IL-6 and JAK inhibition in COVID-19

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July 16, 2022

RAVENSWOOD RHEUMATOLOGY

Great Lakes Clinical Trials at Ravenswood

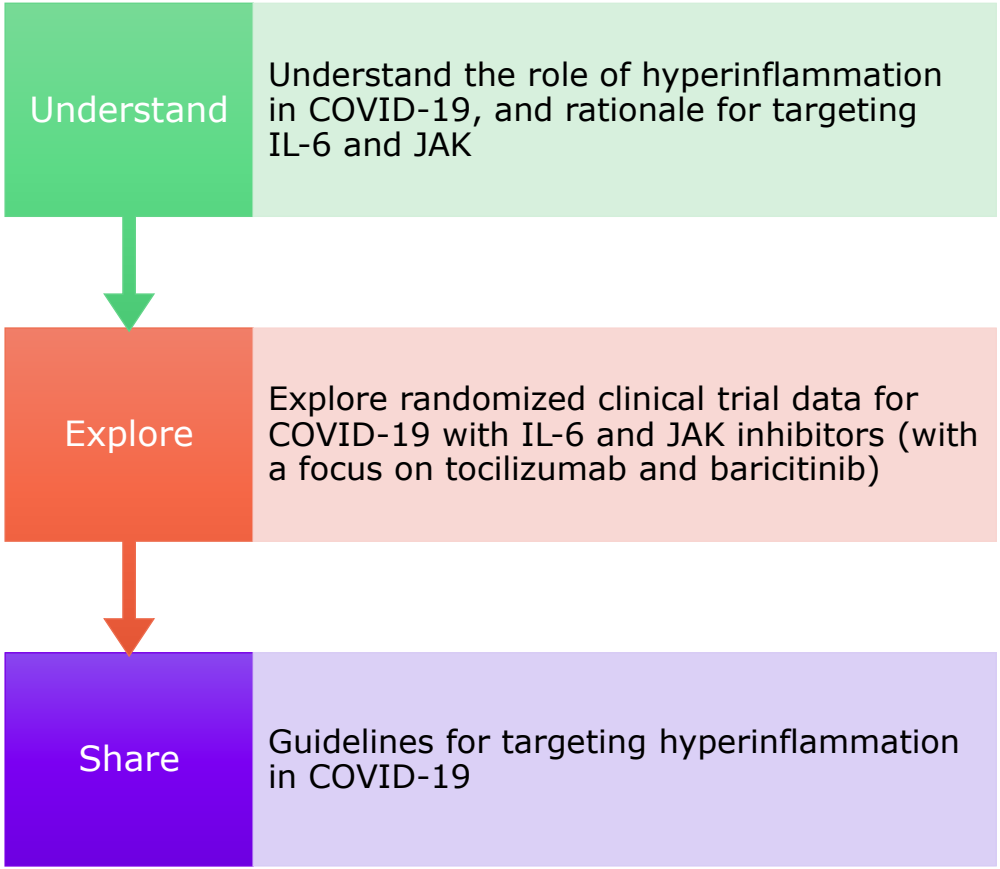
Disclosures

I have received funds for trial support or consulting/speaking related to COVID-19 from Genentech, Eli Lilly, Novartis, Janssen, AstraZeneca, Amgen, Abbott, Regeneron, Vir, and NIH.

For the next hour…

From Sharp scores, DAS28-CRPs, MDA, ASDAS, SLEDAI, etc.

Outline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Explore
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Share
Guidelines for targeting hyperinflammation in COVID-19

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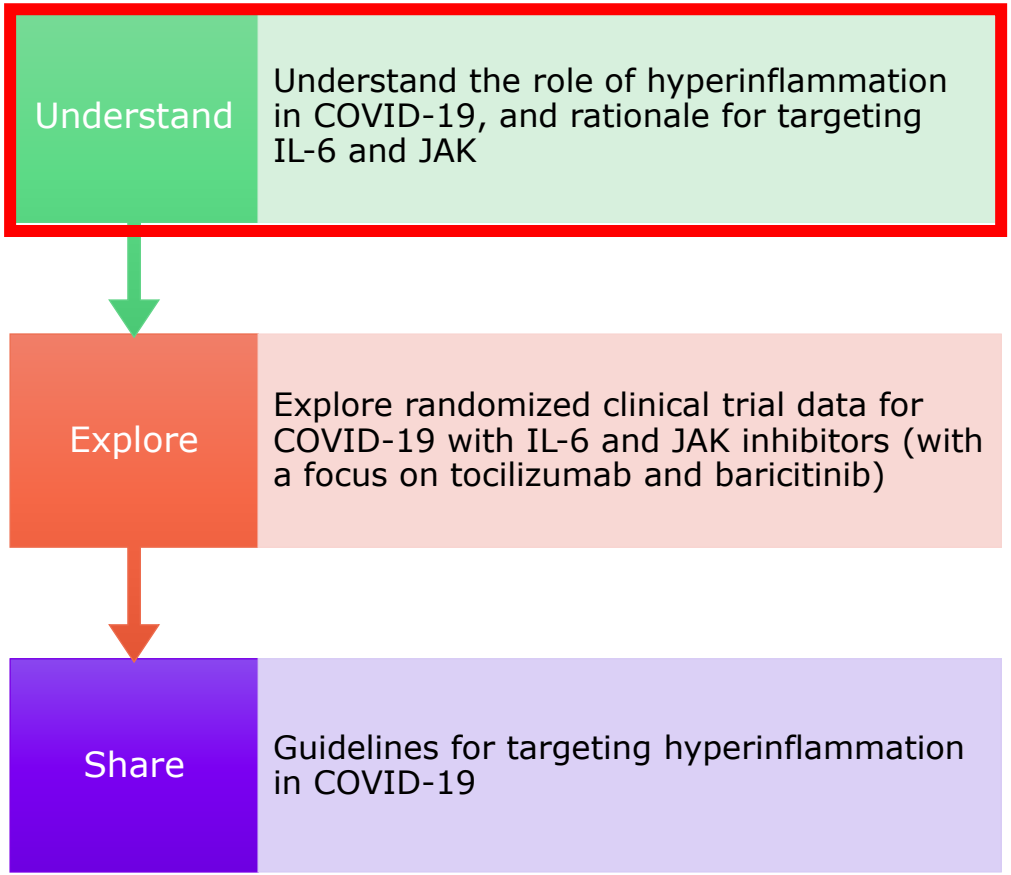
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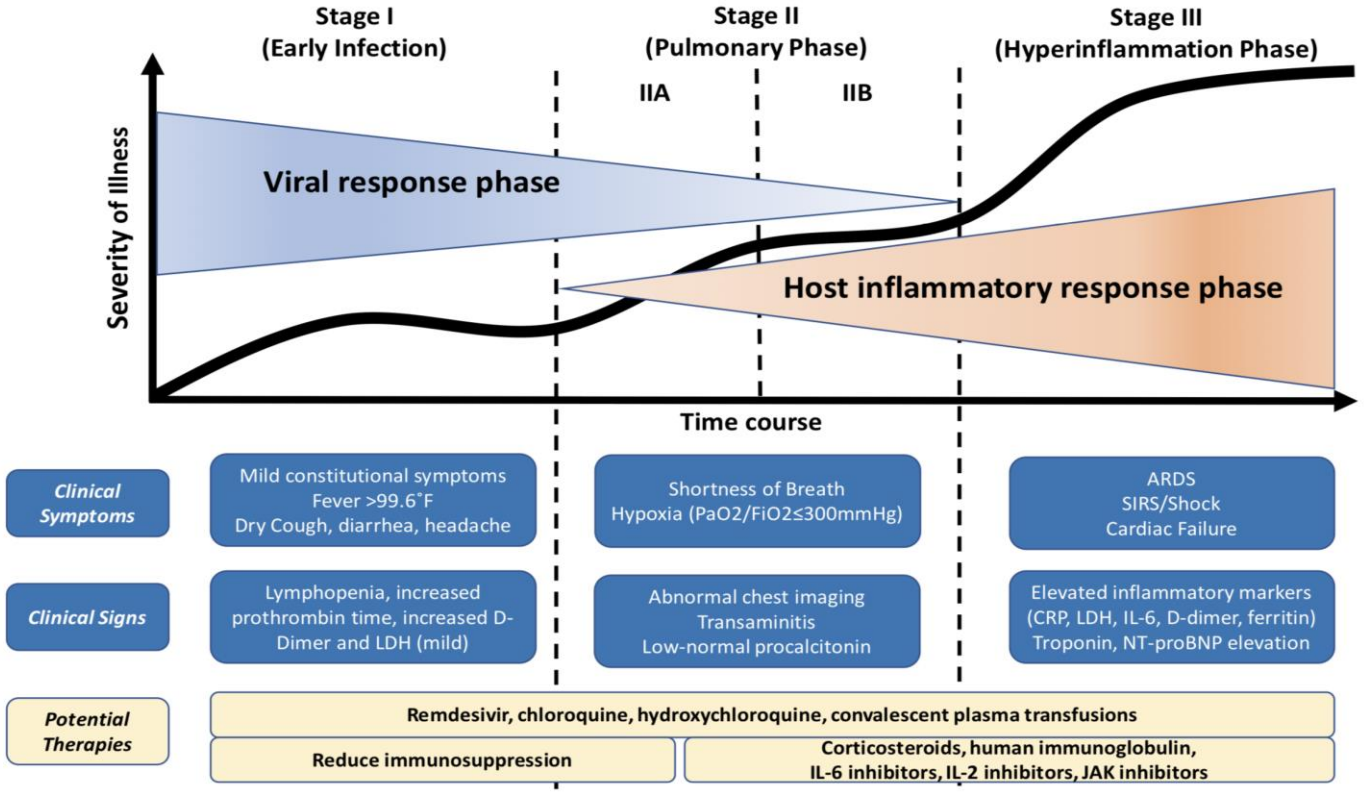
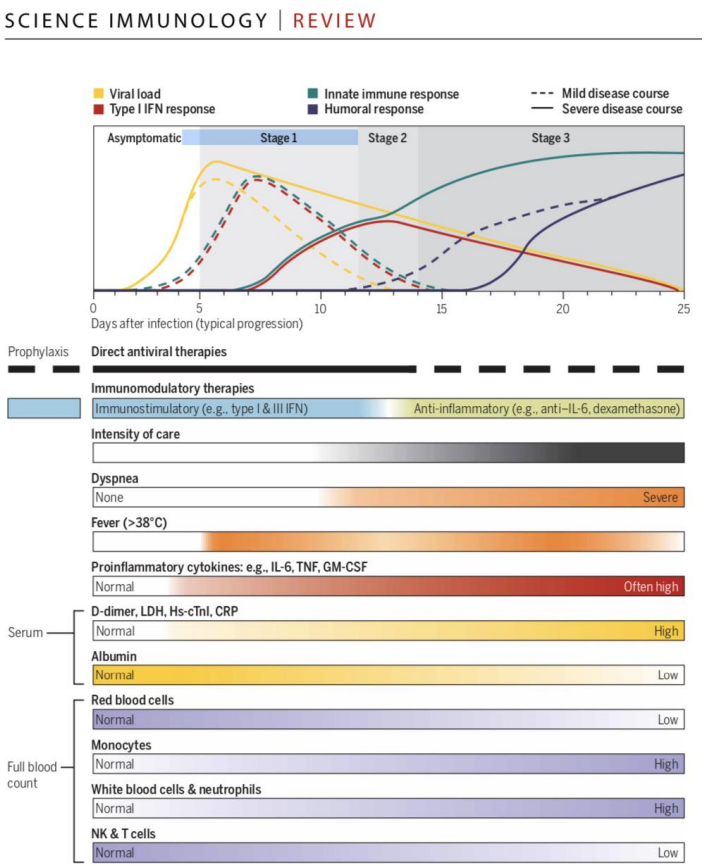
Hyperinflammation and COVID-19 early in the pandemic… If only it were this simple (March 2020)



A newer paradigm for hyperinflammation (September 2021)



COVID-19 disease course and clinical markers of severity.
The clinical course of COVID-19 can be categorized into stages:
(1) preclinical/mild
(2) moderate
(3) severe/critical.

…"the disease advances beyond stage 1 if the anti-inflammatory checkpoints of the host's immune responses fail and the balance between virus control and inflammation is lost "

Role for IL-6 inhibition in COVID-19 – Early case reports, and CRS as a model

Effective Treatment of Severe COVID-19 Patients with Tocilizumab

Xiaoling Xu[1,#*], Mingfeng Han[2,#], Tiantian Li[1], Wei Sun[2], Dongsheng Wang[1], Binqing Fu[3,4], Yonggang Zhou[3,4], Xiaohu Zheng[3,4], Yun Yang[5], Xiuyong Li[6], Xiaohua Zhang[2], Aijun Pan[5], Haiming Wei[3,4*]

- Published in April 2020 PNAS (Pre-print sooner).
- O2 requirements reduced 16/21; fever resolved 21/21; resolution of chest opacities on imaging (19/21); *"19 out of 21 patients discharged; 2 others remain hospitalized"*
- Why the initial comfort level and excitement for IL-6i? Familiar drug, approved for RA, GCA, **CRS**.

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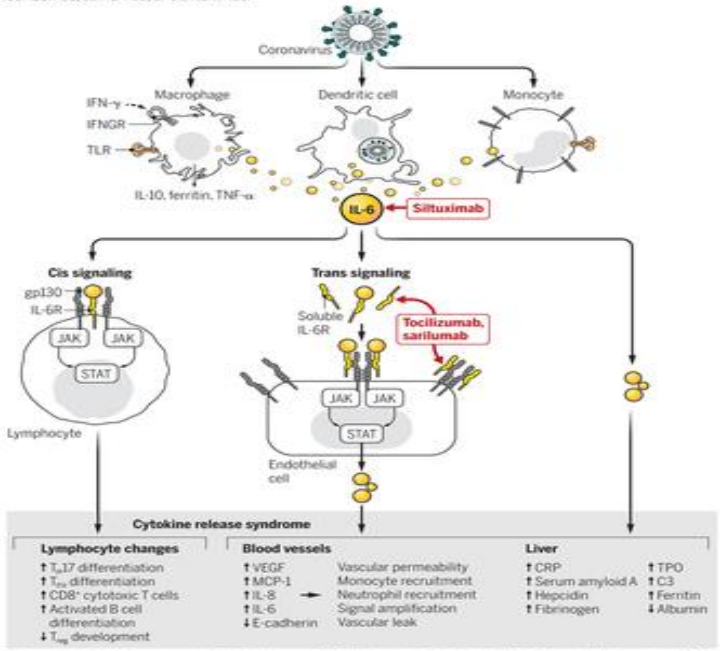
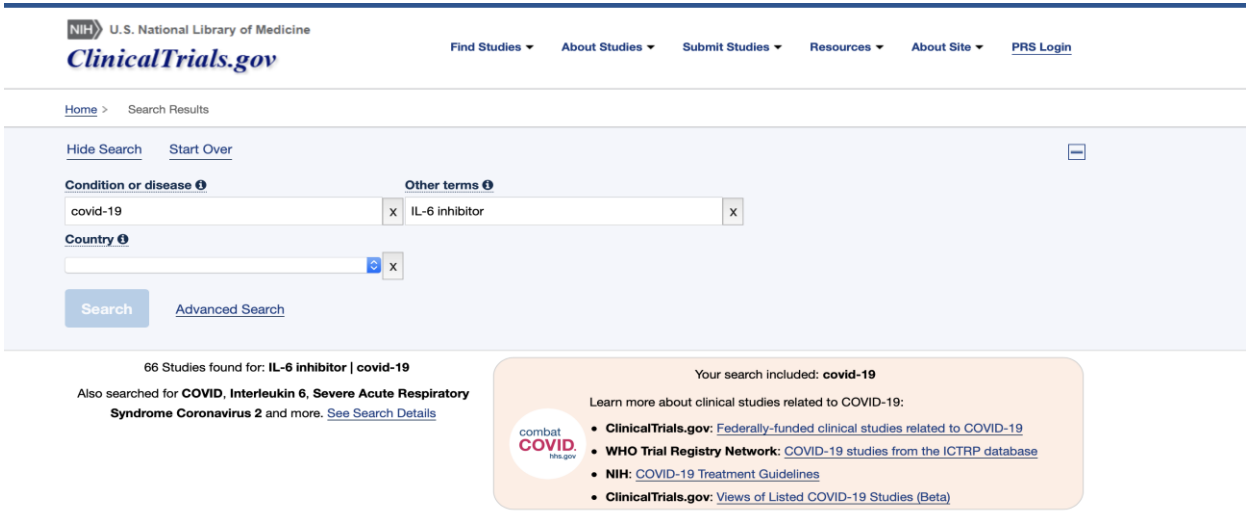
Pathways leading to cytokine release syndrome

Coronavirus infection results in monocyte, macrophage, and dendritic cell activation. IL-6 release then instigates an amplification cascade that results in cis signaling with T_H17 differentiation, among other lymphocytic changes, and trans signaling in many cell types, such as endothelial cells. The resulting increased systemic cytokine production contributes to the pathophysiology of severe COVID-19, including hypotension and acute respiratory distress syndrome (ARDS), which might be treated with IL-6 antagonists such as tocilizumab, sarilumab, and siltuximab.



C3, complement 3; CRP, C reactive protein; IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF-α, tumor necrosis factor-α; TLR, Toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.

An early explosion in trials and utilization of IL-6 inhibitors (IL-6i)



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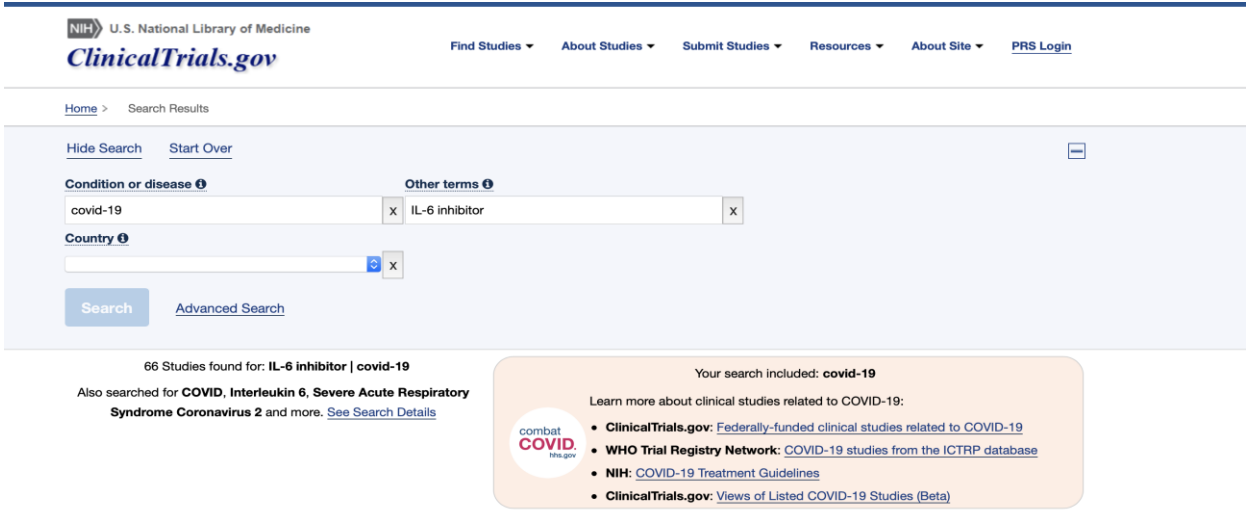
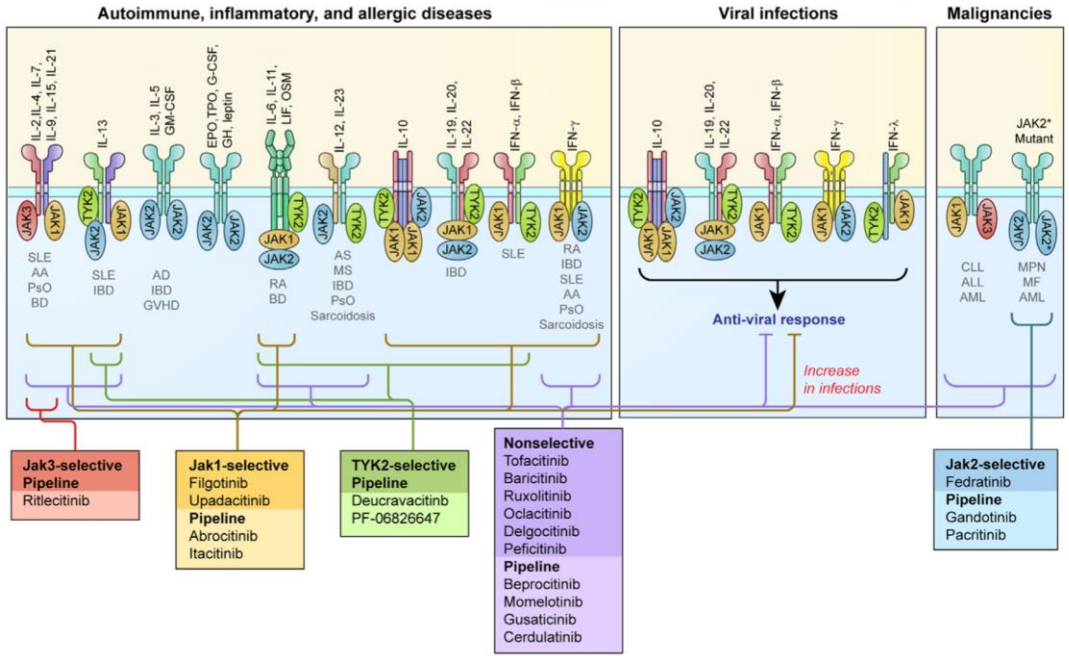


Tocilizumab COVID-19 utilization at AMITA (Chicagoland community based health system)

4/6/2020 to present: 570 patients
Vast majority treated prior to EUA (6/24/2021)
Helps explain shortages in our rheumatology practices

JAK inhibition in inflammation

- JAKs (JAK1/2/3 and TyK 2) have inflammatory, anti-viral, and hematopoetic effects via the JAK/STAT pathway
- Potential for broader downstream immunologic effects than single cytokine blockade
- JAKinibs block JAKs with specificity but clinical relevance unknown
- Interest in COVID-19:
  - **Baricitinib – JAK1 & JAK2**
  - Tofacitinib – pan-Jak (especially JAK3)
  - Ruxolitinib – JAK1 & JAK2



BenevolentAI: Interest of baricitinib early in pandemic

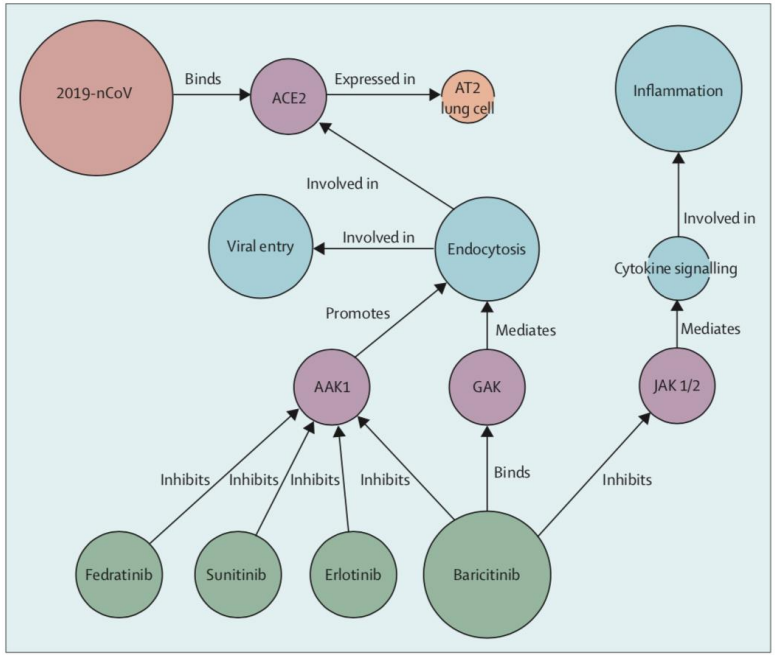


Figure: **The BenevolentAI knowledge graph**
The BenevolentAI knowledge graph integrates biomedical data from structured and unstructured sources. It is queried by a fleet of algorithms to identify new relationships to suggest new ways of tackling disease. 2019-nCoV=2019 novel coronavirus. AAK1=AP2-associated protein kinase 1. GAK=cyclin G-associated kinase. JAK1/2=janus kinase 1/2.

- Baricitinib identified as an early molecule of interest based on "machine based learning algorithm"
- Artificial intelligence matched known pathways in COVID-19 with known therapeutics
- Beyond JAK 1/2, Baricitinib other effects on the kinome, blocking kinases (AAK1) implicated in viral entry
- Published in Lancet February 2020

Flurry of COVID-19 inpatient RCTs with no standardization across primary endpoints

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)

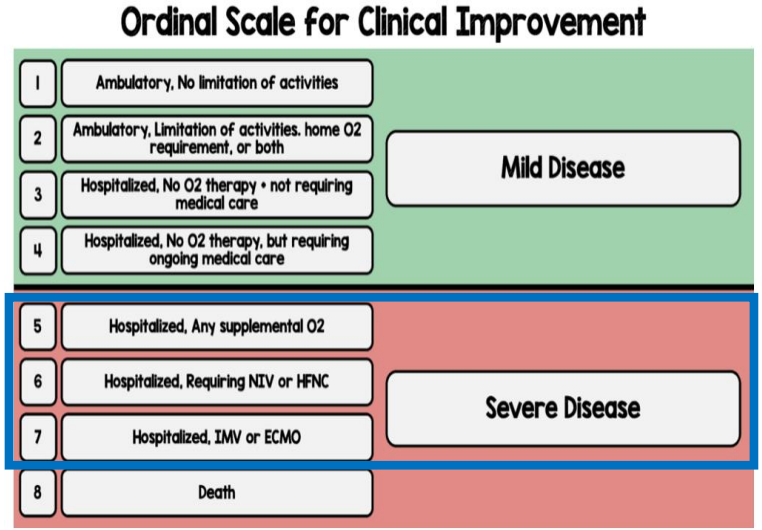
How much do endpoints other than mortality matter?

No initial standardization across clinical status assessments

WHO

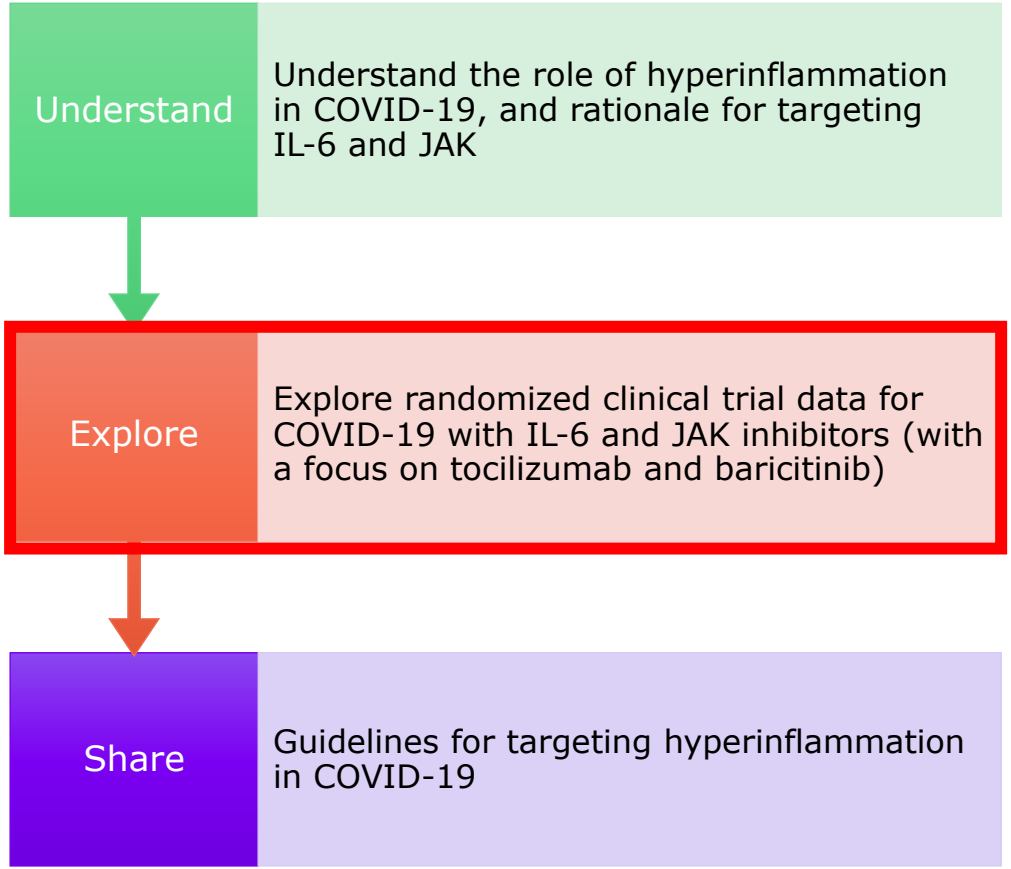
Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

NIAID



NIAID OS5-7 eventual sweet spot for inpatient clinical trials (trial eligibility and subgroup analysis)

Outline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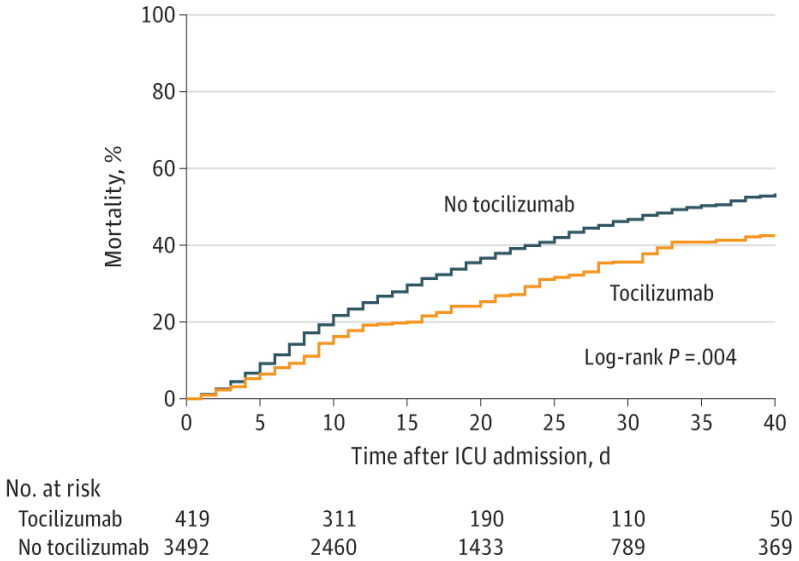
Tocilizumab studies 0.0: Case reports & observational studies generate promise and excitement

- Typical dose 8 mg/kg as single IV infusion but some reports (and subsequent trials) described/allowed 2nd dose

- STOP-COVID – **observational** multicenter cohort study with 3924 critically ill patients (of whom 433 received tocilizumab within 2 days of ICU admission); the risk of in-hospital death was estimated to be lower with tocilizumab treatment compared with no tocilizumab.
  - 30-day mortality toci 27.5% vs no toci 37.1%, (risk difference 9.6%; 95% CI 3.1%-16%*);* NNT ~ 10



Tocilizumab studies 1.0: Double-blind, placebo-controlled RCTs fail to show mortality benefit

	Target population	Key eligibility criteria	Treatment *	Primary endpoint	Enrollment dates
COVACTA	Hospitalized adults with hypoxia	COVID-19 (PCR) Pneumonia (CXR or CT) SpO2≤93% or PaFiO2/FiO2<300 mmHg	TCZ 8 mg/kg vs PBO	Clinical status at day 28 on 7-category ordinal scale	03 Apr 2020 – 28 May 2020
EMPACTA	Hospitalized adults with hypoxia	COVID-19 (PCR) Pneumonia (CXR or CT) SpO2≤94%; NI/I MV excluded	TCZ 8 mg/kg vs PBO	Mechanical ventilation or death by day 28	14 May 2020 – 21 Jul 2020
REMDACTA	Hospitalized patients >12 yrs old with hypoxia	COVID-19 (PCR) Pneumonia (CXR or CT) SpO2≤93% on >6L/min oxygen; renal failure excluded	TCZ 8mg/kg + RDV vs PBO + RDV	Time to discharge or ready for discharge to day 28	16 Jun 2020 – 04 Jan 2021

*TCZ in these trials was typically given in lieu of, and not in addition to steroids (RECOVERY-dex press release 6/16/2020)

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Tocilizumab studies 1.0 – placebo-controlled RCTs, failing to show mortality benefit

	COVACTA		EMPACTA		REMDACTA	
	TCZ N=294	PBO N=144	TCZ N=249	PBO N=128	TCZ N=430	PBO N=210
Mortality	19.7%	19.4%	10.4%	8.6%	18.1%	19.5%
Weighted difference (95%CI)	0.3% (-7.6, 8.2)		2.0% (-5.2, 7.8)		-1.3% (-7.8, 5.2)	
Time to hospital DC/ Ready for DC	56.8%	50.0%	87.1%	82.8%	66.0%	67.1%
Median days	20	28	6	7.5	14	14
HR (95%CI)	1.35 (1.02, 1.79)*		1.16 (0.91, 1.48)		0.965 (0.78, 1.19)	
MV or death	27.9%	36.7%	11.6%	18.8%	27.5%	29.8%
Weighted difference/ HR (95%CI)	-8.9% (-20.7, 3.0)		0.56 (0.33, 0.97)*		-2.2% (-10.2, 5.9)	

*TCZ in these trials was typically given in lieu of, and not in addition to steroids (RECOVERY-dex press release 6/16/2020)

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Safety of tocilizumab in RCTs

	COVACTA		EMPACTA		REMDACTA	
	TCZ N=295	PBO N=143	TCZ N=250	PBO N=127	TCZ N=429	PBO N=213
AE	240 (81.4%)	118 (82.5%)	127 (50.8%)	67 (52.8%)	332 (77.4%)	153 (71.8%)
SAE	116 (39.3%)	64 (44.8%)	38 (15.2%)	25 (19.7%)	141 (32.9%)	76 (35.7%)
Deaths	72 (24.4%)	36 (25.2%)	29 (11.6%)	15 (11.8%)	98 (22.8%)	55 (25.8%)
Infections	127 (43.1%)	63 (44.1%)	25 (10.0%)	16 (12.6%)	143 (33.3%)	76 (35.7%)
Serious infections	71 (24.1%)	42 (29.4%)	13 (5.2%)	9 (7.1%)	97 (22.6%)	59 (27.7%)
Opportunistic infections	1 (0.3%)	3 (2.1%)	0	0	6 (1.4%)	5 (2.3%)
Anaphylactic reactions	0	0	0	0	2 (0.5%)	0
Hepatic events	7 (2.4%)	3 (2.1%)	2 (0.8%)	0	8 (1.9%)	3 (1.4%)
Bleeding events	47 (15.9%)	18 (12.6%)	12 (4.8%)	8 (6.3%)	61 (14.2%)	24 (11.3%)

*TCZ in these trials was typically given in lieu of, and not in addition to steroids (RECOVERY-dex press release 6/16/2020)

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Dampening enthusiasm after Tociluzimab 1.0…

Editorial

October 20, 2020

Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia

Jonathan B. Parr, MD, MPH[1]

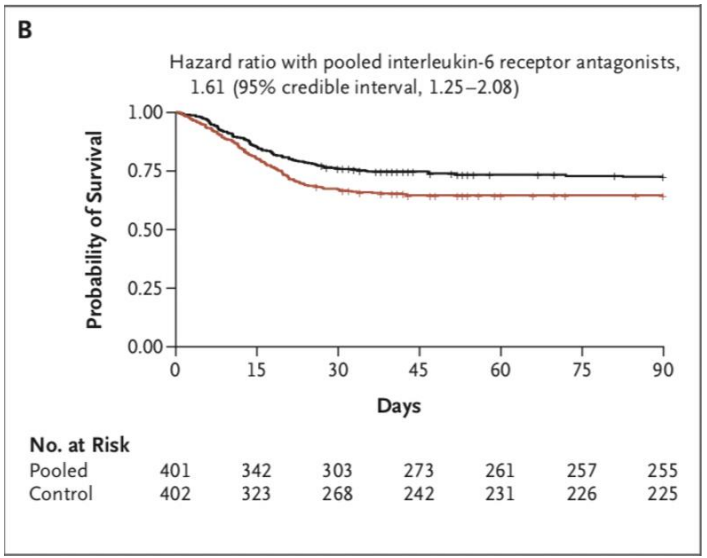
» Author Affiliations | Article Information

JAMA Intern Med. 2021;181(1):12-15. doi:10.1001/jamainternmed.2020.6557

Tocilizumab 2.0 – A New Hope
Two open label studies show mortality benefit

REMAP-CAP: Open-label, randomized, controlled study with COVID-19 inpatients with ICU admission within 24 hours

- tocilizumab (353) or sarilumab (48) IV vs standard care (402)
- 70%+ on dexamethasone; 30%+ on remdesivir
- Pooled IL6i mortality: 27% vs placebo: 36%. NNT ~ 11



Tocilizumab 2.0 – A New Hope (open label studies show mortality benefit)

RECOVERY-toci:

Open-label, randomized, controlled, UK majority sites. COVID-19 inpatients with hypoxia (<92%, NC→MV), *CRP ≥ 75 mg/dl*

- tocilizumab n=2022 vs standard care n=2094
- 80%+ on dexamethasone; broadly used after RECOVERY-dex announcement June 2020

	Tocilizumab group (n=2022)	Usual care group (n=2094)
Respiratory support at second randomisation		
No ventilator support†	935 (46%)	933 (45%)
Non-invasive ventilation‡	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)
Biochemistry at second randomisation		
Latest C-reactive protein, mg/L	143 (107–203)	144 (106–205)
Ferritin, ng/mL	947 (497–1599)	944 (507–1533)
Creatinine, µmol/L	77 (62–98)	77 (62–100)

	Tocilizumab group (n=2022)	Usual care group (n=2094)
Use of systemic corticosteroids††		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

RECOVERY-toci: Mortality & safety results

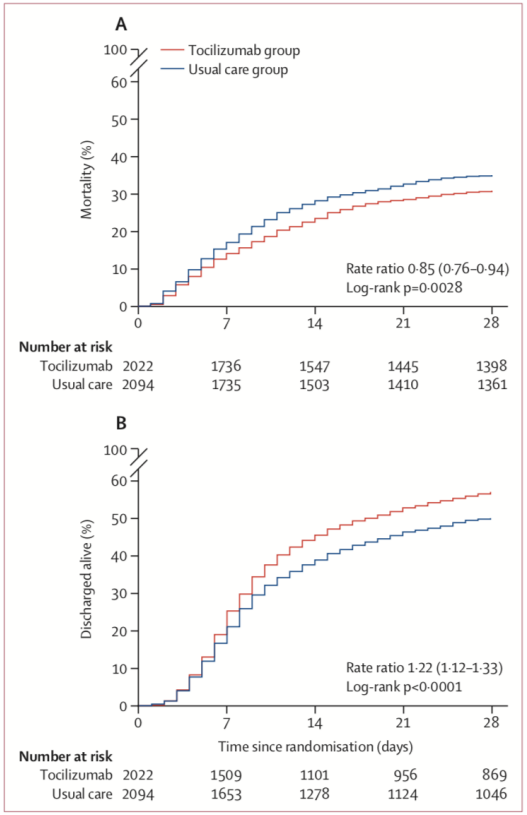


Figure 2: **Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab group (n=2022)	Usual care group (n=2094)		
Primary outcome				
28-day mortality	621 (31%)	729 (35%)	0·85 (0·76–0·94)	0·0028
Secondary outcomes				
Median time to being discharged, days	19	>28	..	..
Discharged from hospital within 28 days	1150 (57%)	1044 (50%)	1·22 (1·12–1·33)	<0·0001
Receipt of invasive mechanical ventilation or death*	619/1754 (35%)	754/1800 (42%)	0·84 (0·77–0·92)	<0·0001
Invasive mechanical ventilation	265/1754 (15%)	343/1800 (19%)	0·79 (0·69–0·92)	0·0019
Death	490/1754 (28%)	580/1800 (32%)	0·87 (0·78–0·96)	0·0055
Subsidiary clinical outcomes				
Receipt of ventilation†	290/935 (31%)	323/933 (35%)	0·90 (0·79–1·02)	0·10
Non-invasive ventilation	281/935 (30%)	309/933 (33%)	0·91 (0·79–1·04)	0·15
Invasive mechanical ventilation	67/935 (7%)	86/933 (9%)	0·78 (0·57–1·06)	0·11
Successful cessation of invasive mechanical ventilation‡	95/268 (35%)	98/294 (33%)	1·08 (0·81–1·43)	0·60
Use of haemodialysis or haemofiltration§	120/1994 (6%)	172/2065 (8%)	0·72 (0·58–0·90)	0·0046

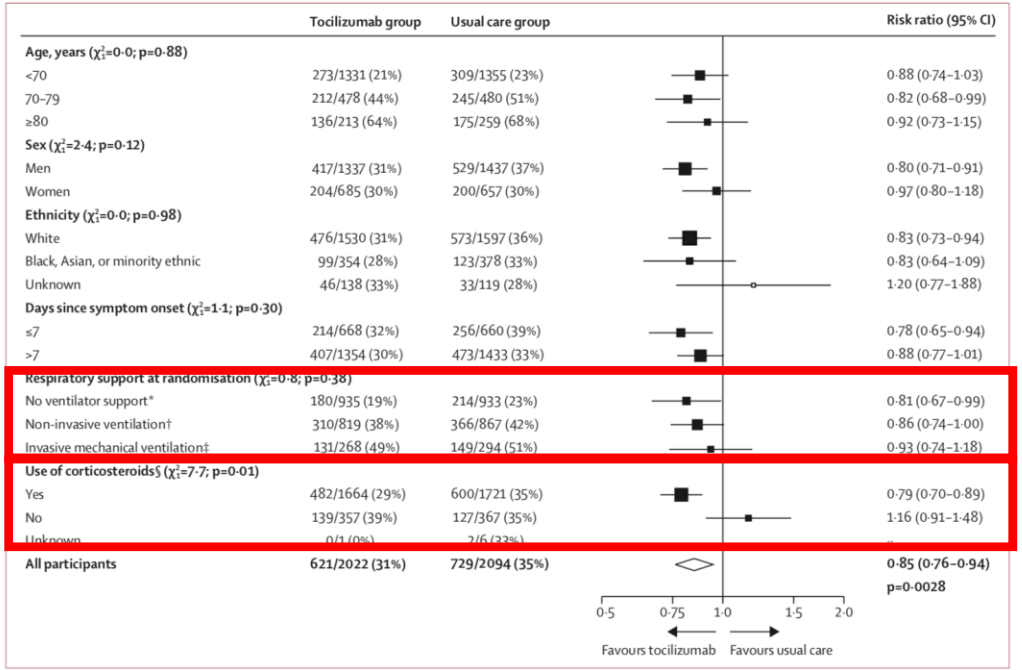
Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

Table 2: **Effect of allocation to tocilizumab on main study outcomes**

28-day mortality:
toci 31% vs placebo 35%,
NNT = 25

Safety: pre-specified safety outcomes including cause-specific mortality and major cardiac arrythmias showed "no difference between treatment arms"

RECOVERY-toci: Subgroup analysis



	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Age, years (χ^2_1=0·0; p=0·88)			
<70	273/1331 (21%)	309/1355 (23%)	0·88 (0·74–1·03)
70–79	212/478 (44%)	245/480 (51%)	0·82 (0·68–0·99)
≥80	136/213 (64%)	175/259 (68%)	0·92 (0·73–1·15)
Sex (χ^2_1=2·4; p=0·12)			
Men	417/1337 (31%)	529/1437 (37%)	0·80 (0·71–0·91)
Women	204/685 (30%)	200/657 (30%)	0·97 (0·80–1·18)
Ethnicity (χ^2_1=0·0; p=0·98)			
White	476/1530 (31%)	573/1597 (36%)	0·83 (0·73–0·94)
Black, Asian, or minority ethnic	99/354 (28%)	123/378 (33%)	0·83 (0·64–1·09)
Unknown	46/138 (33%)	33/119 (28%)	1·20 (0·77–1·88)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	..
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94) p=0·0028**

0·5 0·75 1·0 1·5 2·0

Favours tocilizumab Favours usual care

Figure 3: **Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics**

Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. *Includes nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only. †Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation. ‡Includes patients receiving invasive mechanical ventilation and extracorporeal membranous oxygenation. §Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids. In a model adjusted for all six baseline subgroups (in the categories shown) the overall rate ratio was 0·88 (95% CI 0·79–0·98).

- Data weaker for NIV (OS6) and IMV (OS7) subsets - *keep in mind for JAKi data*
- What's more clinically relevant to identify patients – CRP levels or clinical status?
- ONLY significant for toci *with concurrent steroid use*

Overall tociluzimab performance in meta-analysis

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017

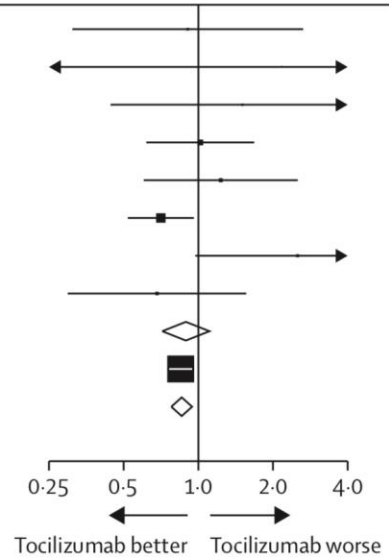


Figure 4: **Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19**

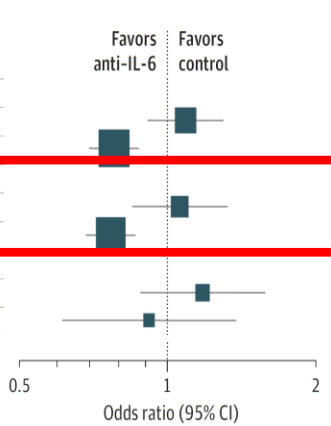
O–E=observed–expected. Var=variance. *Log–rank O–E for RECOVERY, O–E from 2 × 2 contingency tables for the other trials. Rate ratio is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O–E or V values. Heterogeneity between RECOVERY and eight previous trials combined, χ_1^2=0·2 (p=0·7).

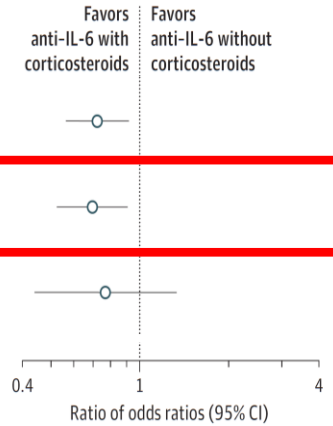
WHO meta-analysis: Background steroid use with tocilizumb demonstrates mortality benefit

- Prospective meta-analysis of 27 IL6i trials by WHO REACT Working Group

World Health Organization

Outcome and treatment	I^2, %	No. of events/total patients: Control	Anti-IL-6	Odds ratio (95% CI)	Ratio of odds ratios (95% CI)	I^2, %	P value
All anti-IL-6							
No corticosteroid use	0	293/1280	537/2357	1.09 (0.91-1.30)	0.72 (0.56-0.92)	0	.008
Corticosteroid use	0	838/2848	827/3468	0.78 (0.69-0.88)			
Tocilizumab							
No corticosteroid use	0	211/898	254/1192	1.06 (0.85-1.33)	0.69 (0.52-0.91)	0	.008
Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)			
Sarilumab							
No corticosteroid use	0	83/384	283/1134	1.18 (0.88-1.58)	0.77 (0.44-1.33)	0	.34
Corticosteroid use	0	48/281	124/607	0.92 (0.61-1.38)			





A willingness to explore IL6i with concomitant steroids (bit different from JAKi)

Adapted with permission from Genentech

Tocilizumab summary & EUA highlights

- MOA excitement & comfort + success in early case reports & observational studies = lots of utilization → shortages for our rheumatology patients

- Most trials including double-blind placebo-controlled RCTs did **not** show a mortality benefit

- Open-label studies including RECOVERY showed mortality benefit
  - RECOVERY patients selected in part by elevated CRP but clinical status (NC vs BiPAP vs IMV) did not seem to matter
  - Success limited to concomittant steroid-treated patients across trials

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EUA granted 6/24/2021 – Factsheet highlights:

- *Receipt of systemic corticosteroids required*
- Adults and kids > 2 years of age requiring oxygen support of any degree
- Adult dosing: 8 mg/kg max 800 mg IV
- If clinical signs/symptoms worsen or do not improve after 1st dose, 2nd dose may be given at least 8 hours after 1st

JAKi to treat COVID-19

Honorable mentions

Tofacitinib: STOP-COVID. 289 patients – tofa vs pbo +SOC
-met primary endpoint: death or respiratory failure
-not powered to detect mortality differences, but trends favored

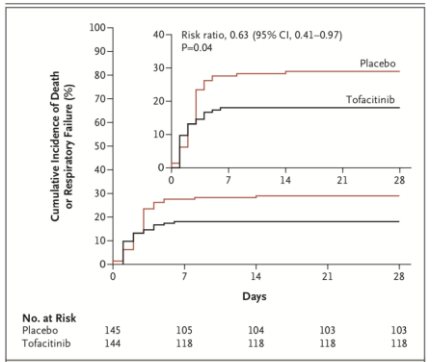

Figure 2. Cumulative Incidence of the Primary Outcome.
The primary outcome was death or respiratory failure through day 28. The risk ratio and P value for the primary outcome were calculated by means of binary regression with Firth correction, with trial group and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded y axis.

Ruxolitinib: RUXCOVID – 432 patients rux vs pbo + SOC
-negative study

		Ruxolitinib (n=287)	Placebo (n=145)	Comparison (95% CI)
Primary endpoint				
Composite endpoint of death, respiratory failure requiring mechanical ventilation, or ICU care by day 29*		34/284 (12%)	17/144 (12%)	OR 0·91 (0·48–1·73); p=0·77
Secondary endpoints				
Mortality rate by day 29		9/286 (3%)	3/145 (2%)	OR 1·21 (0·35–5·11)
Respiratory failure by day 29*		22/286 (8%)	10/145 (7%)	OR 0·99 (0·45–2·21)
ICU care by day 29*†		30/284 (11%)	17/144 (12%)	OR 0·81 (0·42–1·55)
Change in WHO (0–8) clinical status at day 29‡				
	≥1-point improvement	261/286 (91%)	136/145 (94%)	OR 0·79 (0·35–1·79)
	≥2-point improvement	252/286 (88%)	129/145 (89%)	OR 1·00 (0·52–1·92)

Baricitinib for the treatment of COVID-19

FDA approved for COVID-19 5/10/2022, also approved for RA and alopecia areata):

1) NIH ACTT-2

2) Initial safety hesitations/considerations & evolution in use

3) Pivotal COV-BARRIER & COV-BARRIER addendum trial

4) RECOVERY-baricitinib

5) Package insert highlights

NIH ACTT-2: First pivotal trial with baricitinib

- Adaptive platform trial: Baricitinib (BAR) + remdesivir (RDV) for hospitalized patients
  - Patients could be enrolled if ”admitted to hospital with symptoms suggestive of COVID-19”
  - No CRP or supplemental O2 requirements *(most were on O2)*
- BAR (4 mg/d x 14 days for GFR>60) + RDV (n=515) vs PBO + RDV (n=518)
- Dexamethasone not routinely used at the time. 20% on steroids for “standard indications” including asthma, adrenal insufficiency, septic shock, and ARDS.

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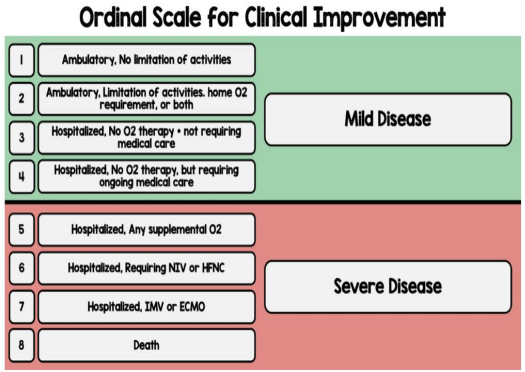
- Primary endpoint: **time to recovery by day 28** (i.e. how many days to get to OS1-3)
- Secondary endpoints: status at day 15 **and mortality day 28**



Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)

Baricitinib, ACTT-2: Median time to recovery

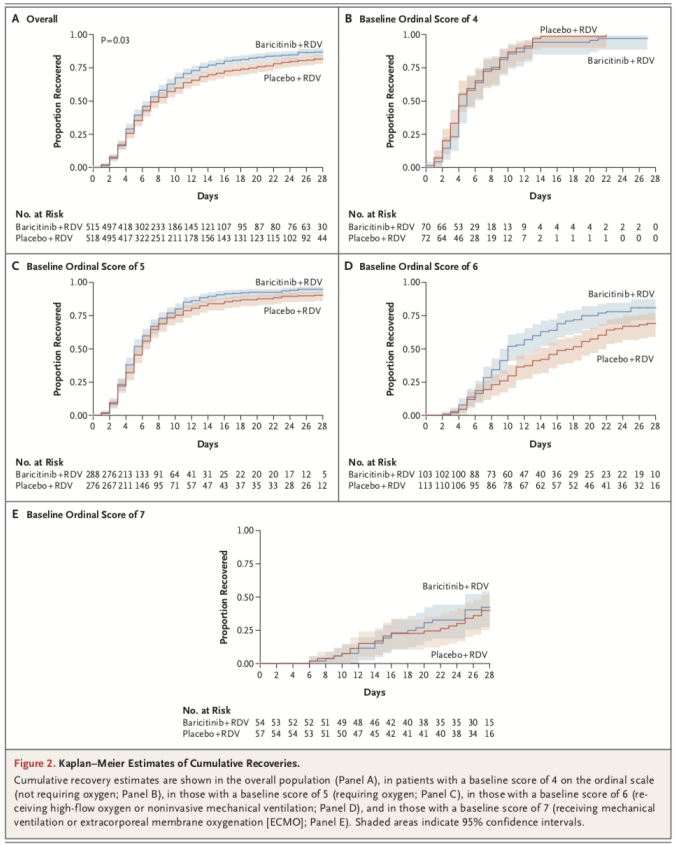
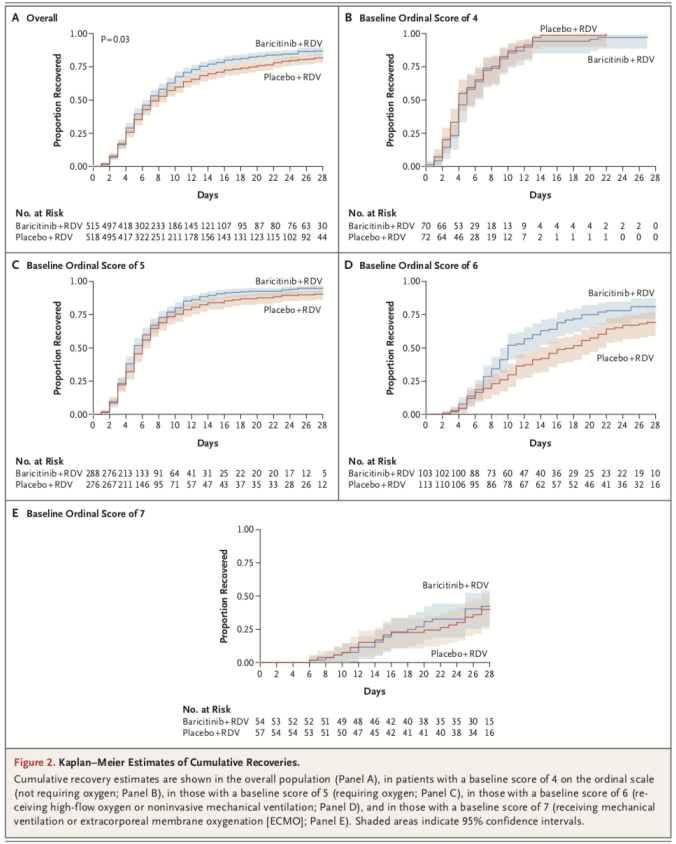


Figure 2. Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

Baricitinib, ACTT-2: Median time to recovery



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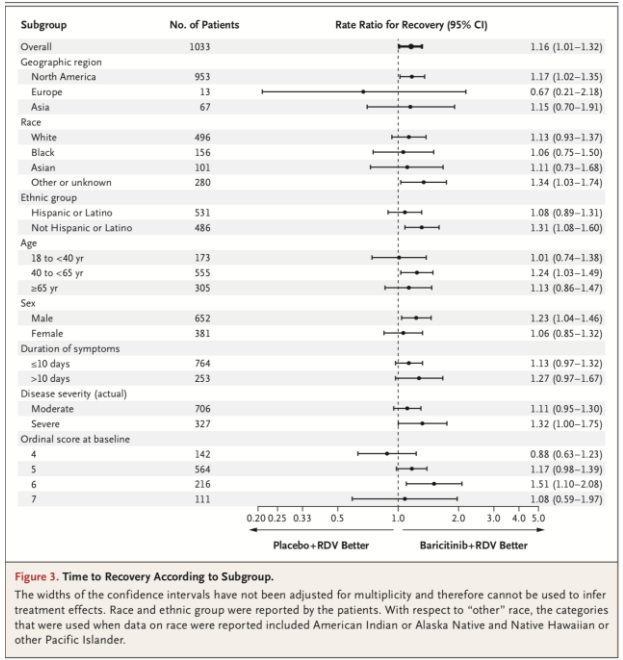
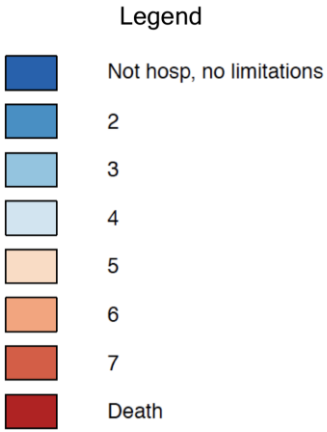


Figure 3. Time to Recovery According to Subgroup.

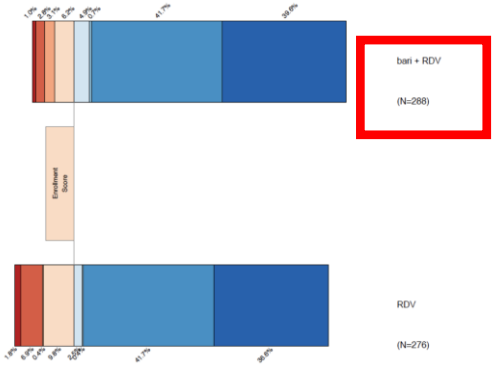
The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

Improved median time to recovery most pronounced in OS6 (high-flow/NIV) – OVERALL: BAR 7 days vs PBO + RDV 8 days
OS6: BAR 10 days vs PBO + RDV 18 days

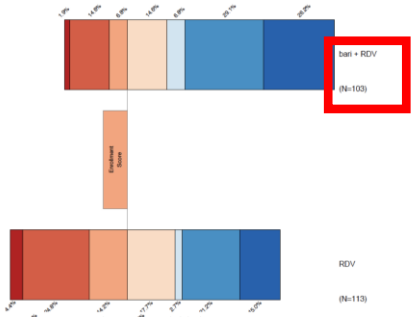
Baricitinib, ACTT-2: Outcomes on day 15 based on baseline severity



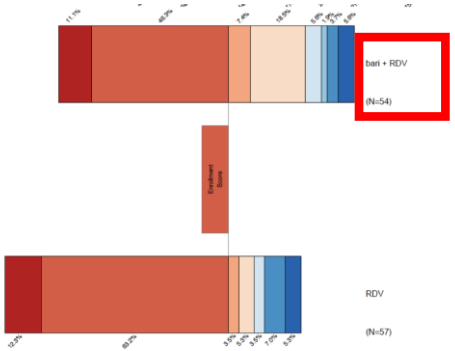
Baseline: OS5 (Nasal canula O2)



Baseline: OS6 - BiPAP



Baseline: OS7 – IMV or ECMO



Baricitinib, ACTT-2: Mortality and safety

Mortality

- Kaplan–Meier estimates of mortality at day 28
  - BAR + RDV: 5.1% vs PBO + RDV: 7.8% (HR 0.65)
  - Study not powered to detect a difference in mortality but both the survival rate and the time-to-death analyses favored combination treatment

Safety

- SAEs: BAR + RDV: 16% vs PBO + RDV: 21%
- 20% of patients who received steroids: Infections (serious/non-serious) 25.1% (56 of 223) vs 5.5% (44 of 793)

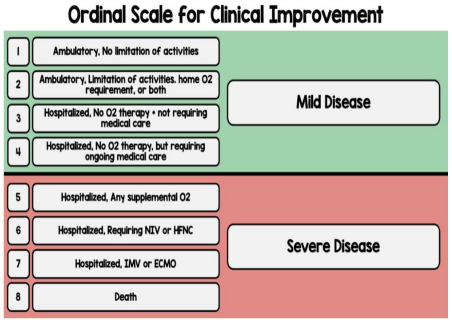
Outcome	Overall	
	Baricitinib (N=515)	Placebo (N=518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)	
No. of deaths by day 14	8	15
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.65 (0.39–1.09)	
No. of deaths by day 28	24	37
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)

Baricitinib, ACTT-2: Reception

- Results were not received with initial acclaim; questionable clinical importance of 1 day of earlier recovery
- Class-related VTE safety concerns (signal not seen in ACTT-2)
- EUA granted 11/19/2020. Initial use in EUA tied to remdesivir which had its skeptics.
- Concern over combining with steroids. Placed initially in niche when tocilizumab unavailable, or as an alternative to dexamethasone – ACTT-4 Study BARI vs DEX started and eventually stopped for futility (though AEs lower in bari than in dex)

Baricitinib, COV-BARRIER: Second pivotal trial

- Phase 3, international, double-blind, placebo-controlled trial comparing baricitinib 4 mg daily or placebo for up to 14 days in COVID-19+ hospitalized patients receiving standard of care (e.g., steroids and antivirals such as remdesivir but not required unlike ACTT-2)
- Hospitalized patients (OS4-6), special amendment: enrollment expanded for OS7 (IMV/ECMO)
- At least one elevated inflammatory marker (CRP, ferritin, d-dimer, LDH) required
- BARI (n= 764) + SOC vs PBO (n = 761) + SOC
- Primary endpoint: progression to high-flow, NIV, IMV, or death by day 28.
- Secondary endpoints: all-cause mortality by day 28, day 60 (exploratory endpoint)



Baricitinib, COV-BARRIER: Demographics

	Baricitinib group (n=764)	Placebo group (n=761)
Age, years		
Mean (SD)	57·8 (14·3)	57·5 (13·8)
<65	508/764 (66%)	518/761 (68%)
≥65	256/764 (34%)	243/761 (32%)
Sex		
Male	490/764 (64%)	473/761 (62%)
Female	274/764 (36%)	288/761 (38%)
Race		
American Indian or Alaskan Native*	148/752 (20%)	168/741 (23%)
Asian	80/752 (11%)	94/741 (13%)
Black or African American	39/752 (5%)	36/741 (5%)
Native Hawaiian or other Pacific Islander	3/752 (<1%)	2/741 (<1%)
White	480/752 (64%)	440/741 (59%)
Multiple	2/752 (<1%)	1/741 (<1%)
Ethnicity†		
Hispanic or Latino	54/162 (33%)	46/158 (29%)
Not Hispanic or Latino	92/162 (57%)	94/158 (59%)
Not reported	16/162 (10%)	18/158 (11%)
Region and country		
Europe	73/764 (10%)	70/761 (9%)
Germany	9/764 (1%)	11/761 (1%)
Italy	15/764 (2%)	10/761 (1%)
Spain	45/764 (6%)	42/761 (6%)
UK	4/764 (1%)	7/761 (1%)
USA (including Puerto Rico)	162/764 (21%)	158/761 (21%)
Rest of world	529/764 (69%)	533/761 (70%)
Argentina	107/764 (14%)	101/761 (13%)
Brazil	172/764 (23%)	165/761 (22%)
India	19/764 (2%)	31/761 (4%)
Japan	19/764 (2%)	19/761 (2%)
South Korea	16/764 (2%)	20/761 (3%)
Mexico	138/764 (18%)	143/761 (19%)
Russia	58/764 (8%)	54/761 (7%)
Body-mass index (kg/m²)	30·4 (6·4)	30·6 (6·6)

(Table 1 continues in next column)

	Baricitinib group (n=764)	Placebo group (n=761)
(Continued from previous column)		
Duration of disease symptoms before enrolment, days		
<7	137/762 (18%)	116/756 (15%)
≥7	625/762 (82%)	640/756 (85%)
Score on NIAID-OS		
4 (hospitalised, not requiring supplemental oxygen)	89/762 (12%)	97/756 (13%)
5 (hospitalised, requiring supplemental oxygen)	490/762 (64%)	472/756 (62%)
6 (hospitalised, receiving non-invasive ventilation or high-flow oxygen)	183/762 (24%)	187/756 (25%)
Concomitant medications of interest		
Remdesivir	140/762 (18%)	147/756 (19%)
Systemic corticosteroids	612/762 (80%)	592/756 (78%)
Dexamethasone	566/612 (92%)	533/592 (90%)
Pre-existing comorbidities of interest		
Obesity	250/764 (33%)	253/761 (33%)
Diabetes (types 1 and 2)	224/764 (29%)	233/761 (31%)
Chronic respiratory disease	34/764 (4%)	36/761 (5%)
Hypertension	365/764 (48%)	366/761 (48%)

Data are mean (SD) or n/N (%). NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale. *Includes participants from Mexico and Latin America. †Reporting required in the USA only.

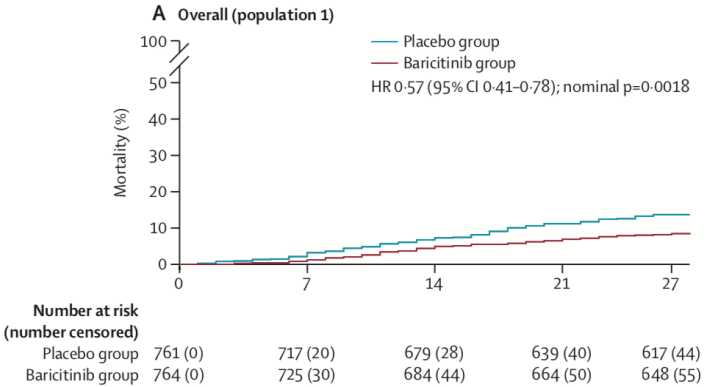
Table 1: **Baseline demographics and clinical characteristics**

~ 20% remdesivir, 80% dex; evenly distributed

Baricitinib, COV-BARRIER: Results

	Baricitinib group (n=764)	Placebo group (n=761)	Baricitinib vs placebo	
			Point estimate (95% CI)	p value*
Primary outcome				
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation (including ECMO), or death, by day 28†				
Population 1‡	27·8%	30·5%	OR 0·85 (0·67 to 1·08)	0·18
Population 2§	28·9%	27·1%	OR 1·12 (0·58 to 2·16)	0·73

Study did not meet primary endpoint (progression to increased O2 support or death), however bari showed 5% absolute reduction in all-cause mortality resulting in NNT=20



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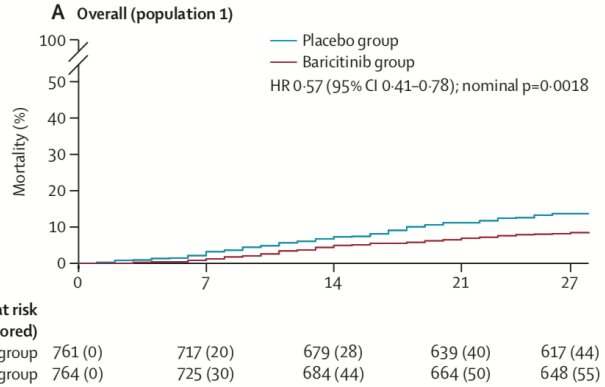
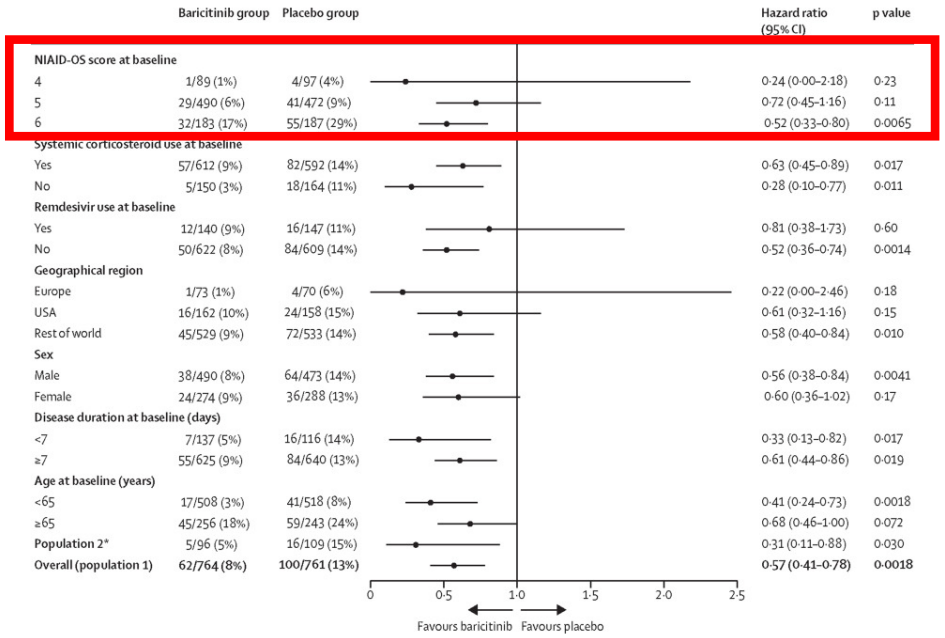
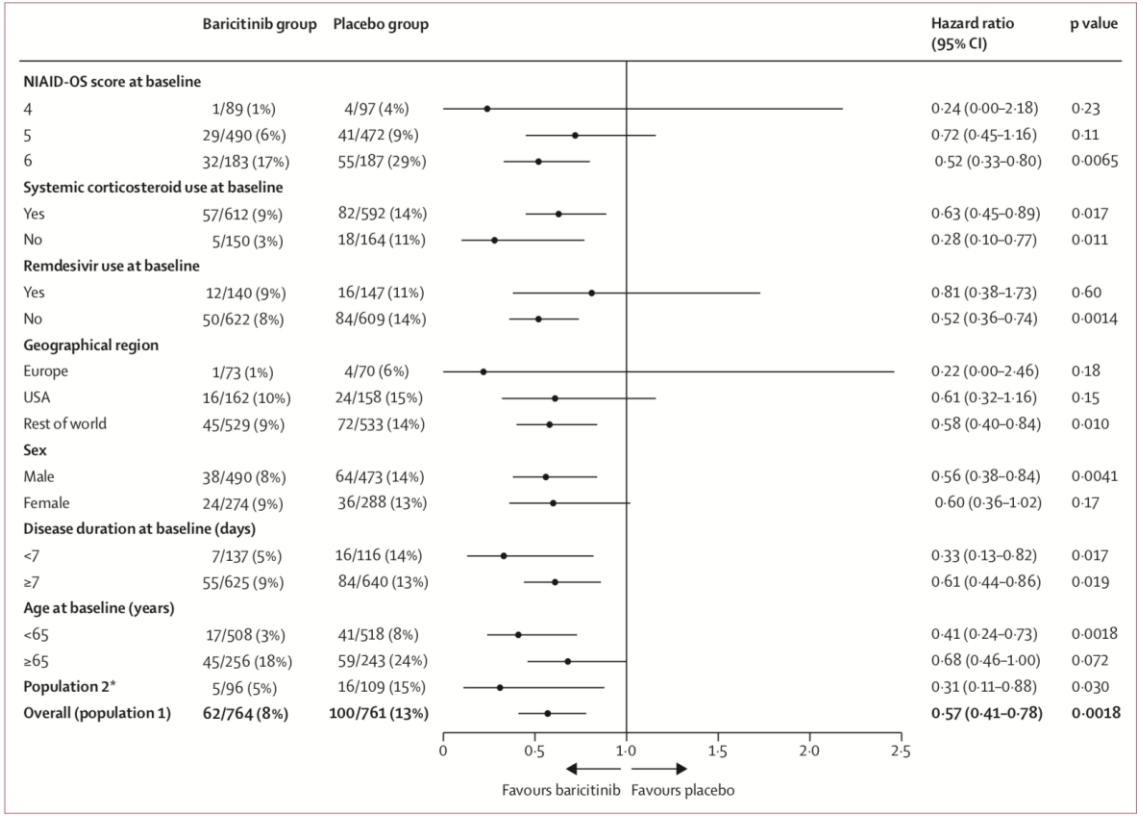




OS6 group NNT=8
Mortality benefit most driven by sickest patients (OS6 – HFNC/BiPAP). Treat 8 patients to save 1 OS6 life.

Baricitinib, COV-BARRIER: Subgroup analysis



	Baricitinib group	Placebo group	Hazard ratio (95% CI)	p value
NIAID-OS score at baseline				
4	1/89 (1%)	4/97 (4%)	0·24 (0·00–2·18)	0·23
5	29/490 (6%)	41/472 (9%)	0·72 (0·45–1·16)	0·11
6	32/183 (17%)	55/187 (29%)	0·52 (0·33–0·80)	0·0065
Systemic corticosteroid use at baseline				
Yes	57/612 (9%)	82/592 (14%)	0·63 (0·45–0·89)	0·017
No	5/150 (3%)	18/164 (11%)	0·28 (0·10–0·77)	0·011
Remdesivir use at baseline				
Yes	12/140 (9%)	16/147 (11%)	0·81 (0·38–1·73)	0·60
No	50/622 (8%)	84/609 (14%)	0·52 (0·36–0·74)	0·0014
Geographical region				
Europe	1/73 (1%)	4/70 (6%)	0·22 (0·00–2·46)	0·18
USA	16/162 (10%)	24/158 (15%)	0·61 (0·32–1·16)	0·15
Rest of world	45/529 (9%)	72/533 (14%)	0·58 (0·40–0·84)	0·010
Sex				
Male	38/490 (8%)	64/473 (14%)	0·56 (0·38–0·84)	0·0041
Female	24/274 (9%)	36/288 (13%)	0·60 (0·36–1·02)	0·17
Disease duration at baseline (days)				
<7	7/137 (5%)	16/116 (14%)	0·33 (0·13–0·82)	0·017
≥7	55/625 (9%)	84/640 (13%)	0·61 (0·44–0·86)	0·019
Age at baseline (years)				
<65	17/508 (3%)	41/518 (8%)	0·41 (0·24–0·73)	0·0018
≥65	45/256 (18%)	59/243 (24%)	0·68 (0·46–1·00)	0·072
Population 2*	5/96 (5%)	16/109 (15%)	0·31 (0·11–0·88)	0·030
Overall (population 1)	**62/764 (8%)**	**100/761 (13%)**	**0·57 (0·41–0·78)**	**0·0018**

Figure 3: **28-day all-cause mortality by subgroup**
HRs and 95% CIs were calculated with a Cox proportional hazards model. The treatment effect was adjusted by all baseline randomisation factors, except when redundant (eg, for age group [<65 or ≥65 years] in the age subgroup analyses). HR=hazard ratio. NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale. *Participants who, at baseline, required oxygen supplementation and were not receiving dexamethasone or other systemic corticosteroids for the primary study condition.

- Clinical status appears to be more important than CRP (resonated with ID/pulm)
- Supports use with concomitant steroids (dex quickly became the SOC), but unclear if really needed – would love to see a trial address this
- Patients who received baseline RDV use did not benefit

Baricitinib, COV-BARRIER addendum – Use in patients with OS7

- Later, COV-BARRIER expanded to include IMV/ECMO (OS7) patients.
- Pre-planned analysis targeting 100 patients. - Mortality and VFDs pre-specified primary endpoints.
- Results published in a later manuscript

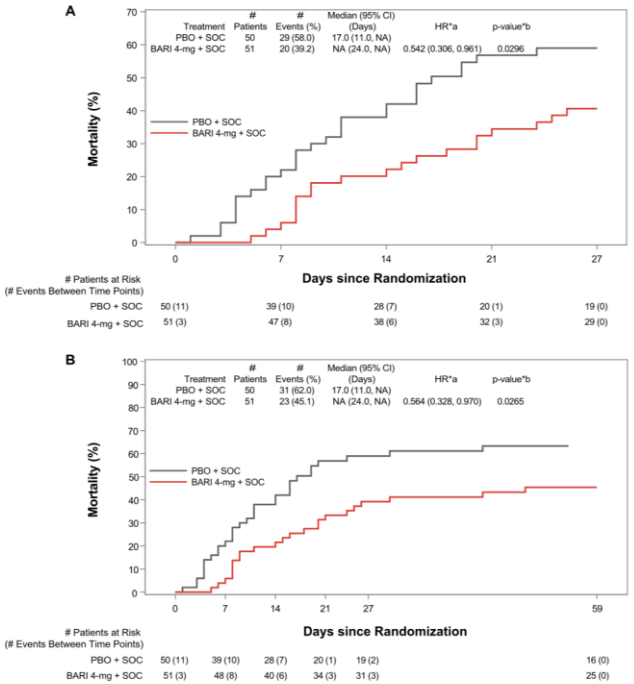


Figure 1: Kaplan-Meier estimates of all-cause mortality (including potentially related with COVID-19 and attributed to adverse events) at Day 28 (A) and Day 60 (B). The numbers at risk at Days 27 and 59 represent the numbers of participants with available data at Days 28 and 60, respectively.
***a HR and 95% CIs were calculated using cox proportional hazard regression model adjusted for age (<65 years, >=65 years), region (United States, rest of world); unstratified.**
***b p-value was calculated from unstratified log-rank test.**
BARI, baricitinib; CI, confidence interval; HR, hazard ratio; NA, not applicable; PBO, placebo; SOC, standard of care.

28 DAY MORTALITY
NNT = 5

60 DAY MORTALITY
NNT=6

Baricitinib, COV-BARRIER: Safety

OS4-6

	Baricitinib group (n=750)	Placebo group (n=752)
Treatment-emergent adverse event	334 (45%)	334 (44%)
Mild	133 (18%)	115 (15%)
Moderate	90 (12%)	89 (12%)
Severe	111 (15%)	130 (17%)
Death due to adverse event*	12 (2%)	31 (4%)
Serious adverse event	110 (15%)	135 (18%)
Discontinuation from study treatment due to adverse event (including death)	56 (7%)	70 (9%)
Treatment-emergent infection	119 (16%)	123 (16%)
Serious infections	64 (9%)	74 (10%)
Herpes simplex	1 (<1%)	4 (1%)
Herpes zoster	1 (<1%)	4 (1%)
Tuberculosis	1 (<1%)	0
Opportunistic infections	6 (1%)	7 (1%)
Candida infection	1 (<1%)	0
Eye infection, fungal	0	1 (<1%)
Fungal retinitis	1 (<1%)	0
Herpes zoster	1 (<1%)	3 (<1%)
Listeriosis	0	1 (<1%)
Oropharyngeal candidiasis	0	1 (<1%)
Pulmonary tuberculosis	1 (<1%)	0
Systemic Candida	2 (<1%)	0
Varicella zoster virus infection	0	1 (<1%)
Venous thromboembolic event†	20 (3%)	19 (3%)
Deep vein thrombosis	4 (1%)	2 (<1%)
Pulmonary embolism	13 (2%)	9 (1%)
Other peripheral venous thrombosis	8 (1%)	10 (1%)
Major adverse cardiovascular event	8 (1%)	9 (1%)
Cardiovascular death	1 (<1%)	3 (<1%)
Myocardial infarction	4 (1%)	4 (1%)
Stroke	4 (1%)	4 (1%)
Gastrointestinal perforation	0	0

Data are n (%). Data were assessed from days 1–28. *Included in overall mortality together with deaths due to disease progression. †Positively adjudicated by an independent external blinded clinical event committee.

***Table 3*: Adverse events in the safety population**

Baricitinib, COV-BARRIER: Safety

OS4-6

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Table 3: **Adverse events in the safety population**

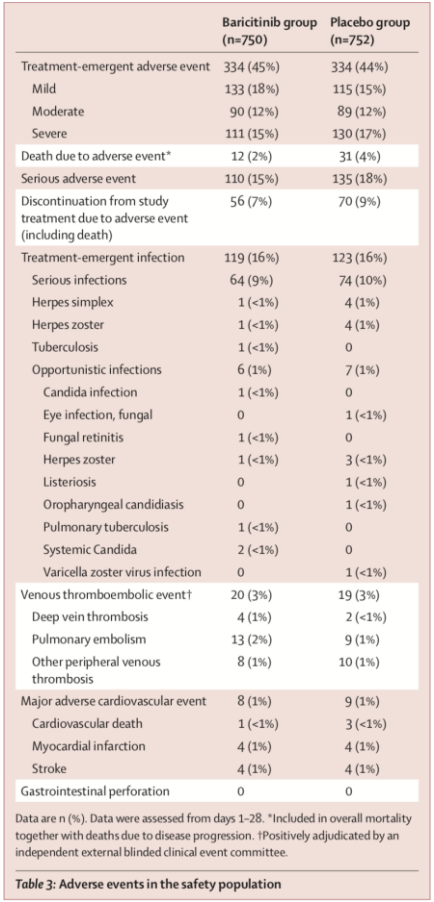
Table S11. Safety overview by baseline systemic corticosteroid use

	Placebo + SOC (N=752)		Baricitinib 4-mg + SOC (N=750)	
Baseline systemic corticosteroid use	Yes (N-obs=590)	No (N-obs=162)	Yes (N-obs=605)	No (N-obs=145)
Treatment-emergent adverse event	269 (45.6)	65 (40.1)	259 (42.8)	75 (51.7)
Death due to adverse event	27 (4.6)	4 (2.5)	11 (1.8)	1 (0.7)
Serious adverse event	112 (19.0)	23 (14.2)	95 (15.7)	15 (10.3)
Treatment-emergent infection	100 (16.9)	23 (14.2)	101 (16.7)	18 (12.4)
Serious infections	63 (10.7)	11 (6.8)	58 (9.6)	6 (4.1)

Data are n (%). N=number of participants in the analysis population. N-obs=number of participants in the analysis. n=number of participants in the specified category.

Baricitinib, COV-BARRIER: Safety

OS4-6



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Death due to adverse event	27 (4.6)	4 (2.5)	11 (1.8)	1 (0.7)
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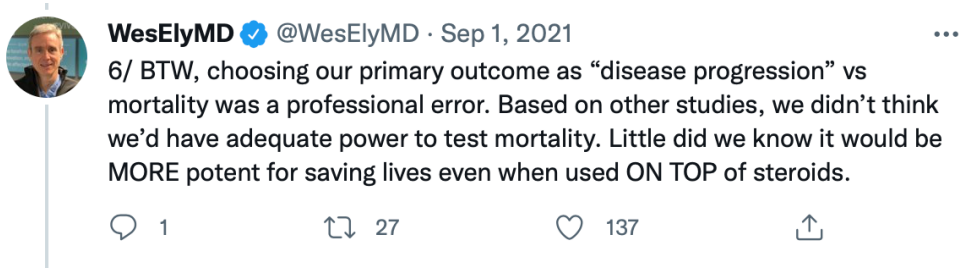
OS7

Adverse Events[b] Data are presented as n (%) unless otherwise specified	Placebo + SOC (N= 49)	Baricitinib + SOC (N= 50)	Total (N=99)
Treatment-emergent adverse event[c] (TEAE)	47 (95.9)	44 (88.0)	91 (91.9)
Mild	3 (6.1)	3 (6.0)	6 (6.1)
Moderate	11 (22.4)	17 (34.0)	28 (28.3)
Severe	33 (67.3)	24 (48.0)	57 (57.6)
Death due to AE[d]	3 (6.1)	5 (10.0)	8 (8.1)
Serious adverse event	35 (71.4)	25 (50.0)	60 (60.6)
Discontinuation from study treatment due to AE (including death)	17 (34.7)	14 (28.0)	31 (31.3)
VTE[e]	3 (6.1)	3 (6.0)	6 (6.1)
DVT	2 (4.1)	1 (2.0)	3 (3.0)
PE	0	2 (4.0)	2 (2.0)
Other peripheral venous thrombosis	1 (2.0)	1 (2.0)	2 (2.0)

COV-BARRIER: Strengths, limitations, and reception

- Do non-mortality primary endpoints matter?



- Large, well-done double-blind placebo-controlled RCT
- Emphasis on clinical subgroups >> inflammatory markers
- Well-powered – OS6 (bipap) – treat 8 to save 1 life; OS7 (IMV) – treat 5 to 6
- Clear data on adding onto dexamethasone. Remdesivir did not add much
- Clear data on safety, especially VTE
- Based on study, EUA use changed (ok to use with dex, ok to use without remdesivir)

Baricitinib, COV-BARRIER: Our experience

- How I got involved
- How we ran the study successfully in a community-based setting
- How it changed my clinical trial career

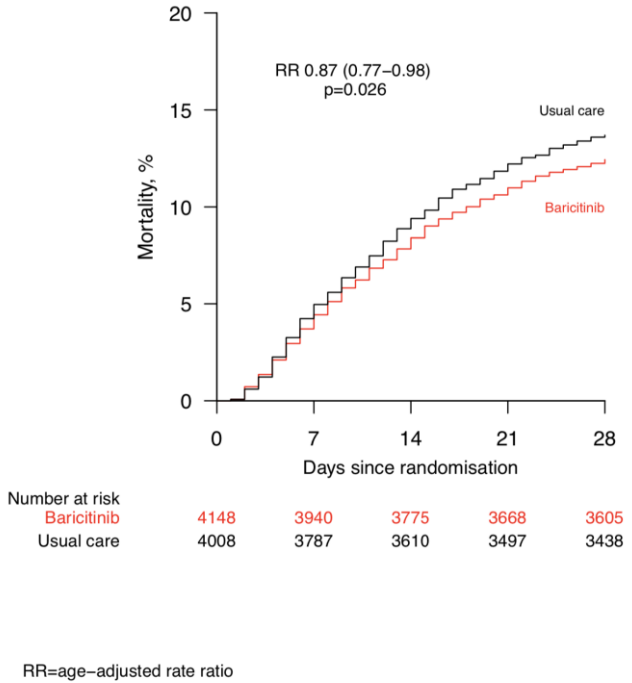
RECOVERY-bari

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- Randomized, controlled, open-label platform trial assessing multiple possible treatments for patients hospitalized for COVID-19. Preprint only, awaiting manuscript
- Hypoxic hospitalized inpatients randomized to receive usual care plus baricitinib 4 mg/day x 10 days/discharge (n=4148) vs placebo (n=4008)
- Primary endpoint was mortality at day 28
- Prior or subsequent administration of tocilizumab was permitted at the discretion of the managing doctor (!)
- 95% of patients were receiving corticosteroids; *23% receiving tocilizumab (with planned use within the next 24 hours recorded for a further 9%*

RECOVERY-bari: Results

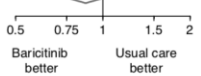
Figure 2: Effect of allocation to baricitinib on 28–day mortality



RR=age–adjusted rate ratio

Figure 3: Effect of allocation to baricitinib on 28–day mortality by pre–specified baseline characteristics

	Baricitinib	Usual care	RR (95% CI)
Age, years (χ^2_1= 1.7; p=0.19)			
<70	225/3142 (7%)	269/3086 (9%)	0.81 (0.68–0.97)
≥ 70 <80	158/665 (24%)	175/655 (27%)	0.87 (0.70–1.08)
≥ 80	130/341 (38%)	102/267 (38%)	1.01 (0.78–1.31)
Sex (χ^2_1= 0.0; p=0.91)			
Men	351/2740 (13%)	371/2638 (14%)	0.88 (0.76–1.01)
Women	162/1408 (12%)	175/1370 (13%)	0.86 (0.70–1.07)
Ethnicity (χ^2_1=0.1; p=0.73)			
White	437/3192 (14%)	443/3104 (14%)	0.92 (0.81–1.05)
Black, Asian and Minority Ethnic	40/457 (9%)	45/455 (10%)	0.85 (0.56–1.30)
Unknown	36/499 (7%)	58/449 (13%)	0.53 (0.35–0.81)
Days since symptom onset (χ^2_1= 0.2; p=0.62)			
≤ 7	255/1495 (17%)	262/1451 (18%)	0.90 (0.76–1.07)
>7	257/2649 (10%)	284/2556 (11%)	0.85 (0.71–1.00)
Respiratory support at randomisation (χ^2_1= 0.9; p=0.33)			
None	15/228 (7%)	19/237 (8%)	0.78 (0.39–1.53)
Simple oxygen	256/2770 (9%)	253/2743 (9%)	0.94 (0.79–1.12)
Non invasive ventilation	204/1016 (20%)	230/911 (25%)	0.75 (0.62–0.90)
Invasive mechanical ventilation	38/134 (28%)	44/117 (38%)	0.90 (0.58–1.39)
Use of corticosteroids (χ^2_1= 0.7; p=0.41)			
Yes	487/3962 (12%)	523/3809 (14%)	0.86 (0.76–0.97)
No	25/183 (14%)	22/197 (11%)	1.09 (0.62–1.92)
All participants	**513/4148 (12%)**	**546/4008 (14%)**	**0.87 (0.77–0.98) p=0.026**



Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The days since onset and use of corticosteroids subgroups exclude patients with missing data, but these patients are included in the overall summary diamond.
RR=age adjusted rate ratio.

- "No significant excess in death or infection due to non-COVID-19 causes and no excess of thrombosis, or other safety outcomes"
- Toci+bari tolerated fine but no real additional benefit

Baricitinib in COVID-19: Package insert highlights

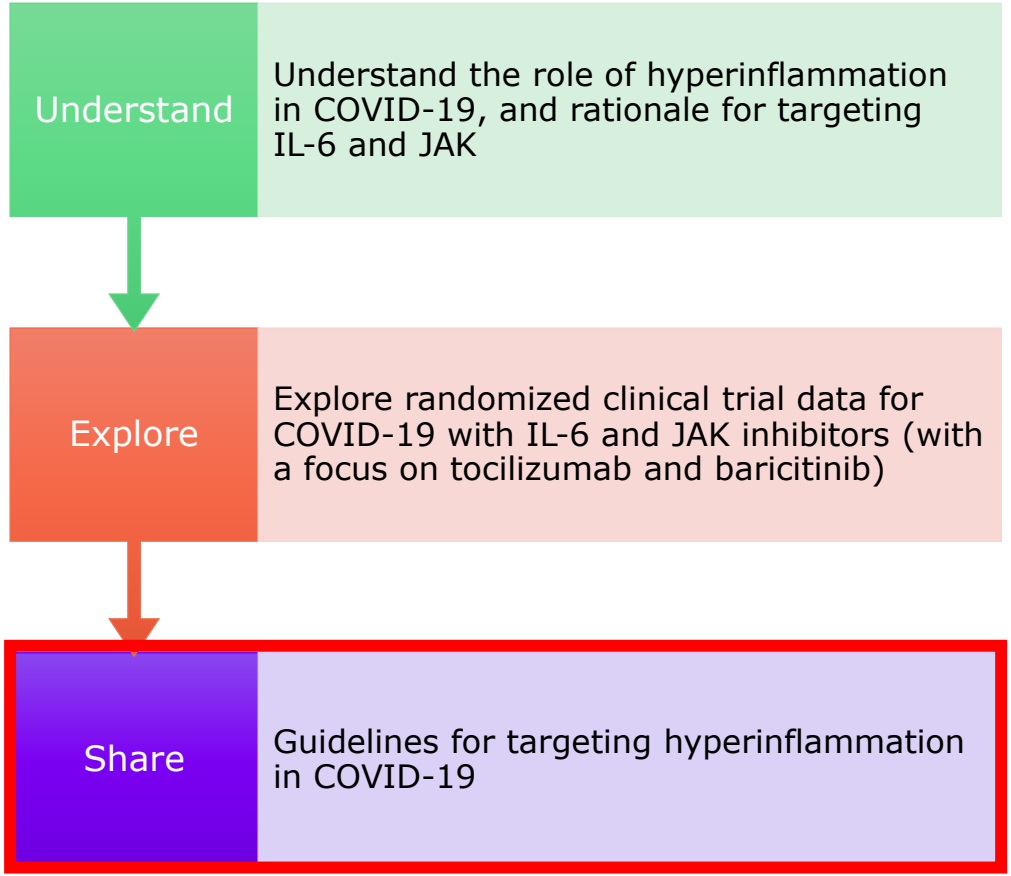
Indication: COVID-19 treatment in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. (EUA remains in place kids 2+)

Dosage: 4 mg orally daily for up to 14 days. Dose reduction for renal failure; do not use eGFR <15 mL/min/1.73m2 (vs gfr 30 for RA/Alopecia). May be crushed and used through NG tube.

Monitoring:

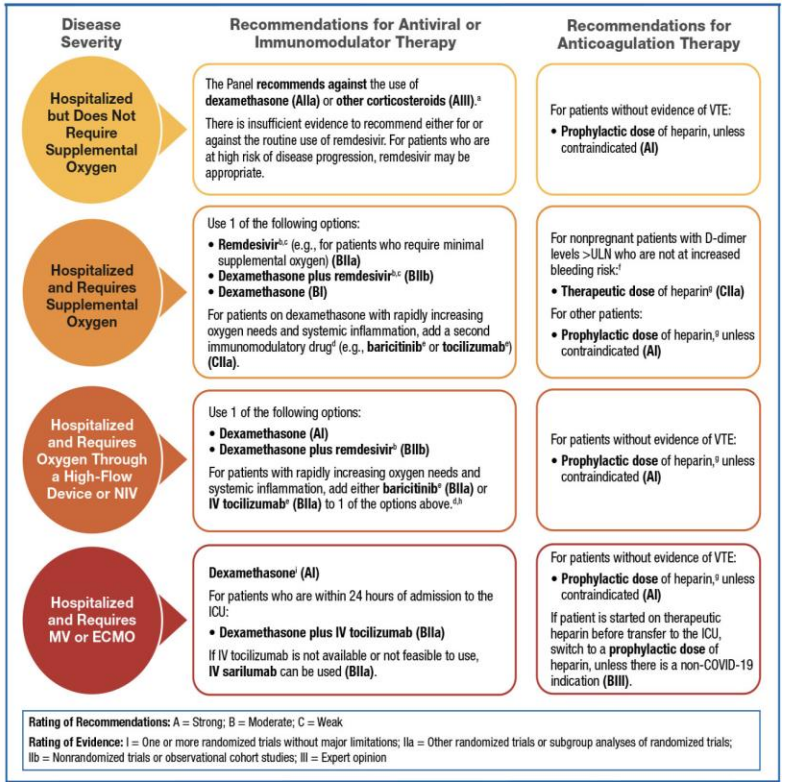
- Latent TB testing not required for COVID-19
- Avoid initiation or interrupt baricitinib in patients with lymphopenia (ALC <200 cells/mm3) or neutropenia (ANC <500 cells/mm3)
- If increases in ALT or AST are observed and drug-induced liver injury is suspected, interrupt OLUMIANT until this diagnosis is excluded
- Patients with symptoms of thrombosis should discontinue drug and be promptly evaluated
- In patients with COVID-19, monitor for signs and symptoms of new infections during and after treatment with OLUMIANT. There is limited information regarding the use of OLUMIANT in patients with COVID-19 and concomitant active serious infections. The risks and benefits of treatment with OLUMIANT in COVID-19 patients with other concurrent infections should be considered.

Outline


Understand
Understand the role of hyperinflammation in COVID-19, and rationale for targeting IL-6 and JAK
Explore
Explore randomized clinical trial data for COVID-19 with IL-6 and JAK inhibitors (with a focus on tocilizumab and baricitinib)
Share
Guidelines for targeting hyperinflammation in COVID-19

Guidelines – NIH (updated 4/8/22) vs IDSA (updated 6/29/22)

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity



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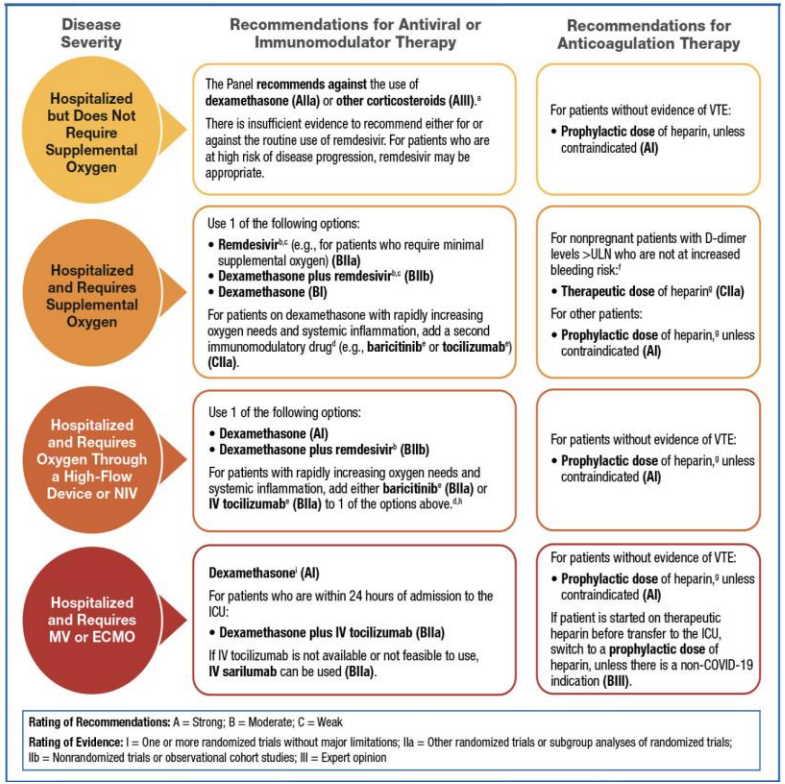

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

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

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

Overview of IDSA COVID-19 Treatment Guidelines

Version 9.0.0 – June 10, 2022 – INCLUDES UPDATE ALERT FOR COLCHICINE (released 7/7/2022)

	Pre- and post-exposure prophylaxis: *healthy people w/o symptoms or diagnosis*	***Ambulatory care:*** *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (SpO_2 ≤94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
Baricitinib + corticosteroids	NA	NA	NA	**Suggest use** ⊕⊕⊕◯ **R:** Baricitinib 4 mg per day (or appropriate renal dosing) up to 14 days or until discharge from hospital. **R:** Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline. **R:** Limited additional data suggest a mortality reduction even among patients requiring mechanical ventilation.	NA
Tocilizumab	NA	NA	NA	**Suggest use** ⊕⊕◯◯ **R:** Patients, particularly those who response to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab. **R:** In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L	**Suggest use** ⊕⊕◯◯ **R:** Patients, particularly those who response to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab. **R:** In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L

Certainty of evidence

⊕⊕⊕⊕ high

⊕⊕⊕◯ moderate

⊕⊕◯◯ low

⊕◯◯◯ very low

Conclusions

- Hyperinflammation recognized early in COVID-19, and rheumatic drugs of high interest as possible treatments – leading to shortages for tocilizumab in our practices
- Heterogeneity in study design and mixed results (particularly with tocilizumab)
- Tocilizumab, when showing benefit in trials, required background steroids. Safety in RCTs overall reassuring
- Baricitinib effect more consistent across studies, pronounced effect in OS6 (high flow O2/BiPAP). Unclear need for steroids. Safety (VTE/infection) overall reassuring. FDA approved for adult inpatients requiring oxygen
- Implications for blocking infection related inflammation beyond COVID-19? Other causes of ARDS? Suspect there will be much more to follow…

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Thank you

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