COVID-19 Treatment: Focus on Immune-Based Therapies

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Objectives

- To discuss the cytokine storm and hypercoagulable state during COVID-19
- To discuss the role of immune-based therapies for COVID-19.
- To discuss where each of the treatment options fits in the paradigm of care.
Cytokine Storm
3 Stages of COVID-19 Infection

Stage I (Early Infection)
- Viral response phase
- Clinical Symptoms: Mild constitutional symptoms, Fever >99.6°F, Dry Cough
- Clinical Signs: Lymphopenia
- Potential Therapies: Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions

Stage II (Pulmonary Phase)
- Host inflammatory response phase
- IIA: Shortness of Breath without (IIA) and with Hypoxia (IIB)
  - PaO2/FiO2 ≤ 300 mmHg
- IIB: Abnormal chest imaging, Transaminitis, Low-normal procalcitonin

Stage III (Hyperinflammation Phase)
- ARDS, SIRS/Shock, Cardiac Failure
- Elevated inflammatory markers: CRP, LDH, IL-6, D-dimer, ferritin, Troponin, NT-proBNP elevation

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Corticosteroids
Overview

- **MOA:** Anti-inflammatory/immunomodulatory

- Dexamethasone is the only drug found to have a mortality benefit in SARS-CoV-2 infection in a controlled trial.

- **Dosing:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier). Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
RECOVERY Trial

- Hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2

- **Study population:**
  - 6,425 patients admitted with COVID-19 disease to 176 National Health Service hospitals in the U.K., of whom 2,104 were randomly allocated to receive dexamethasone (6 mg/day for up to 10 days) + SOC and 4,321 received SOC alone.

- **Primary endpoint:**
  - All-cause mortality within 28 days of randomization.

The Recovery Collaborative Group. *NEJM* July 2020
Results

Key findings:

- 482 patients (22.9%) in the dexamethasone arm and 1,110 patients (25.7%) in the standard of care group died within 28 days of randomization (p< 0.001).

- In the dexamethasone group, the incidence of death was lower than the SOC arm in patients receiving mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51-0.81), as well as those receiving oxygen without mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72-0.94).

- In patients who were moderately ill but did not require oxygen at baseline, use of dexamethasone was associated with a non-statistically significant finding of increased mortality (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91-1.55).

The Recovery Collaborative Group. NEJM July 2020
Conclusions

- Overall, in this controlled open label trial, dexamethasone reduced mortality in those patients receiving mechanical ventilation or oxygen.

- There was no benefit for patients who did not require respiratory support; in fact, there was a non-statistically significant trend toward increased mortality.
WHO Pooled Data

- Pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials).

- 1703 patients (678 randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial.

- 28-day mortality was lower in patients randomized to corticosteroids: 32.7% corticosteroids vs. 41.5% usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53, -0.82]; $P < 0.001$).
CRP & Corticosteroids

- **Study population:**
  - 1,806 patients admitted with COVID-19

- **Primary endpoint:**
  - Mortality or need for mechanical ventilation.

- **Key findings:**
  - 140 patients (7.7%) were treated with corticosteroids, while 1,666 (92.3%) never received corticosteroids.
  - Corticosteroid use in patients with initial CRP levels >20 mg/dL was correlated with significantly reduced risk of mortality or mechanical ventilation (OR, 0.23; 95% CI, 0.08-0.70).
  - Corticosteroid use in patients with CRP levels <10 mg/dL was associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI, 1.39-5.03).

What do the Guidelines State?

- The Surviving Sepsis Campaign guidelines for COVID-19 issued a weak recommendation to use corticosteroids in patients with COVID-19 and ARDS who required mechanical ventilation, but also indicated that some expert panel members preferred not to make a recommendation until further high-quality evidence was available.

- Guidelines from IDSA recommends dexamethasone in those hospitalized critically ill patients or severe patients with COVID-19.

My Thoughts

- Corticosteroids should be started in patients with moderate-severe hypoxemic respiratory sufficiency
  - P/F ratio < 250 +requiring supplemental O₂

- Also factor in rise in inflammatory markers
  - CRP
  - Ferritin
  - D-dimer (inflammation drives coagulation)
  - IL-6

- Methylprednisolone 1 mg/kg or dexamethasone 6 mg/day for at least 7 days with a slow taper over a few weeks.
Convalescent Plasma
Overview

- **Class:** Biologic, passive antibody treatment
- **Dosing:** No standard recommended
  - The National Convalescent Plasma Expanded Access COVID-19 Protocol is studying a dose of 1 unit of plasma (at least 200 ML)
- **August 2020:** FDA announced EUA for convalescent plasma in patients with COVID-19.

https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/
Concept of Using Convalescent Plasma to Treat COVID-19

J Clin Invest. 2020. https://doi.org/10.1172/JCI138003
Convalescent Plasma in Argentine Hemorrhagic Fever (AHF)

- Randomized, double-blind, placebo-controlled trial
- **Primary Endpoint**: Efficacy of convalescent plasma in patients with AHF ≤ 8 days from symptom onset (N=188)
- **Intervention**: Randomized to receive 500 mL of convalescent plasma or healthy donor plasma
- **Results**: Case fatality rate: 1.1% convalescent plasma vs. 16.5% healthy plasma donor

RCT in China: Convalescent Plasma for Severe or Life-Threatening COVID-19

- Open-label study enrolling patients from 7 medical centers in Wuhan, China (February-April 2020)

- Intervention:
  - Standard treatment + convalescent plasma (N=52)
  - Standard treatment alone (N=51)

- Study terminated early due to containment of pandemic in China.

- **Dose**: 4-13 mL/kg, S-RBD-specific IgG titer $\geq 1:640$

- **Primary endpoint**: time to clinical improvement (i.e., discharged alive or 2-point reduction on 6-point disease severity scale) within 28 days

- **Secondary outcomes**: 28-day mortality, time to discharge, rate of viral PCR result changing from BL positive to negative within 72 hours

Li et al. JAMA June 2020
Results

Time to Clinical Improvement

Secondary Outcomes
- 28 day mortality: 15.7% convalescent plasma vs. 24% standard treatment
- Discharge by day 28: 51% convalescent plasma vs. 36% standard treatment

Li et al. JAMA June 2020
Conclusion

- In patients with severe or life-threatening COVID-19, convalescent plasma therapy with standard of care did not significantly improve the time to clinical improvement within 28 days.

- In subgroup analysis of patients with severe, but not life-threatening disease, clinical improvement was seen in patients who received plasma, despite patients being symptomatic for a median of 33 days in this group.
RCT in Netherlands (ConCOVID)

- Open-label RCT enrolled patients from 14 secondary and academic hospitals in the Netherlands (April-June 2020)

- **Intervention:**
  - Standard treatment + convalescent plasma (N=43)
  - Standard treatment alone (N=43)

- Study terminated early due to finding of substantial baseline autologous anti-SARS-CoV-2 antibodies in 79% patients, which would prevent any conclusion on efficacy of convalescent plasma

- **Dose:** 300 mL plasma; anti-SARS-CoV-2 neutralizing titers ≥ 1:80

- **Primary endpoint:** 60-day mortality

- **Secondary outcomes:** length of hospital stay, improvement by WHO 8-point severity scale on day 15, safety

Gharbharan et al. NOTE: Not peer-reviewed; July 2020; NCT04342182
Results

- 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.
- A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40).
- No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58).
Mayo Clinic Observational Data from Expanded Treatment Protocol

- Single-arm open label study executed in 2,807 acute care hospitals in the U.S. (April-July 2020)
- N=35,322 adults hospitalized with severe or life-threatening COVID-19; 52.3% patients in the ICU; 27.5% received mechanical ventilation.
- Patients transfused with ≥ 1 unit of human COVID-19 convalescent plasma
- 7-day mortality rate was 8.7% in patients transfused within 3 days of COVID-19 diagnosis but 11.9% in patients transfused after 3 days (p<0.001).
- 30-day mortality was 21.6% vs. 26.7% (p<0.0001).
- The pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days versus those transfused with low antibody level plasma units.
- AEs: 15 deaths were reported within 4 hours of transfusion (0.3%), with 4 deaths (0.08%) considered possibly or probably related to convalescent plasma transfusion

My Thoughts

- May work best for patients earlier in the disease course
- Treating patients relatively later in disease – patients may already generate their own neutralizing antibodies at baseline
- Questions remain about the antibody titer that should be used when treating patients with COVID-19, and if timing of administration is an important consideration.
Tocilizumab/IL-6 Inhibitors
Overview

- **Class:** Interleukin-6 (IL-6) receptor blocker

- **Dose:** Initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg). One additional dose may be given if symptoms worsen or show no improvement.

- **Rationale:**
  - Increased levels of inflammatory cytokines, including IL-6 has been affiliated with increased mortality from acute respiratory distress syndrome (ARDS)
  - Patients with COVID-19 have increased IL-6 levels and other inflammatory markers consistent with cytokine storm
COVACTA Trial

- Trial did not meet its primary endpoint of improved clinical status in patients with COVID-19–associated pneumonia or the secondary endpoint of reduced patient mortality.
- The trial did show a positive trend in time to hospital discharge among patients who received tocilizumab.
EMPACTA Trial

- Preliminary results found hospitalized patients who received tocilizumab were 44% less likely to progress to mechanical ventilation or death vs. patients who received placebo plus standard of care.

- The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab group vs. 19.3% in the placebo arm.

- The time to hospital discharge and mortality by Day 28 was not statistically significant

Biran et al.

- **Study population:**
  - Retrospective study of 764 COVID-19 patients admitted to the ICU in 13 New Jersey hospitals; 210 (27%) received tocilizumab.
  - Propensity score-matched population included these 210 patients and 420 who did not receive tocilizumab.
  - Tocilizumab was administered a median of 9 days (IQR 6–12) after the start of patient-reported symptoms.

- **Primary endpoint:**
  - Hospital-related mortality

Results

- 358 (57%) of 630 patients died; of these, 102 (49%) received tocilizumab and 256 (61%) did not.

- A primary multivariable Cox regression analysis with propensity matching noted an association between receiving tocilizumab and decreased hospital-related mortality (HR 0.64; p=0.0040).

- In post-hoc analysis of the 558 patients (89%) who had a CRP >15 mg/dL at baseline, tocilizumab exposure was associated with decreased hospital-related mortality (HR 0.48; p=0.0025). This was not seen in patients with a CRP <15 mg/dL.

- The frequency of secondary bacterial infections was 17% in patients who received tocilizumab and 13% in those who did not.
My Thoughts

- Can see a benefit in patients with cytokine storm
- Use inflammatory markers to guide you:
  - CRP
  - Ferritin
  - D-dimer (inflammation drives coagulation)
  - IL-6
Anticoagulation
Anticoagulant in Patients With Severe COVID-19 and Coagulopathy

- Single-center, retrospective study in Wuhan, China
- **Primary Endpoint:** 28-day mortality
- **Intervention:** prophylactic heparin vs. low-molecular-weight heparin for ≥ 7 days vs no heparin or heparin for < 7 days in patients with severe COVID-19 (N = 449)
  - Severe COVID-19: RR ≥ 30 breaths/min, SaO₂ ≤ 93% at rest, or PaO₂/FiO₂ ratio ≤ 300 mm Hg
- No difference in 28-day mortality between those administered heparin vs. nonheparin in overall population (30.3% vs 29.7%; p = 0.910)

Prophylactic Dose vs Therapeutic Dose Anticoagulation in COVID-19

- Retrospective, cohort study compared in-hospital mortality with prophylactic dose (N=299) vs therapeutic dose anticoagulation with heparin or low-molecular-weight heparin (N=75) upon admission in patients with COVID-19.
  - Excluded patients receiving therapeutic anticoagulation for thrombotic indication; prophylactic anticoagulation group received only prophylactic dosing for whole inpatient duration

- Results:
  - In-hospital mortality: 14.4% prophylactic vs. 38.7% treatment
  - Adjusted risk ratio: 2.3 (1.0-4.9; p=0.04)

Motta. *medRxiv*. 2020;[Preprint]. Note: This study has not been peer reviewed.
ASH Guidance

- All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk.
- Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia.
- In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g., pneumatic compression devices).
- Encourage participation on clinical trials rather than empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation.
Inflammatory risk

- Low Risk
  - Low D-dimer
  - Relatively normal inflammatory markers
- High Risk
  - High D-dimer (>2000 ng/mL)
  - PT>3 seconds over control
  - PTT>5 seconds over control
  - Elevated inflammatory markers

Clinical suspicion for VTE

- Absent
- Present

Imaging feasible?

- Imaging feasible
- Imaging not feasible

Management

- Standard dose VTE prophylaxis
- Treatment depending on imaging results
- Full dose anticoagulation
- Higher dose VTE prophylaxis

Consider VTE Imaging
Questions??