsis Campaign organized a subcommittee dedicated to COVID-19 and similarly recommended against routine implementation of corticosteroids in patients without ARDS, even in the context of respiratory failure requiring invasive ventilation. This subcommittee does acknowledge the benefit of corticosteroids in patients with COVID-19 and refractory shock with a recommendation for the use of low doses (200 mg hydrocortisone). They also acknowledge a weak recommendation for the use of low dose corticosteroids for a short duration in more severe patients with ARDS without shock.[7] Regarding use in pregnancy, the American Academy of Obstetricians and Gynecologists (ACOG) generally recommend against the use of corticosteroids for fetal benefit in the late preterm period (34-36 weeks) due to lack of clear benefits.[8]

The RECOVERY trial has recently gained attention as the first randomized, controlled trial that has detected preliminary results suggesting the benefit of dexamethasone treatment in severe cases of COVID-19. Sponsored by the University of Oxford, this trial is a multi-centered, open-label, randomized, controlled, adaptive platform trial comparing treatment with dexamethasone, hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, and convalescent plasma with standard of care for efficacy against COVID-19. The primary outcome is 28-day all-cause mortality, with secondary outcomes including duration of hospital stay, requirement of ventilation, and a composite endpoint of death, mechanical ventilation, or extracorporeal membrane oxygenation. Patients were randomized 2:1 to receive standard of care or dexamethasone, dosed at 6 mg daily for 10 days or until discharge. The preliminary results, as displayed in figure 1, show a significant difference in 28-day mortality between patients receiving standard of care (24.6%) vs. dexamethasone (21.6%) (RR=0.83; 95% CI 0.74-0.92, $p<0.001$). In a pre-specified subgroup analysis performed based on levels of respiratory support, results indicated a significant effect of dexamethasone in patients receiving invasive mechanical ventilation with a 35% reduction in the primary outcome (RR=0.65 [95% CI 0.51 to 0.82]; $p<0.001$) and supplemental oxygen with a 20% reduction (RR=0.80 [95% CI 0.70 to 0.92]; $p=0.002$). This benefit was not extended to those who did not experience acute respiratory failure (RR=1.22 [95% CI 0.93 to 1.61]; $p=0.14$). Regarding secondary outcomes, the dexamethasone arm did see shorter duration of hospitalization with a median stay of 12 days compared to 13 in the standard of care arm. This group also showed significantly greater probability of discharge within 28 days (RR=1.11 [95% CI 1.04 to 1.19]; $p=0.002$).[9]

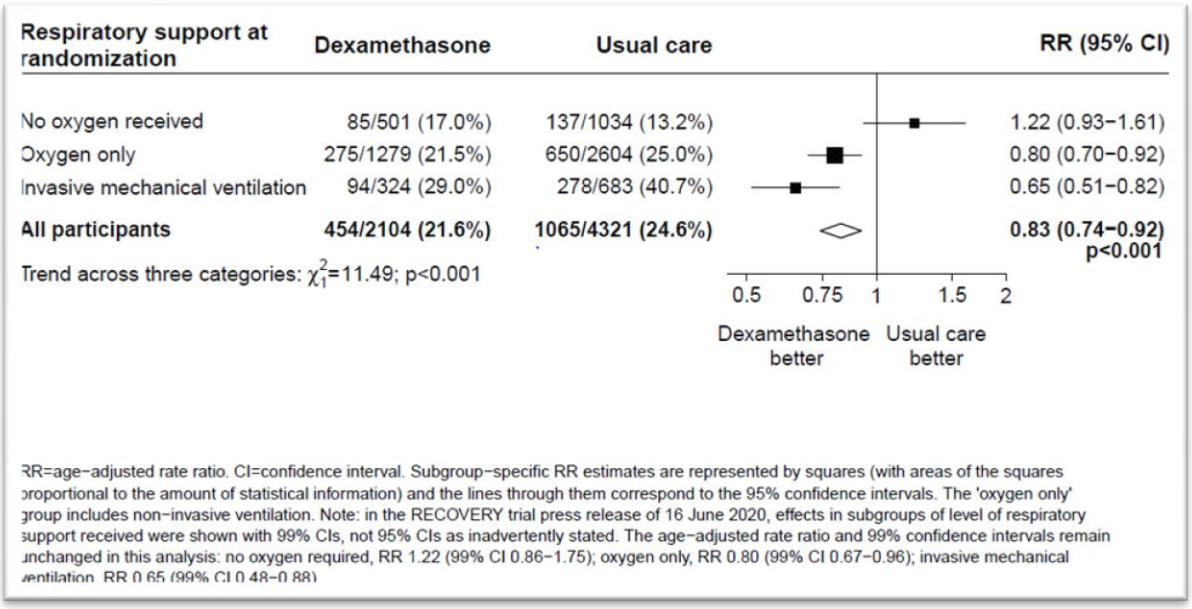

Figure 1.

The RECOVERY Collaborative Group. Effect of dexamethasone in hospitalized patients with COVID-19—preliminary report. 22 Jun 2020 (preprint).

As the first study to provide significant mortality data in the context of patients with COVID-19, dexamethasone has become the first to provide evidence for use in patients with acute respiratory failure (requirement of oxygen or invasive mechanical ventilation). However, the data produced from this study cannot justify the use of dexamethasone outside of the context of respiratory failure as no benefit was extended to patients without receipt of oxygen or ventilation. As discussed earlier this echoes, along with previous investigations, that the use of corticosteroids too early in the disease process offers no clear benefit and may possibly pose greater risk. The study did allow for equivalent doses of corticosteroid as prednisolone 40 mg or intravenous hydrocortisone 80 mg twice daily for patients who were pregnant or breastfeeding. This is helpful information to consider as the pharmaceutical drug market reacts to shifts in demand with newly published literature on COVID-19 treatments.[10] Should substitutions be considered, it is important to consider the relative glucocorticoid and mineralocorticoid effects of each corticosteroid.

As the preliminary results of the RECOVERY trial highlight, corticosteroids may play a role in SARS-CoV-2 for select patients. Our understanding of the pathophysiology of this disease process has identified a maladaptive inflammatory response triggered by infection as one of the primary reasons for progression to ARDS. Literature assessing the use of corticosteroids in the previous SARS and MERS viral epidemics cast doubt on the safety and efficacy of this therapy with mixed results. The RECOVERY trial displayed early significant results potentially clarifying the confusion around corticosteroid use. It is theorized that corticosteroids may prove harmful when used too early in the disease course through immunosuppression which only exacerbates the severity of infection. As the results of RECOVERY suggest, corticosteroid use is optimal for patients at the point of respiratory failure requiring supplemental oxygen or ventilation. As this study ages and we continue to see widespread demand of dexamethasone and the subsequent emergence of recommendations for substitutions it will be important to reflect on the relative glucocorticoid and mineralocorticoid profiles of alternative corticosteroids in the context of each individual patient.

References:

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Continuing Education Quiz and Evaluation

Complete the quiz and evaluation online at:
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