Dexamethasone for COVID-19
= Randomized Evaluation of COVID-19 Therapy (RECOVERY trial) =

Background:1,2,3,4
COVID-19 is a novel illness with high morbidity and mortality for which there is a lack of approved treatments. Remdesivir, currently available under an FDA Emergency Use Authorization, has been shown to reduce time to recovery among inpatients with COVID-19 (11 vs 15 days, p<0.001). According to RCT data from the RECOVERY Trial (published in pre-print), dexamethasone for the treatment of inpatients with severe COVID-19 has been demonstrated to improve survival. The IDSA Guidelines currently recommend glucocorticoids for hospitalized patients with severe COVID-19 (SpO2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO).

Methods5:
- The RECOVERY study is a randomized, controlled, open-label, adaptive platform clinical trial comparing numerous potential COVID-19 treatments to usual care (placebo) in hospitalized patients with confirmed COVID-19.
- 11,320 patients were enrolled at 176 hospitals across the United Kingdom. Active arm participants were given dexamethasone 6mg daily, either orally or IV for ten days or until discharge. A 2:1 ratio of usual care (N= 4,321) to dexamethasone patients (N=2,104) was used. The study began in March 2020 and was halted on June 8, 2020.
- Mean age of participants was 66.1 years, and 36% were female. A history of diabetes was present in 24% of patients, heart disease in 27%, and chronic lung disease in 21%. Fifty-six percent of participants had at least one major comorbidity. The primary efficacy outcome was 28-day mortality.

Results5:
- In total, 28-day mortality occurred in 24.6% (1065/4321) of usual care patients and 21.6% (454/2104) in patients receiving dexamethasone (Rate Ratio 0.83; 95% CI 0.74-0.92, p<0.001). In a subgroup analysis, researchers reported the following outcomes in various patient characteristic groups:

<table>
<thead>
<tr>
<th></th>
<th>Deaths in Usual Care</th>
<th>Deaths in Dexamethasone</th>
<th>RR / Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ventilated patients</td>
<td>278 of 683 (40.7%)</td>
<td>94 of 324 (29.0%)</td>
<td>RR: 0.65; 95% CI: 0.51-0.82, p&lt;0.001</td>
</tr>
<tr>
<td>In oxygenated patients</td>
<td>650 of 2604 (25.0%)</td>
<td>275 of 1279 (21.5%)</td>
<td>RR: 0.80; 95% CI: 0.70-0.92; p&lt;0.002</td>
</tr>
<tr>
<td>No respiratory support</td>
<td>137 of 1034 (17.0%)</td>
<td>85 of 501 (13.2%)</td>
<td>RR: 1.22; 95% CI: 0.93-1.61; p=0.14</td>
</tr>
</tbody>
</table>

- In ventilated patients, dexamethasone reduced 28-day mortality by a statistically significant 35% vs. usual care.
- In patients on supplemental oxygen, 28-day mortality was statistically significantly reduced by 20% in patients receiving dexamethasone.
- In patients who received no oxygen (moderately ill), no difference was noted with dexamethasone vs. usual care.

Impact and Points to Consider5,6:
- Dexamethasone is the first medication to demonstrate a reduction in mortality due to COVID-19.
- Methodologically well-designed trial (multi-site, randomized, placebo comparator, blinded) with large effect size.
- Drug characteristics are well known (inexpensive, low dose) with a history of safety/use in various populations.
- Study limitations include:
  - Reporting of subgroup analyses (e.g. ventilated patients) that were not pre-specified and may be misleading;
  - Final outcome was unknown in 28% of enrolled patients; 1807 patients remained hospitalized at end of trial;
  - Reporting of dexamethasone patients >28 days could identify if harm occurred with mild-moderate illness.

References: