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CLINICAL REVIEW

Nevada Society of Health-System Pharmacists

COVID-19 SPOTLIGHT: THE ROLE OF STEROID USE IN COVID-19 TREATMENT

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SARS-CoV-2 is a severe acute respiratory syndrome caused by the novel coronavirus, COVID-19. This virus was first noted in December 2019 in china. The virus quickly spread across the world, causing a pandemic in March 2020. Many treatments have been examined, however glucocorticoids were the first to demonstrate reduced mortality in patients with COVID-19. Elevated levels of inflammatory markers such as interleukin-1. Interleukin-6, C-reactive protein, procalcitonin and other inflammatory infiltrates are seen in patients with severe COVID-19. This leads to lung damage, multi-organ failure and death. Therefore, the use of anti-inflammatory agents such as glucocorticoids may help modulate the inflammation associated with lung injury and can reduce or prevent the progression of respiratory failure.

DEXA-ARDS AND CoDEX trials[1,2]:

DEXA-ADRS trial is a multicenter, randomized controlled trial. This trial evaluated treatment options on patients with established moderate-to-severe acute respiratory distress syndrome (ADRS) at 17 intensive care units (ICUs) in Spain. A total of 277 patients were enrolled in the trial. 139 patients were randomized receiving dexamethasone 20 mg intravenous (IV) from day 1 to day 5, then 10 mg IV once daily from day 6 to day 10; and 138 patients were in the control group. All patients were on ventilation with lung-protective mechanical ventilators. Although the study was terminated early due to the low enrollment rate, the result showed a higher number of ventilator-free days in treatment group vs control group (between-groups difference 4.8 days [95% CI 2.57 to 7.03]; p<0.0001). 60-days mortality in the treatment group was [21%] compared to [36%] in the control group (between-group difference -15.3% [-25.9 to -4.9]; p=0.0047). The adverse events did not differ between the treatment and control groups. The common adverse effect on the dexamethasone group was hyperglycemia [76%] vs [70%] in the control group.

CoDEX trial, published in September 2020 studied a similar dosing regimen on COVID-19 positive patients with moderate to severe ARDS. The trial enrolled a total of 299 patients, with 151 in the dexamethasone group and 148 to usual care. The primary outcome was ventilator-free days during the first 28 days and some of the secondary outcomes included all-cause mortality at 28 days and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days. The results showed that the treatment group had significant increasing number of ventilator-free days than standard care group [6.6 vs 4 days; p=0.04]. At day 7, the treatment group had significant lower mean Sequential Organ Failure Assessment (SOFA) scores than the standard care group [6.1 vs 7.5; p=0.004]. However, no significant difference in all-cause mortality between the treatment group and the control group.

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RECOVERY trial preliminary report[3,5]:

RECOVERY trial was designed to evaluate various treatment options for hospitalized COVID-19 patients. The trial was set at 176 National Health Service organizations in the United Kingdom. In this controlled, open-label trial patients were randomly assigned to receive oral (PO) or IV dexamethasone at 6 mg once daily for up to 10 days compared to patients receiving usual care. A total of 2104 patients were randomized to receive dexamethasone either PO or IV versus 4321 to receive usual care. The primary outcome was 28-day mortality and preliminary results showed a 28-day mortality benefit highest in patients who required mechanical ventilation (41%) (RR 0.65 [95% CI 0.48-0.88]; p=0.0003, intermediate in those who required oxygen only (25%) (RR 0.80 [0.67-0.96]; p=0.0021) and no difference among those who did not require supplemental oxygen. The trial concluded that in hospitalized COVID-19 patients, the use of dexamethasone resulted in lower 28-day mortality in those who were receiving either invasive mechanical ventilation or oxygen, but not among those who were without respiratory support.

Special Populations[4,6]:

Glucocorticoids can cross the placenta. Betamethasone and dexamethasone have been used in pregnant women to decrease neonatal complications of prematurity and prevent preterm delivery. Based on the low risk of fetal adverse effects and potential benefit of maternal mortality reduction, COVID-19 Treatment Guidelines Panel recommends to use dexamethasone on pregnant patients with COVID-19 on mechanically ventilated or who require oxygen supplement. The risks and benefits of dexamethasone in children have not been studied. The RECOVERY trial did not include a significant number of pediatric patients. However, the COVID-19 Treatment Guidelines Panel indicates that dexamethasone can be considered in treatment for hospitalized children with COVID-19 who require mechanical ventilation, however the decision of treatment should be evaluated on a case-by-case basis.

Clinical Implications:

Some institutions have adopted the two different treatment therapies. For patients presenting with COVID-19 but less severe symptoms and without ARDS, they follow the RECOVERY trial dosage (dexamethasone 10 mg IV or PO once daily for 10 days). For patients presenting with ARDS requiring high flow nasal cannula, mechanical ventilation and ICU stay, dosing regimen from DEXA-ARDS and CoDEX trials is recommended (dexamethasone 20mg IV daily for 5 days, then 10 mg IV daily for days or until discharge, plus standard of care). Giving dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily plus standard of care significantly improved the number of ventilator-free days on these patients, compared to the standard of care alone. In addition, this treatment regimen showed a significant reduction of ICU days in critically ill patients with COVID-19 positive.

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In contrast, the utilization of dexamethasone 6 mg daily for 10 days strategy has been utilized, even in severe ARDS patients requiring ventilation. This is based on the preliminary report of the RECOVERY trial, which is the only trial to demonstrate mortality benefits with the use of glucocorticoids. This trial was large with over 6000 patients and included over 1000 patients that were on mechanical ventilation. Barring substantial evidence to suggest otherwise, this approach is now the standard of therapy for all hospitalized COVID-19 patients requiring oxygen therapy. It is preferred to have PO dexamethasone than IV, if the patient is able to tolerate PO medications. In the event of dexamethasone shortage, alternative glucocorticoids such as prednisone or methylprednisolone with equivalent dose can be utilized.

Conclusions:

Based on the recently published literature, The COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone 6 mg per day for up to 10 days, patients requiring supplemental oxygen. ARDS patients that require mechanical ventilation, can be considered for the dose of dexamethasone 20 mg IV once daily for the first 5 days, then 10 mg PO or IV once daily afterwards. Special populations such as pediatric and pregnant patients with COVD-19 and requiring oxygen supplement should be considered for glucocorticoids. COVID-19 is a novel virus that affects patients with a wide range of symptoms, there is still limited evidence to support effective treatment or cure. The recommendations in this newsletter are based on currently available information, it is important to note that information is changing rapidly. Our readers are encouraged to stay updated.

References:

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