Η επίδραση των αντιρευματικών φαρμάκων στην εξέλιξη της νόσου COVID-19

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Ρευματολόγος

Επιμελήτρια Β' ΕΣΥ

Παν. Γεν. Νοσ. Πατρών "Παναγία η Βοήθεια"

Σύγκρουση συμφερόντων

Καμία γι'αυτή την παρουσίαση

Treatment of COVID-19 by medications used in rheumatology

Corticosteroids/Dexamethazone

Chloroquine/Hydroxychloroquine

Tocilizumab, Sarilumab anti IL-6 receptor mAb

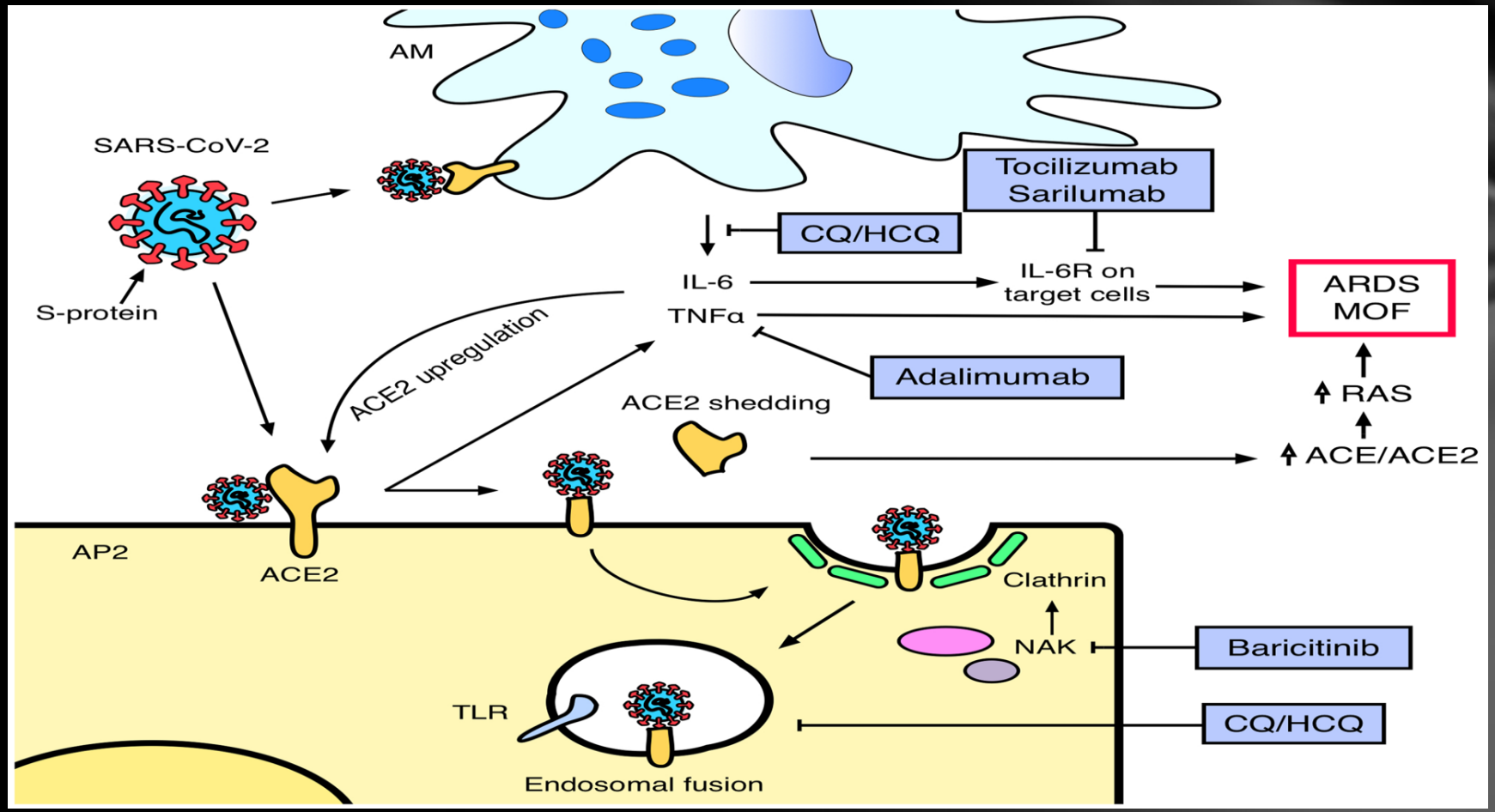
siltuximab anti-IL-6 mAb

Anakinra IL-1 inhibitor

Tyrosine kinase inhibitors

- NAK(numb-associated kinase)
- JAK (Janus –kinase) Baricitinib ,ruxolitinib
- Anti-TNF α Adalimumab (ChiCTR2000030089)

Antiviral mechanisms of action of anti-rheumatic drugs in COVID-19
ACE: angiotensin-converting enzyme; AM: ...



Rheumatology (Oxford), Volume 59, Issue 6, June 2020, Pages 1200–1203, https://doi.org/10.1093/rheumatology/keaa194

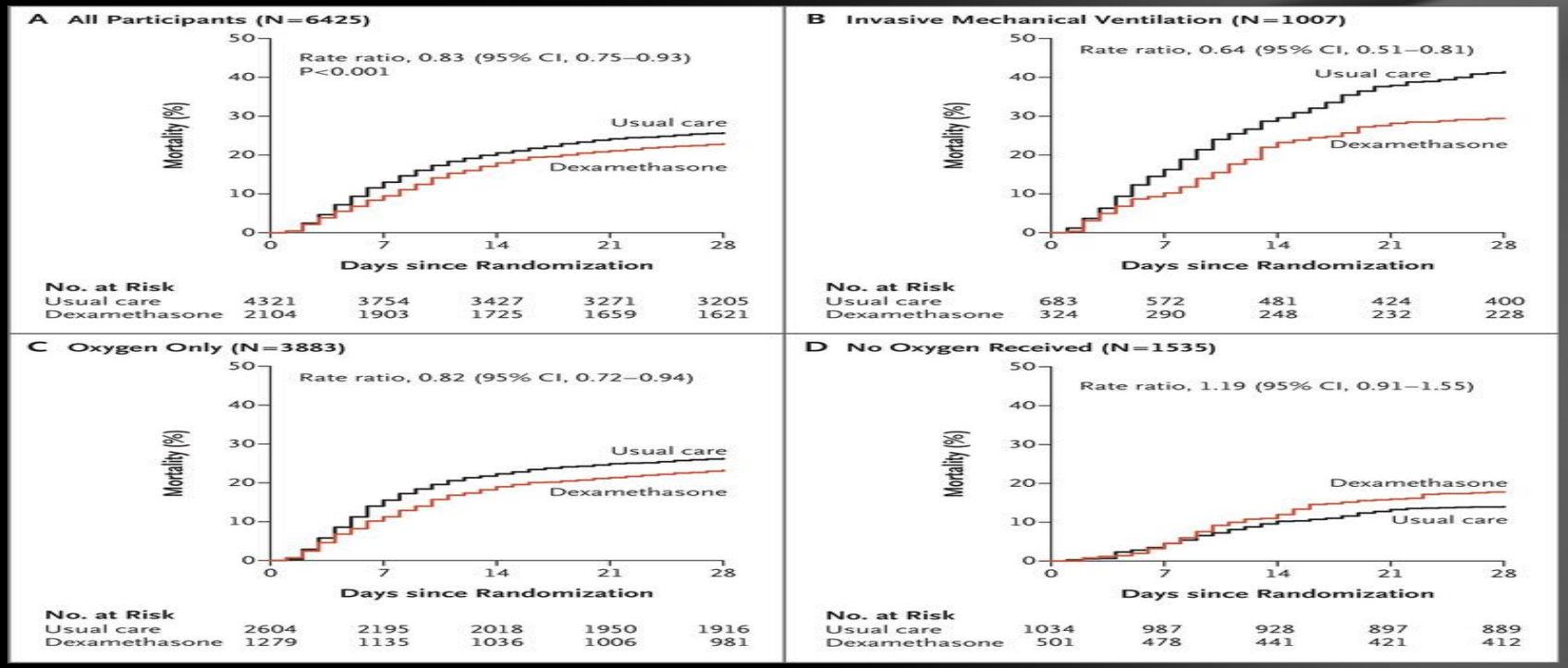
Dexamethazone

RECOVERY dexamethasone 6 mg daily for 10 days or until discharge

2,104 pts dexamethasone

4,321 pts standard Tx alone

pts with severe COVID-19 who required mechanical ventilation died at 28 days: 29,3% dexamethasone VS standard Tx 41.4%



Hydroxychloroquine/chloroquine

Increases endosomal PH

Inhibits fusion of SARS-Covid 2 and host cell membrane

Inhibits glycosylation of ACE2 receptor

Hydroxychloroquine/chloroquine studies

- HCQ in mild/serious cases
- HCQ±Azythromycin in mild/serious cases
- Low dose HCQ vs high dose HCQ

No favorable effect of HCQ alone or in combination with Azithromycin in Tx Covid-19 infection in comparison to standard treatment

HCQ High dose ⇨serious AE

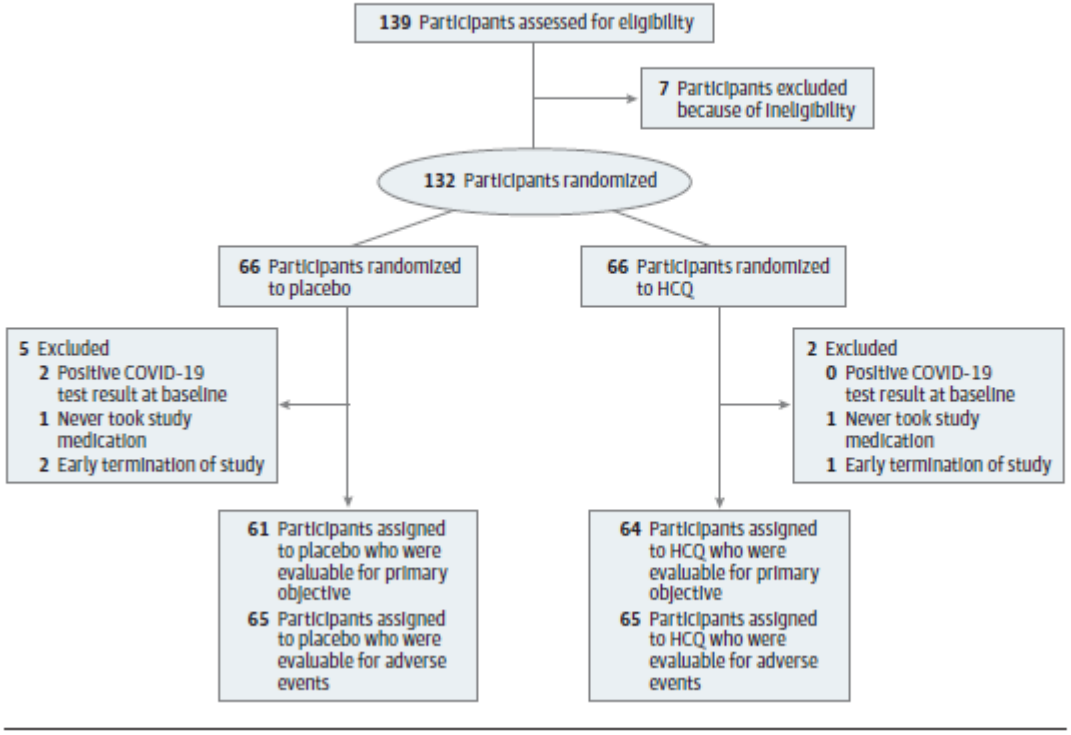
LIMITATIONS

- the potential for residual confounding,
- small sample sizes,
- Concomitant CS Tx
- incomplete reporting,
- a lack of comparison groups

JAMA Internal Medicine | Original Investigation

Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers
A Randomized Clinical Trial

Figure 1. Participant Enrollment and Treatment Assignment



COVID-19 indicates coronavirus disease 2019; HCQ, hydroxychloroquine.

HCQ 600mg /d for 8 weeks SARS CoVID 2 negative

Infection rates HCQ 6,3% vs Placebo 6,6%

Mild AE : HCQ 45% vs Placebo 26% p=0,04

ANAKINRA

Anakinra for severe forms of COVID-19: a cohort study. Huet T, Beaussier H, Voisin O, et al.*Lancet Rheumatology*. 2020

IL-1 elevated in Sars covid 2 infection

52 pts ANAKINRA 100mgx2 for 72 h then 100mg day

for 7 days VS 44 pts cnt (HCQ,AZI,βLAC)

25% ANA group VS 73% cnt group ventilation or

death

AE no difference

ANAKINRA

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study.Cavalli G, De Luca G, Campochiaro C, et al. *Lancet Rheumatology*. 2020

29 pts moderate to severe ARDS no ventilation required and

hyperinflammation high dose ANA IV for 9 days then sc 100mg

twice /d plus HCQ+lopinavir/ritonavir VS 16 pts HCQ+lopinavir

/ritonavir only

Reduction of CRP in ANA group

21-day survival rate (90% vs. 56%, respectively; *P* = 0.009)

IL-6 inhibition

dose-dependent production of IL-6 from bronchial epithelial cells.

COVID-19- systemic inflammation and hypoxic respiratory failure can be associated with heightened cytokine release :

↑ IL-6, C-reactive protein (CRP), D-dimer, ferritin

Tocilizumab, sarilumab IL-6 receptor mAbs

Siltuximab IL-6 mAb

Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19

randomized (2:2:1), double-blind, placebo-controlled trial

Sarilumab 400mg , 200mg, Placebo

No clinical benefit of Sarilumab for any group

AE dose dependent high ALT AST, low WBC, low PLTs

A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)

450 pts receive TOCI IV or Placebo

No significant differences

- in the primary outcome (improved clinical status)
- in ventilator free days

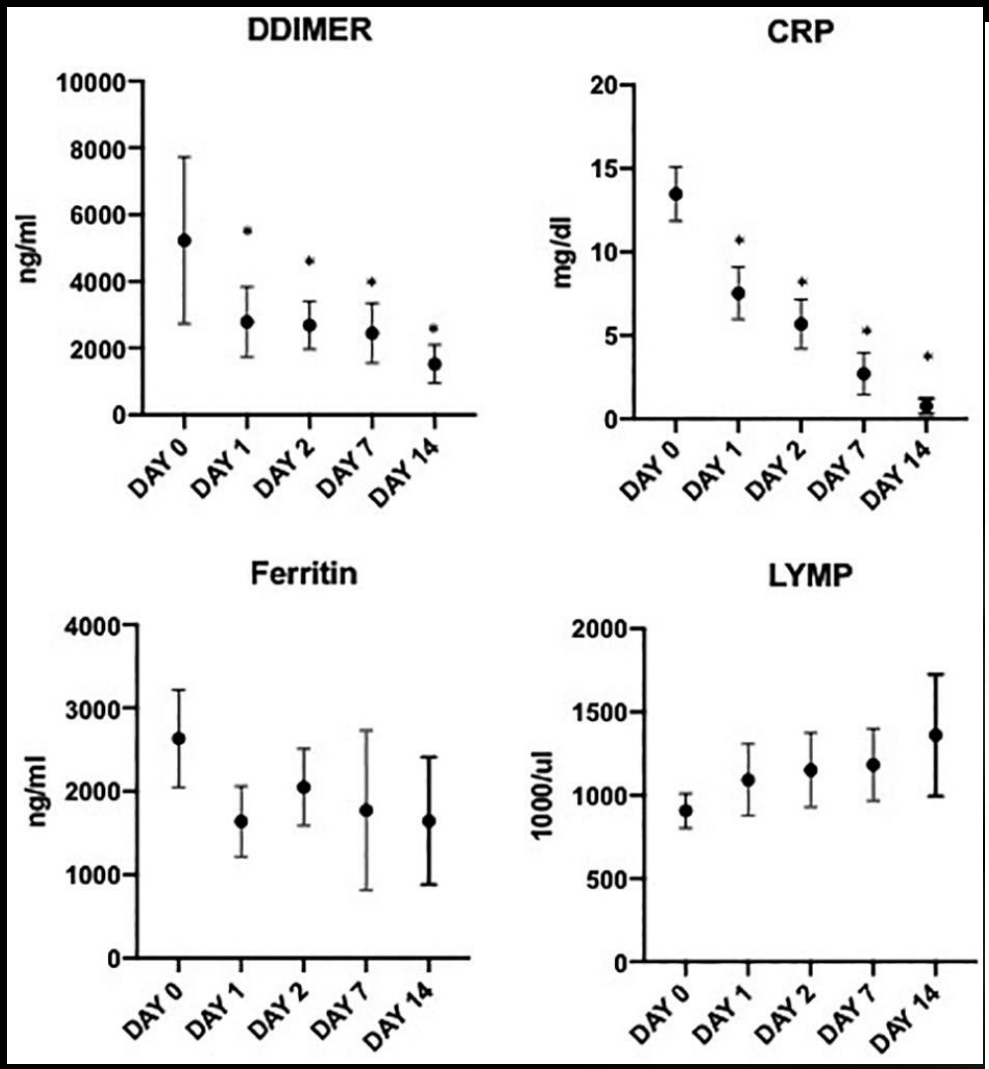
Pilot prospective open, single-arm multicentre study on off-label use of
tocilizumab in patients with severe COVID-19.
Sciascia S, Apra F, Baffa A, et al *Clin Exp Rheumatol*. 2020

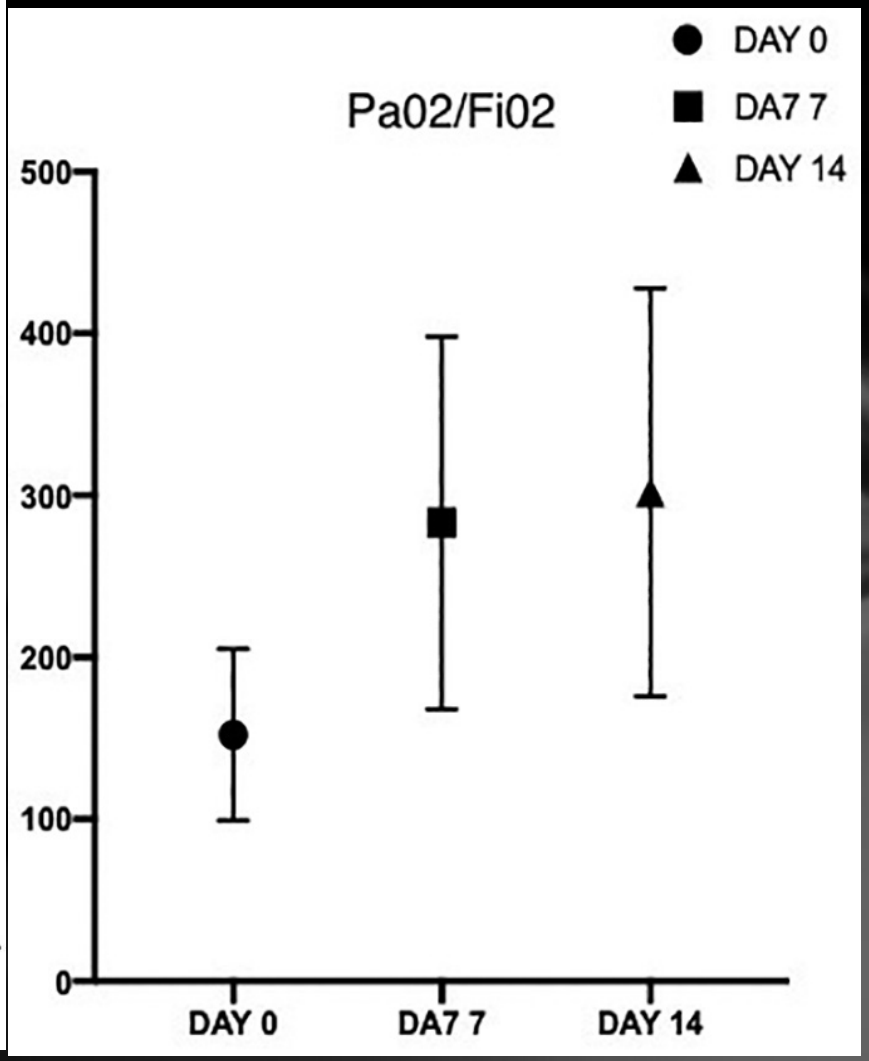
63 pts Sars covid 2,

- SO2<93%
- High CRP, ferritin, D-dimer on antiretroviral Tx

received TOCI IV or Sc

On second Day fever resolved in all pts except one





inflammation markers reduced

Earlier use of tocilizumab and reduced mortality

LIMITATION : No comparison group

Tocilizumab in patients with severe COVID-19: a retrospective cohort study

*Giovanni Guaraldi*et al* ***Lancet Rheumatol* 2020**

365 pts severe pneumonia standard care O2,

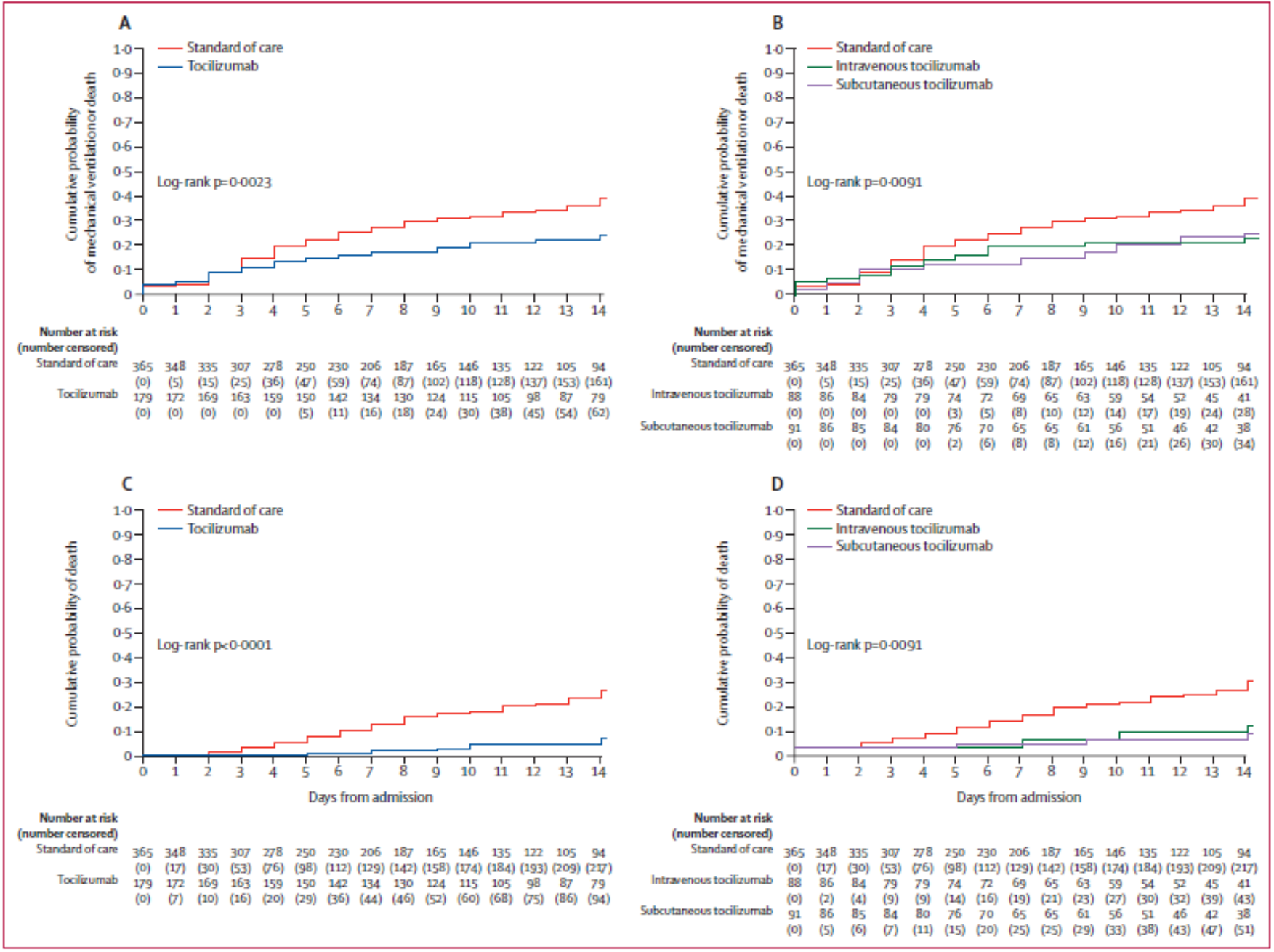
HCQ,AZI,ANTIRETROVIRAL

88 pts IV TOCI

91 pts SC TOCI

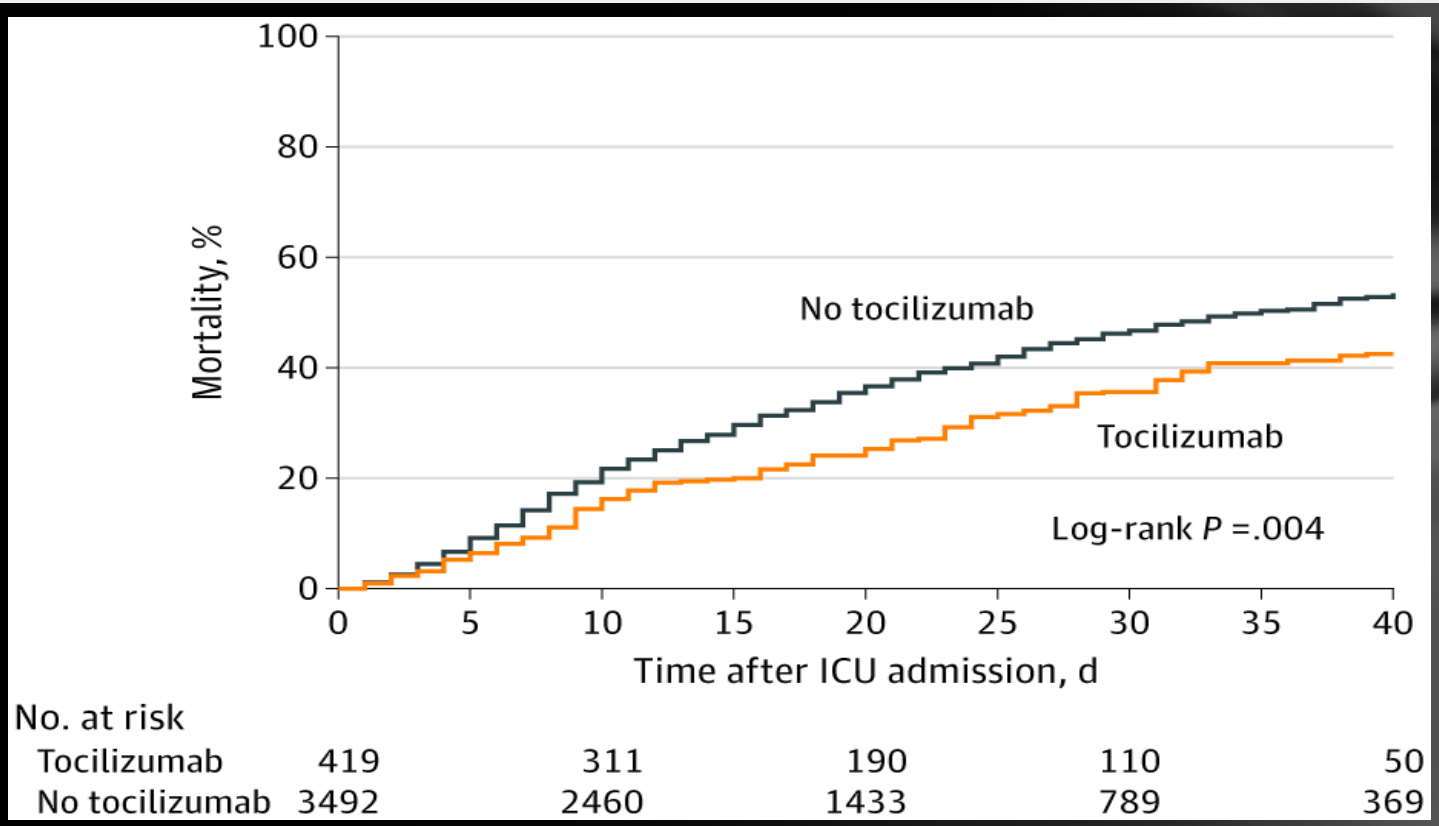
Mechanical ventilation : 17/365 (16%) vs 33/179 (18%) **p=0·41**

Death : 73 / 365 (20%) vs 13/179 (7%) **p<0·0001)**


A
Standard of care
Tocilizumab
Cumulative probability of mechanical ventilation or death
Log-rank p=0·0023
Number at risk (number censored)
Standard of care 365 348 335 307 278 250 230 206 187 165 146 135 122 105 94
(0) (5) (15) (25) (36) (47) (59) (74) (87) (102) (118) (128) (137) (153) (161)
Tocilizumab 179 172 169 163 159 150 142 134 130 124 115 105 98 87 79
(0) (0) (0) (0) (0) (5) (11) (16) (18) (24) (30) (38) (45) (54) (62)
B
Standard of care
Intravenous tocilizumab
Subcutaneous tocilizumab
Cumulative probability of mechanical ventilation or death
Log-rank p=0·0091
Number at risk (number censored)
Standard of care 365 348 335 307 278 250 230 206 187 165 146 135 122 105 94
(0) (5) (15) (25) (36) (47) (59) (74) (87) (102) (118) (128) (137) (153) (161)
Intravenous tocilizumab 88 86 84 79 79 74 72 69 65 63 59 54 52 45 41
(0) (0) (0) (0) (0) (3) (5) (8) (10) (12) (14) (17) (19) (24) (28)
Subcutaneous tocilizumab 91 86 85 84 80 76 70 65 65 61 56 51 46 42 38
(0) (0) (0) (0) (0) (2) (6) (8) (8) (12) (16) (21) (26) (30) (34)
C
Standard of care
Tocilizumab
Cumulative probability of death
Log-rank p<0·0001
Days from admission
Number at risk (number censored)
Standard of care 365 348 335 307 278 250 230 206 187 165 146 135 122 105 94
(0) (17) (30) (53) (76) (98) (112) (129) (142) (158) (174) (184) (193) (209) (217)
Tocilizumab 179 172 169 163 159 150 142 134 130 124 115 105 98 87 79
(0) (7) (10) (16) (20) (29) (36) (44) (46) (52) (60) (68) (75) (86) (94)
D
Standard of care
Intravenous tocilizumab
Subcutaneous tocilizumab
Cumulative probability of death
Log-rank p=0·0091
Days from admission
Number at risk (number censored)
Standard of care 365 348 335 307 278 250 230 206 187 165 146 135 122 105 94
(0) (17) (30) (53) (76) (98) (112) (129) (142) (158) (174) (184) (193) (209) (217)
Intravenous tocilizumab 88 86 84 79 79 74 72 69 65 63 59 54 52 45 41
(0) (2) (4) (9) (9) (14) (16) (19) (21) (23) (27) (30) (32) (39) (43)
Subcutaneous tocilizumab 91 86 85 84 80 76 70 65 65 61 56 51 46 42 38
(0) (5) (6) (7) (11) (15) (20) (25) (25) (29) (33) (38) (43) (47) (51)

From: **Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19**

JAMA Intern Med. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252



Mortality in Tocilizumab-Treated vs Non-Tocilizumab–Treated Patients A total of 63 tocilizumab-treated and 259 non-tocilizumab–treated patients were still hospitalized at last follow-up and thus could not be fully assessed for the primary outcome. ICU indicates intensive care unit.

the risk of in-hospital mortality in this study was lower in patients treated with tocilizumab in the first 2 days of ICU admission

From: **Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial**

JAMA Intern Med. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

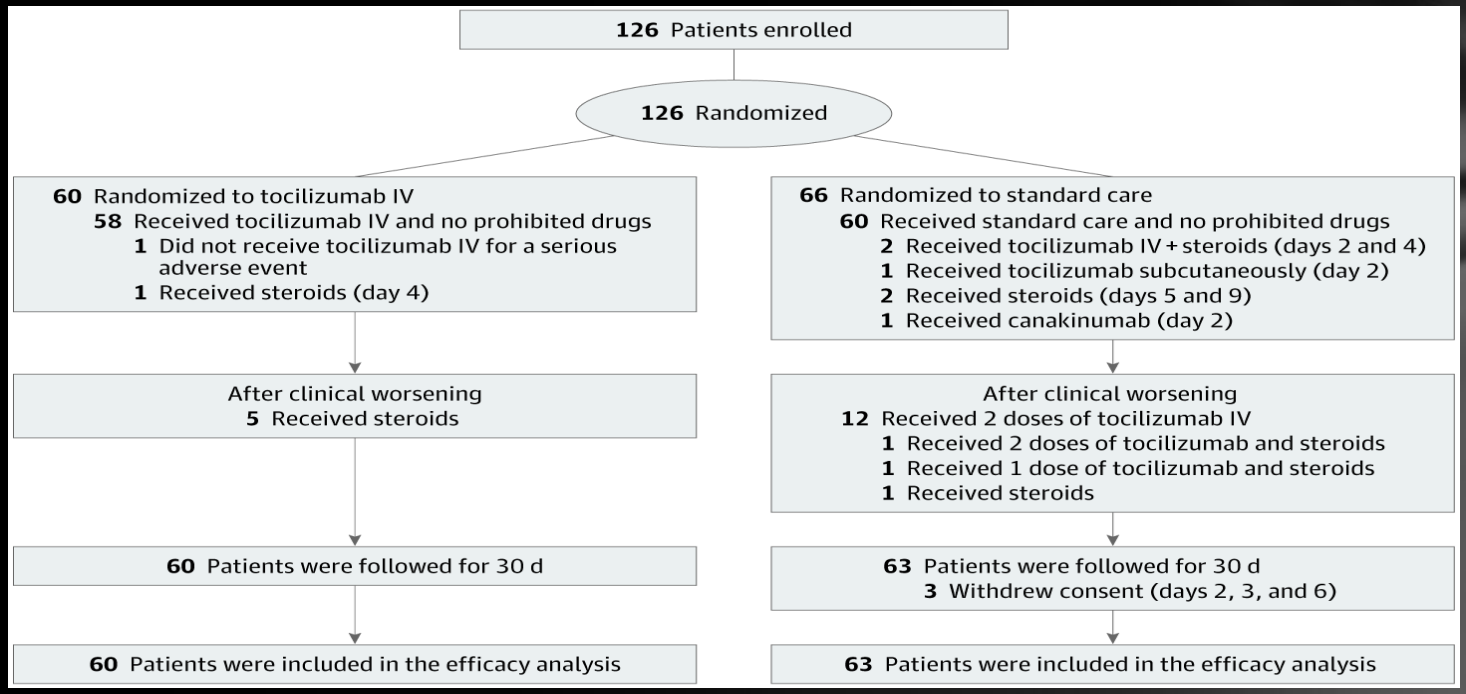


Figure Legend:

Flowchart of the Study IV indicates intravenous.

JAMA Network™

From: **Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial**

JAMA Intern Med. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

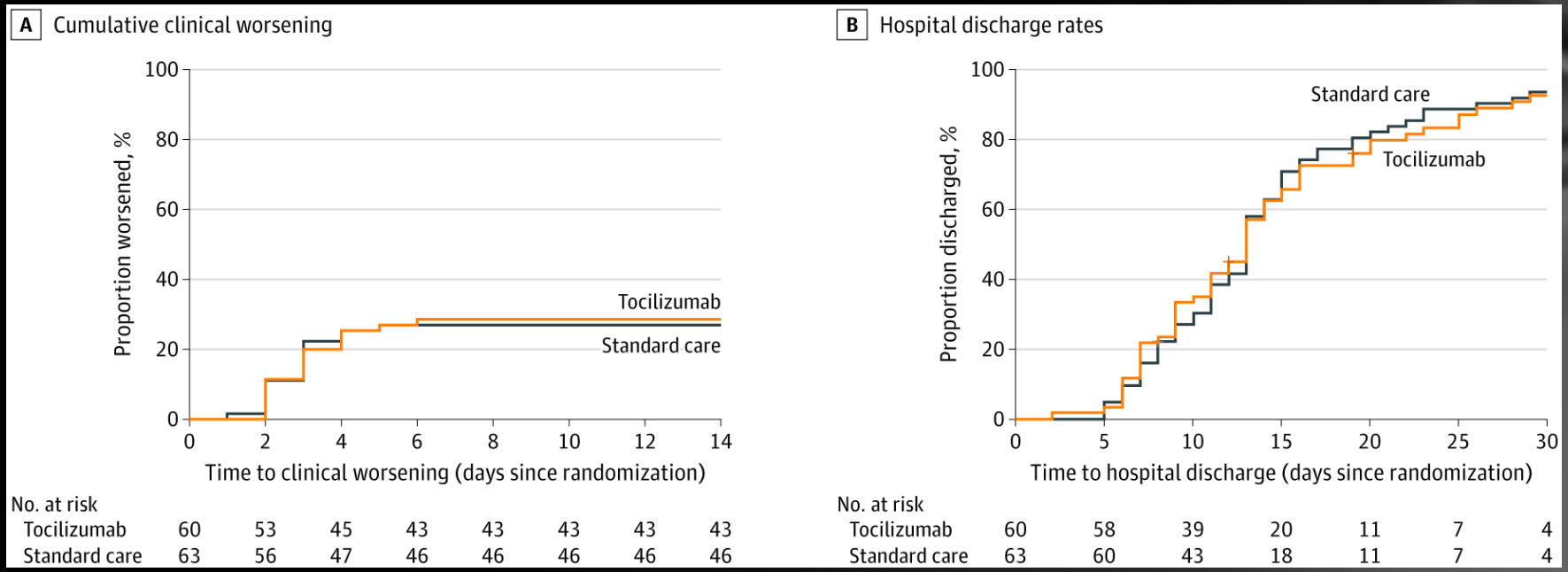
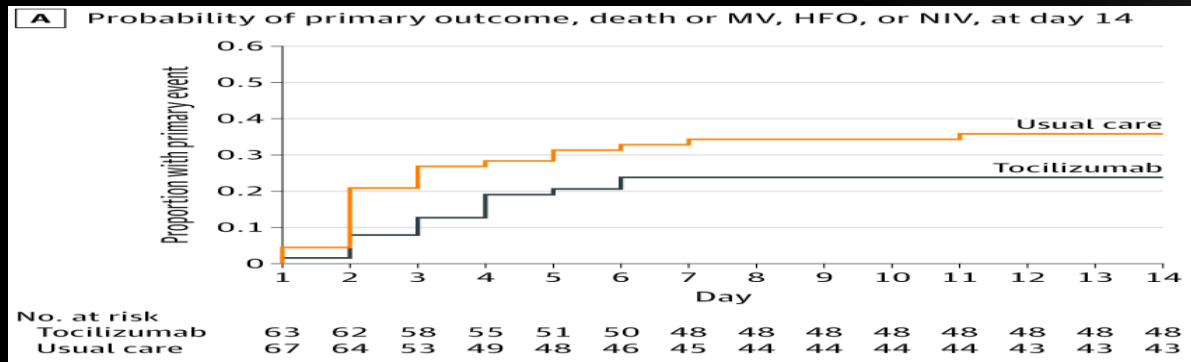


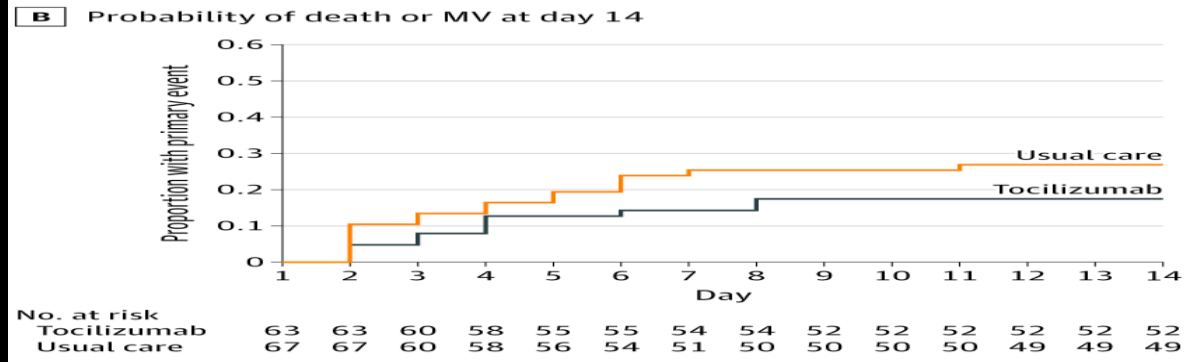
Figure Legend:

Kaplan-Meier Estimates of Cumulative Clinical Worsening and Hospital DischargeKaplan-Meier estimates of cumulative clinical worsening (A) and hospital discharge (B).

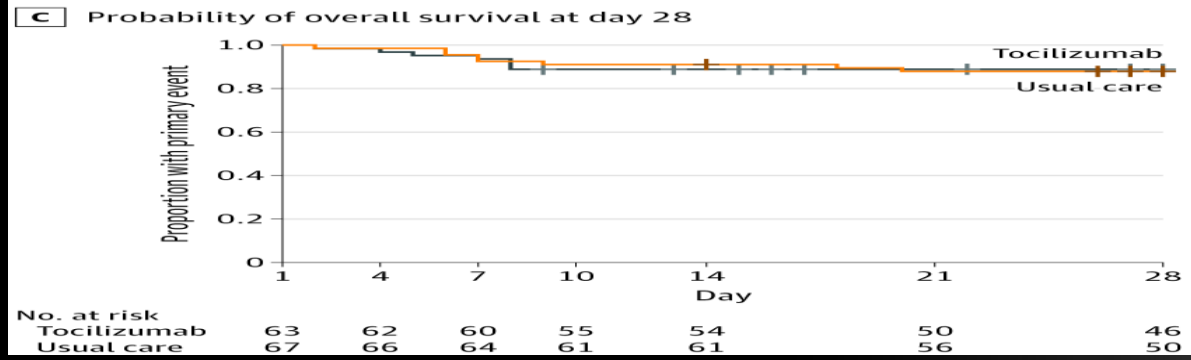
From: **Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial**



Parameter	Value
Median HR	0.58
90% CrI	0.33–1.00
95% CrI	0.30–1.11
P (HR <1)	0.95
P (HR <0.95)	0.93
P (HR <0.85)	0.87
P (HR <0.8)	0.83



Parameter	Value
Median HR	0.58
90% CrI	0.30–1.09
95% CrI	0.26–1.23
P (HR <1)	0.925
P (HR <0.95)	0.903
P (HR <0.85)	0.844
P (HR <0.8)	0.804



siltuximab

Blocks IL6 receptor membrane and soluble Castleman disease

Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020 Gritti G, Raimondi F, Ripamonti D, et al.

Baricitinib

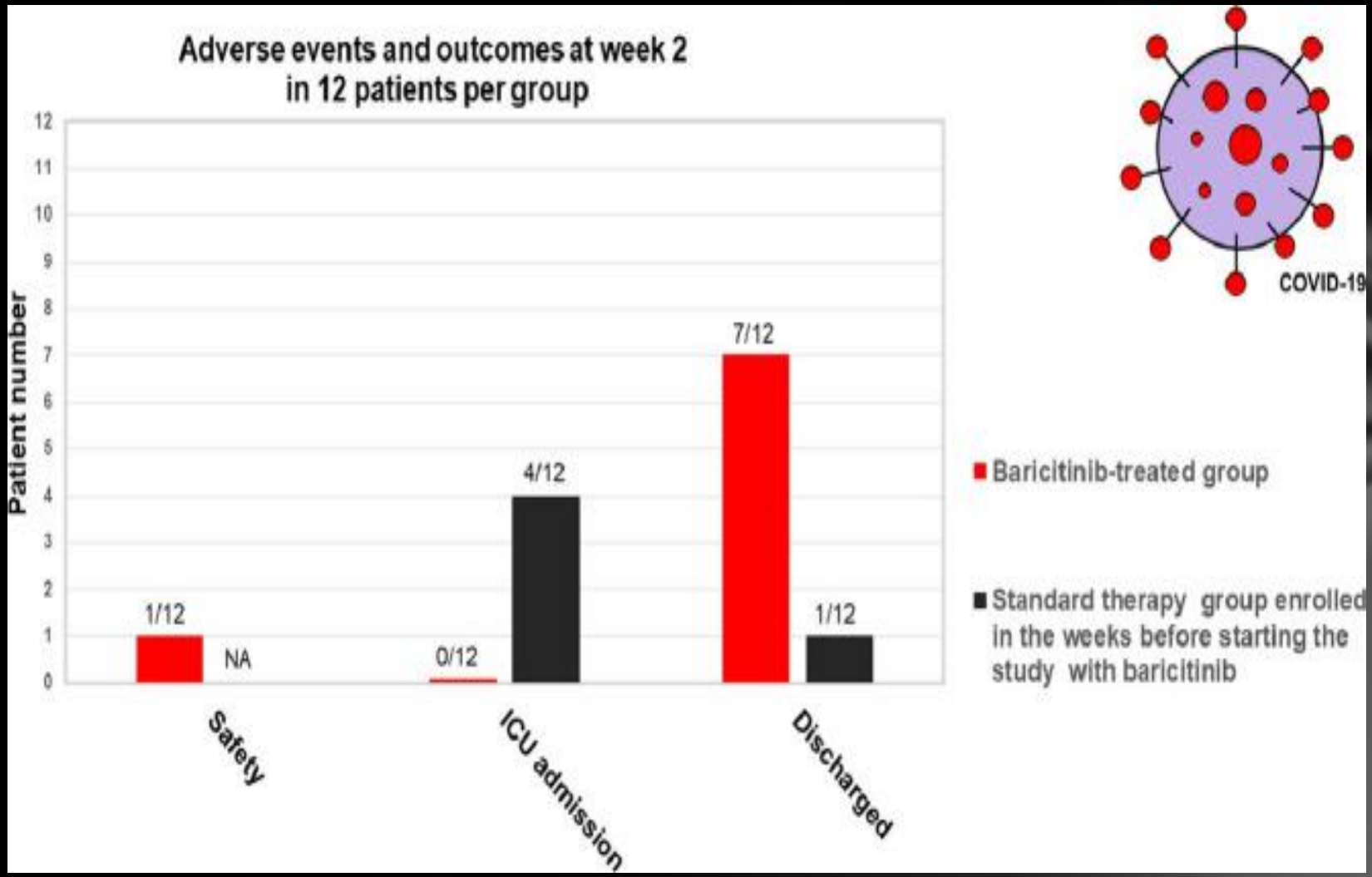
Baricitinib therapy in COVID-19:
a pilot study on safety and clinical impact. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. *Infect*. 2020

JAK1 JAK2 kinase selective inhibitor ; affinity for adaptor-associated kinase-1 (AAK1)

A small, nonrandomized study in patients with moderate COVID-19 pneumonia

A)12 pts Baricitinib+lopinavir/ritonavir

B)12 pts standard tx : lopinavir/ritonavir +HCQ



A) Tx shorter time to improvement of clinical and respiratory symptoms and a greater reduction of CRP

Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial Cao Y, Wei J, Zou L, et al. *J Allergy Clin Immunol*. 2020

Selective JAK1JAK2 kinase inhibitor GVHD myelofibrosis

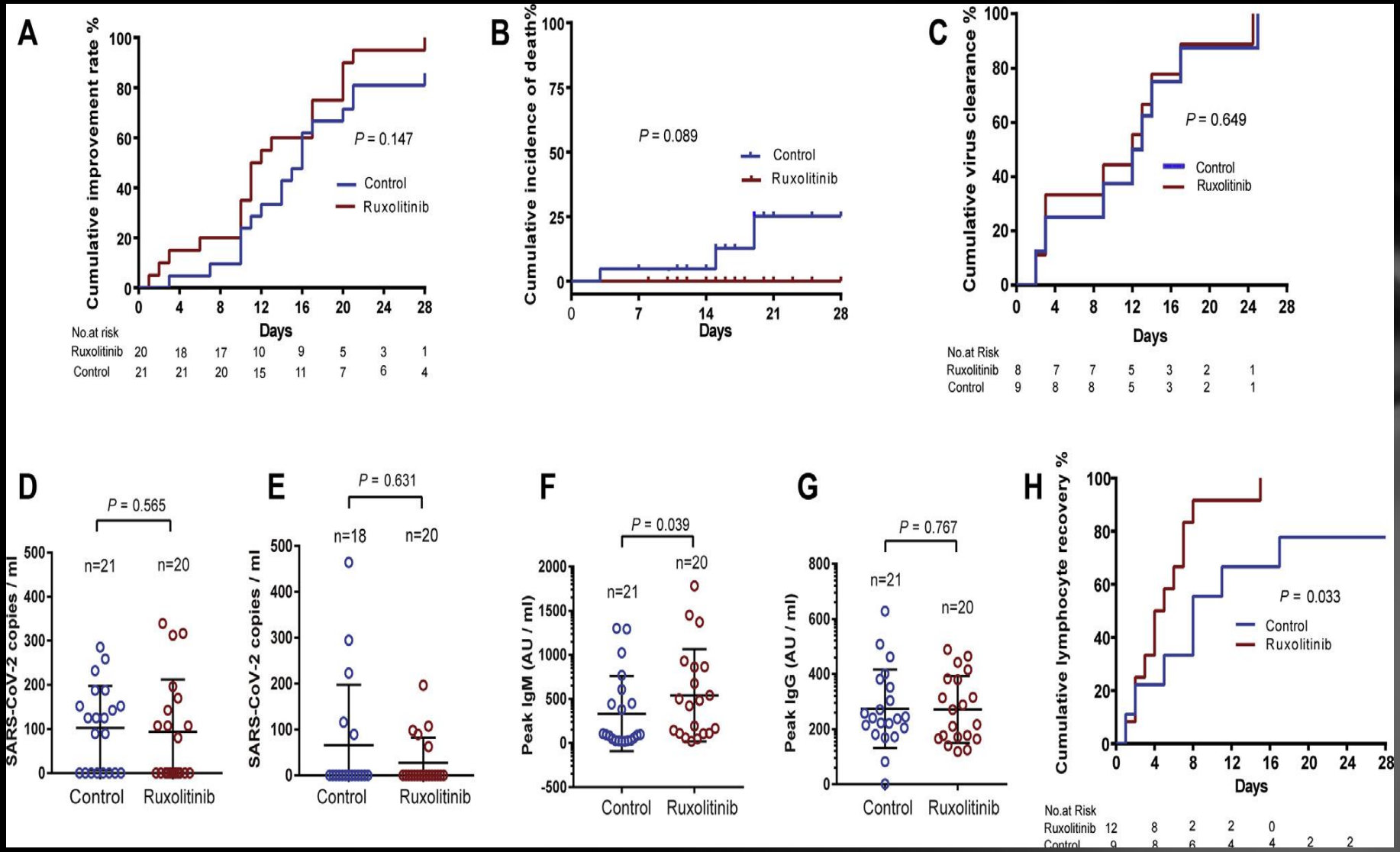
20 pts Ruxolitinib 5mg twice/d +standard Tx

21 pts Placebo+standard Tx

No significant differences in time of clinical improvement or disharge

radiographic improvement on chest CT at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$)

Ruxolitinib : Faster recovery from lymphocytopenia; favorable safety profile



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VOLUME 146, NUMBER 1

CAO ET AL

tofacitinib

Tofacitinib JAK1JAK3 selective kinase inhibitor　RA

No clinical study for COVID

Chinese Trial Clinical Registry. A randomized, open-label, controlled trial for the efficacy and safety of Adalimumab Injection in the treatment of patients with severe novel coronavirus pneumonia (COVID 19) (ChiCTR2000030089

SARS COVID2

through ACE2 receptor

enters cell

enhanced TNFα-production and TNFα-converting enzyme (TACE)-dependent shedding of the ectodomain of ACE2

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Immunomodulators					
Corticosteroids					
Dexamethasone	**For COVID-19:** • Dexamethasone 6 mg daily IV or PO, for up to 10 days[6] • Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • When used during outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.[7,8]	• Blood glucose • Blood pressure • Sign and symptoms of new infection • When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm temperate regions or who engage in agricultural activities) or fulminant reactivations of HBV should be considered.[9-11]	• Moderate CYP3A4 inducer • CYP3A4 substrate • Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020).	• On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, 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)**. • The Panel **recommends against** using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. • If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone **(AIII)**. • The approximate daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. • In the RECOVERY trial, only 5 patients received RDV; therefore, the safety and efficacy of coadministering RDV and dexamethasone are not known. • In the United States, dexamethasone is available in the following formulations: oral tablet, oral solution, oral elixir, and IV solution. • A list of clinical trials is available: Dexamethasone

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is anakinra 100 mg SQ once daily • Has also been used IV • Duration unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend either for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies					
Sarilumab[18]	**Clinical Trial Dosing (See *ClinicalTrials.gov* Identifier NCT04315298):** • Sarilumab 400 mg IV (single dose)[19] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• The Panel **recommends against** the use of sarilumab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Sarilumab

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[20]	**Clinical Trial Dosing:** • Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see *ClinicalTrials.gov* Identifier NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• The Panel **recommends against** the use of tocilizumab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • The SQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab
Anti-Interleukin-6 Monoclonal Antibody					
Siltuximab	• Siltuximab 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[21] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR • Monitor for infusion reaction • Neutrophils	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• The Panel **recommends against** the use of siltuximab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Janus Kinase Inhibitors					
Baricitinib[22]	**For Rheumatoid Arthritis:** • Baricitinib 2 mg PO once daily **Doses for COVID-19 in Clinical Trials:** • Baricitinib 2 mg–4 mg PO once daily for 7–14 days	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• CBC with differential • Renal function • Liver enzymes • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Baricitinib **is not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib
Ruxolitinib	• Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. • Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days.	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors. • **Avoid** use with fluconazole doses >200 mg.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose modification may be required in patients with moderate or severe renal impairment, hepatic impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Doses for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis) • Tofacitinib 10 mg PO twice daily (ulcerative colitis) • Dose and duration for COVID-19 is unknown; a planned COVID-19 clinical trial will be evaluating tofacitinib 10 mg twice daily for 14 days.	• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • Gastrointestinal perforation • Diarrhea • Headache • Herpes zoster reactivation • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors, or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. • **Avoid** live vaccines.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid use in patients with ALC <500 cells/mm^3, ANC <1,000 cells/mm^3, or Hgb <9 grams/dL. • Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib

ολοκληρώνοντας

Cytokine storm needs to be controlled by antirrheumatic drugs

Promising results by targeting cytokines

Trials with combination of antiviral and antirrheumatic drugs are expected

More studies needed carefully designed in patients traits and primary outcomes avoiding confounding factors