Medical Management of Kidney Transplant Recipients with COVID-19

Maria Ajaimy, MD

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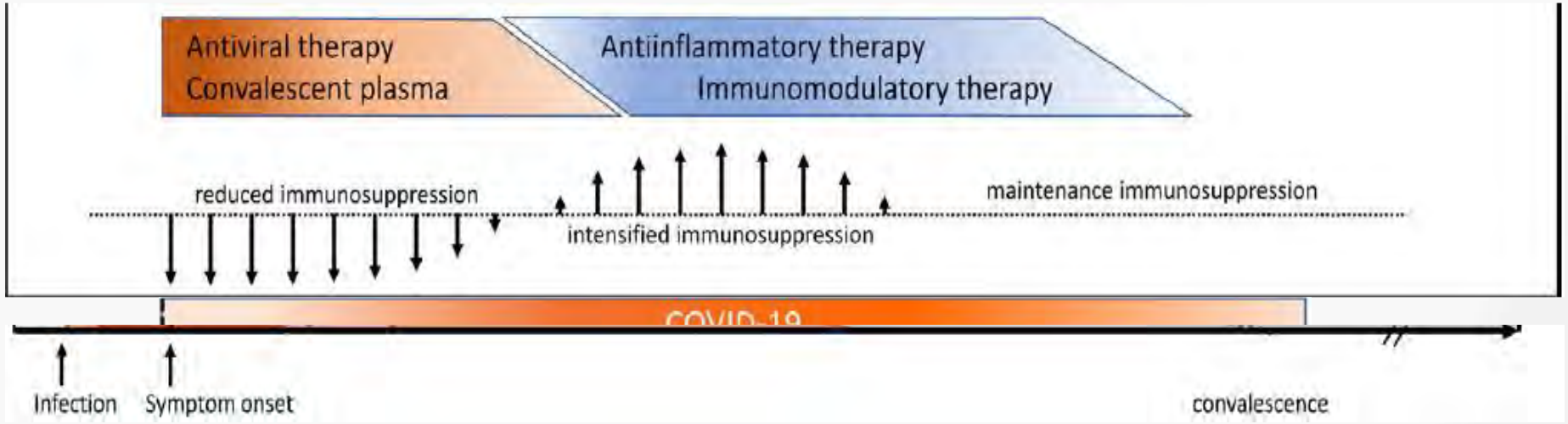

Stepwise reduction of immunosuppression according to the severity of the clinical presentation

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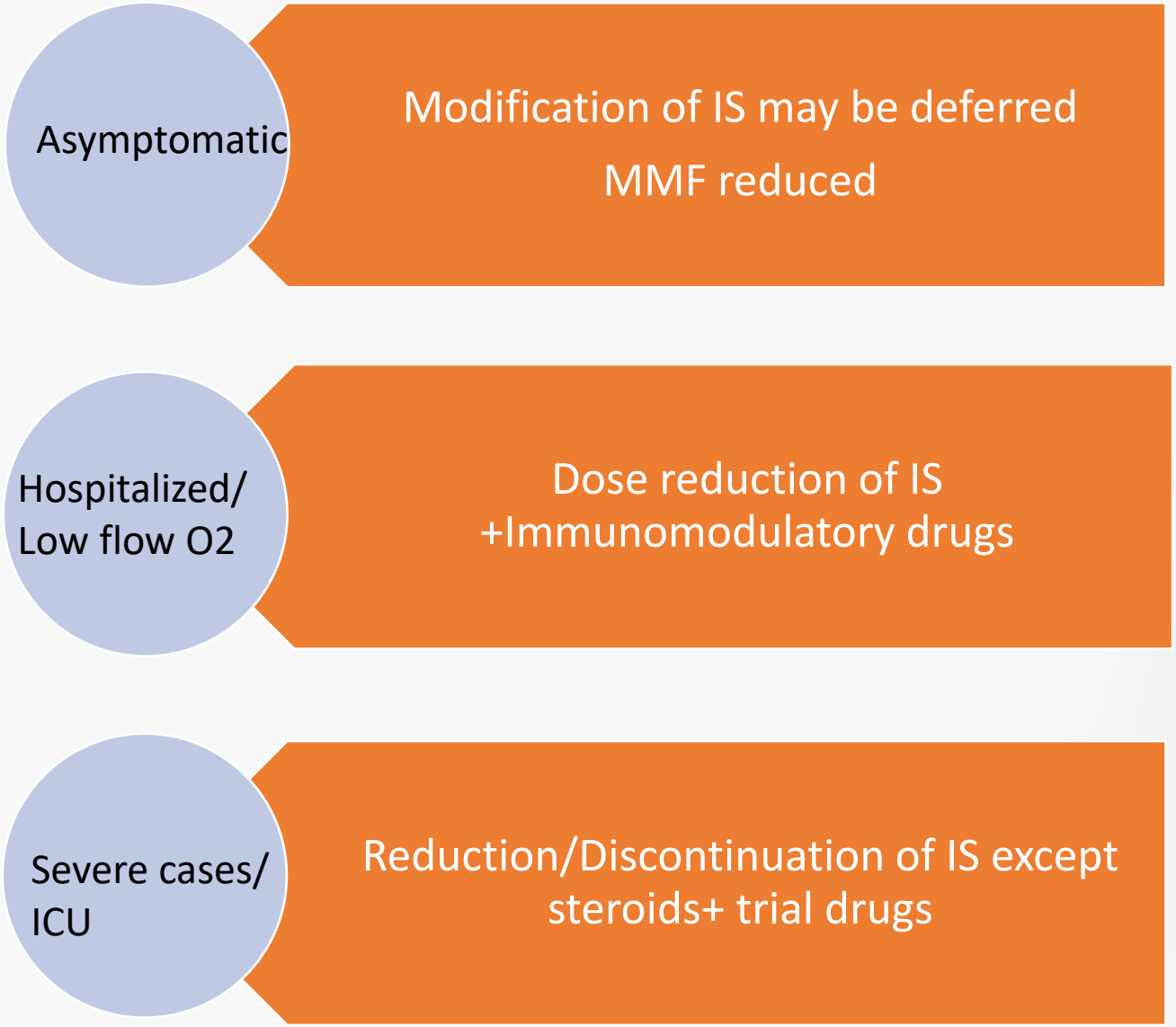

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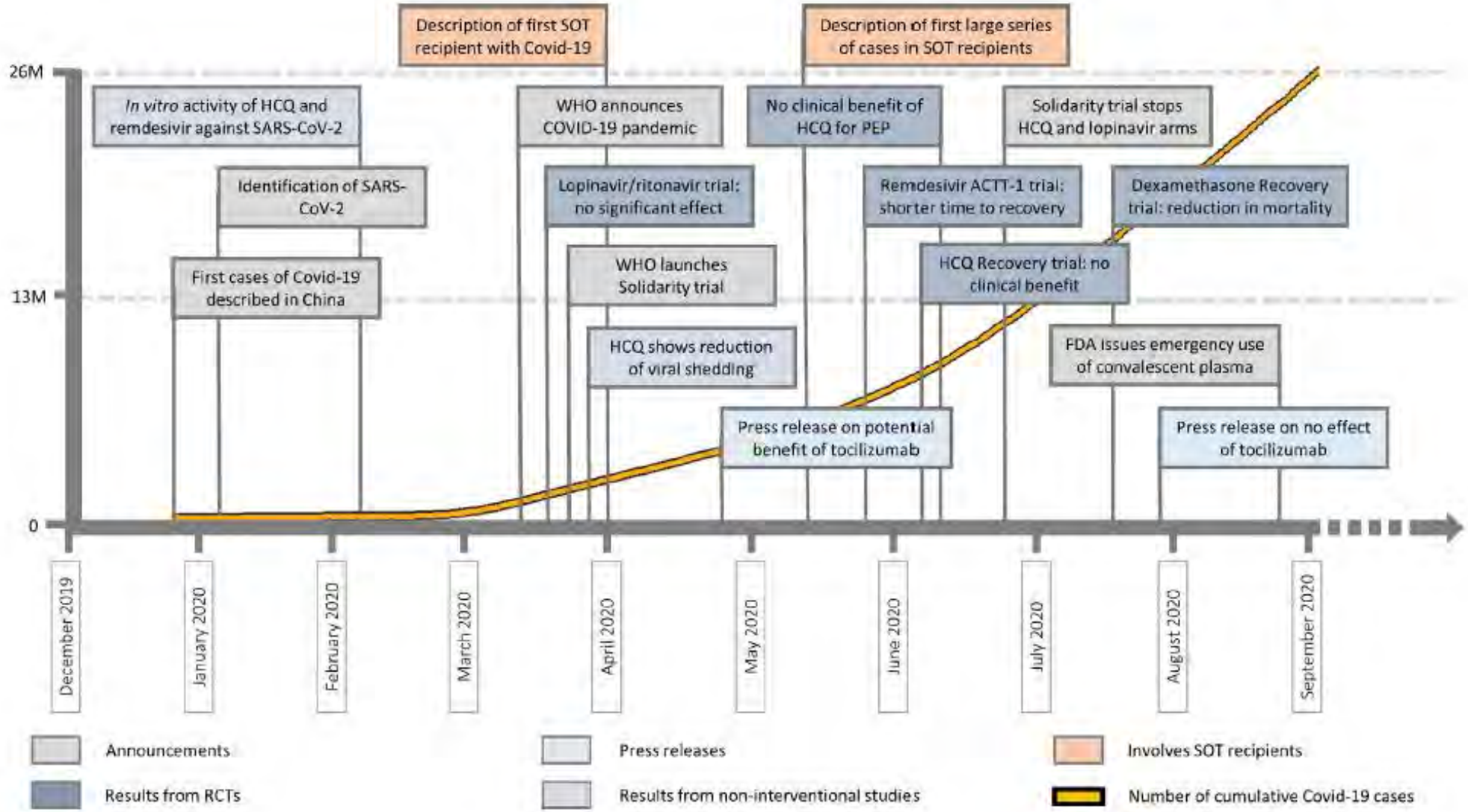

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Non-Hospitalized COVID 19

Treatment with monoclonal antibody therapy: The FDA issued Emergency Use Authorizations (EUAs) for two monoclonal antibodies (**bamlanivimab; and casirivimab + imdevimab cocktail)** for non-hospitalized COVID-19 patients presenting early in the course of illness after randomized trials demonstrating benefit in terms of **prevention of disease progression, hospitalization, and reduction in viral loads**. This treatment is available for patients who will be managed as outpatients **with <3 days of symptoms**.

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101 Patients were enrolled and assigned to 700 mg of LY-CoV555 monotherapy

107 Patients were enrolled and assigned to 2800 mg of LY-CoV555 monotherapy

101 Patients were enrolled and assigned to 7000 mg of LY-CoV555 monotherapy

143 Patients were enrolled and assigned to placebo

Interim Analysis

Positive SARS-CoV-2 test ≤3 days before infusion
Mild or moderate Covid-19 symptoms
Primary end point: change from baseline to day 11 (±4 days) in SARS-CoV-2 viral load
Secondary end points include safety, symptom severity, hospitalization, and time points for viral clearance

Figure 1. Enrollment and Trial Design.

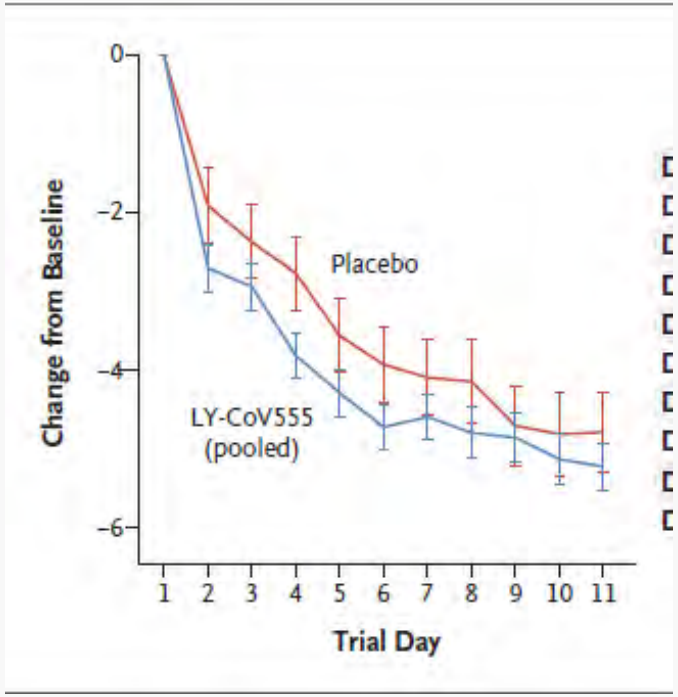

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

n engl j med 384;3

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ORIGINAL ARTICLE

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, B.J. Musser, Y. Soo, D. Rofail, J. Im, C. Perry, C. Pan, R. Hosain, A. Mahmood, J.D. Davis, K.C. Turner, A.T. Hooper, J.D. Hamilton, A. Baum, C.A. Kyratsous, Y. Kim, A. Cook, W. Kampman, A. Kohli, Y. Sachdeva, X. Graber, B. Kowal, T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, and G.D. Yancopoulos, for the Trial Investigators*

ABSTRACT

BACKGROUND

Recent data suggest that complications and death from coronavirus disease 2019 (Covid-19) may be related to high viral loads.

METHODS

In this ongoing, double-blind, phase 1–3 trial involving nonhospitalized patients with Covid-19, we investigated two fully human, neutralizing monoclonal antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, used in a combined cocktail (REGN-COV2) to reduce the risk of the emergence of treatment-resistant mutant virus. Patients were randomly assigned (1:1:1) to receive placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). Key end points included the time-weighted average change from baseline in viral load from day 1 through day 7 and the percentage of patients with at least one Covid-19–related medically attended visit through day 29. Safety was assessed in all patients.

RESULTS

Data from 275 patients are reported. The least-squares mean difference (combined REGN-COV2 dose groups vs. placebo group) in the time-weighted average change in viral load from day 1 through day 7 was −0.56 $\log_{10}$ copies per milliliter (95% confidence interval [CI], −1.02 to −0.11) among patients who were serum antibody–negative at baseline and −0.41 $\log_{10}$ copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population. In the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

CONCLUSIONS

In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group. (Funded by Regeneron Pharmaceuticals and the Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services; ClinicalTrials.gov number, NCT04425629.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (Covid-19), which is most frequently mild yet can be severe and life-threatening. Virus-neutralizing monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalization.

METHODS

In this ongoing phase 2 trial involving outpatients with recently diagnosed mild or moderate Covid-19, we randomly assigned 452 patients to receive a single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo and evaluated the quantitative virologic end points and clinical outcomes. The primary outcome was the change from baseline in the viral load at day 11. The results of a preplanned interim analysis as of September 5, 2020, are reported here.

RESULTS

At the time of the interim analysis, the observed mean decrease from baseline in the log viral load for the entire population was −3.81, for an elimination of more than 99.97% of viral RNA. For patients who received the 2800-mg dose of LY-CoV555, the difference from placebo in the decrease from baseline was −0.53 (95% confidence interval [CI], −0.98 to −0.08; P=0.02), for a viral load that was lower by a factor of 3.4. Smaller differences from placebo in the change from baseline were observed among the patients who received the 700-mg dose (−0.20; 95% CI, −0.66 to 0.25; P=0.38) or the 7000-mg dose (0.09; 95% CI, −0.37 to 0.55; P=0.70). On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a Covid-19–related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group.

CONCLUSIONS

In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)

Hospitalized COVID 19

a. Blood, urine and sputum culture
b. CBC, BMP, LDH, CPK, liver function tests, PT/PTT
c. ABG if hypoxic
d. Inflammatory markers: Ferritin, D-dimer, CRP, fibrinogen, IL6, procalcitonin
e. CD3, CD4, CD8
f. Urine legionella and strep antigen, Fungitell and galactomanan
g. EKG
h. Daily BMP, CBC with diff, LDH, and liver function tests. Inflammatory markers should be monitored every 48 hours to monitor the progression of the disease
i. Repeat CXR with clinical deterioration
j. Goal O2 sat 92-96%, can titrate up to 6L nasal cannula, monitor O2 every 4 hours
k. Can transition from NC to NRB or HFNC as needed for hypoxia/work of breathing
l. Avoid nebulizers, CPAP/BIPAP as possible due to aerosols

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Hospitalized COVID 19

-Patients do not need prophylactic antibiotics unless positive culture/test result or CXR is suspicious for superimposed bacterial pneumonia

-Patients with mild or severe disease(requiring HPNC/mechanical ventilation/CPAP/BiPAP or pressor):**Thrombophylaxis**

-Patients with moderate disease(not requiring HPNC/mechanical ventilation/CPAP/BiPAP or pressor):**Therapeutic AC**

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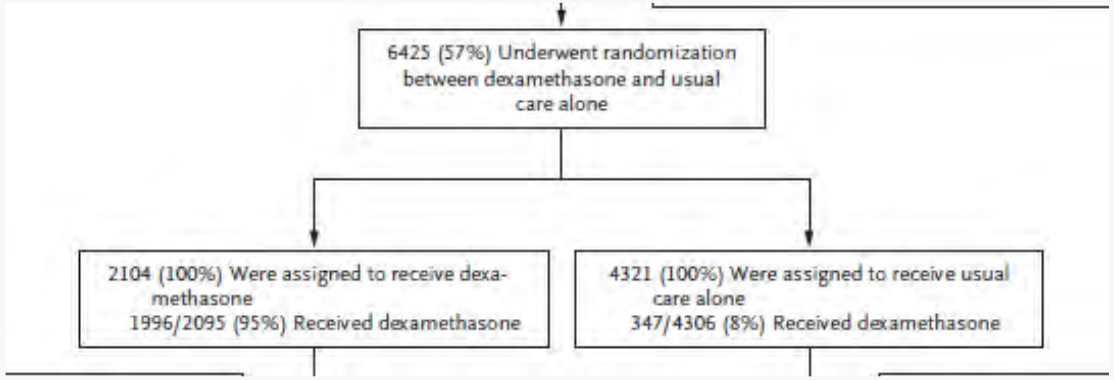

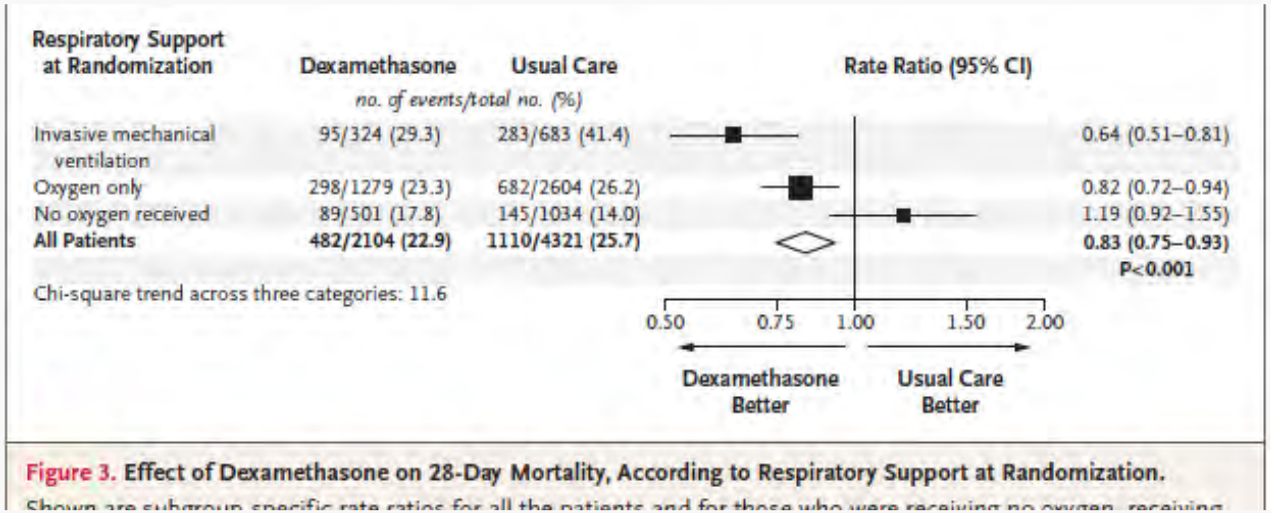

Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving

RECOVERY trial demonstrated mortality benefit in treatment with dexamethasone 6 mg daily(total of 10 days) for patients with COVID-19 requiring oxygen(Standard of Care)

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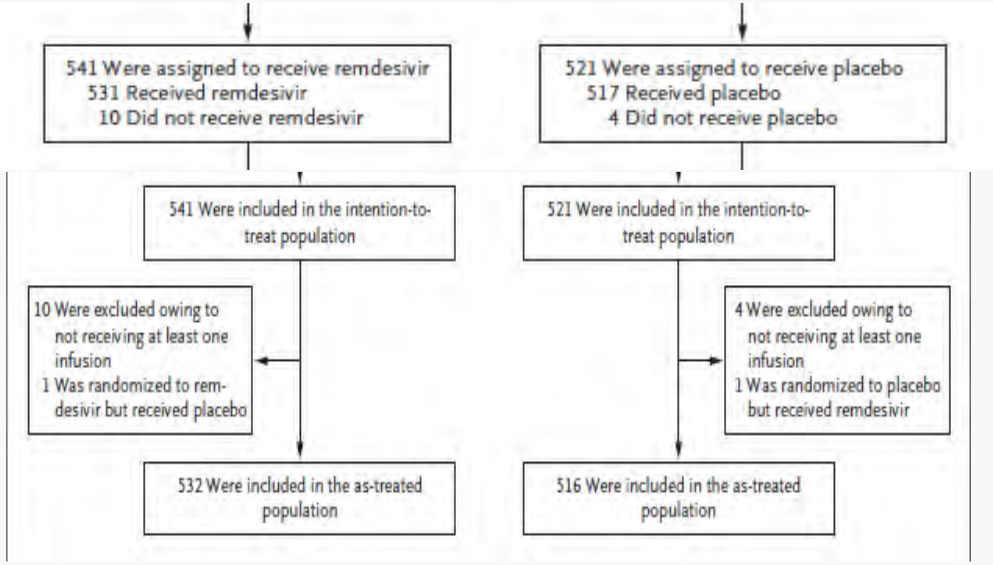
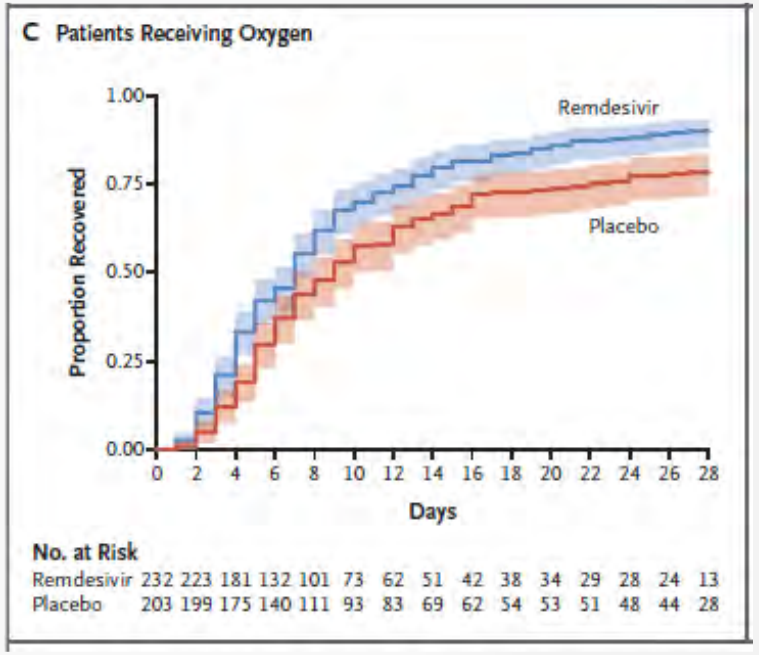
N Engl J Med 2021;384:693-704.

Remdesivir is used for hospitalized patients with COVID-19 for those requiring low-flow supplemental oxygen since data suggest it reduces time to recovery





- RCT, double blinded
- 10 days duration of treatment

Shorter time to recovery (median, 10 days vs. 15 days; rate ratio for recovery, 1.29 [95% CI, 1.12 to 1.49]

n engl j med 383;19

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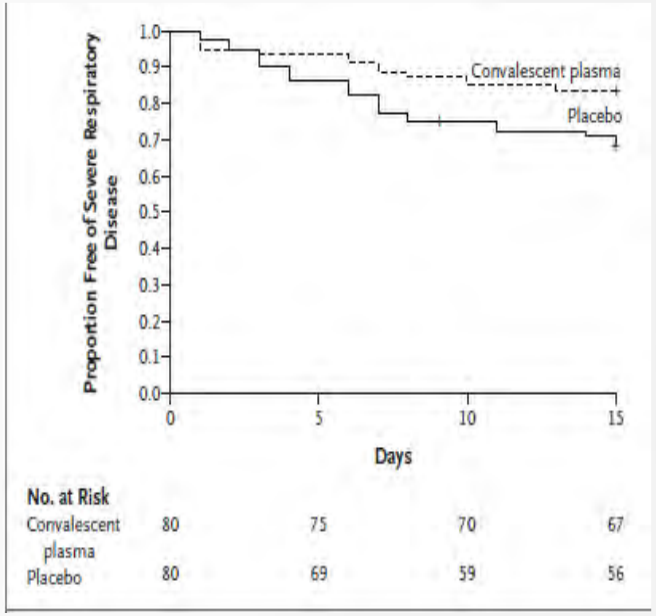
Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19.

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.



Randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against severe SARS-CoV-2 in older adult patients within 72 hours after the onset of mild Covid-19 symptoms. N=180

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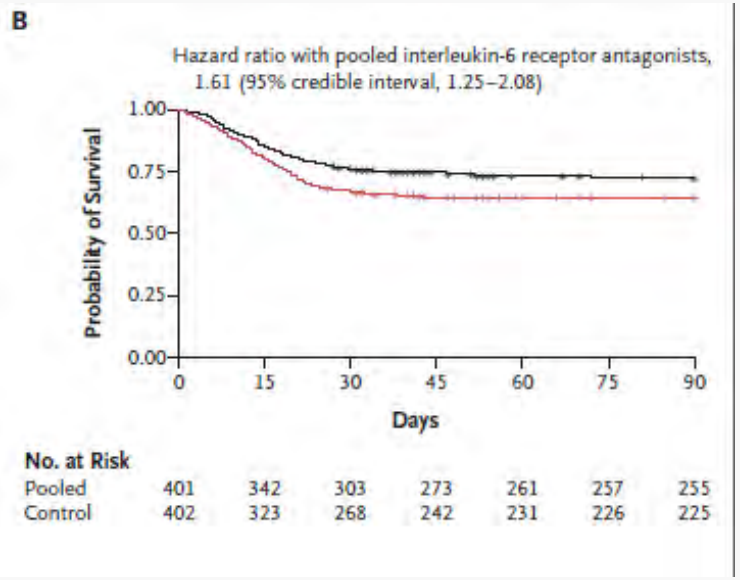
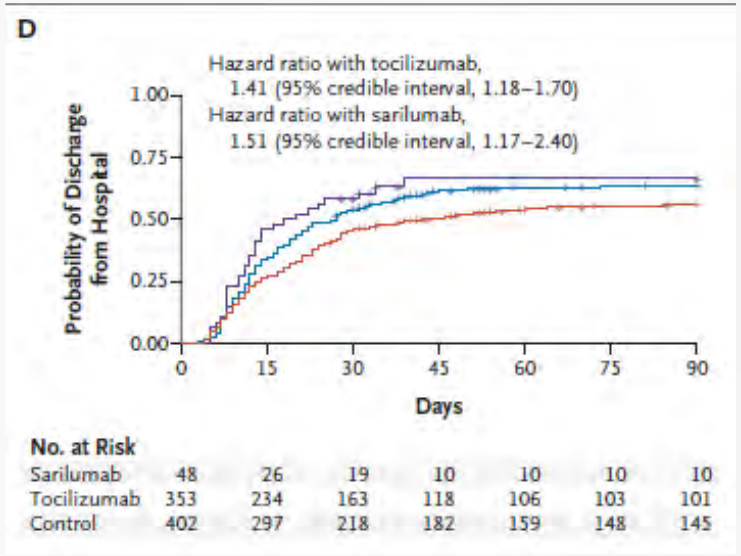
n engl j med 384;7

-For hospitalized adults with COVID-19 who, within the prior 24 to 48 hours, have initiated high-flow supplemental oxygen, non-invasive ventilation, or mechanical ventilation, may suggest adding tocilizumab to usual care (which includes dexamethasone) (Grade 2C).

-Tocilizumab and sarilumab are monoclonal antibodies that inhibit both membrane-bound and soluble interleukin-6 receptors.





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COVID-19 infection in kidney transplant recipients at the epicenter of pandemics

see commentary on page 1404

Yorg Azzi[1,2], Michael Parides[3], Omar Alani[2], Pablo Loarte-Campos[1,2], Rachel Bartash[4], Stefanie Forest[5], Adriana Colovai[2], Maria Ajaimy[1,2], Luz Liriano-Ward[1,2], Cindy Pynadath[1,2], Jay Graham[2,3], Marie Le[2,3], Stuart Greenstein[2,3], Juan Rocca[2,3], Milan Kinkhabwala[2,3] and Enver Akalin[1,2]

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Treatment	Total patients (*N* = 79)	Survivors (*N* = 51)	Nonsurvivors (*N* = 28)
Antimetabolite withdrawal	74 (94)	48 (94)	26 (93)
Calcineurin inhibitor withdrawal	11 (14)	4 (8)	7 (25)
Antibiotics	65 (82)	38 (75)	27 (96)
Hydroxychloroquine	59 (75)	35 (69)	24 (86)
Remdesivir[a]	6 (8)	5 (10)	1 (4)
High-dose corticosteroids	35 (44)	14 (28)	21 (75)
Tocilizumab	11 (14)	5 (10)	6 (21)
Sarilumab[a]	2 (3)	0 (0)	2 (7)
Leronlimab	6 (8)	3 (6)	3 (11)
Convalescent plasma	7 (9)	3 (6)	4 (14)
i.v. Ig	1 (1)	0 (0)	1 (4)
Anakira	1 (1)	0 (0)	1 (4)
Anticoagulation	44 (56)	26 (51)	18 (64)

MONITORING AFTER DISCHARGE

-Communicate every other day for 2 weeks

-Telehealth visit within 7 days after discharge

-Inhouse lab service is available

-Routine clinic visits can be resumed 4 weeks after COVID-19 diagnosis

-Resume pre COVID IS regimen

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Questions

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