Tabriz University of Medical Sciences

COVID-19 treatment

Haleh Mikaeili, MD

Associate Professor

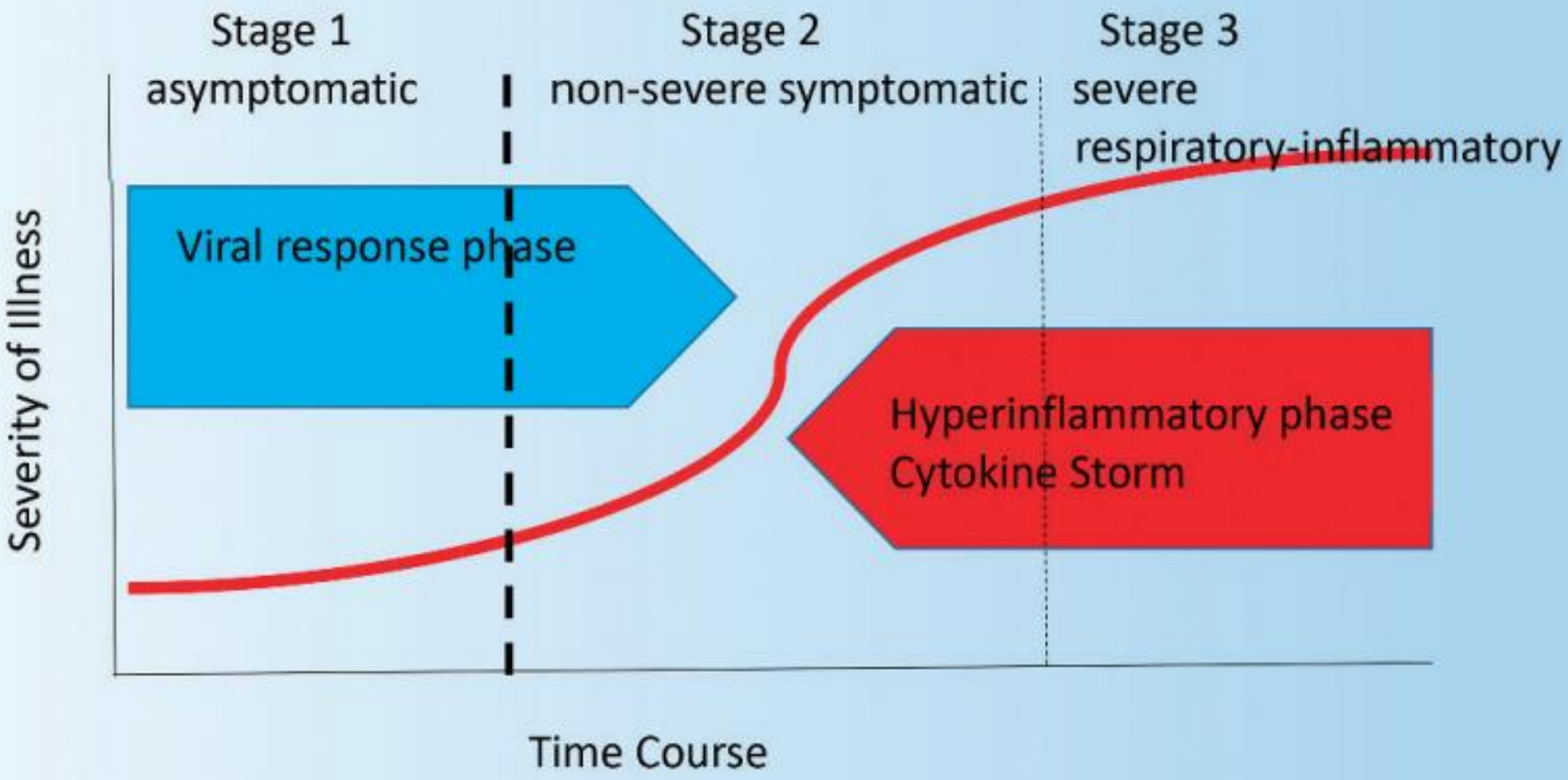
Pulmonologist , Intensivist

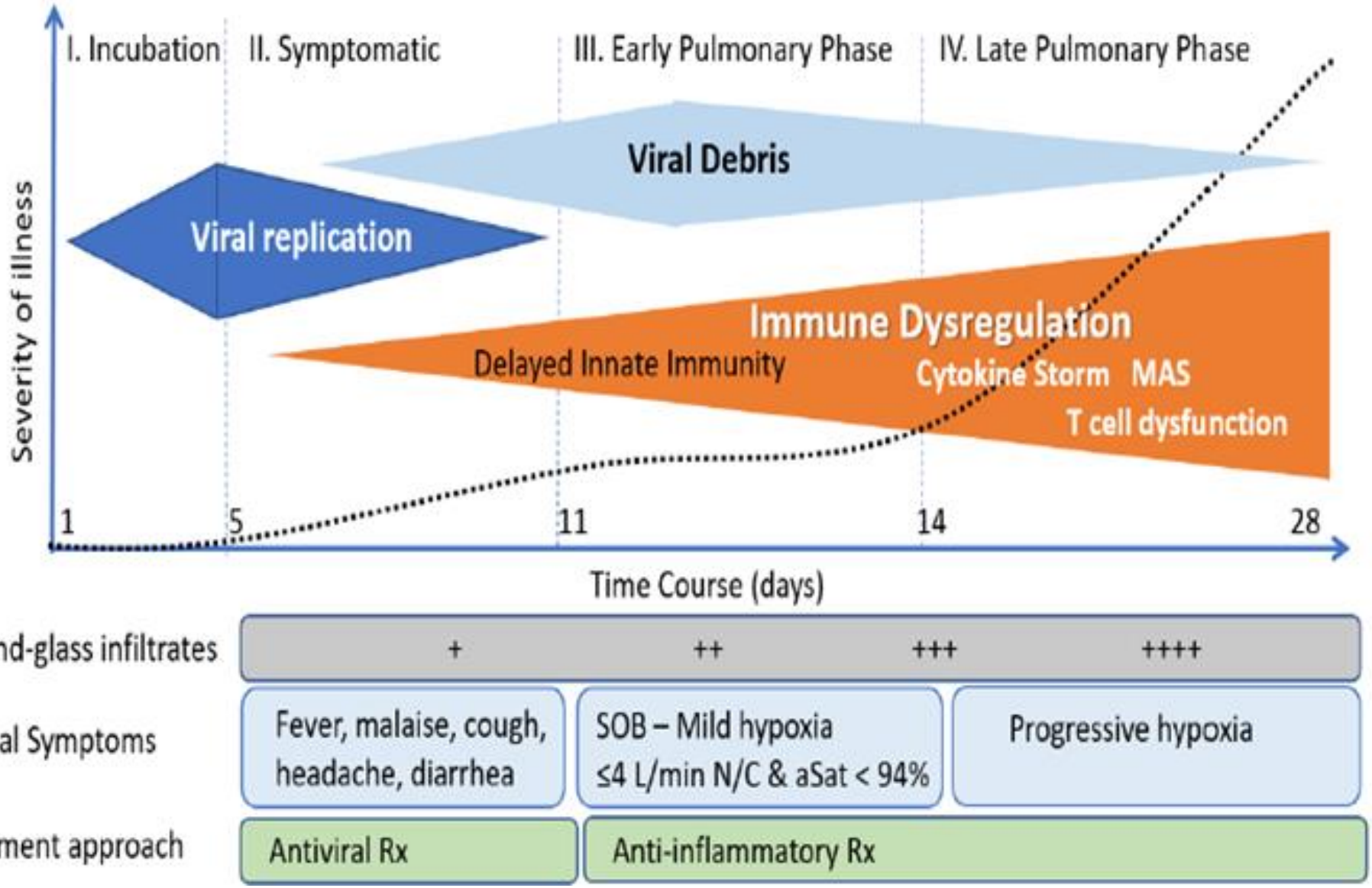
Tabriz University of Medical Sciences

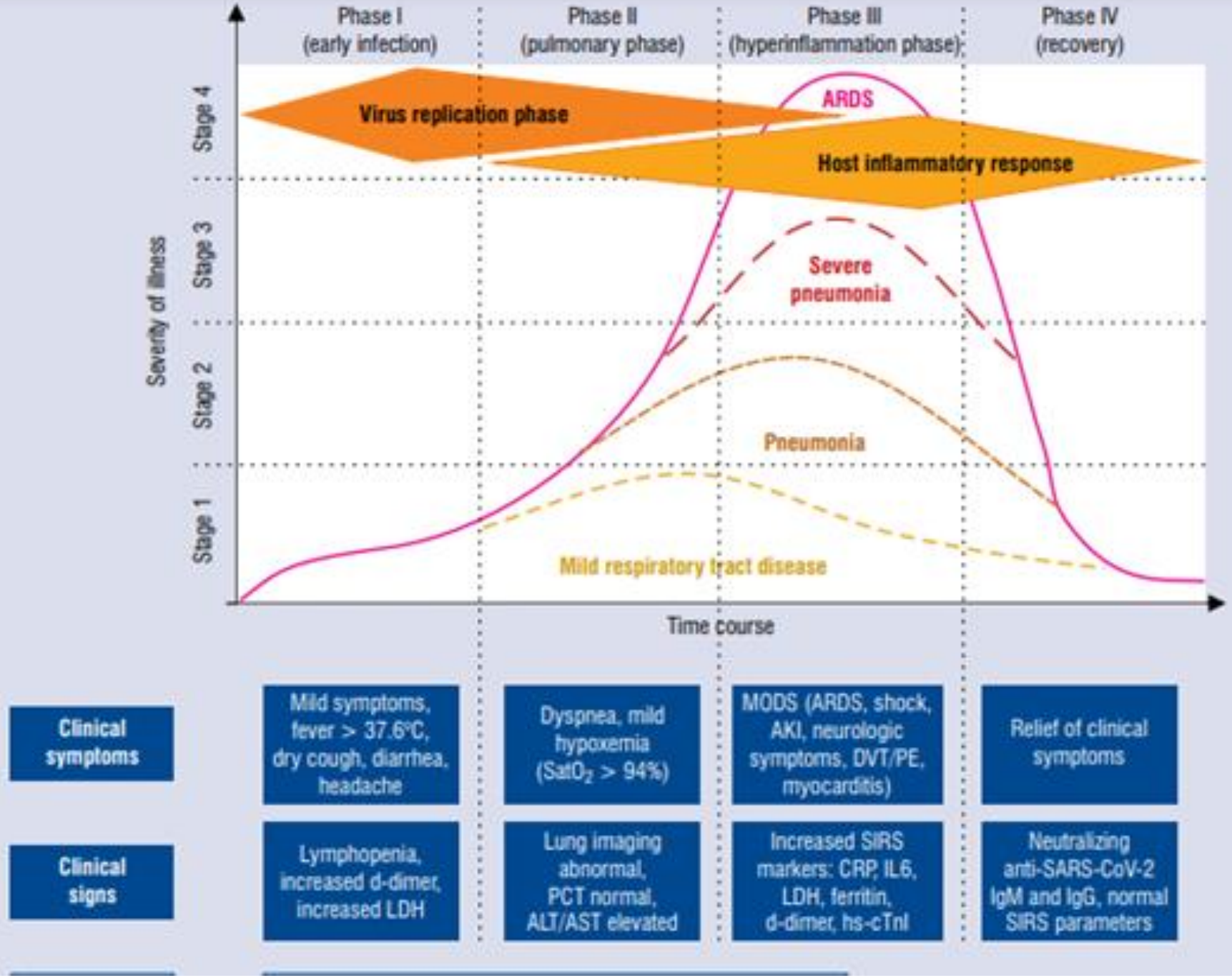
severity of illness categorization:

- ***Asymptomatic or Presymptomatic Infection:*** test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- ***Mild Illness:*** Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
- ***Moderate Illness:*** Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.
- ***Severe Illness:*** Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%.
- ***Critical Illness:*** Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

Course of COVID-19 Infection




I. Incubation
II. Symptomatic
III. Early Pulmonary Phase
IV. Late Pulmonary Phase
Viral Debris
Viral replication
Immune Dysregulation
Delayed Innate Immunity
Cytokine Storm MAS
T cell dysfunction
Severity of illness
1
5
11
14
28
Time Course (days)
Ground-glass infiltrates
+
++
+++
++++
Clinical Symptoms
Fever, malaise, cough, headache, diarrhea
SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%
Progressive hypoxia
Treatment approach
Antiviral Rx
Anti-inflammatory Rx


Phase I
(early infection)
Phase II
(pulmonary phase)
Phase III
(hyperinflammation phase)
Phase IV
(recovery)
Virus replication phase
ARDS
Host inflammatory response
Severe pneumonia
Pneumonia
Mild respiratory tract disease
Severity of illness
Stage 1
Stage 2
Stage 3
Stage 4
Time course
Clinical symptoms
Mild symptoms, fever > 37.6°C, dry cough, diarrhea, headache
Dyspnea, mild hypoxemia ($SatO_2$ > 94%)
MODS (ARDS, shock, AKI, neurologic symptoms, DVT/PE, myocarditis)
Relief of clinical symptoms
Clinical signs
Lymphopenia, increased d-dimer, increased LDH
Lung imaging abnormal, PCT normal, ALT/AST elevated
Increased SIRS markers: CRP, IL6, LDH, ferritin, d-dimer, hs-cTnI
Neutralizing anti-SARS-CoV-2 IgM and IgG, normal SIRS parameters

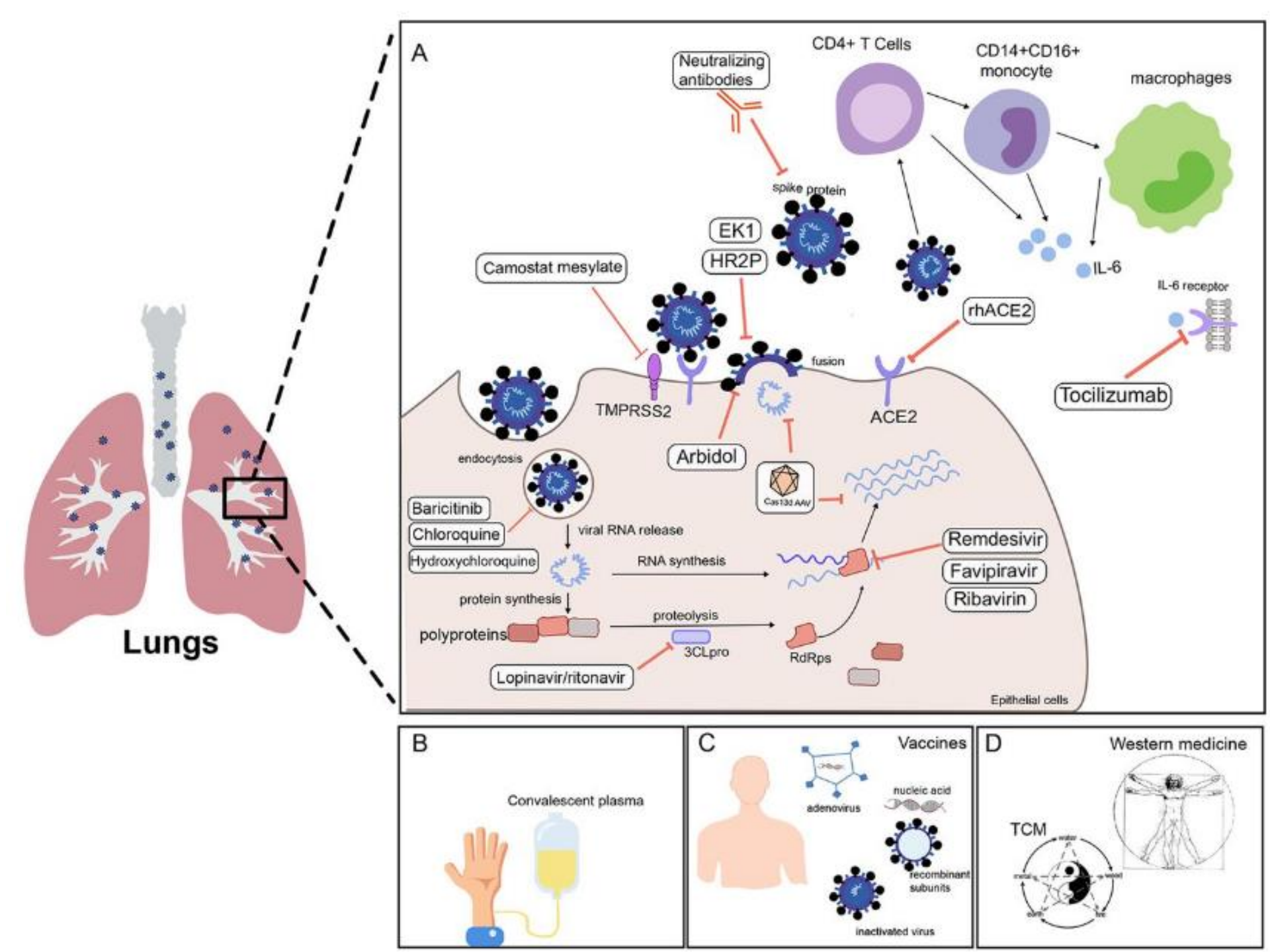
Pharmacologic Interventions

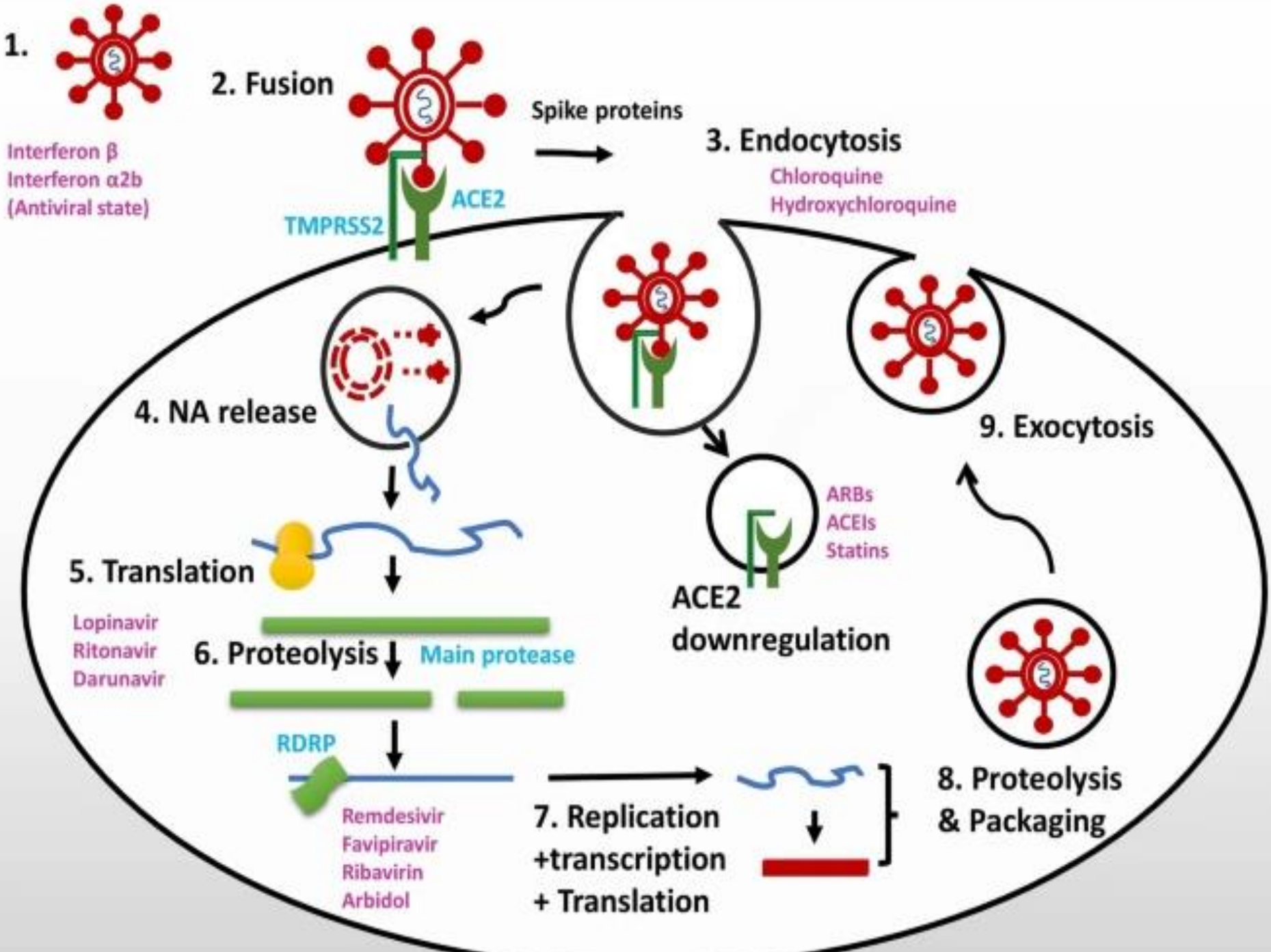
1-Antiviral Therapy

2-Immune-Based Therapy

- target the virus (antibodies)
- modulate the immune response (corticosteroids, IL-1 or IL-6 inhibitors)

3- Adjunctive Therapy


Lungs
A
Neutralizing antibodies
CD4+ T Cells
CD14+CD16+ monocyte
macrophages
spike protein
EK1
HR2P
Camostat mesylate
IL-6
IL-6 receptor
rhACE2
fusion
TMPRSS2
ACE2
Tocilizumab
endocytosis
Arbidol
Cas13d AAV
Baricitinib
Chloroquine
Hydroxychloroquine
viral RNA release
RNA synthesis
Remdesivir
Favipiravir
Ribavirin
protein synthesis
proteolysis
polyproteins
3CLpro
RdRps
Lopinavir/ritonavir
Epithelial cells
B
Convalescent plasma
C
Vaccines
adenovirus
nucleic acid
recombinant subunits
inactivated virus
D
Western medicine
TCM


1.
Interferon β
Interferon α2b
(Antiviral state)
2. Fusion
Spike proteins
3. Endocytosis
Chloroquine
Hydroxychloroquine
TMPRSS2
ACE2
4. NA release
5. Translation
Lopinavir
Ritonavir
Darunavir
6. Proteolysis
Main protease
RDRP
Remdesivir
Favipiravir
Ribavirin
Arbidol
7. Replication
+transcription
+ Translation
8. Proteolysis
& Packaging
9. Exocytosis
ARBs
ACEIs
Statins
ACE2
downregulation

Antiviral Therapy

- **Remdesivir**
- Favipiravir
- HCQ +/- Azithromycin
- Lopinavir/Ritonavir or HIV PIs
- Ivermectin

Remdesivir

Remdesivir is *approved by (FDA)* for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg)

Remdesivir

- nucleotide pro drug of an adenosine analog
- Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription
- It has demonstrated in vitro activity against 2 (SARS-CoV-2)
- In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals

Multinational Randomized Controlled Trial of **Remdesivir** Versus Placebo in Hospitalized Patients

1-The Adaptive COVID-19 Treatment Trial (ACTT-1) is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial(1,062 participants)

2-China:a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19(237 patients)

3-Multinational, Randomized Trial of Different Durations of Remdesivir Treatment in Hospitalized Patients:

a manufacturer-sponsored, multinational, randomized, open-label trial(402 patients)

4-Remdesivir Versus Standard Care in Hospitalized Patients with Moderate COVID-19

open-label, randomized trial compared the use of 10 or 5 days of remdesivir “standard in hospitalized patients(600 patients)

Adaptive COVID-19 Treatment Trial (ACTT-1)

- Remdesivir significantly reduced the time to recovery compared to placebo (10 vs. 15 days $P < 0.001$)
- Clinical improvement based on the ordinal scale was significantly higher at Day 15 $P < 0.001$).
- The benefit for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment ,there was no observed difference in time to recovery
- Among the patients who were on mechanical ventilation or ECMO at study enrollment,there was no observed difference in time to recovery
- Among patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery

Adaptive COVID-19 Treatment Trial (ACTT-1)

- There was no statistically significant difference in mortality by Day 29 between the remdesivir (11.4%) and placebo (15.2%) arms (*P* = 0.07)
- The benefit of remdesivir was greater in participants who were randomized during the first 10 days after symptom onset.
- The percentages of participants with serious adverse effects (AEs) were similar in the remdesivir and placebo groups (25% vs. 32%).
- Transaminase elevations occurred in 6% of remdesivir recipients and 10.7% of placebo recipients.

Remdesivir

- Recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days.
- For mechanically ventilated patients and/ or patients on ECMO, the recommended treatment duration is 10 days.
- *For Patients Aged <12 Years and Weighing ≥40 kg:*

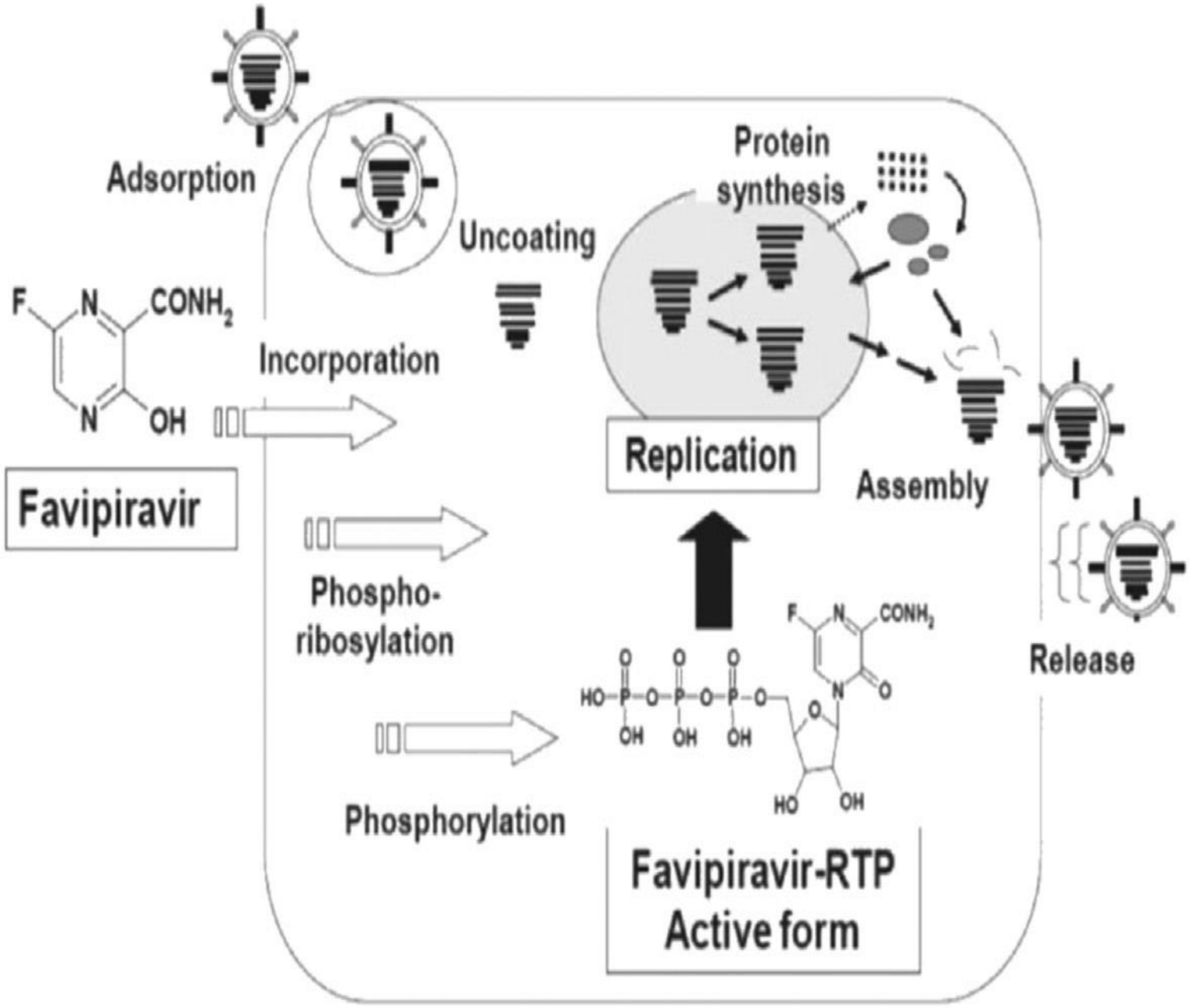
Same dose as for adults and children aged >12 years and weighing >40 kg

Favipiravir

- a. This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, thus inhibiting its activity leading to termination of viral protein synthesis

- b. It gets incorporated in the viral RNA strand, preventing further extension. This mechanism of action, along with preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains the broad spectrum of activity of this drug.

- c. It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.


Adsorption
Uncoating
Protein synthesis
Incorporation
Favipiravir
Replication
Assembly
Release
Phospho-ribosylation
Phosphorylation
Favipiravir-RTP
Active form

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Review Article

Favipiravir: A new and emerging antiviral option in COVID-19

Umang Agrawal [a], *Reyma Raju* [b], *Zarir F. Udwadia* [c,*]

[a] *Associate Consultant (Infectious Diseases), PD Hinduja National Hospital and Medical Research Centre, Mumbai, India*

[b] *Clinical Assistant (Pulmonary Medicine), PD Hinduja National Hospital and Medical Research Centre, Mumbai, India*

[c] *Consultant Pulmonologist, PD Hinduja National Hospital and Medical Research Centre, Mumbai, India*

ARTICLE INFO

Article history:
Received 27 July 2020
Accepted 17 August 2020
Available online 2 September 2020

Keywords:
Favipiravir
SARS-CoV-2
COVID-19
Antiviral drugs

ABSTRACT

With over 16 million cases reported from across the globe, the SARS-CoV-2, a mere 125 microns in diameter, has left an indelible impact on our world. With the paucity of new drugs to combat this disease, the medical community is in a race to identify repurposed drugs that may be effective against this novel coronavirus. One of the drugs which has recently garnered much attention, especially in India, is an anti-viral drug originally designed for influenza, called favipiravir. In this article, we have tried to provide a comprehensive, evidence-based review of this drug in the context of the present pandemic to elucidate its role in the management of COVID-19.

Clinical trials of Favipiravir in COVID-19

1-open-label multicentric trial in China to compare two treatment arms Conventional therapy plus umifenovir (Arbidol) (200 mg thrice

a day) or favipiravir (1600 mg twice daily followed by 600 mg

twice daily) for 7 days (extendable to 10 days

The authors found that the clinical recovery rate at day 7 did not differ significantly between the two groups

2-open-labeled nonrandomized study from

China compared the effect of favipiravir (day 1: 1600 mg

twice daily; days 2e14: 600 mg twice daily) vs lopinavir/ritonavir

(day 1e14: 400/100 twice daily) in the treatment of

COVID 19

Multivariate analysis showed that favipiravir was independently associated with faster viral clearance and chest CT scan improvement

- Non randomized

3- Japon without control arm

Ongoing trials : Russia- Saudi Arabia- USA stanford- India

Favipiravir

- similar mechanism of action to remdesivir
- Oral
- less strong supportive data to back its use
- but is nevertheless emerging as an agent that is worth considering in mild to moderate cases
- administered early after the onset of symptoms for it to be effective in reducing viremia.

Ivermectin

- inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host antiviral response
- host-directed agent

Ivermectin

Recommendation

against: for COVID-19, except in a clinical trial **(AIII)**

- inhibit the replication of (SARS-CoV-2) in cell cultures
- plasma concentrations necessary for the antiviral efficacy detected *in vitro* would require administration of doses up to 100-fold higher than those approved for use in humans
- ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 µM, the half-maximal inhibitory concentration (IC50) *in vitro*
- Ivermectin is not approved for the treatment of any viral infection
- The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans.

Immune-Based Therapy for COVID-19

human blood-derived products

immunomodulatory therapies

human blood-derived products

human blood-derived products are obtained from recovered patients :

1- convalescent plasma

2-Anti-SARS-CoV-2 Antibody Products

A- specific(concentrated)
B- specific(monoclonal)
B- nonspecific(IVIG)

convalescent plasma

1- against the use of **low-titer COVID-19 convalescent plasma (AIIb)**

no longer authorized through the convalescent plasma EUA

2- hospitalized patients on MV who do not have impaired immunity: **against** the use of **COVID-19 convalescent plasma (AI)**

3- hospitalized patients not on MV : **against** the use of **high-titer COVID-19 convalescent plasma**, except in a clinical trial **(AI)**

4- hospitalized patients with impaired immunity:

There are insufficient data to recommend either for or against the use of high-titer COVID-19 convalescent plasma

5- non hospitalized patients :insufficient data to recommend either for or against the use of high-titer COVID-19 convalescent plasma

Anti-SARS-CoV-2 Antibody Products

A- specific(concentrated)

insufficient data for the Panel to recommend either for or against the use

B- nonspecific(IVIG)

against

except when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19 **(AIII)**

Anti-SARS-CoV-2 Antibody Products

B- specific(monoclonal)

Recommendation to treat

outpatients with mild to moderate COVID-19 who are at high risk of clinical progression **by (EUA)**

1-Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa)

or

2-Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa)

B- specific(monoclonal)

- started as soon as possible after the patient receives a positive result and within 10 days of symptom onset.
- variants, particularly the **mutation E484K**, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro
- Recommendation against the for hospitalized patients **(AIIa)**
- should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

Immunomodulators for COVID-19

Interferon

-IL-6 receptor antibodies (sarilumab, tocilizumab) or IL-6 antibody (siltuximab)

Corticosteroids

Interleukin (IL)-1 inhibitors (anakinra)

Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib

Janus kinase inhibitors (baricitinib, ruxolitinib, tofacitinib)

interferons

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of interferons for the treatment of patients with severe or critical COVID-19, except in a clinical trial **(AIII)**.
- There are insufficient data to recommend either for or against the use of **interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Colchicine

- several potential mechanisms of action:

1-reduce the chemotaxis of neutrophils

2- inhibit inflammasome signaling

3- decrease the production of cytokines such as IL-1 beta

- Administeration early in the course :

may potentially mitigate or prevent inflammation-associated manifestations of the disease.

- These anti-inflammatory properties (as well as the drug's limited immunosuppressive potential, widespread availability, and favorable safety profile) have prompted investigation of colchicine for the treatment of COVID-19.

Colchicine

- insufficient data either or against for nonhospitalized patients
- A large, randomized trial in outpatients, the Colchicine Coronavirus SARS-CoV-2 Trial **(COLCORONA)** did not reach its primary efficacy endpoint of reducing hospitalizations and death. However, a slight reduction in hospitalizations was observed in the subset of patients whose diagnosis was confirmed by a positive nasopharyngeal swab on a SARS-CoV-2 polymerase chain reaction (PCR) test.
- **recommends against** the use of colchicine in hospitalized patients **(AIII)**

Fluvoxamine

- selective serotonin reuptake inhibitor (SSRI)
- Anti-Inflammatory Effect :

1- bind to the sigma-1 receptor in immune cells, resulting in reduced production of inflammatory cytokines

2-in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes

insufficient data to recommend either or against

Interleukin-1 Inhibitors

- insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors (**anakinra)**

Interleukin-6 Inhibitors

1-anti-IL-6 receptor monoclonal antibodies **(sarilumab, tocilizumab)**

2-anti-IL-6 monoclonal antibodies **(siltuximab)**

Tocilizumab

RECOVERY trial and REMAP-CAP

a with corticosteroids, offers a modest **mortality benefit** in certain patients :

1-who are severely ill

2-rapidly deteriorating with increasing oxygen needs

3-have a significant inflammatory response

Tocilizumab

- Recommendation:

tocilizumab (single IV 8 mg/kg up to 800 mg) **in combination with dexamethasone** (6 mg/d up to 10 days) in certain hospitalized patients with rapid respiratory decompensation

Tocilizumab

These patients are:

1- Recently hospitalized (within first 3 days of admission) in (ICU) within the prior 24 hours and who require invasive MV, NIV, or (HFNC) oxygen (>0.4 FiO2/30 L/min) (BIIa)

2- Recently hospitalized (within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require NIV or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥75 mg/L) (BIIa)

Tocilizumab

hospitalized patients with hypoxemia who require conventional oxygen therapy:

insufficient evidence of benefit

Some Panel members would also give tocilizumab in rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L, but who do not yet require NIV or HFNC oxygen.

Tocilizumab

should be avoided in

1-significantly immunosuppressed, particularly in recent use of other biologic immunomodulating drugs

2-alanine aminotransferase >5 times

3- high risk for GI perforation

4- uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral

Sarilumab , siltuximab

- insufficient data to recommend

either for or against sarilumab for hospitalized patients who are within 24 hours of admission to the ICU and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO2/30 L/min of oxygen flow)

- The Panel **recommends against** the use of anti-IL-6 monoclonal antibody therapy (**siltuximab**) **(BI)**.

Janus Kinase Inhibitors

- prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).
- Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins2,3 that are involved in vital cellular functions, including signaling, growth, and survival.

1-Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19

2- particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells

baricitinib

- ***Recommendations***

1-insufficient data to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients, when on corticosteroids

2- In the rare circumstance when corticosteroids cannot be used, **baricitinib** in combination with **remdesivir** for hospitalized, non-intubated patients who require oxygen supplementation **(BIIa)**

3-recommends against the use of **baricitinib without remdesivir**, except in a clinical trial **(AIII)**

4- insufficient data to recommend either for or against the use of baricitinib in combination with corticosteroids

Because both baricitinib and corticosteroids are potent immunosuppressants, there is potential for an additive risk of infection.

5-The Panel **recommends against** the use of **JAK inhibitors other than baricitinib** for the treatment of COVID-19 **(AIII)**.

baricitinib

Rationale

- data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), a multinational, randomized, placebo-controlled trial of baricitinib use in hospitalized patients with COVID-19 pneumonia

Participants (n = 1,033) were randomized 1:1 to oral baricitinib 4 mg or placebo, for up to 14 days, in combination with intravenous (IV) remdesivir, for up to 10 days. Participants who received baricitinib had a shorter time to clinical recovery than those who received placebo (median recovery time of 7 vs. 8 days, respectively). This treatment effect was most pronounced among those who required high-flow oxygen or non-invasive ventilation but were not on invasive mechanical ventilation.

The difference in mortality between the treatment groups was not statistically significant.

baricitinib

On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Corticosteroids

- data from the RECOVERY trial, a large, multicenter, randomized, open-label trial performed in the United Kingdom
- This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. Mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.1 This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollme

The RECOVERY study

The RECOVERY study is an ongoing, multicenter, open-label, adaptive trial sponsored by the National Health Service in the United Kingdom

In patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days. The benefit of dexamethasone was most apparent in hospitalized patients who were mechanically ventilated. There was no observed benefit of dexamethasone in patients who did not require oxygen support.

The RECOVERY study

Overall, 22.9% of participants in the dexamethasone arm and 25.7% in the standard of care arm died within 28 days of study randomization (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$).

- There was an interaction between baseline severity of COVID-19 and the treatment effect of dexamethasone.
- Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization: 29.3% of participants in the dexamethasone arm died within 28 days versus 41.4% in the standard of care arm (rate ratio 0.64; 95% CI, 0.51–0.81).
- Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 23.3% of participants in the dexamethasone arm and 26.2% in the standard of care arm died within 28 days (rate ratio 0.82; 95% CI, 0.72–0.94).
- No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.8% of participants in the dexamethasone arm and 14.0% in the standard of care arm died within 28 days (rate ratio 1.19; 95% CI, 0.91–1.55).
- The risk of progression to invasive mechanical ventilation was lower in the dexamethasone arm than in the standard of care arm (rate ratio 0.77; 95% CI, 0.62–0.95).

The RECOVERY study

Limitations

- The study was randomized, but open label.
- In this preliminary report, the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), potential adverse events, and efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities) have not been reported.
- Study participants with COVID-19 who required oxygen but not mechanical ventilation had variable disease severity; it is unclear whether all patients in this heterogeneous group derived benefit from dexamethasone, or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device.
- The age distribution of participants differed by respiratory status at randomization.
- The survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown, because only 1% of this group was ventilated.
- It is unclear if younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. If so, then the disease severity would vary by age within the oxygen group, contributing to the difficulty in interpreting the observed mortality benefit in this heterogeneous group.
- Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of dexamethasone for the treatment of COVID-19 in children or in pregnant individuals are unknown.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)**. For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**

Hospitalized but Does Not Require Supplemental Oxygen

There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

Hospitalized and Requires Supplemental Oxygen

Use one of the following options:

- **Remdesivir**[a,b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**
- **Dexamethasone**[c] **plus remdesivir**[a,b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[d,e]
- **Dexamethasone**[c] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**

Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation

Use one of the following options:

- **Dexamethasone[c] (AI)[e]**
- **Dexamethasone[c] plus remdesivir[a,b] (BIII)[d,e]**

For patients who were recently hospitalized[f] with rapidly increasing oxygen needs and systemic inflammation:

- Add **tocilizumab[g]** to one of the two options above **(BIIa)**

Hospitalized and Requires Invasive Mechanical Ventilation or ECMO

- **Dexamethasone[c] (AI)[h]**

For patients who are within 24 hours of admission to the ICU:

- **Dexamethasone[c] plus tocilizumab[g] (BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

The combination of dexamethasone and remdesivir has not been studied in clinical trials.

In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.

The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.

The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.