COVID 19 THERAPEUTICS
REMDESIVIR AND STEROIDS
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WHAT IS REMDESIVIR

Nucleotide analog

Broad spectrum activity (in vitro and in vivo) in animal models against multiple viral pathogens, including Ebola, MERS and SARS.

Remdesivir acts by causing premature termination of viral RNA transcription thereby inhibiting virus replication.

In rhesus macaques therapeutic treatment with Remdesivir showed reduction in SARS-CoV-2 loads, pathologic changes and progression of clinical disease.
Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Díaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescure, M.D., Ph.D., Emanuele Nicastri, M.D., Rentaro Oda, M.D., et al.


Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial


Summary

Background No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro.
1059 patients randomized across groups – Remdesivir Vs Placebo

Primary endpoint time to recovery to reach ordinal scale of 1-3 (Not requiring Oxygen)

Preliminary results

- Time to recovery 11 days for Remdesivir group vs 15 days for placebo
- No change in mortality, trend 7% vs 12% placebo 14 day outcomes

Figure 3. Time to Recovery According to Subgroup.

Recommendation for Patients With Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19.

Recommendations for Patients with COVID-19 Who Require Supplemental Oxygen

For Patients Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first (AI).

- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.
Recommendation 9: In hospitalized patients with severe* COVID-19 (SpO₂ ≤94% on room air; on supplemental oxygen, mechanical ventilation, or ECMO, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

*Severe illness is defined as patients with SpO₂ ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

Recommendation 10: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

- **Remark:** In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

Recommendation 11: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)
Enrolled in ACCT 1 Trial

Engaged a multidisciplinary best practice council with clinical experts

Developed a Stewardship program

Shared guidelines in weekly town-halls, allow forums for discussion
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group
A All Participants (N=6425)

Rate ratio, 0.83 (95% CI, 0.75–0.93) 
P<0.001

Usual care
Dexamethasone

B Invasive Mechanical Ventilation (N=1007)

Rate ratio, 0.64 (95% CI, 0.51–0.81)

Usual care
Dexamethasone

C Oxygen Only (N=3883)

Rate ratio, 0.82 (95% CI, 0.72–0.94)

Usual care
Dexamethasone

D No Oxygen Received (N=1508)

Rate ratio

Usual care
Dexamethasone

Respiratory Support at Randomization

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Dexamethasone</th>
<th>Usual Care</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>95/324 (29.3)</td>
<td>285/683 (41.4)</td>
<td>0.64 (0.51–0.81)</td>
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<tr>
<td>Oxygen only</td>
<td>298/1279 (23.3)</td>
<td>682/2604 (26.2)</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>No oxygen received</td>
<td>89/501 (17.8)</td>
<td>145/1034 (14.0)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
<tr>
<td>All Patients</td>
<td>482/2104 (22.9)</td>
<td>1110/4321 (25.7)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
</tbody>
</table>

Chi-square trend across three categories: 11.5

Dexamethasone Better
Usual Care Better

No. at Risk

Usual care
Dexamethasone

0.50
0.75
1.00
1.50
2.00

P<0.001
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19
The CoDEX Randomized Clinical Trial
Bruno M. Tomazini, MD1,2; Israel S. Maia, MD, MSc3,4; Alexandre B. Cavalcanti, MD, PhD3,4; et al

JAMA. Published online September 2, 2020. doi:10.1001/jama.2020.17021

Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19
A Randomized Clinical Trial
Pierre-François Dequin, MD, PhD1,2; Nicholas Heming, MD, PhD1,5; Ferhat Meziani, MD, PhD6,7; et al

JAMA. Published online September 2, 2020. doi:10.1001/jama.2020.16761
Findings  In this prospective meta-analysis of 7 randomized trials that included 1703 patients of whom 647 died, 28-day all-cause mortality was lower among patients who received corticosteroids compared with those who received usual care or placebo (summary odds ratio, 0.66).

Meaning  Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19.
Recommendations for Patients with COVID-19

- On the basis of the preliminary report from the RECOVERY trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (BI).


- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (see Additional Considerations below for dosing recommendations) (AlII).

Recommendation 4: Among hospitalized critically ill patients* with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)

- Remark: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 5: Among hospitalized patients with severe**, but non-critical, COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)

- Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 6: Among hospitalized patients with non-severe*** COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

Severity definitions:

- *Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS
- **Severe illness is defined as patients with SpO₂ ≤ 94% on room air, including patients on supplemental oxygen.
- ***Non-severe illness is defined as patient with a SpO₂ > 94% not requiring supplemental oxygen.
Engaged clinical experts across hospitals
Developed protocols and therapeutics Order sets
Disseminated recommendations including recognizing areas of uncertainty
- Virus clearance
- Unclear benefit when combined with other active therapeutics
- Rebound inflammation after steroids discontinuation
THANK YOU