# Update on Therapeutic Options for COVID-19

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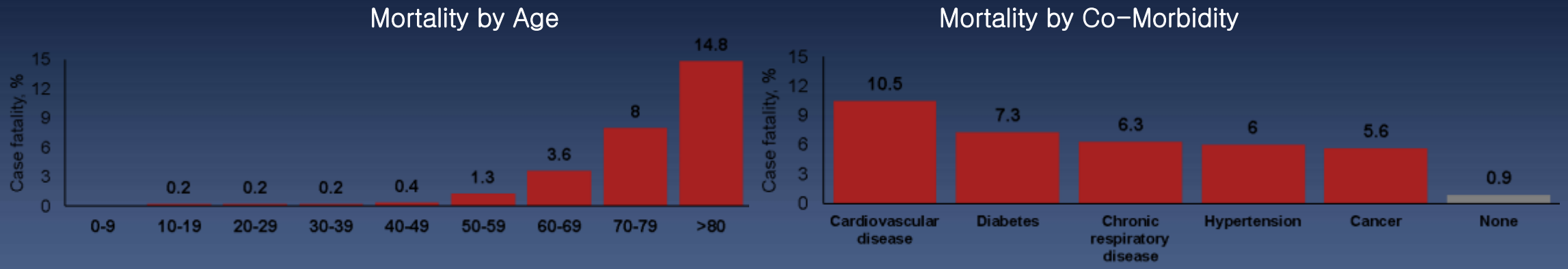
# COVID-19 Therapeutic Options: Overview

- Brief Overview of SARS-CoV-2 Treatment Strategies
- Status of Antiviral Agents
  - Remdesivir
  - Hydroxychloroquine
- Status of Immune-Based Treatments
  - Dexamethasone
  - IL-6 Blockers (e.g., tocilizumab)
  - Convalescent plasma

Disclosures:
Speakers fees from Gilead

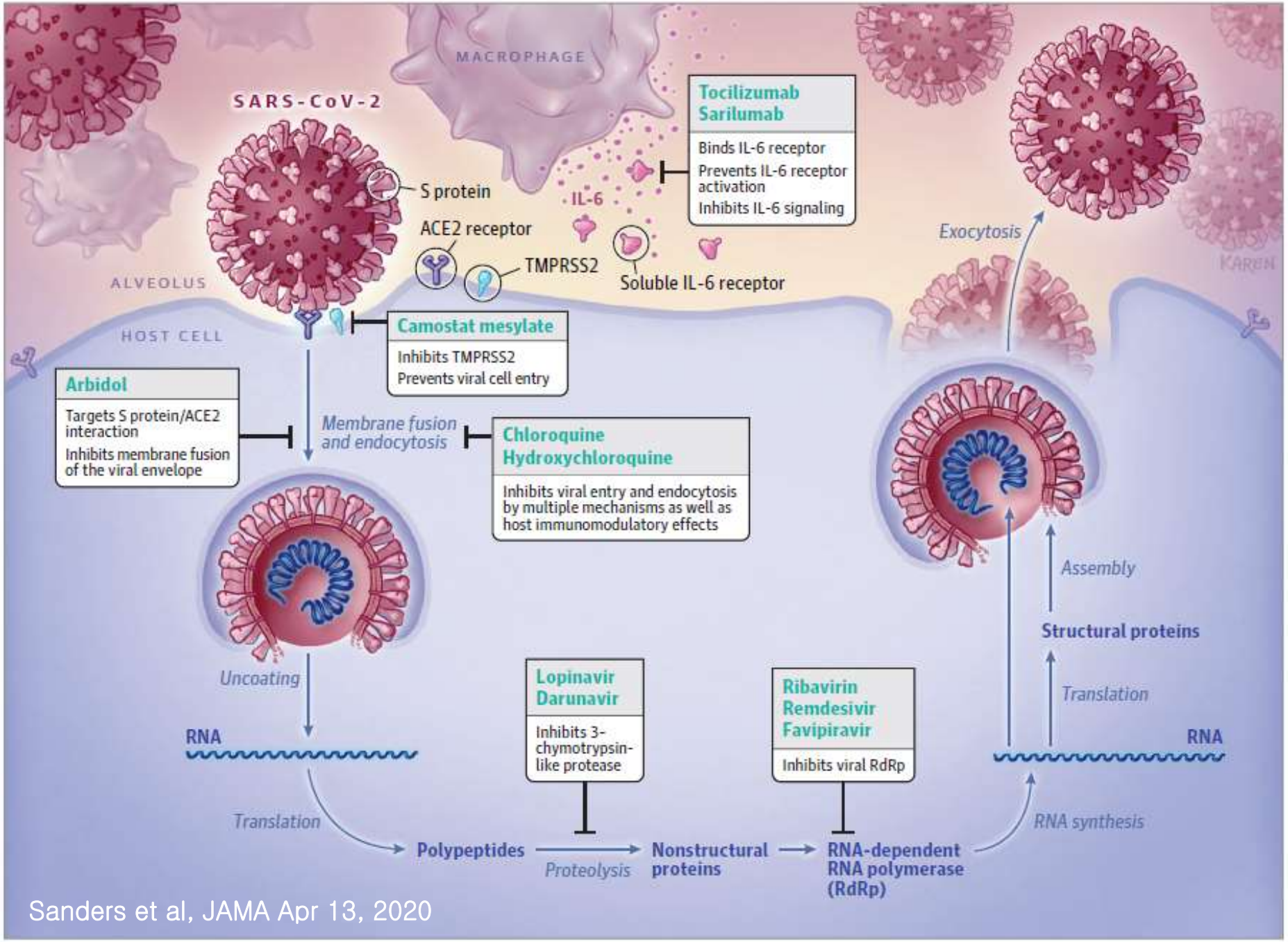
# Brief Overview of SARS-CoV-2 Treatment Strategies




- Risk factors for mortality include older age and presence of co-morbidities
- Currently there are no FDA-approved treatments for COVID-19
- Remdesivir received Emergency Use Authorization for *severe* COVID-19 disease on May 1
- Numerous clinical trials underway

China CDC Weekly Feb 17, 2020 http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

Figure. Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets



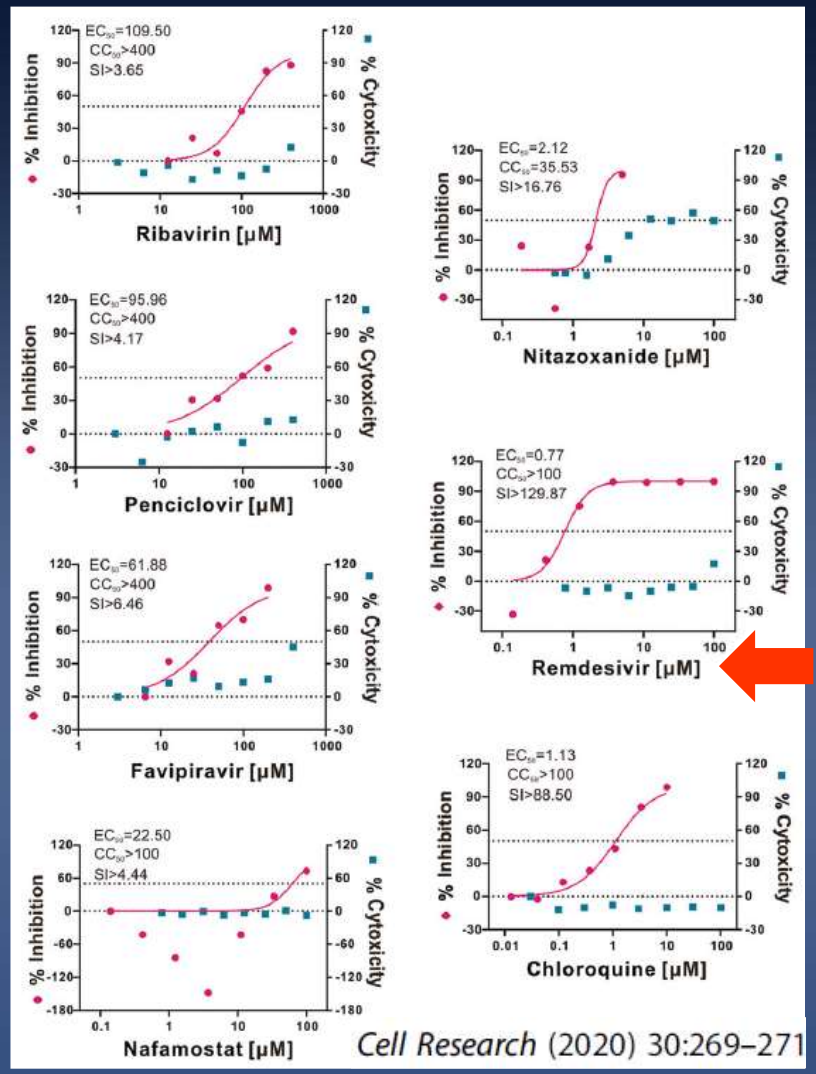

Sanders et al, JAMA Apr 13, 2020

# Anti-Viral Agents

## Remdesivir

# Remdesivir: Pre-Clinical Data

- Nucleoside analogue- inhibits viral RNA polymerase
- Broad in vitro antiviral activity, highly active against SARS-CoV-2 (low $EC_{50}$)
- Animal Models (Mice)
  - SARS: reduces SARS lung viral load and improves pulmonary function
  - MERS: Superior to lopinavir/ritonavir + IFN-beta in reducing viral load and improving pulmonary function





Wang W et al, Cell Research 2020; 30: 269–271
Sheahan TP et al, *Sci Transl Med.* 2017;9(396)
Sheahan TP et al, *Nat Commun.* 2020;11(1):222
de Wit E et al, *Proc Natl Acad Sci USA.* 2020;117(12):6771–6776

# Remdesivir: Brief Summary of Clinical Data

Phase 1 Data:
- Generally well tolerated; reversible Grade 1-2 elevation in AST and ALT
- GI side effects (N/V, diarrhea)

PALM Trial (Ebola)
- 175 patients received remdesivir; found to be inferior to other agents for Ebola
- 1 serious adverse event (death), unclear if related to Ebola infection or remdesivir

Compassionate Use of Remdesivir for severe COVID-19
- Data for 53 patients (median age 64 years, 57% on mechanical ventilation)
- 68% showed improvement in oxygenation; 13% mortality (18% in ventilated patients) appears lower than existing published data (no control group)

RCT (placebo-controlled) in hospitalized patients with severe COVID-19 (China)
- No difference in time to clinical improvement at 28d (HR 1.23, 95%CI 0.87-1.75) or viral clearance, but study was significantly under-enrolled (237 patients enrolled, target 453))

5-day vs. 10-day Remdesivir for Severe COVID-19
- 5-day course as effective as 10-day course (no control group)
- Suggestion that ventilated patients may benefit from 10-day course

https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf
Mulangu et al, NEJM 2019; Dec 12
Grein J et al, NEJM April 10, 2020
Wang Y et al, Lancet 2020; May 16
Goldman et al, NEJM 2020; May 27

# Adaptive COVID-19 Treatment Trial (ACTT): Remdesivir vs Placebo

- Placebo-controlled RCT sponsored by NIAID
- Enrolled 1063 hospitalized patients across 68 sites
- Baseline characteristics
  - Avg age 58.9 years; 52% with ≥2 comorbidities (HTN, obesity, DM)
  - 51% of patients on either no oxygen or nasal cannula
- Trial halted by DSMB given preliminary evidence of benefit in primary outcome
  - Remdesivir associated with 31% faster recovery time (p=<0.001)
  - Trend towards improved mortality
  - Greatest benefit for non-ventilated patients on supplemental oxygen
- Contributed to FDA decision to grant EUA

| Intervention | Recovery Time (days, median) | 14d Mortality |
|---|---|---|
| Remdesivir | 11 days | 7.1% |
| Placebo | 15 days | 11.9% |
| | p=<0.001 | HR 0.70<br>95% CI, 0.47 to 1.04 |

Beigel et al, NEJM 2020; May 22

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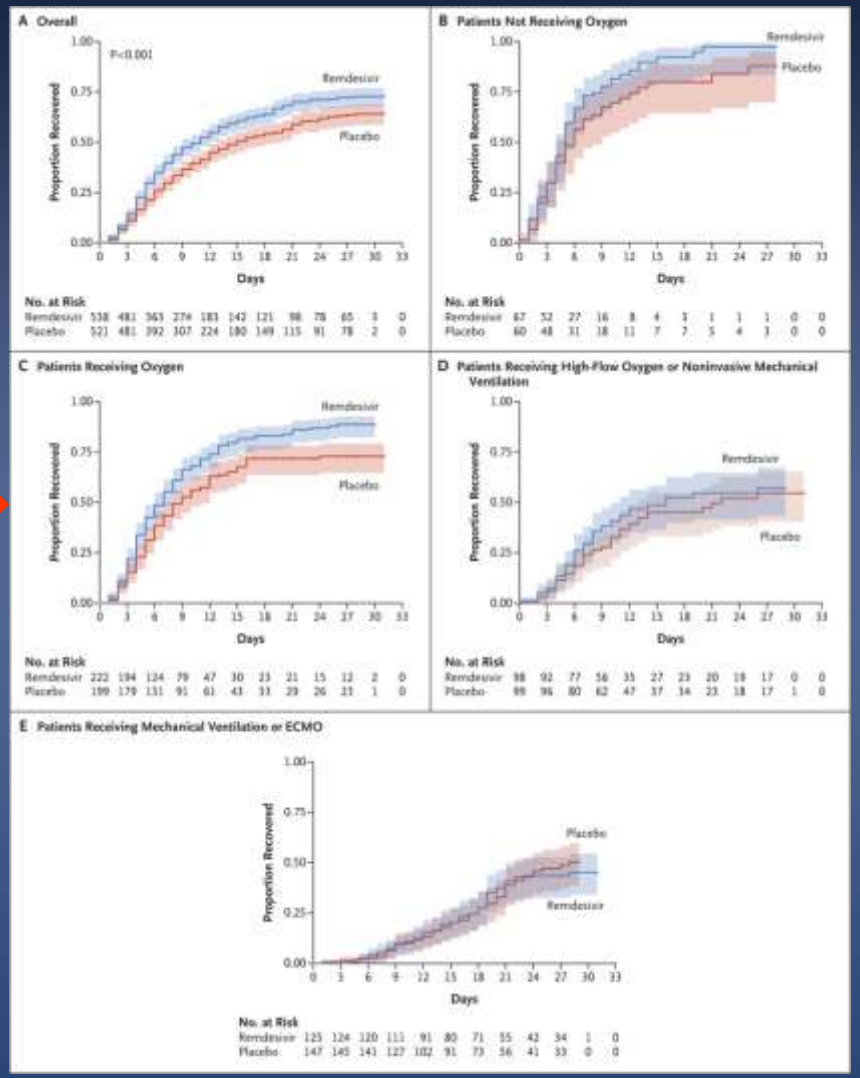



Beigel et al, NEJM 2020; May 22

# Adaptive COVID-19 Treatment Trial (ACTT): Remdesivir vs Placebo

| Subgroup | No. of Patients | Recovery Rate Ratio (95% CI) |
|---|---|---|
| All patients | 1059 | 1.32 (1.12–1.55) |
| Geographic region | | |
| North America | 844 | 1.33 (1.11–1.59) |
| Europe | 163 | 1.40 (0.90–2.16) |
| Asia | 52 | 1.20 (0.65–2.22) |
| Race | | |
| White | 563 | 1.39 (1.12–1.73) |
| Black | 219 | 1.14 (0.81–1.61) |
| Asian | 134 | 1.04 (0.68–1.57) |
| Other | 143 | 1.89 (1.15–3.10) |
| Ethnic group | | |
| Hispanic or Latino | 247 | 1.23 (0.88–1.72) |
| Not Hispanic or Latino | 748 | 1.33 (1.10–1.61) |
| Age | | |
| 18 to <40 yr | 119 | 2.03 (1.31–3.15) |
| 40 to <65 yr | 558 | 1.16 (0.94–1.44) |
| ≥65 yr | 382 | 1.37 (1.02–1.83) |
| Sex | | |
| Male | 682 | 1.31 (1.07–1.59) |
| Female | 377 | 1.38 (1.05–1.81) |
| Symptoms duration | | |
| ≤10 days | 664 | 1.28 (1.05–1.57) |
| >10 days | 380 | 1.38 (1.05–1.81) |
| Baseline ordinal score | | |
| 4 (not receiving oxygen) | 127 | 1.38 (0.94–2.03) |
| 5 (receiving oxygen) | 421 | 1.47 (1.17–1.84) |
| 6 (receiving high-flow oxygen or noninvasive mechanical ventilation) | 197 | 1.20 (0.79–1.81) |
| 7 (receiving mechanical ventilation or ECMO) | 272 | 0.95 (0.64–1.42) |


Beigel et al, NEJM 2020; May 22

# Remdesivir and COVID-19: Summary

- Remdesivir is associated with faster time to clinical improvement in hospitalized patients with severe COVID-19
  - Non-intubated patients on supplemental oxygen may benefit the most
- Remdesivir is generally well-tolerated; watch for GI symptoms and transaminitis
- In the US remdesivir is available through EUA. Criteria include:
  - Hospitalized with confirmed COVID-19 with severe pneumonia (SpO2 ≤ 94% on room air or requiring supplemental O2)
  - AST/ALT levels < 5 X ULN
  - Cr clearance > 30 mL/min
  - Review and consent to EUA fact sheet
- Treatment duration: 5 days for non-intubated patients; 10 days for intubated patients

# Anti-Viral Agents:
## Hydroxychloroquine

# Hydroxychloroquine

Currently no high-quality clinical data to support the use of hydroxychloroquine for COVID-19

NIH Treatment Guidelines Panel recommend AGAINST the use of:

- Chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII).
- Hydroxychloroquine + azithromycin (AIII), because of the potential for toxicities.

June 15: FDA revokes Emergency Use Authorization for chloroquine and hydroxychloroquine "based on new information, including clinical trial data results, that have led BARDA to conclude that this drug may not be effective"

- Newer data suggests current dosing levels are unlikely to have an antiviral effect
- Initial reports of reduced viral shedding with HCQ have not been consistently replicated
- No evidence of clinical benefit to date (mortality, LOS, ventilation)

https://www.covid19treatmentguidelines.nih.gov/tables/table-2a/
https://www.fda.gov/media/138945/download

# Hydroxychloroquine: Clinical Data

## Observational Study of HCQ at a Large Medical Center in New York City

- Observational evaluation of 1,376 consecutive hospitalized adults; 811 (58.5%) received HCQ
- Baseline characteristics: more risk factors for severe disease in HCQ group
- HCQ use not associated with intubation or death using propensity score analysis (HR 1.04; 95% CI, 0.82–1.32). Similar findings with HCQ + azithromycin

## Randomized, Controlled Trial of HCQ vs. SOC for Mild/Moderate COVID-19

- RCT of HCQ (n=75) compared to placebo (n=75)
- No difference in negative PCR conversion rate within 28 days (85.4% vs. 81.3%, respectively), and no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.
- Adverse events more common in the HCQ arm (30%) compared to SOC (9%) (diarrhea most frequent)

## RECOVERY Trial (UK)

- Ongoing trial of hospitalized COVID-19 patients evaluating multiple treatments to evaluate all-cause 28-d mortality
- Preliminary data (HCQ n=1542 vs usual care n=3121): No mortality benefit with HCQ (25.7%) compared to usual care (23.5%), HR 1.11, 95% CI 0.98–1.26, p=0.10. Similar findings with LOS and need for mechanical ventilation


https://www.covid19treatmentguidelines.nih.gov/tables/table-2a/
Geleris J, Sun Y, Platt J, et al.. *N Engl J Med*. 2020.
Tang W, Cao Z, Han M, et al. *BMJ*. 2020;369:m1849.
https://www.fda.gov/media/138945/download

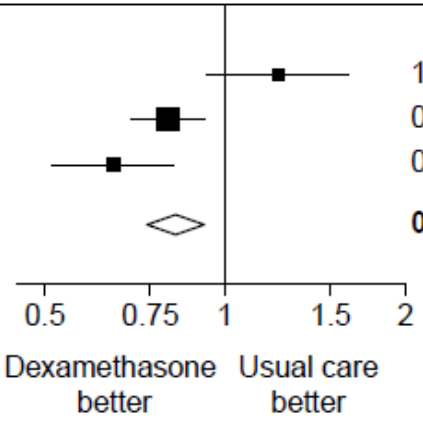
# Immune-Based Treatments:
## Dexamethasone

# Dexamethasone

- RECOVERY Trial (randomized, open-label, controlled trial in UK)
- 2104 patients randomized to dexamethasone (6mg IV/PO daily x10 days)
- Baseline characteristics
  - Age 66.1 years (mean), 64% male, 56% with ≥1 co-morbidity
  - Mechanical ventilation 16%, supplemental O2 in 60%, no supplemental O2 in 24%
- Compared to usual care, 28-d mortality was lower with dexamethasone (21.6% vs 24.6%); biggest impact in those on mechanical ventilation

| Respiratory support at randomization | Dexamethasone | Usual care | RR (95% CI) |
|---|---|---|---|
| No oxygen received | 85/501 (17.0%) | 137/1034 (13.2%) | 1.22 (0.93–1.61) |
| Oxygen only | 275/1279 (21.5%) | 650/2604 (25.0%) | 0.80 (0.70–0.92) |
| Invasive mechanical ventilation | 94/324 (29.0%) | 278/683 (40.7%) | 0.65 (0.51–0.82) |
| **All participants** | **454/2104 (21.6%)** | **1065/4321 (24.6%)** | **0.83 (0.74–0.92) p<0.001** |

Trend across three categories: $\chi^2_1$=11.49; p<0.001




https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf

# Immune-Based Treatments:
## IL-6 Blockade

# IL-6 Inhibitors

## Sarilumab

•Preliminary data of Phase 2/3 clinical trial of hospitalized COVID-19 patients randomized to sarilumab 400 mg (n=145), sarilumab 200 mg (n=136), or placebo (n=77).

•Of 226 critical patients:
- •Lower mortality/ventilator requirement in the 400mg sarilumab (28%) compared to 200mg sarilumab (46%) or placebo (55%)

•Benefit not observed in the "severe" cohort

## Tocilizumab

•Preliminary data an open-label randomized trial across 7 French hospitals (CORIMUNO-TOCI trial)

•Patients with mod/severe disease randomized to tocilizumab (n = 65) or usual care (n = 64).

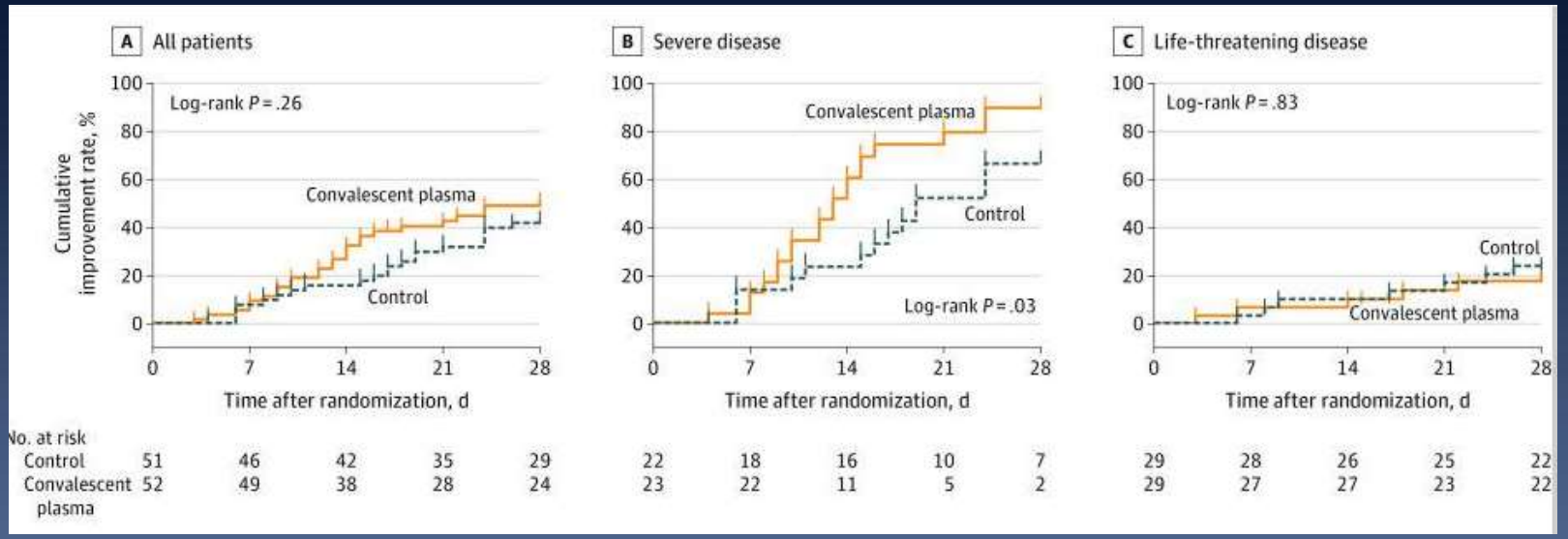
•Tocilizumab 8 mg/kg on Day 1; repeat dose on Day 3 if no response

•Preliminary finding of lower mortality or ventilation requirement in the tocilizumab cohort (data not yet reported)

https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19
https://www.covid19treatmentguidelines.nih.gov/tables/table-3a/

# Immune-Based Treatments:
## Convalescent Plasma

# SARS-CoV-2 Convalescent Plasma




•Very limited data available; potential benefit from limited data with SARS

•Open-label RCT from 7 hospitals (Wuhan) for patients with severe or life-threatening COVID-19 comparing convalescent plasma (n=52) to usual care (n=51). *Note: Only plasma with high SARSCo-V-2 IgG titers were used*

•Findings:

- •Trend towards 28-d clinical improvement (51.9% vs 43.1%, HR 1.40 [95% CI, 0.79-2.49])
- •Significant clinical improvement in those with severe disease (91.3% vs 68.2%, HR 2.15 [95% CI, 1.07-4.32]; P = .03); no improvement in those with life-threatening disease
- •No significant improvement in 28-d mortality or time-to-discharge
- •Higher viral PCR conversion rate with convalescent plasma (87.2% vs. 37.5%, p<0.001)
- •2 adverse events observed in convalescent plasma group that improved with supportive care.

Li L et al, JAMA 2020; Jun 3

# Summary: COVID-19 Therapeutics

- No role for hydroxychloroquine in COVID-19 treatment
- Preliminary data demonstrates remdesivir can improve time to recovery in hospitalized patients on supplemental oxygen, particularly those not mechanically ventilated
- Preliminary data demonstrates dexamethasone can improve mortality in hospitalized patients requiring supplemental oxygen (including mechanical ventilation)
- Encouraging data supports a possible role of IL-6 inhibitors in critically ill patients; high-quality data needed
- Encouraging data supports a possible role of convalescent plasma in severe but non-life threatening illness; high-quality data needed
- This is a rapidly changing topic; stay tuned