TAMING THE IMMUNE SYSTEM IN COVID-19

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POTENTIAL CONFLICT OF INTEREST

I have read and understood ICMJE policy on declaration of interest and I declare that in the past five years

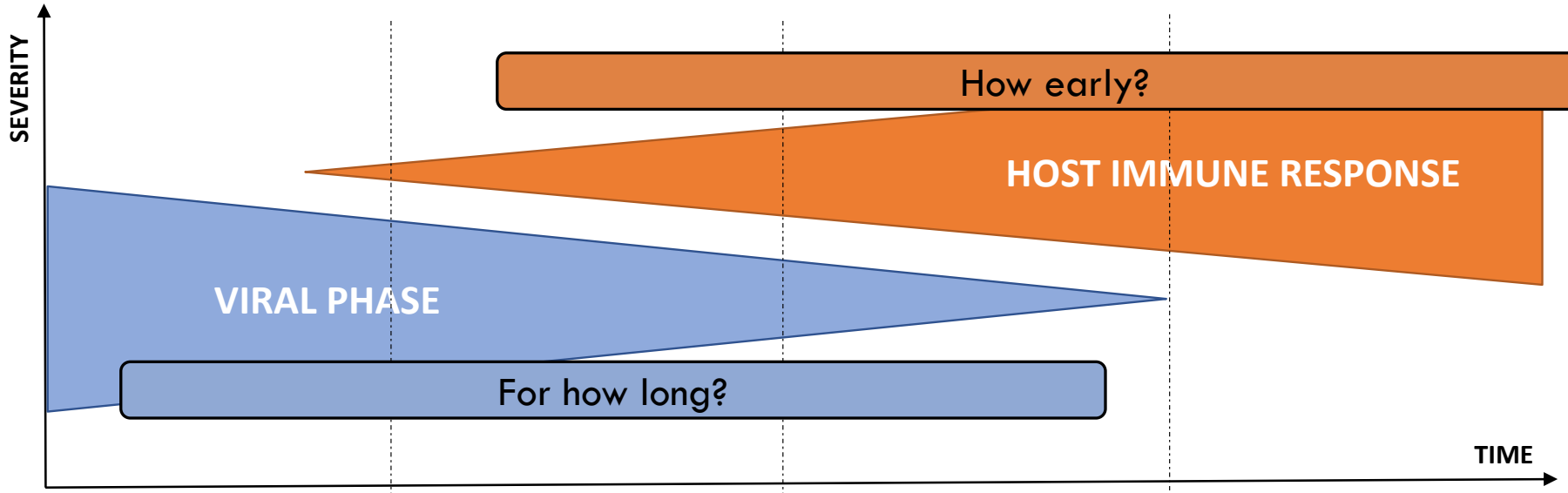
- My Institution has received research grants from Abbvie, Gilead, BMS, Janssen-Cilag and ViiV;
- I received speaker's and consultancy honoraria from Gilead, Insmed, Janssen-Cilag, MSD and ViiV.

TRUE SCIENCE TEACHES, ABOVE ALL, TO DOUBT AND TO BE IGNORANT.

Miguel de Unamuno

COVID-19 - PATHOGENESIS

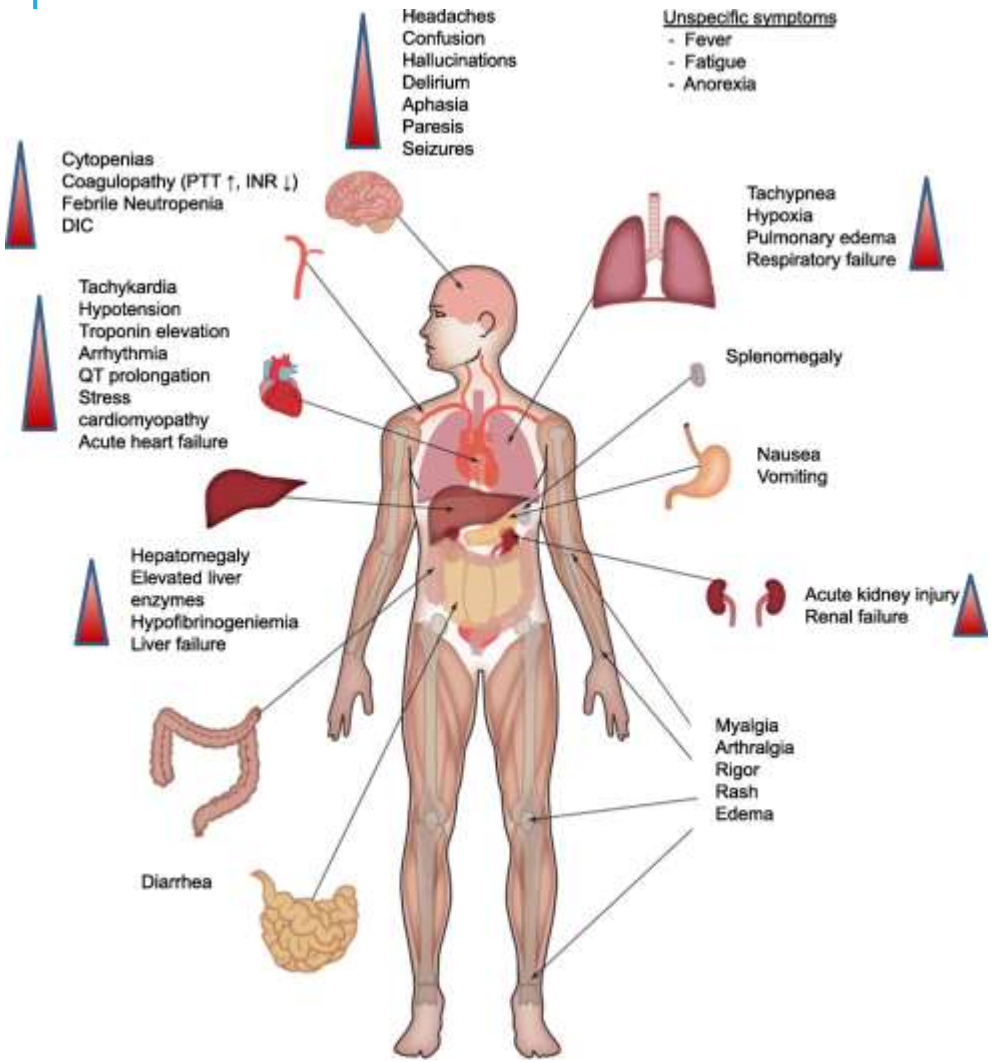
Biomarker Trehsolds??



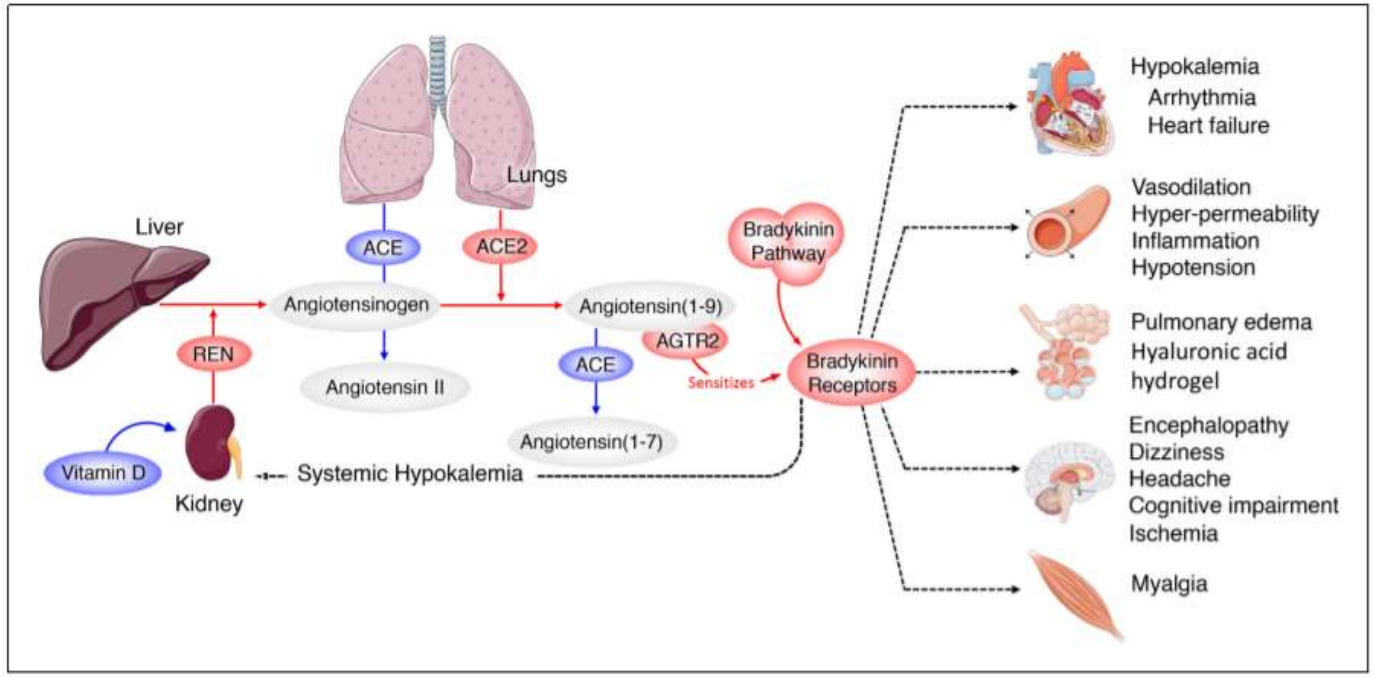
SIGNS & SYMPTOMS	Asymptomatic, fever <37.5°C, diarrhea, headache, asthenia, anosmia and ageusia, conjunctivitis		Dry cough, fever >37,5°C, arthro-myalgia	Shortness of breathe, Hypoxia, arrythmia	ARDS, SIRS, Shock, MOF, cardiac failure, MAS /HLH (Enlarged liver/spleen/lymph nodes), skin rash, Easy bruising and/or abnormal bleeding, fever >38.5°C.
LAB	Normal routine lab tests, mild lymphopenia, normal blood gas		Increasing lymphopenia, mild increase of PT and/or ferritin and/or D-Dimer and/or LDH, mild hypoxia >92	progressive increase of d-dimer and ferritin, increase transaminases and triglycerides, abnormal blood gas (hypoxia <92-hypocapnia etc.), mild increase NT-proBNP and troponin, IL6, CRP, reduction of platelet count	Elevation of inflammatory markers and ferritin, progressive cytopenias, increase in NT-proBNT, troponin and renal function markers
LUNG US	Normal	Localized B-lines	Diffuse B-lines – pleural line thickening	Diffuse B-lines – pleural line thickening – Subpleural consolidation, localized pleural effusion	Diffuse B-lines – pleural line thickening – Subpleural and alveolar consolidation – air bronchograms
CT SCAN	Normal	Localized supleural ground glass	Ground glass		Crazy paving

"RheumaPain Academy" available at http://www.rheumapainacademy.com/wp-content/uploads/2020/03/Algoritmo-COVID19.pdf.

Cytokine Release Syndrome

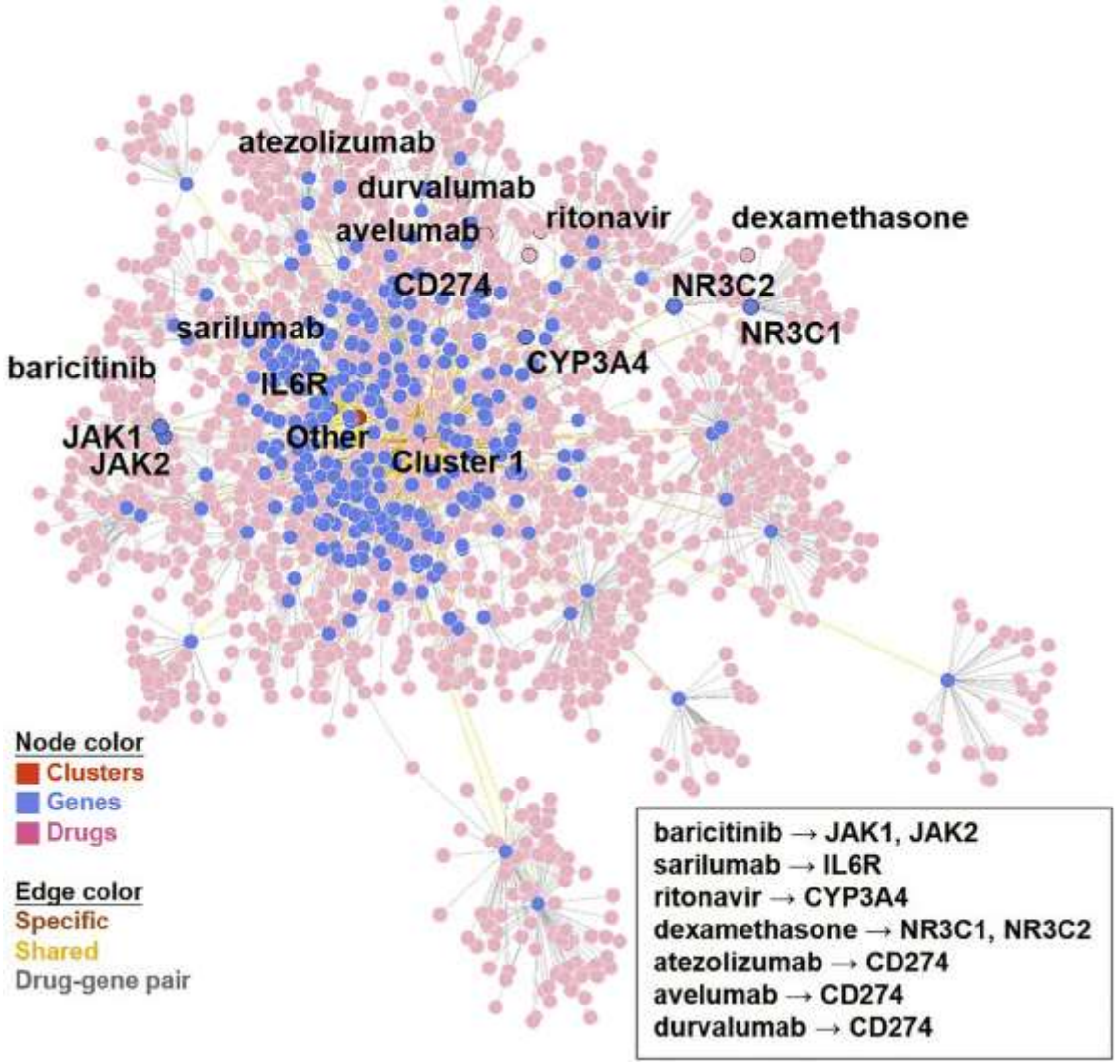


Bradykinin Storm Syndrome



Shimabukuro-Vornhagen A, et al. J Immun Ther Cancer 2018; Garvin MR et al. eLife 2020;9:e59177

TRANSCRIPTOME NETWORK ANALYSIS



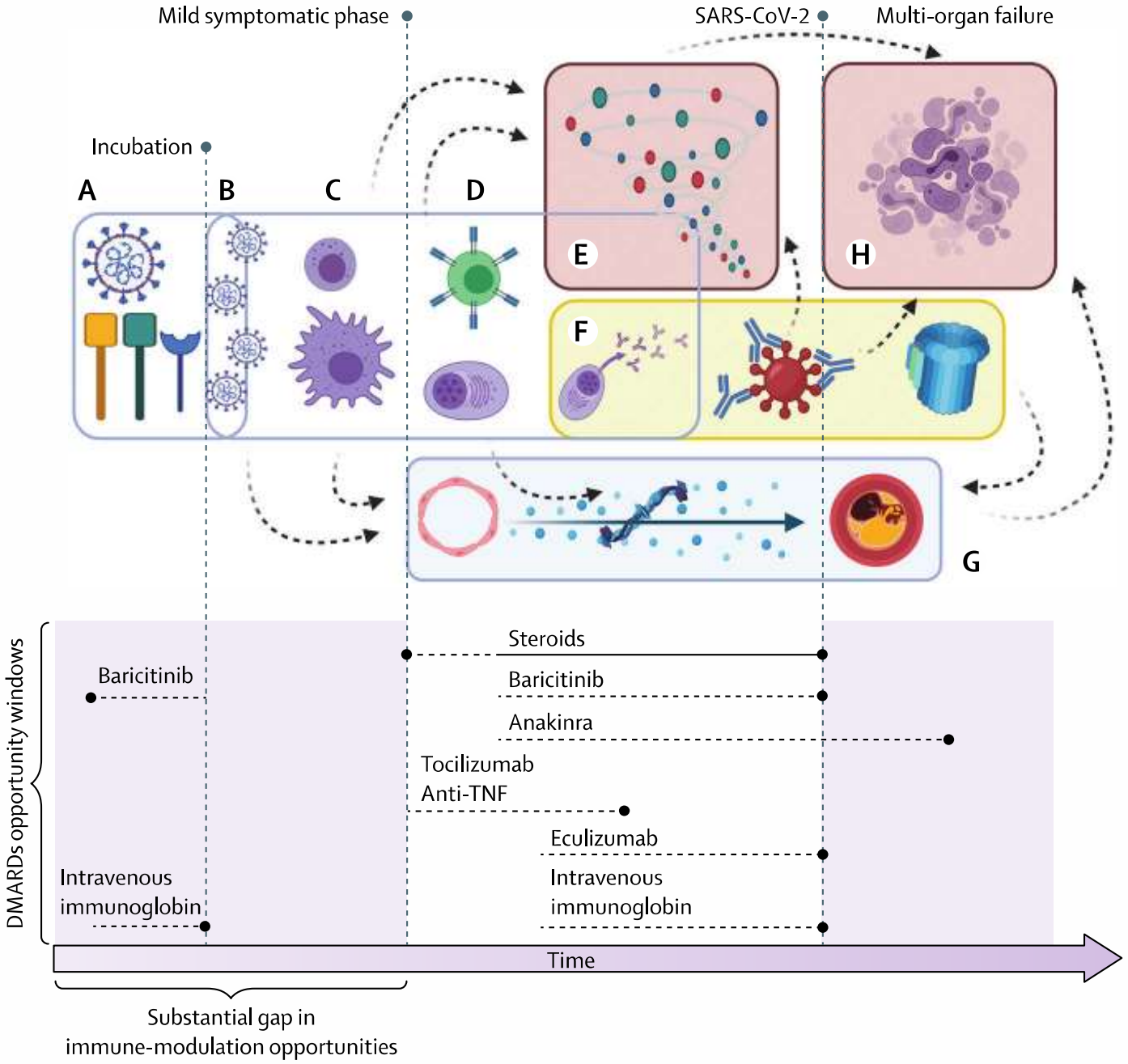
Wong HS, et al. Genomics 2021

THE ROLE OF ANTIRHEUMATICS IN PATIENTS WITH COVID-19

NISSEN CB, ET AL. LANCET RHEUMATOL 2021

	Caricchio R et al (2020)*[13]	Webb BJ et al (2020)†[14]
Signs or symptoms of COVID-19	Presence of any COVID-19 signs or symptoms	Fever >38·0°C
Diagnostic test for COVID-19	RT-PCR positive for COVID-19	..
HRCT or chest x-ray	+Ground Glass Opacities by HRCT or chest X-ray	..
Ferritin	>250 µg/L	≥700 µg/L
C-reactive protein	>4·6 mg/dL	≥15 mg/dL (or IL-6 ≥15 pg/mL or triglyceride ≥150 mg/dL)
Albumin	<2·8 g/dL	..
Lymphocytes (%)	<10·2	Neutrophil to lymphocyte ratio ≥10 cells (or both haemoglobin ≤9·2 g/dL and platelet count [<11 400 cells per µL])
Neutrophils (absolute)	≤110 000 cells per µL	..
Alanine aminotransferase	>60 U/L	..
Aspartate aminotransferase	>87 U/L	..
D-dimers	>4930 ng/mL	≥1500 ng/mL
Lactate dehydrogenase	>416 U/L	≥400 U/L (or AST ≥100 U/L)
Troponin I	>1·09 ng/mL	..
Anion gap	<6·8 mmol/L	..
Chloride	>106 mmol/L	..
Potassium	>4·9 mmol/L	..
BUN to creatinine ratio	>29	..

Entry criteria Cluster 1 Cluster 2 Cluster 3



TREATMENT OF HOSPITALIZED PATIENTS IN

- **Early recognition of high-risk patients with pneumonia**
- **High flow nasal cannula and CPAP/NIV**
  - Pronation
  - Late intubation
- **Low molecular weight heparin**
  - Prophylactic in all patients (potential antiviral effect and prevention of thrombotic complications) 4000/6000 units of enoxaparin (according to weight)
  - Anticoagulant in critical/severe cases (enoxaparin 50→100 UI/Kg x2)?
- **Antivirals**
  - Remdesivir
  - Monoclonal antibodies
- **Antibiotics/Antifungals**
  - If proven/suspected co-infection
- **Anti-inflammatory agents**
  - Dexamethasone 6 mg for 5-10 days in those requiring oxygen
  - Tocilizumab
  - Anakinra?
  - Baricitinib?

CORTICOSTEROIDS

	Mortality	Mechanical ventilation	Adverse events	Admission to hospital	Viral clearance at 7 days‡	Duration of hospital stay	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance	Ventilator free days‡
Standard care*	130 per 1000	116 per 1000	9 per 1000	51 per 1000	500 per 1000	13 days	13 days	15 days	11 days	7 days	12 days
ACEi/ARB	-4 (-59 to 83)	-16 (-55 to 44)	8 (-5 to 58)†			-1.9 (-5.7 to 1.8)					
Anakinra		21 (-52 to 155)									
Anticoagulants	-2 (-33 to 34)										
Azithromycin	-4 (-25 to 21)	-6 (-33 to 28)				-0.9 (-1.7 to 0.3)†					-1.2 (-4.3 to 2.0)
Colchicine	-78 (-110 to -5)	-57 (-90 to 2)		-11 (-34 to 12)		-1.7 (-2.8 to -0.7)†					
Corticosteroids	-20 (-36 to -3)	-25 (-44 to -7)			-82 (-269 to 111)	-0.3 (-1.7 to 1.3)		-1.4 (-3.4 to 0.7)			2.6 (0.3 to 5.0)
Doxycycline + ivermectin	-130 (-130 to -123)		34 (-7 to 547)†								
Favipiravir	-41 (-113 to 207)	-14 (-74 to 120)	2 (-7 to 47)†		50 (-96 to 193)	-1.3 (-2.4 to -0.1)†			-4.3 (-5.9 to -2.14)	-0.6 (-3.2 to 4.2)	
Hydroxy-chloroquine	10 (-8 to 30)	15 (-9 to 45)	8 (-1 to 27)†	-10 (-31 to 26)	2 (-93 to 109)	0.1 (-1.8 to 2.0)			-1.5 (-3.0 to 0.2)	-0.9 (-2.9 to 2.1)	-1.4 (-4.9 to 2.2)
Hydroxy-chloroquine + azithromycin	-42 (-96 to 53)	54 (-22 to 174)	9 (-5 to 60)	-1 (-35 to 83)	-35 (-211 to 154)	0.4 (-1.4 to 2.1)†					
IL-6i	-15 (-30 to 6)	-30 (-46 to -10)	-4 (-9 to 67)†			-4.3 (-8.1 to -0.5)†			-0.7 (-2.7 to 1.7)		1.6 (-0.2 to 3.3)
Interferon beta	2 (-34 to 28)	-7 (-40 to 32)				-0.4 (-1.9 to 1.0)†			-1.8 (-4.0 to 1.0)		
Interferon gamma					419 (41 to 497)						
Interferon kappa + treefoil factor 2					284 (-54 to 451)						
Ivermectin	-103 (-117 to -78)	-54 (-100 to 80)	26 (-2 to 187)	-32 (-47 to 23)	118 (-13 to 241)	-0.5 (-1.7 to 1.1)†			-0.4 (-3.7 to 3.5)	-2.0 (-4.4 to 2.4)	
JAKi	-50 (-84 to 0)	-46 (-74 to -5)				-1.5 (-3.0 to 0.1)†		-3.8 (-7.5 to -0.1)†	-1.0 (-3.8 to 2.8)		
Lopinavir-ritonavir	3 (-17 to 25)	10 (-16 to 41)	46 (9 to 197)	-17 (-39 to 37)	-20 (-165 to 98)	0.7 (-1.1 to 2.7)†			0.1 (-2.5 to 3.5)		
Lopinavir-ritonavir + interferon b1a	62 (-20 to 176)	41 (-17 to 125)	136 (31 to 506)		-93 (-296 to 143)	5.0 (3.7 to 6.3)†			1.2 (-2.8 to 6.9)		
Nitazoxanide			63 (-3 to 725)	0 (-39 to 151)	159 (-97 to 350)						
Peginterferon lambda					206 (-142 to 418)						
Proxalutimide	-130 (-130 to -118)	-116 (-116 to -111)		-50 (-51 to -38)†							
rhG-CSF	-102 (-124 to -43)	-96 (-107 to -76)				-0.7 (-1.8 to 0.5)†			-0.8 (-4.6 to 5.2)		
Remdesivir	-11 (-33 to 12)	-26 (-51 to -2)	1 (-6 to 26)		13 (-242 to 262)	0.4 (-0.1 to 1.4)†		-1.3 (-4.3 to 1.5)	-2.0 (-4.1 to 0.7)		
Sulodexide	-78 (-119 to 50)	-62 (-105 to 81)	3 (-7 to 65)	-24 (-41 to 20)							
Umifenovir	794 (-130 to 870)										
Vitamin C	-50 (-89 to 22)	17 (-41 to 110)				-1.6 (-3.3 to 1.3)†					
Vitamin D	-11 (-86 to 150)	-63 (-96 to 7)				0 (-1.2 to 1.2)†					

*The expected risk of each outcome with standard care is reported in the grey row. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
† The best estimate of effect was obtained from direct evidence
‡ For this outcome, higher risk/mean is a benefit
Empty cells: there was no evidence for the specific intervention
IL-6i: Interleukin 6 inhibitors (tocilizumab, sarilumab); JAKi: Janus kinase inhibitors (baricitinib, ruxolitinib); rhG-CSF: Recombinant human granulocyte colony-stimulating factor

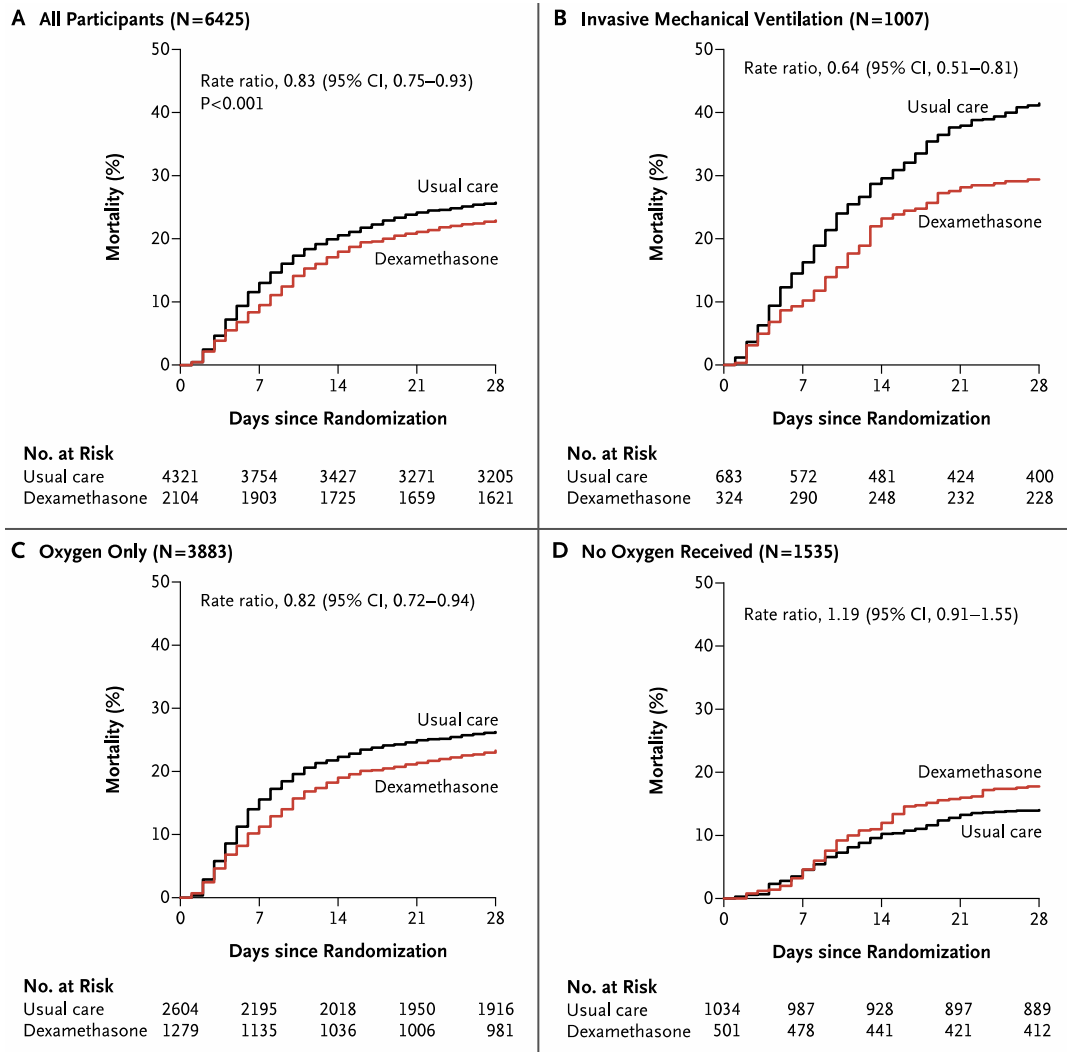
https://www.bmj.com/content/370/bmj.m2980

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

- 2104 vs. 4321
- Oral or iv dexamethasone 6 mg/day up to 10 days (median 7 days, IQR 3-10)



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

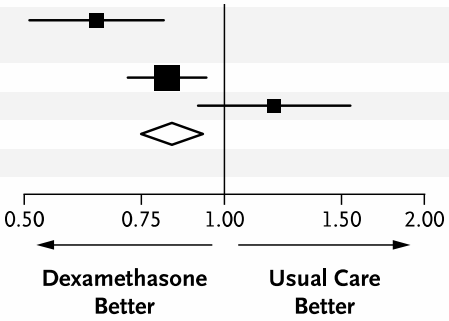


Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

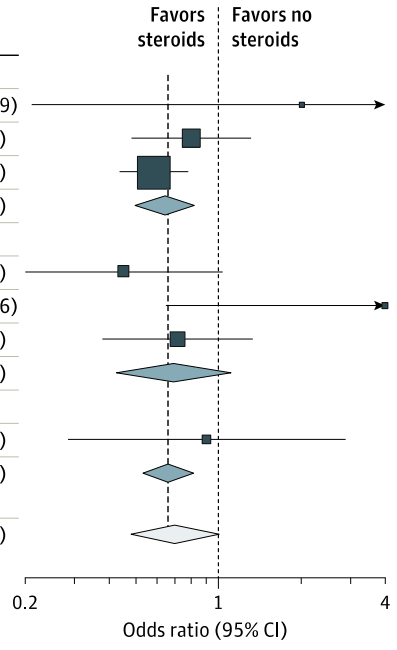
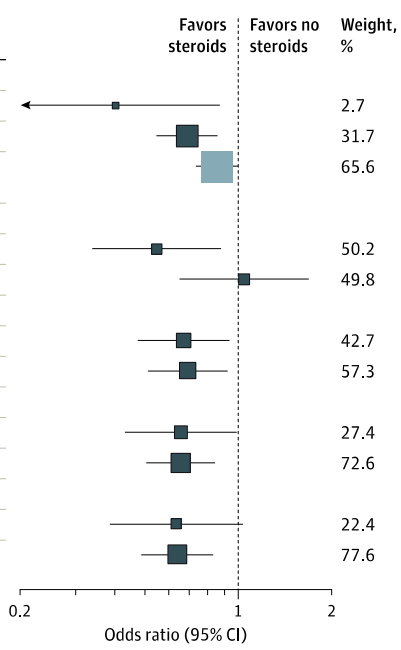


Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No ($I^2 = 0\%$)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes ($I^2 = 44.1\%$)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No ($I^2 = 0\%$)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes ($I^2 = 0\%$)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 ($I^2 = 0\%$)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 ($I^2 = 49.7\%$)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female ($I^2 = 0\%$)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male ($I^2 = 14.7\%$)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 ($I^2 = 69.1\%$)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 ($I^2 = 0\%$)	139/418	293/693	0.64 (0.49-0.83)	77.6



EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Correspondence

Corticosteroids in Covid-19: One size does not fit all

Athena Gogali, Chris Kyriakopoulos, Konstantinos Kostikas

Please cite this article as: Gogali A, Kyriakopoulos C, Kostikas K. Corticosteroids in Covid-19: One size does not fit all. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00224-2021).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

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Ranjbar *et al. BMC Infectious Diseases* (2021) 21:337
https://doi.org/10.1186/s12879-021-06045-3

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial

2 mg/kg and half dose very 5 days

PLOS ONE

RESEARCH ARTICLE

Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia

Miguel Alejandro Pinzón[1]*, Santiago Ortiz[2], Héctor Holguín[3], Juan Felipe Betancur[4], Doris Cardona Arango[5], Henry Laniado[2], Carolina Arias Arias[6], Bernardo Muñoz[7], Julián Quiceno[4], Daniel Jaramillo[8], Zoraida Ramirez[4]

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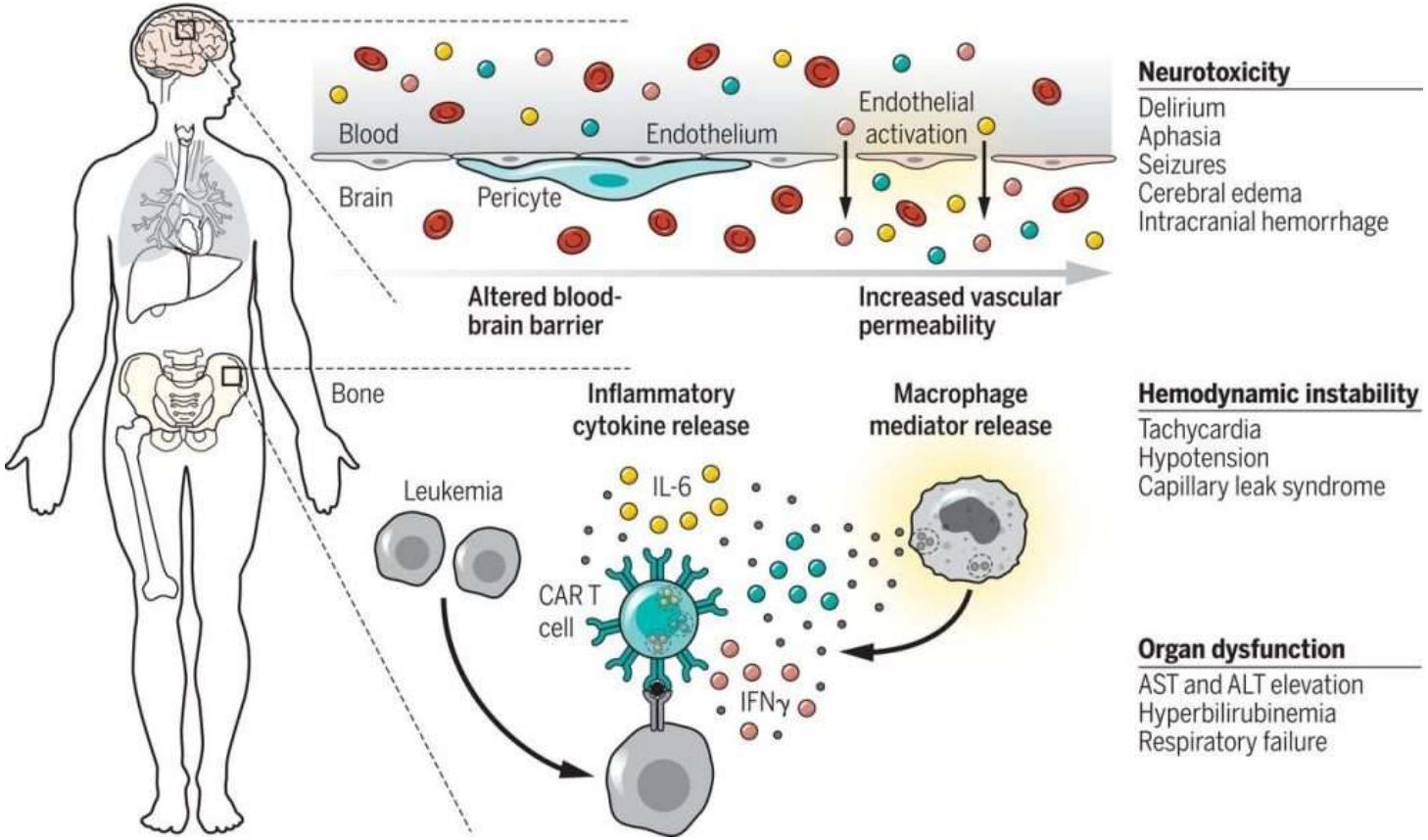
IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)



Treatment of ICANS

GRADE 2 → dexamethasone 10 mg x 4 (3 dd)

GRADE 3 → dexamethasone 20 mg x 2 (3 dd)

GRADE 4 → methylprednisolone 1 g (3dd), then 250/125/60 (2 dd each)

If not succesfull consider high-dose cyclophosphamide, anakinra or siltixumab

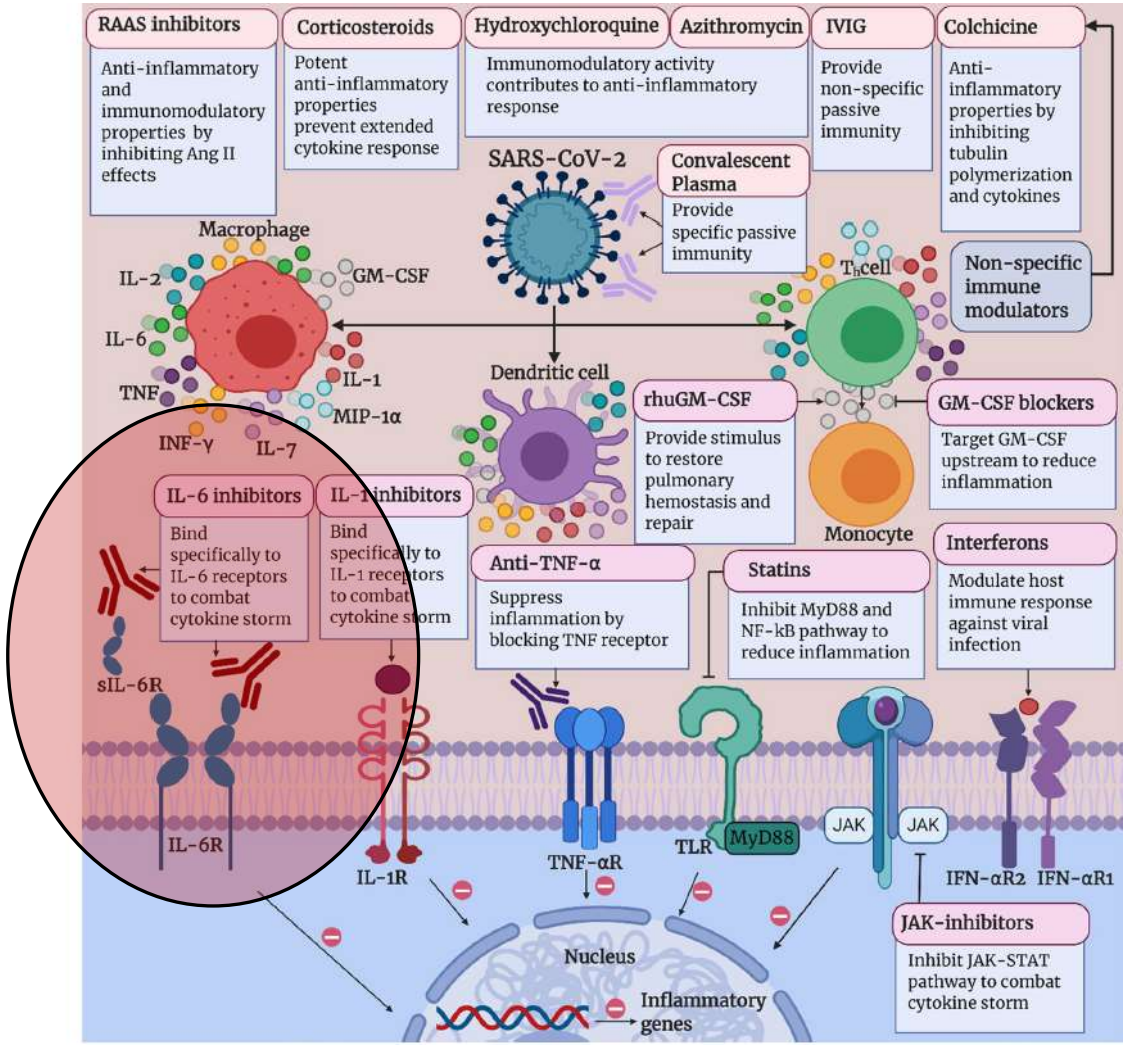
Tallantyre EC, et al. J Neurol 2020

ANTI IL-6/IL-6R MEDICATIONS

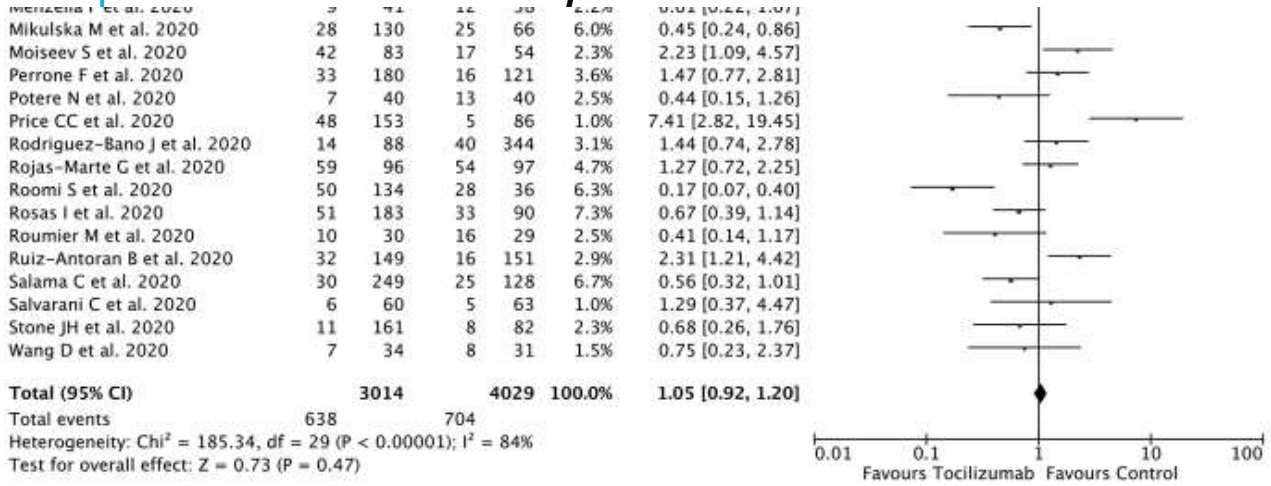
1. **Tocilizumab**
   - Humanized MoA against IL-6R
   - Rheumatoid arthritis and systemic juvenile idiopathic arthritis

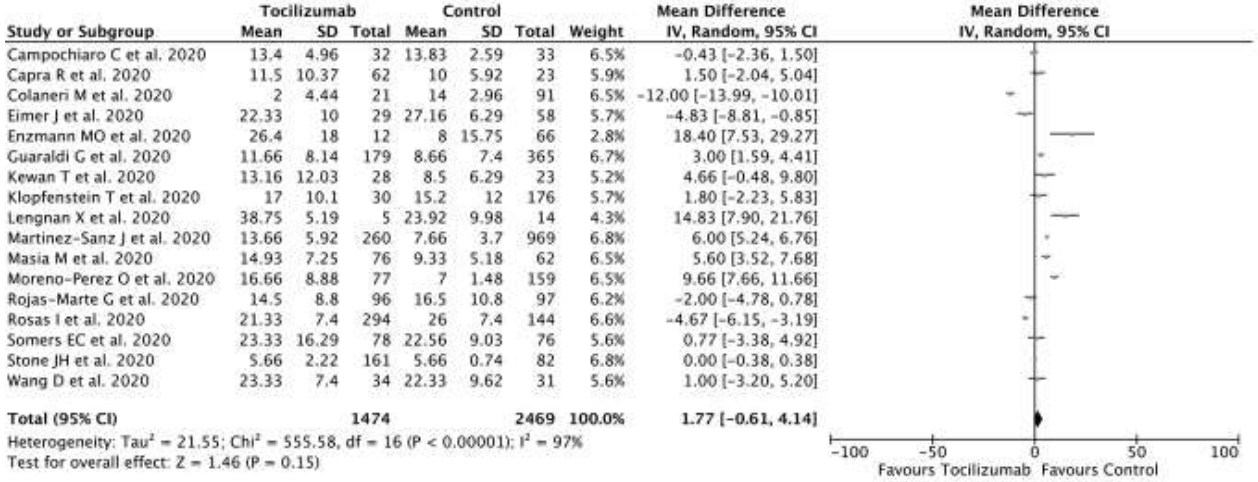
2. **Sarilumab**
   - Human MoAb against IL-6R
   - Rheumatoid arthritis

3. **Siltuximab**
   - Chimeric MoAb that binds IL-6
   - Multicentric Castleman's disease



ANTI IL-6/IL-6R: OBSERVATIONAL STUDIES





Outcomes	Effect size (95 % Confidence Interval), p-value	Heterogeneity (I2), p-value	Begg's test	Egger's test	Number of Studies
Mortality	**OR = 0.54 [0.42–0.71], < 0.00001**	79 %, < 0.00001	0.968	0.284	37
Severe COVID-19	OR = 1.05 [0.92–1.20], 0.47	84 %, < 0.00001	0.464	0.150	30
Length of hospital stay	Mean Difference = 1.77 [− 0.61–4.14], 0.15	97 %, < 0.00001	0.836	0.213	17
Thrombosis incident	OR = 1.02 [0.69–1.50], 0.93	12 %, 0.33	0.916	0.978	9
Secondary infection	OR = 0.86 [0.63–1.18], 0.36	57 %, 0.02	0.558	0.451	16

Hariyanto TI, et al. Drug Res 2020

Figure 1. Association Between IL-6 Antagonists vs Usual Care or Placebo and Primary Outcome of 28-Day All-Cause Mortality

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	2/11	0/10	0.18 (0.01-4.27)	0.09
BACC-Bay	4/82	9/161	1.15 (0.34-3.87)	0.63
CORIMUNO-TOCI-1	8/67	7/63	0.92 (0.31-2.71)	0.79
CORIMUNO-TOCI-ICU	10/43	8/49	0.64 (0.23-1.82)	0.85
COV-AID[a]	7/72	9/81	1.16 (0.41-3.29)	0.84
COVACTA	28/144	58/294	1.02 (0.62-1.68)	3.62
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.09
COVIDSTORM	0/13	0/26	NA[b]	
COVINTOC	15/88	11/91	0.67 (0.29-1.55)	1.30
COVITOZ	0/9	0/17	NA[b]	
EMPACTA	11/128	26/249	1.24 (0.59-2.60)	1.67
HMO-020-0224	8/17	11/37	0.48 (0.15-1.56)	0.65
ImmCoVA	2/27	2/22	1.25 (0.16-9.67)	0.22
PreToVid[c]	34/180	21/174	0.59 (0.33-1.06)	2.63
RECOVERY	729/2094	621/2022	0.83 (0.73-0.95)	53.76
REMAP-CAP[d]	116/358	85/353	0.66 (0.48-0.92)	8.43
REMDACTA	41/210	78/430	0.91 (0.60-1.39)	5.18
TOCIBRAS	6/64	14/65	2.65 (0.95-7.42)	0.87
TOCOVID	0/134	0/136	NA[b]	
Subgroup $I^2 = 3.3\%$	1023/3749	960/4299	0.83 (0.74-0.92)	81.61
Sarilumab				
CORIMUNO-SARI-1	14/76	8/68	0.59 (0.23-1.51)	1.04
CORIMUNO-SARI-ICU	11/33	14/48	0.82 (0.32-2.14)	1.00
REGENERON-P2	19/90	104/367	1.48 (0.85-2.57)	2.97
REGENERON-P3	64/286	264/1044	1.17 (0.86-1.60)	9.45
REMAP-CAP[d]	19/65	10/48	0.64 (0.26-1.53)	1.19
SANOFI	7/84	30/332	1.09 (0.46-2.58)	1.24
SARCOVID	0/10	2/20	2.84 (0.12-64.87)	0.09
SARICOR	4/39	3/76	0.36 (0.08-1.69)	0.38
SARTRE	1/70	2/70	2.03-0.18-22.91)	0.16
Subgroup $I^2 = 0\%$	139/753	437/2073	1.08 (0.86-1.36)	17.51
Siltuximab				
COV-AID[a]	7/72	10/77	1.39 (0.50-3.86)	0.87
Overall $I^2 = 18.2\%$	1158/4481	1407/6449	0.86 (0.79-0.95)	100.00

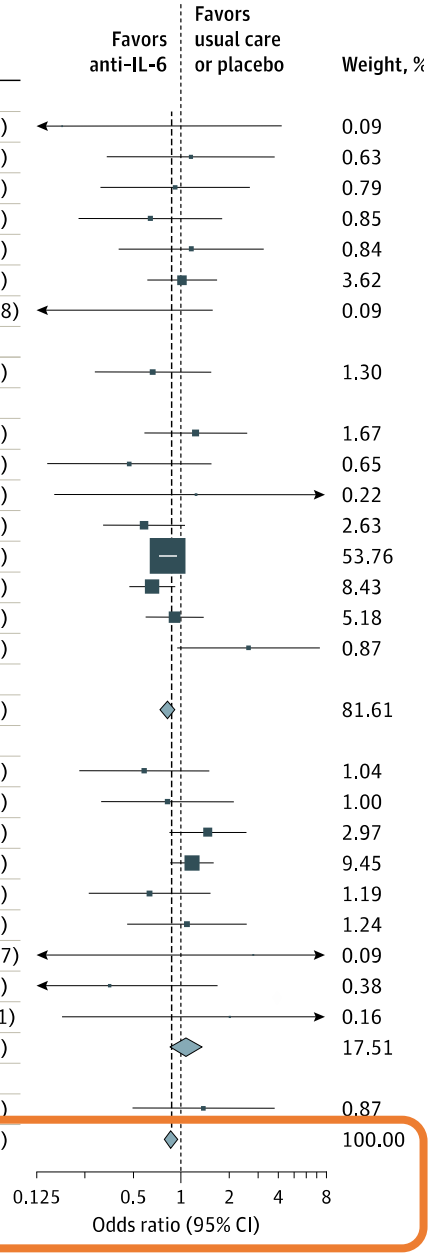
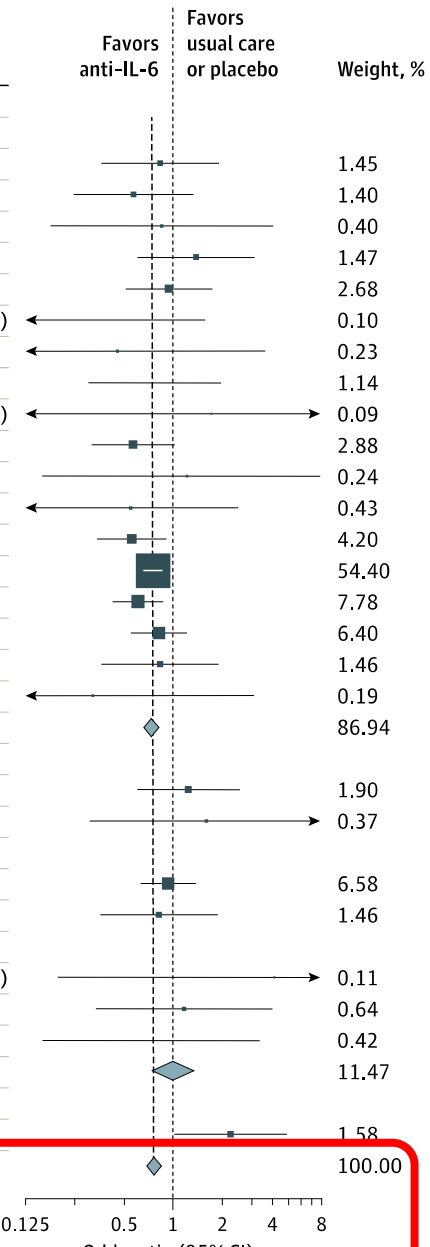


Figure 3. Association Between IL-6 Antagonists vs Usual Care or Placebo and Secondary Outcome of Progression to Invasive Mechanical Extracorporeal Membrane Oxygenation, or Death

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	1/1	0/0	NA[a]	
BACC-Bay	10/81	17/161	0.84 (0.37-1.92)	1.45
CORIMUNO-TOCI-1	18/67	11/63	0.58 (0.25-1.34)	1.40
CORIMUNO-TOCI-ICU	6/12	6/13	0.86 (0.18-4.13)	0.40
COV-AID[b]	12/63	18/73	1.39 (0.61-3.17)	1.47
COVACTA	20/89	39/181	0.95 (0.51-1.75)	2.68
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.10
COVIDSTORM	2/13	2/26	0.46 (0.06-3.69)	0.23
COVINTOC	11/84	9/86	0.78 (0.30-1.98)	1.14
COVITOZ	0/9	1/17	1.73 (0.06-46.77)	0.09
EMPACTA	24/128	29/249	0.57 (0.32-1.03)	2.88
HMO-020-0224	3/5	11/17	1.22 (0.16-9.47)	0.24
ImmCoVA	6/27	3/22	0.55 (0.12-2.52)	0.43
PreToVid[c]	56/179	35/172	0.56 (0.34-0.91)	4.20
RECOVERY	754/1800	619/1754	0.76 (0.66-0.87)	54.40
REMAP-CAP[d]	127/239	102/249	0.61 (0.43-0.88)	7.78
REMDACTA	54/188	91/365	0.82 (0.56-1.22)	6.40
TOCIBRAS	17/54	15/54	0.84 (0.37-1.91)	1.46
TOCOVID	3/134	1/136	0.32 (0.03-3.15)	0.19
Subgroup $I^2 = 0\%$	1126/3181	1009/3657	0.74 (0.66-0.82)	86.94
Sarilumab				
CORIMUNO-SARI-1	20/76	21/68	1.25 (0.61-2.58)	1.90
CORIMUNO-SARI-ICU	4/9	9/16	1.61 (0.31-8.32)	0.37
REGENERON-P2			NA[a]	
REGENERON-P3	43/182	142/631	0.94 (0.64-1.39)	6.58
REMAP-CAP[d]	24/57	15/40	0.83 (0.36-1.89)	1.46
SANOFI			NA[a]	
SARCOVID	0/10	3/20	4.20 (0.20-89.61)	0.11
SARICOR	4/39	9/76	1.18 (0.34-4.09)	0.64
SARTRE	4/70	3/70	0.74 (0.16-3.43)	0.42
Subgroup $I^2 = 0\%$	99/443	202/921	1.00 (0.75-1.35)	11.47
Siltuximab				
COV-AID[b]	12/63	25/72	2.26 (1.02-5.00)	1.58
Overall $I^2 = 0\%$	1220/3609	1236/4650	0.77 (0.70-0.85)	100.00



ANTI IL-6/IL-6R: OPEN QUESTIONS

Timing?

Clinical/Lab test based

Early administration of interleukin-6 inhibitors for patients with severe COVID-19 disease is associated with decreased intubation, reduced mortality, and increased discharge

Sinha P, et al. Int J Infect Dis 2020

Dose (1 or 2?) and route of administration?

Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19

Sciascia S, Exp Rheumatol 2020

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

Guaraldi G, et al. Lancet Rheumatol 2020

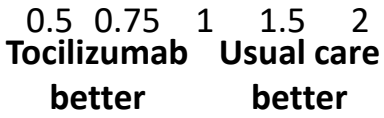
Mono or combination therapy?

Comparative Survival Analysis of Immunomodulatory Therapy for Coronavirus Disease 2019 Cytokine Storm

Narain S, et al. Chest 2020

RECOVERY: 28-DAY MORTALITY BY BL CHARACTERISTICS

	Tocilizumab	Usual Care	RR (95% CI)
Age, yrs (x^2_1 = 0.1; *P* = .80)			
< 70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74-1.04)
≥ 70 to < 80	206/477 (43%)	234/480 (49%)	0.84 (0.69-1.01)
≥ 80	134/213 (63%)	171/260 (66%)	0.93 (0.74-1.17)
Sex (x^2_1 = 2.2; *P* = .14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71-0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80-1.20)
Ethnicity (x^2_1 = 0.3; *P* = .56)			
White	429 /1356 (32%)	519 /1426 (36%)	0.83 (0.73-0.95)
Black, Asian, or minority ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69-1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71-1.41)
Days since symptom onset (x^2_1 = 0.6; *P* = .46)			
≤ 7	210/668 (31%)	245/660 (37%)	0.81 (0.67-0.97)
> 7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77-1.01)
Respiratory support at randomization (x^2_1 = 0.4; *P* = .52)			
No ventilator support	175/935 (19%)	202/933 (22%)	0.84 (0.69-1.03)
Noninvasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74-1.01)
Invasive mechanical ventilation	125/268 (47%)	142/294 (48%)	0.94 (0.73-1.19)
Use of corticosteroids (x^2_1 = 7.1; *P* = .1)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70-0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91-1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77-0.96)** *P* = .0066



82% of patients received corticosteroids as part of usual care

Recovery Collaborative Group. medRxiv. 2021;[Preprint]. Note: this study has not been peer reviewed.

Slide credit: clinicaloptions.com

Tocilizumab 8 mg/kg (max 800 mg) **i.v.** (one single administration, insufficient data to reccomend two doses yet several countries use 2 doses) **in adult hospitalized patients** with

1. **Confirmed SARS-CoV-2 infection**
2. **Respiratory failure as $SatO_2$<92% (room air) or need for oxygen**

when?

In the first 24-72 h after the introduction o HFNC, NIV/CPAP o IV in addition to corticosteroids (REMAP-CAP criteria);

or

progressive oxygen supplementation required and CRP≥ 7.5 mg/dL (while on dexamethasone) **(RECOVERY criteria)**

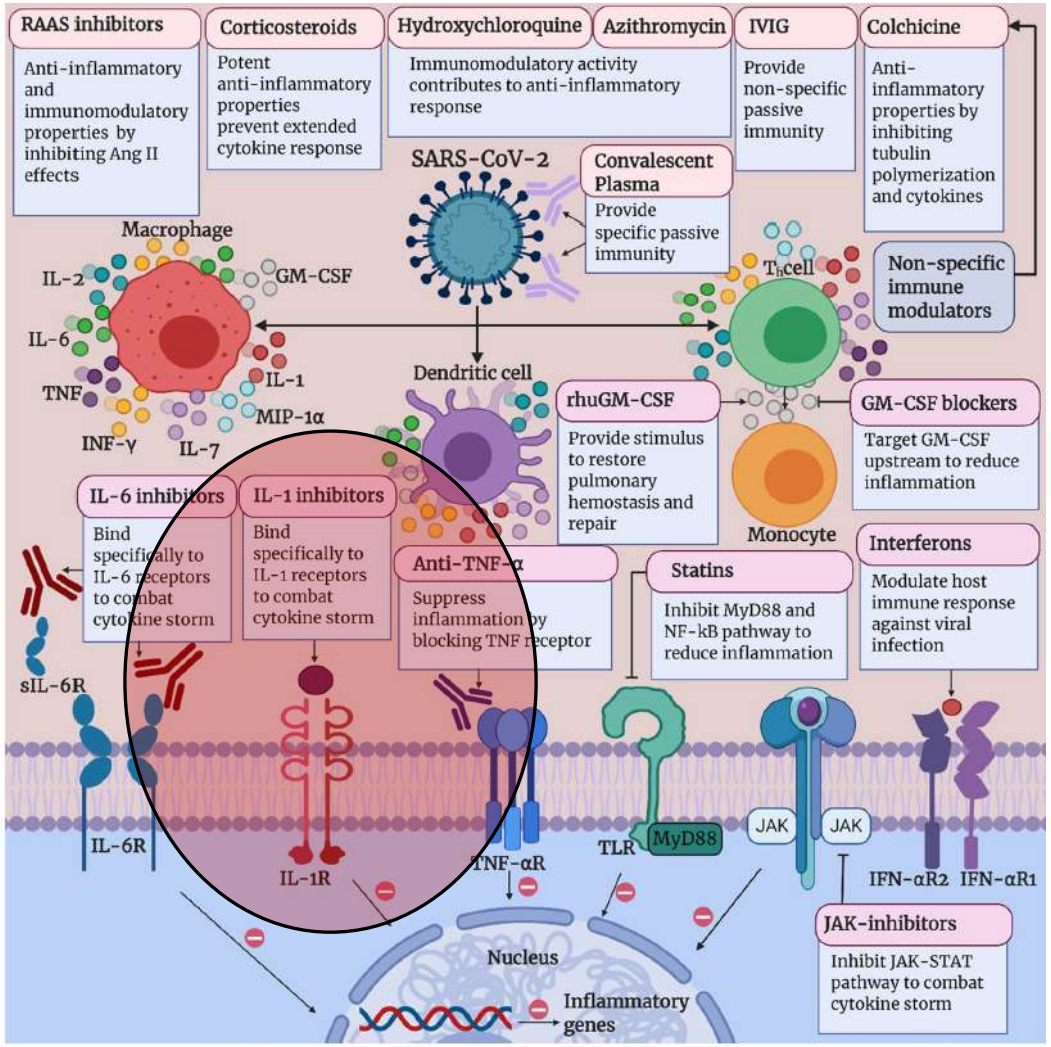
ANTI IL-1R MEDICATIONS

Anakinra

- Recombinant IL-1R antagtonist
- Rheumatoid arthritis
- cryopyrin-associated periodic syndrome
- Macrophage activation syndrome
- Hemophagocytic lymphohistiocytosis

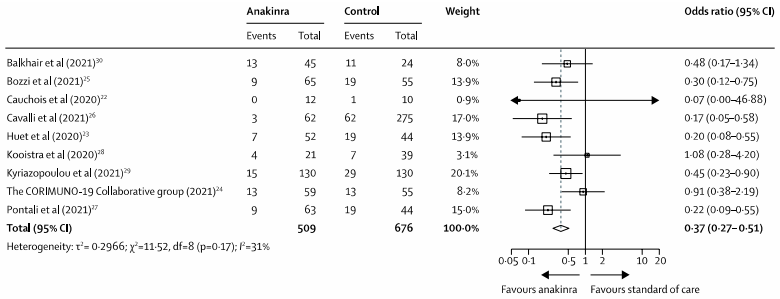
Canakinumab

- Human anti IL-1Beta
- systemic juvenile idiopathic arthritis
- Still's disease
- cryopyrin-associated periodic syndrome



ANAKINRA STUDIES

Dose?



	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Anakinra treatment	0·38 (0·26–0·56)	<0·0001	0·32 (0·20–0·51)	<0·0001
Age >72 years*	4·97 (3·5–7·06)	<0·0001	1·89 (1·12–3·20)	0·018
Charlson comorbidity index >2*	6·35 (4·01–10·06)	<0·0001	3·75 (1·99–7·07)	<0·0001
PaO_2/FiO_2 <100	2·18 (1·50–3·17)	<0·0001	2·89 (1·80–4·64)	<0·0001
CRP >100 mg/L	1·76 (1·21–2·55)	0·003	1·21 (0·76–1·92)	0·42
Lymphopenia (<580 lymphocytes per mm^3)*	3·08 (2·12–4·49)	<0·0001	3·05 (1·90–4·89)	<0·0001
Study	..	0·15	..	..

	Study type; individual patient data available?	Study setting and period	Inflammation criteria for inclusion	Number of patients		Route of administration	Steroid intake
				Anakinra group	Control group		
Cauchois et al (2020)[22]	Observational; yes	France: not mentioned	CRP >110 mg/L	12	10	Intravenous	No dexamethasone as standard of care; no other steroids
Huet et al (2020)[23]	Observational; yes	France: March, 2020 (historical controls); March 24–April 6, 2020 (anakinra group)	..	52	44	Subcutaneous	No dexamethasone as standard of care; steroid pulse in 2 of 52 patients in anakinra group
The CORIMUNO-19 Collaborative group (2021)[24]	Randomised controlled trial; no	France: April 8–26, 2020	CRP >25 mg/L	59	55	Intravenous	Dexamethasone in 1 of 59 in anakinra group; other glucocorticoids in 6 of 59 in anakinra group, and 8 of 55 in control group
Bozzi et al (2021)[25]	Observational; yes	Italy: Feb 25–March 30, 2020	CRP > 100 mg/L or ferritin >1000 µg/L, or both	65	55	Subcutaneous; intravenous if on invasive mechanical ventilation	No dexamethasone as standard of care; methylprednisolone co-administered with anakinra
Cavalli et al (2021)[26]	Observational; yes	Italy: March 10–17, 2020 (historical controls); March–May, 2020 (anakinra group)	CRP >100 mg/L or ferritin >900 µg/L	62	275	Intravenous	Dexamethasone in 54 of 275 controls and in 7 of 62 in anakinra group
Pontali et al (2021)[27]	Observational; no	Italy: Feb 26–April 29, 2020	CRP or ferritin >3 times the normal limits	63	44	Intravenous	No dexamethasone as standard of care; methylprednisolone in 33 of 63 patients in anakinra group
Kooistra et al (2020)[28]	Observational; yes	Netherlands: March 11–April 27, 2020	Ferritin >1800 µg/L; clinical hyperinflammation signs (persistent fever, unexplained progression of multiorgan failure)	21	39	Intravenous	Dexamethasone in 14 of 39 patients on standard of care and in 3 of 21 in anakinra group
Kyriazopoulou et al (2021)[29]	Observational; yes	Greece: April 16–Sept 12, 2020	suPAR >6 µg/L	130	130	Subcutaneous	Dexamethasone as standard of care in 47 of 130 controls and in 52 of 130 in anakinra group
Balkhair et al (2021)[30]	Observational; no	Oman: April 1–June 14, 2020 (historical controls); June 15–July 25, 2020 (anakinra group)	..	45	24	Subcutaneous	Dexamethasone in 24 of 45 in anakinra group, and 3 of 24 controls; methylprednisolone in 1 of 45 in anakinra group, and in 13 of 24 controls

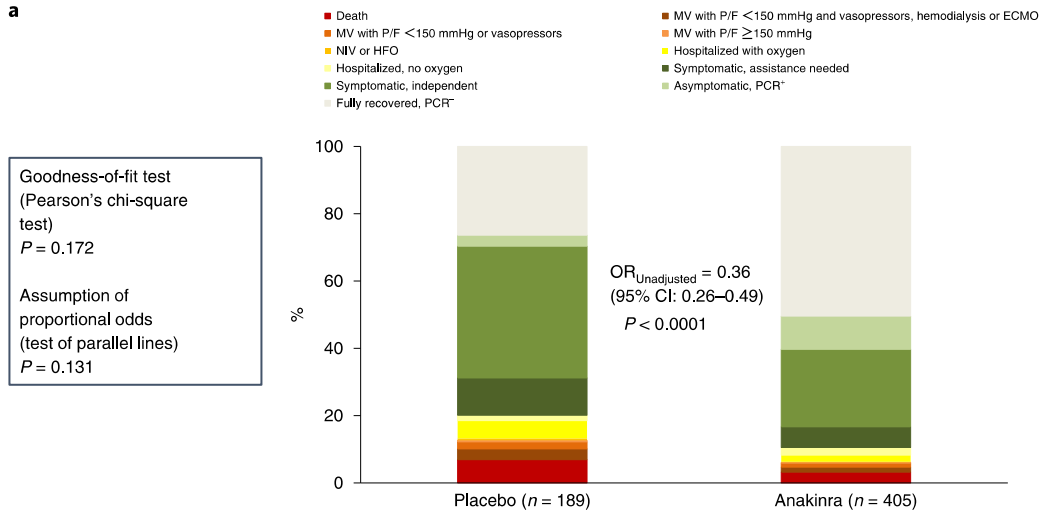
Kyriazopoulou E, et al. Lancet Rheumatol 2021

SAVE MORE

Anakinra 100 mg s.c. once daily for 7-10 days

- RCT, Italy and Greece
- Inclusion criteria:
  - Hospitalized with COVID-19 pneumonia
  - **plasma suPAR ≥6 ng ml−1**
  - no stage IV malignancy
  - no do-not-resuscitate order
  - **p/f >150 mmHg**
  - **no need of NIV (CPAP or BPAP) or MV**
  - no primary immunodeficiency
  - neutrophils >1500/mm3
  - no anti-cytokine biological treatment, including JAK inhibitors, during the last 1 month
  - no severe hepatic failure
  - no end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis

a



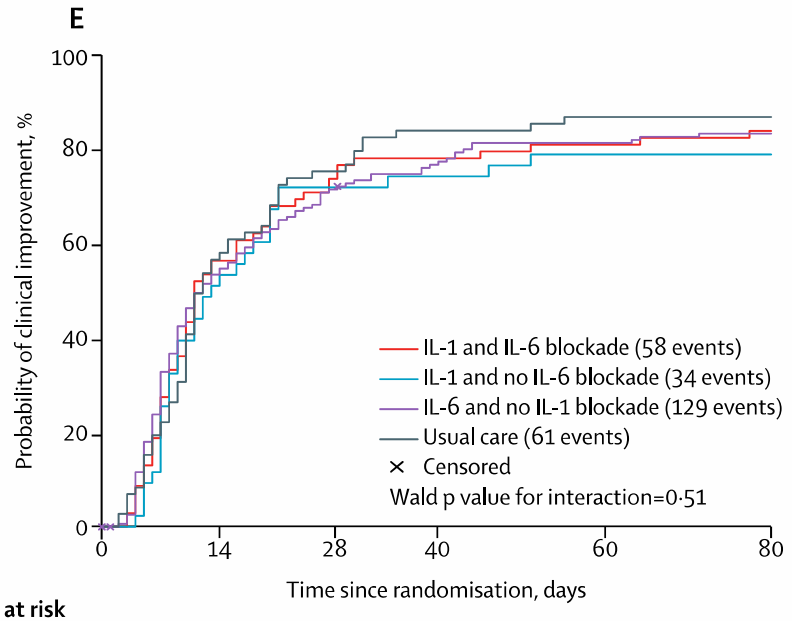
b

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Group of treatment (Anakinra vs placebo)	0.36	0.26–0.49	<0.0001	0.36	0.26–0.50	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.28–2.83	0.002	1.49	0.59–3.80	0.395
Severe COVID-19 by WHO (Yes/No)	1.95	1.31–2.90	0.001	1.29	0.51–3.27	0.582
BMI >30 kg m^{-2} (Yes/No)	1.27	0.87–1.61	0.267	1.10	0.81–1.50	0.530
Country (Italy vs Greece)	1.18	0.74–1.88	0.482	1.25	0.77–2.03	0.350

Kyriazopoulou E, et al. Nature Med 2021

ANTI-INTERLEUKIN TREATMENTS (COV-AID)

- RCT, Belgium, proven COVID-19
- Inclusion/exclusion
  - symptoms 6-16 days
  - p/f <350 mm Hg on room air or <280 mm Hg on supplemental oxygen
  - signs of a cytokine release syndrome in their serum (ferritin>2000 µg/L, rising ferritin >1000 µg/L, lymphopenia <800/mL, LDH >300 IU/L, CRP >70 mg/L, risign D-dimer >1000 ng/mL)
- 342 patients were randomly assigned to IL-1 blockade (n=112) or no IL-1 blockade (n=230) and simultaneously randomly assigned to IL-6 blockade (n=227; 114 for tocilizumab and 113 for siltuximab) or no IL-6 blockade (n=115)



Number at risk (number censored)						
IL-1 and IL-6 blockade	69	30 (0)	18 (0)	15 (0)	13 (0)	11 (0)
IL-1 and no IL-6 blockade	43	21 (0)	12 (0)	11 (0)	9 (0)	9 (0)
IL-6 and no IL-1 blockade	158	72 (3)	44 (3)	35 (4)	28 (4)	25 (4)
Usual care	72	30 (2)	17 (2)	11 (2)	9 (2)	9 (2)

Declercq J, Lancet Resp Med 2021

JANUS KINASE 1-2 (JAK1/JAK2) INHIBITORS

Baricitinib

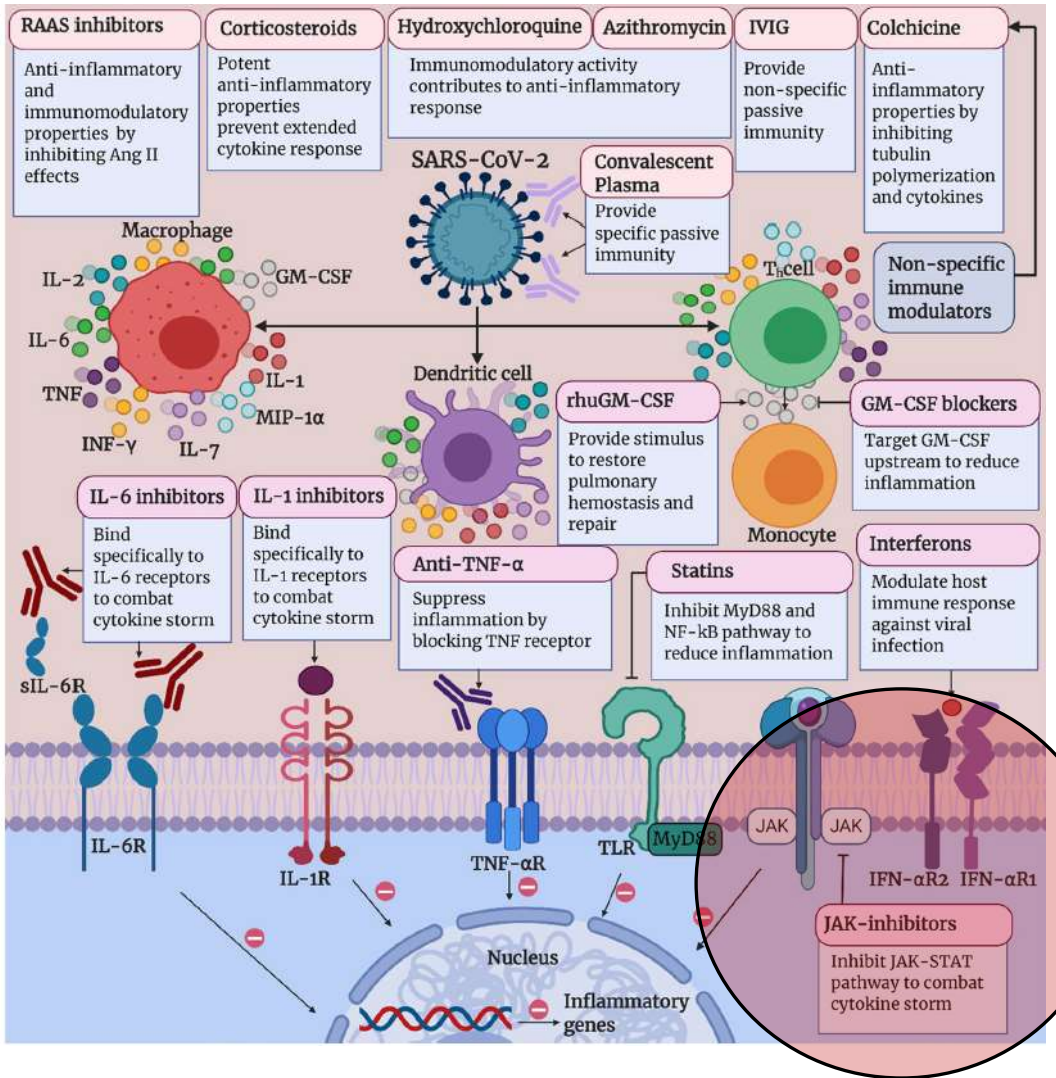
- JAK/JAK2 inhibitor
- Rheumatoid arthritis

Ruxolitinib

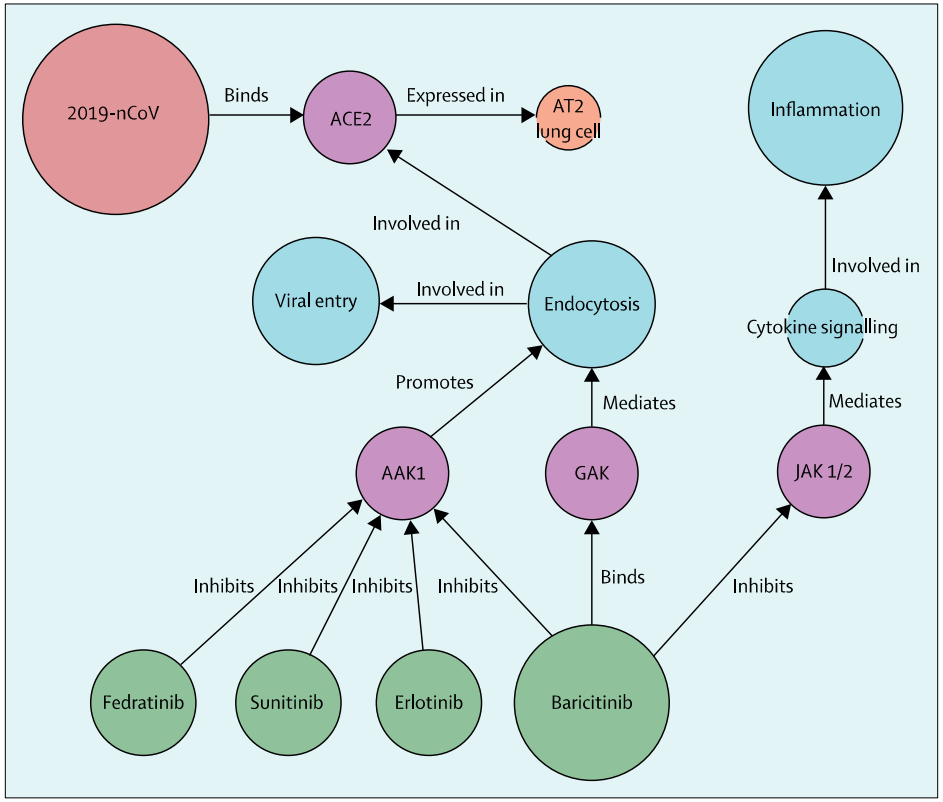
- JAK1/JAK2 inhibitor
- Myelofibrosis, Polycythemia vera, GVHD

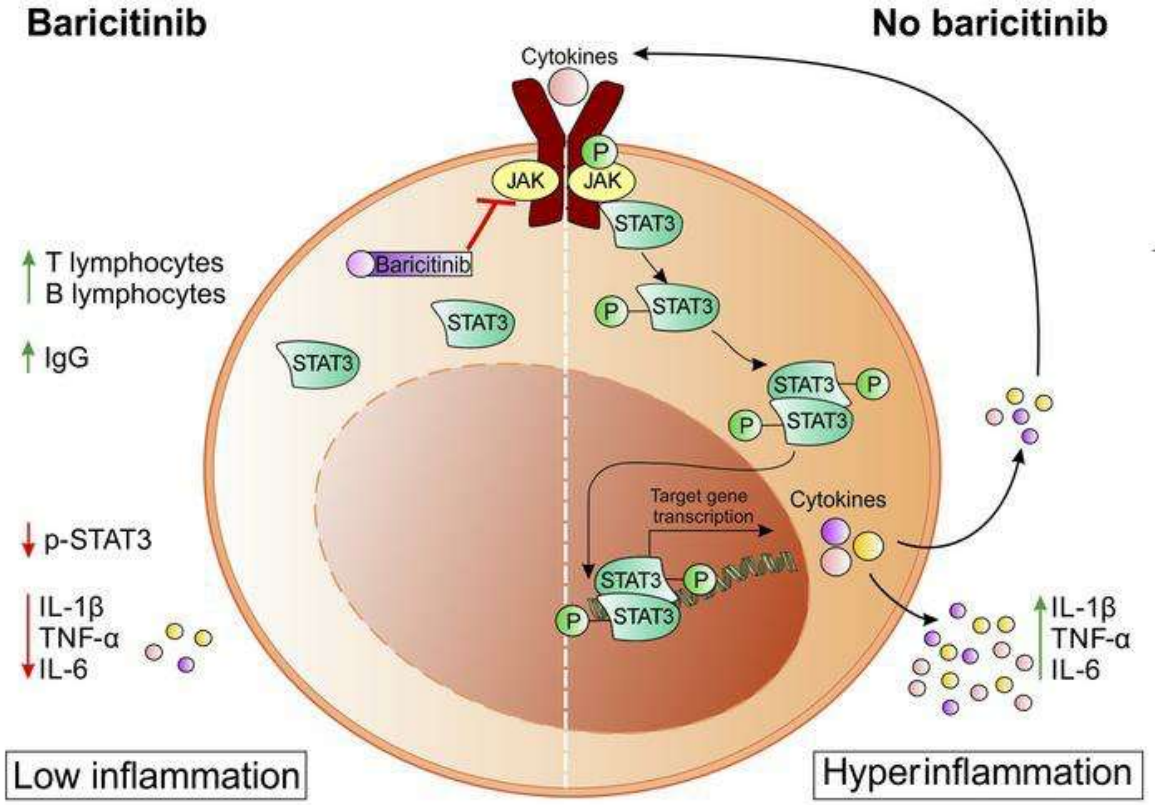
Tofacitinib

- JAK1/JAK3 inhibitor
- Rheumatoid Arthritis, Psoriasic arthritis and Ulcerative colitis



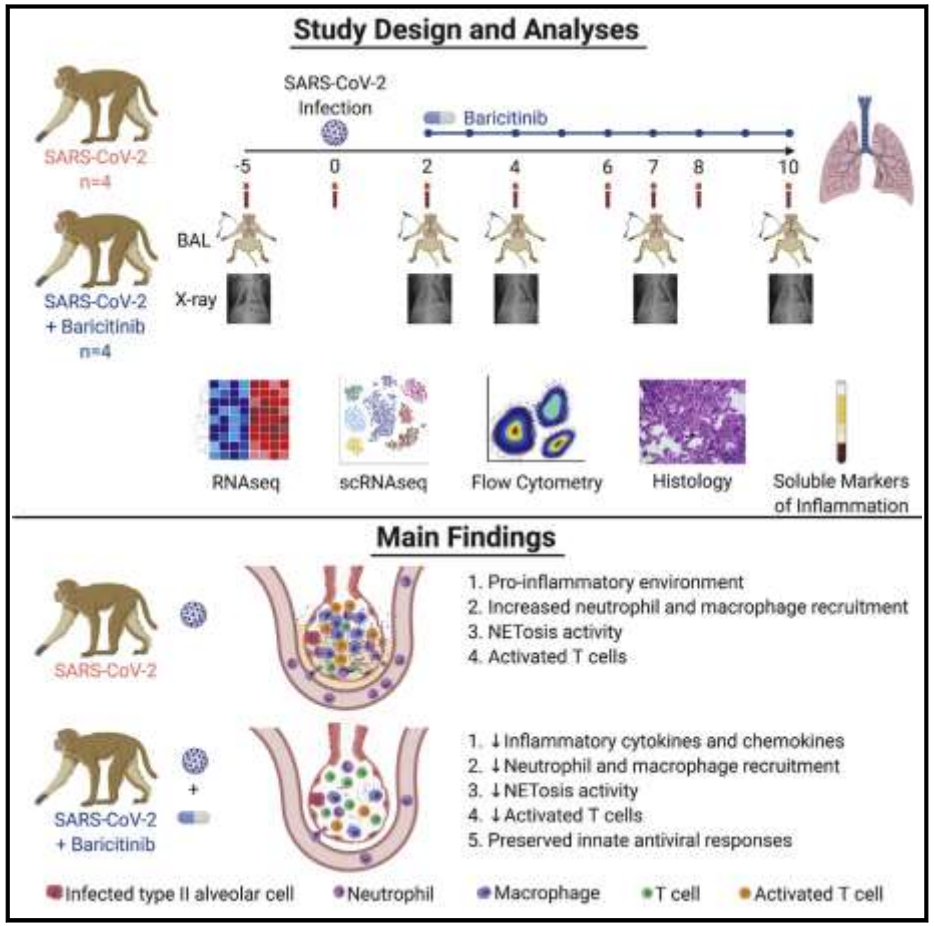
BARICITINIB

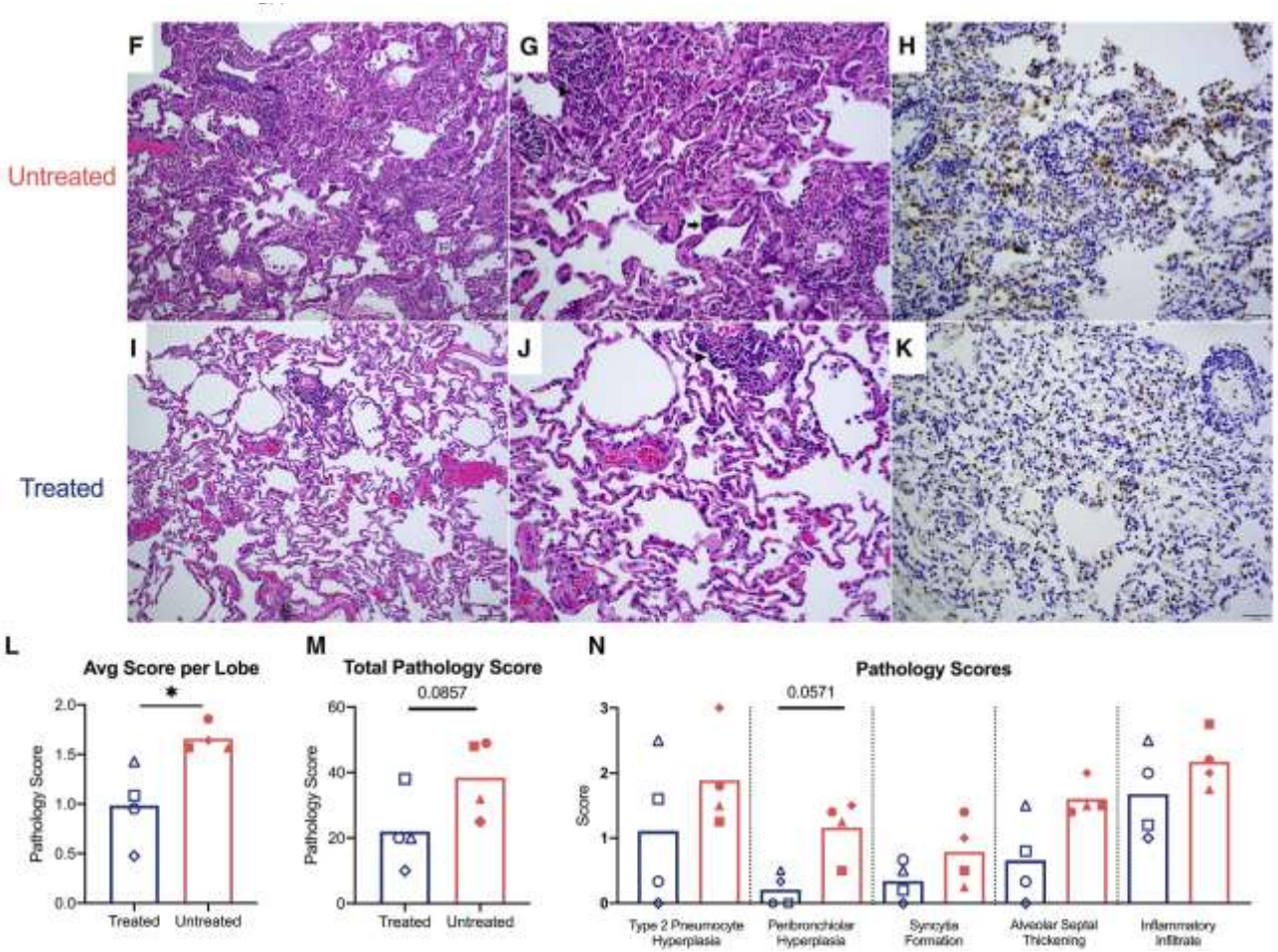




Richardson P, et al. Lancet 2020; Bronte V, et al. JCI 2020

BARICITINIB IN MACAQUES





Hoang TN, et al. Cell 2021

BARICITINIB STUDIES

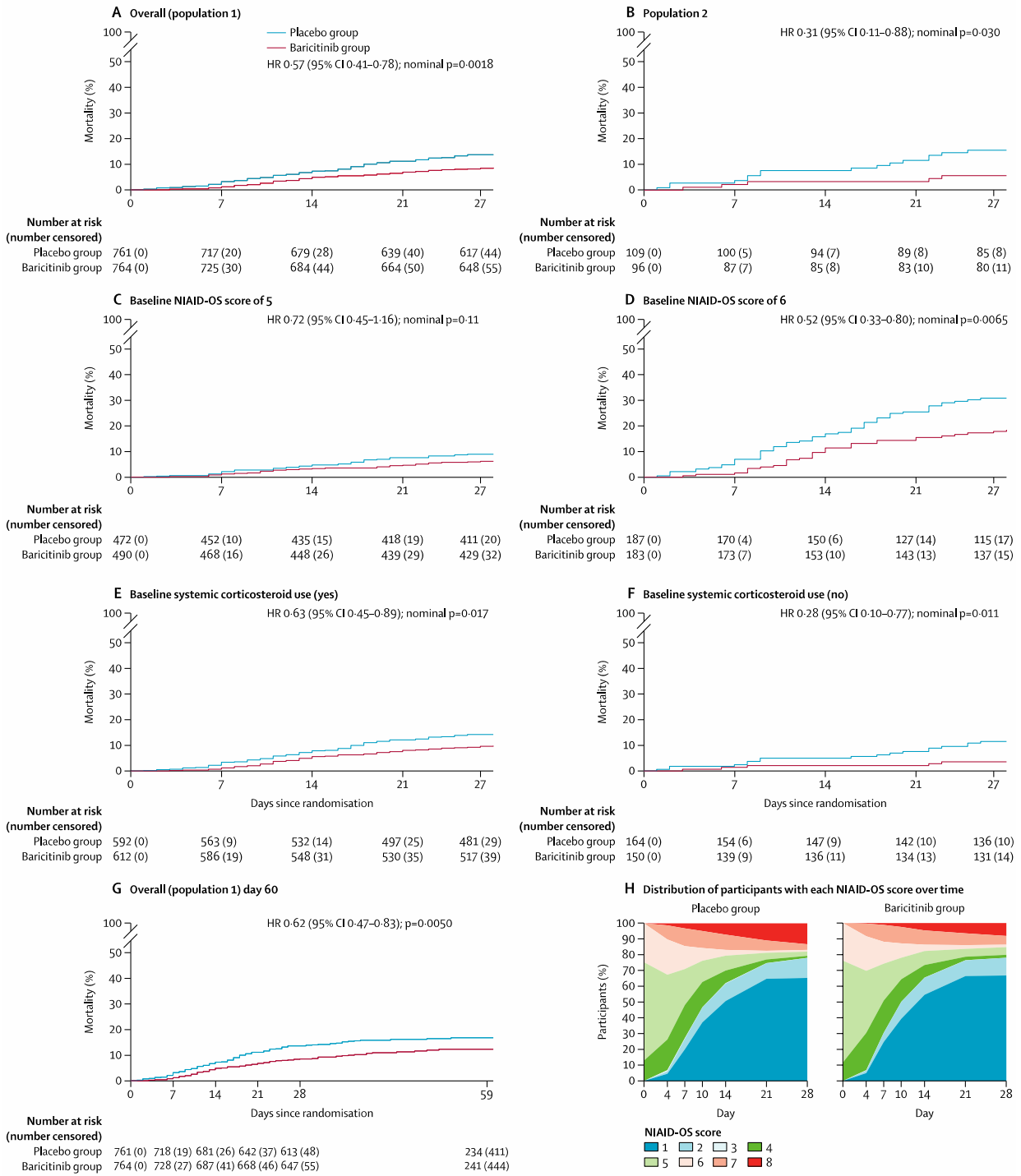
1st author	Design	Setting	N	Main finding
Kalil 2021	**RCT + remd**	**Hosp**	**1033**	**Shorter time to improvement, trend for lower mortality Higher effect in patients on NIV (small sample size)**
Marconi 2021	**RCT vs. SOC**	**Hosp**	**1525**	**38.2% reduction in mortality**
Cantini 2020	Obs	Hosp	191/12	Lower mortality and ICU in the bar arm
Rosas 2020	Obs ±TOC	Hosp	60	Lower mortality and ICU in the bar arm
Hasan 2020	Obs HD/UD	Hosp	37/238	Lower mortality and ICU in the HD arm
Bronte 2020	Obs	Hosp	66	Reduction in inflammatory markers
Stebbing 2020	Obs vs. SOC	Hosp	166	Lower mortality
Rodriguez-Garcia 2021	Obs	Hosp	152	Faster clinical improvement
Tziolos 2021	Obs vs. SOC	Hosp - severe	369	Lower mortality and ICU admission
Garcia-Garcia 2021	Obs vs. Anak	Hosp	342	No difference in mortality
Perez-Alba 2021	Obs vs. SOC	Hosp	197	Lower mortality
Abizanda 2021	Obs.	Hosp	327	Lower mortality (also if age >70)

Bronte V, et al. JCI 2020; Cantini F, et al. J Infect 2020; Stebbing J et al., Sci. Adv. 2020; Rosas J, et al. Reumatolg Clin 2020; Kalil AC, et al. NEJM 2021; Marconi VC, et al. Lancet Respir Med. 2021; Rodrgiuez-Garcia JL, et al. Rheumatology 2021; Tziolos N, et al. Open Forum Infect Dis. 2021; Pérez-Alba E, et al. J Microbiol Immunol Infect. 2021; García-García JA, et al. J Clin Med. 2021; Abizanda P, et al. J Am Geriatr Soc. 2021.

COV-BARRIER

- RCT, world, proven COVID-19
- Inclusion/exclusion
  - hospitalized
  - pneumonia or symptomatic COVID-19
  - at least one elevated inflammatory marker (C-reactive protein, D-dimer, lactate dehydrogenase, or ferritin)
  - no MV
  - no immunosuppressants (high-dose corticosteroids, biologics, T-cell-targeted or B-cell-tar- geted therapies, interferon, or JAK inhibitors)
  - no convalescent plasma or intravenous immunoglobulin for COVID-19
  - no neutropenia, lymphopenia, AST/ALT >X5, eGFR<30 mL/min
- 4 mg baricitinib once daily plus standard of care (n=764) or placebo plus standard of care (n=761)

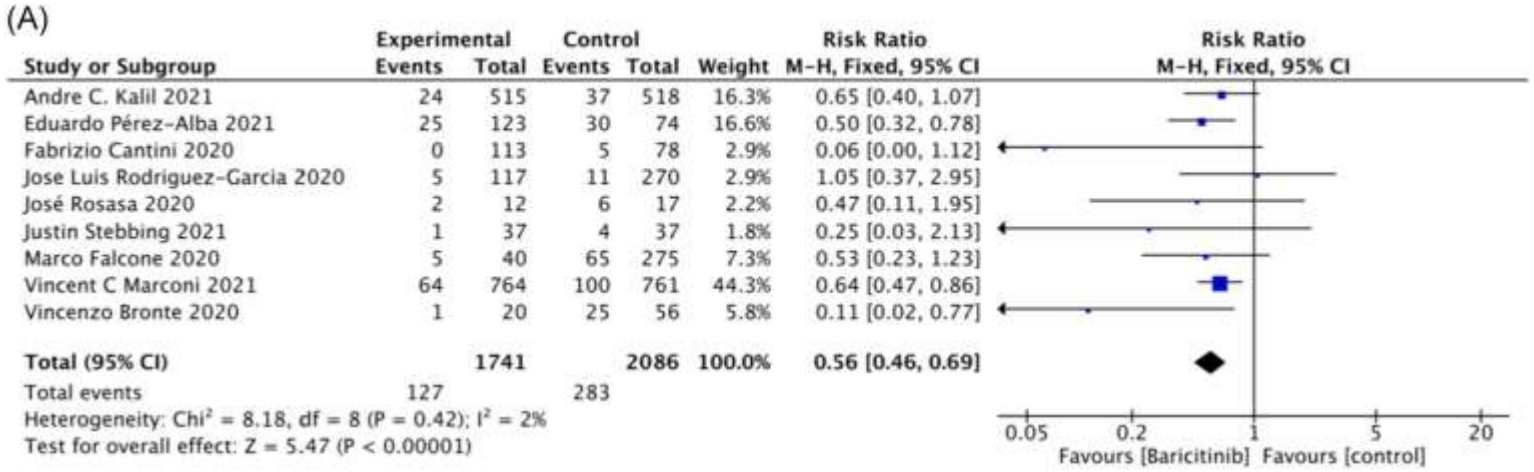
Marconi VC, et al. Lancet Resp Med 2021



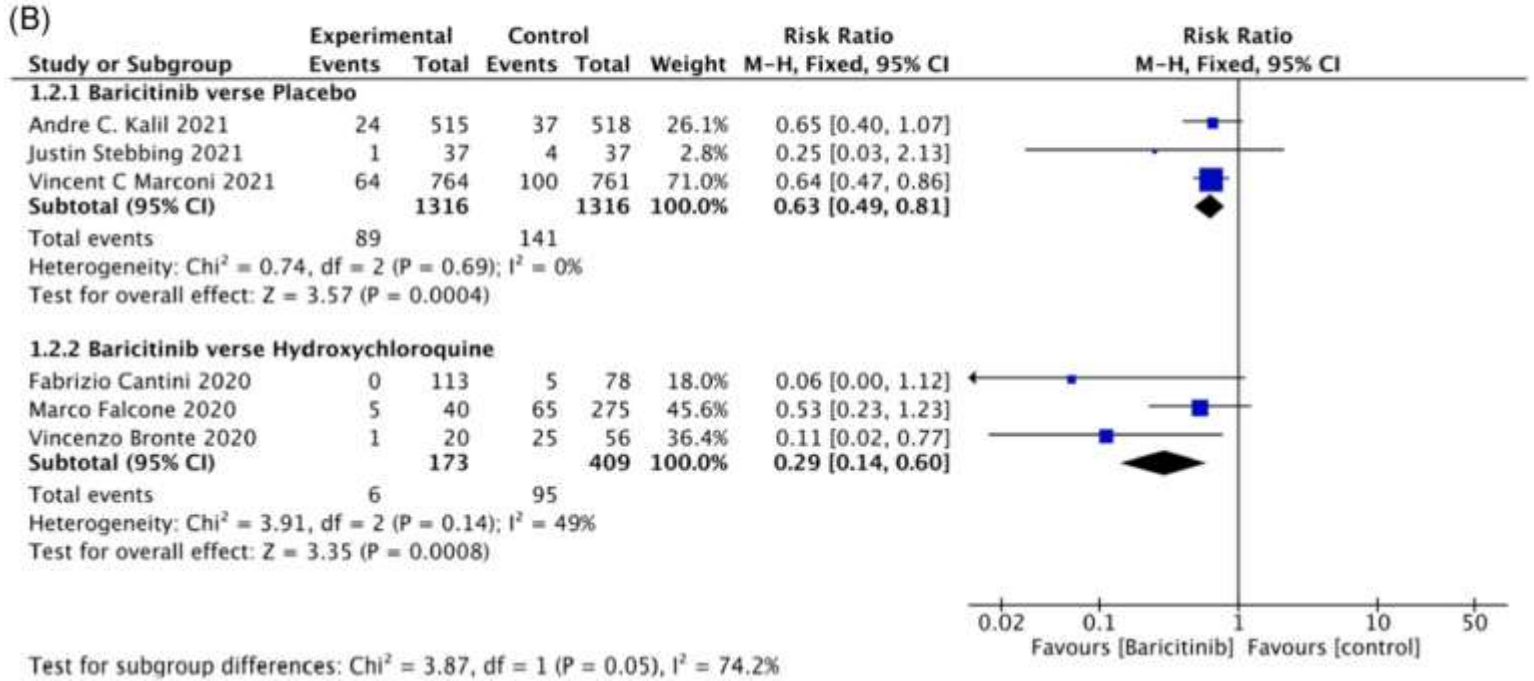
BARICITINIB SYSTEMATIC REVIEW AND META-ANALYSIS

First Author	Year	Study Type	Total	Baricitinib group	Control	Scale
Andre C. Kalil	2021	RCT	1033	515	518	Jadad scale: 8
Vincent C Marconi	2021	RCT	1525	764	761	Jadad scale: 8
Jose Luis Rodriguez-Garcia	2021	Clinical Trial	101	51	50	Jadad scale: 4
Vincenzo Bronte	2021	Clinical Trial	76	20	56	Jadad scale: 4
Md. Jahidul Hasan	2021	Clinical Trial	238	122	116	Jadad scale: 6
Md. Jahidul Hasan	2020	Clinical Trial	37	20	17	Jadad scale: 5
Eduardo Pérez-Alba	2020	Observational	99	74	25	NOS scale: 8
José Rosasa	2021	Observational	29	12	17	NOS scale: 8
Fabrizio Cantini	2020	Observational	191	113	78	NOS scale: 9
Fabrizio Cantini	2020	Observational	24	12	12	NOS scale: 9
Justin Stebbring	2020	Observational	112	62	50	NOS scale: 9
Marco Falcone	2020	Observational	99	74	25	NOS scale: 8

(A)



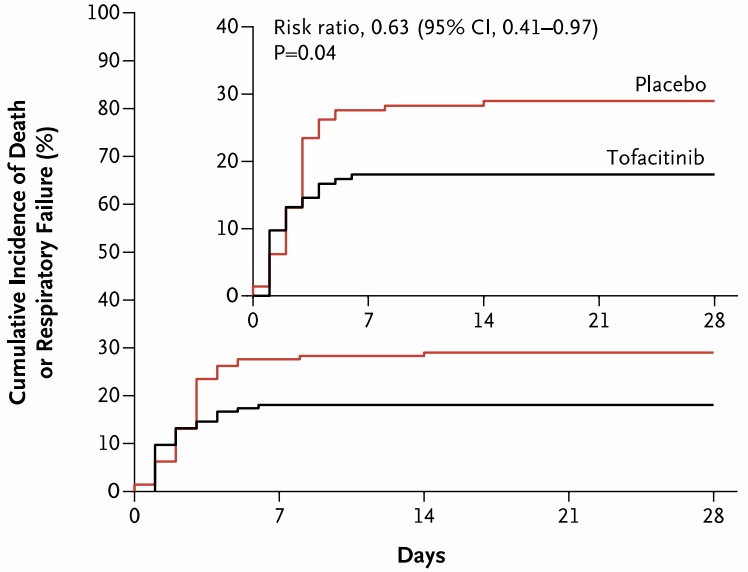
(B)

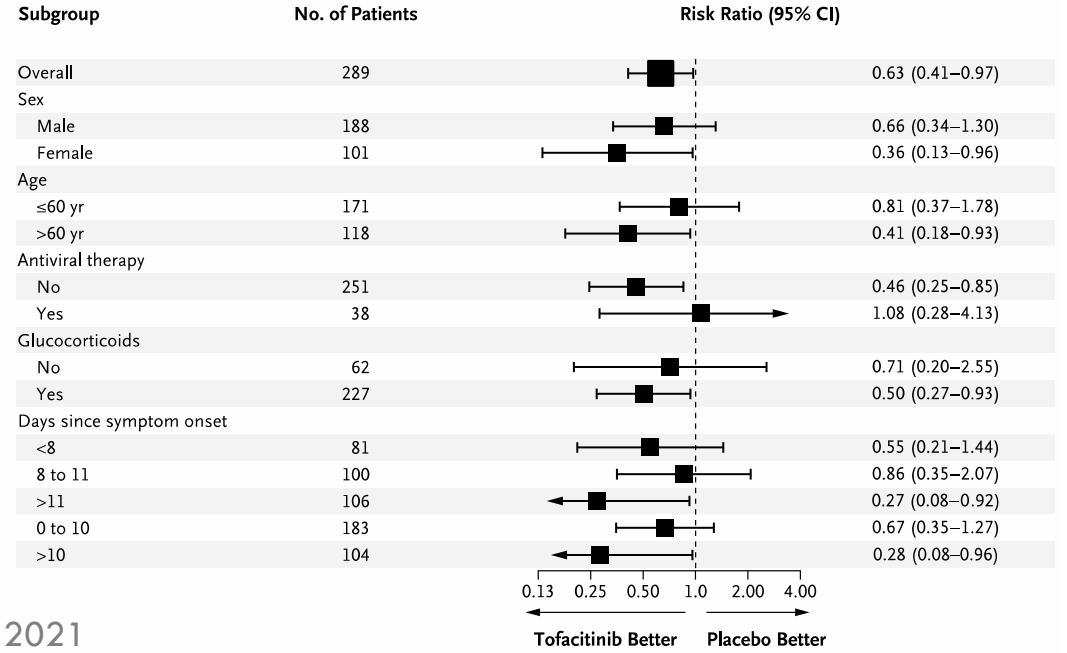


Lin Z, et al. J Med Vir 2021

TOFACITINIB

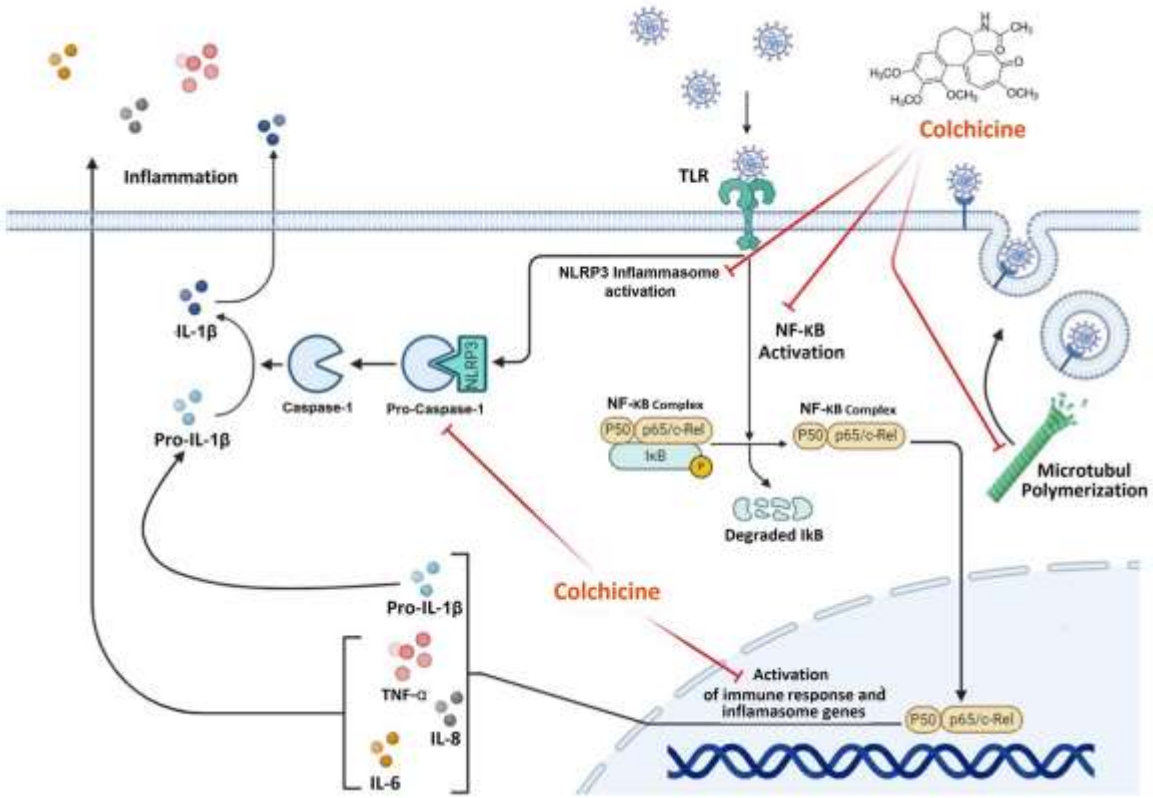
- RCT
- Hospitalized patients with COVID-19 pneumonia
  - Hospitalized <72 hours
  - no NIV/ECMO
  - no history of thrombosis or current thrombosis,
  - no immunosuppression
  - no current cancer on active treatment
- 10 mg or placebo twice daily for up to 14 days or until hospital discharge



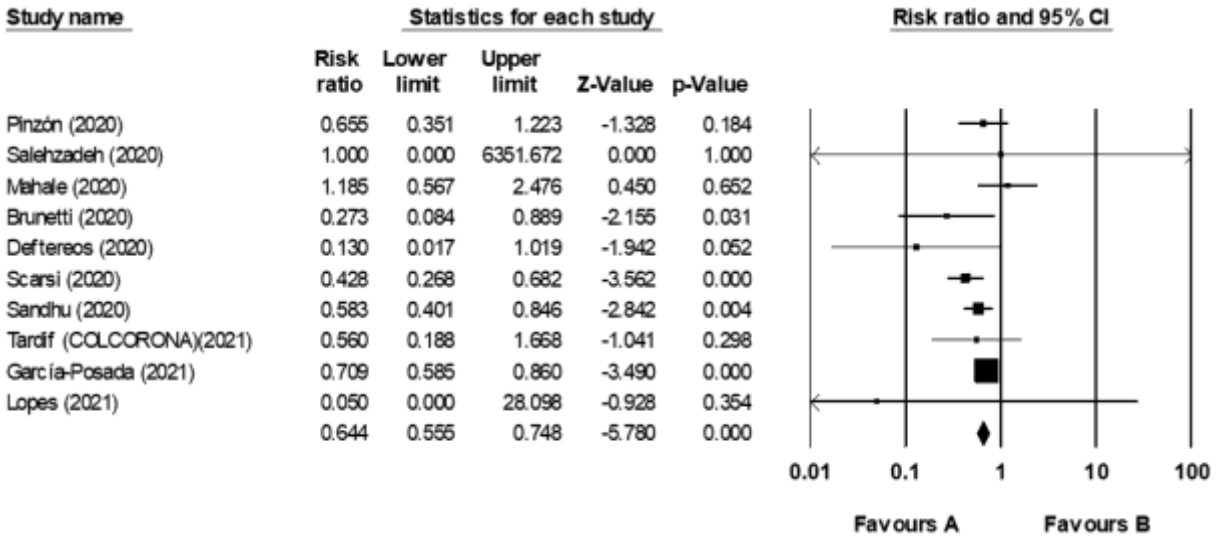


Guimarães PO, et al. NEJM 2021

COLCHICINE

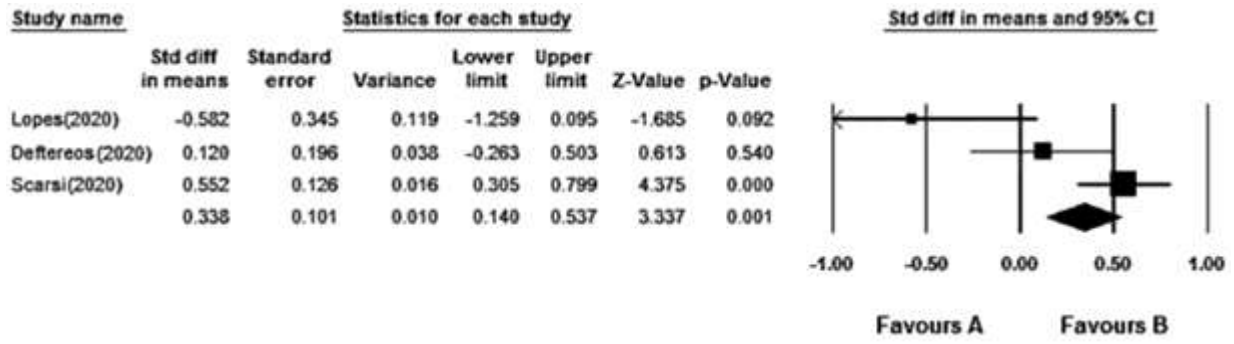


Mortality



Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Pinzón (2020)	0.655	0.351	1.223	-1.328	0.184
Salehzadeh (2020)	1.000	0.000	6351.672	0.000	1.000
Mahale (2020)	1.185	0.567	2.476	0.450	0.652
Brunetti (2020)	0.273	0.084	0.889	-2.155	0.031
Deftereos (2020)	0.130	0.017	1.019	-1.942	0.052
Scarsi (2020)	0.428	0.268	0.682	-3.562	0.000
Sandhu (2020)	0.583	0.401	0.846	-2.842	0.004
Tardif (COLCORONA)(2021)	0.560	0.188	1.668	-1.041	0.298
García-Posada (2021)	0.709	0.585	0.860	-3.490	0.000
Lopes (2021)	0.050	0.000	28.098	-0.928	0.354
	0.644	0.555	0.748	-5.780	0.000

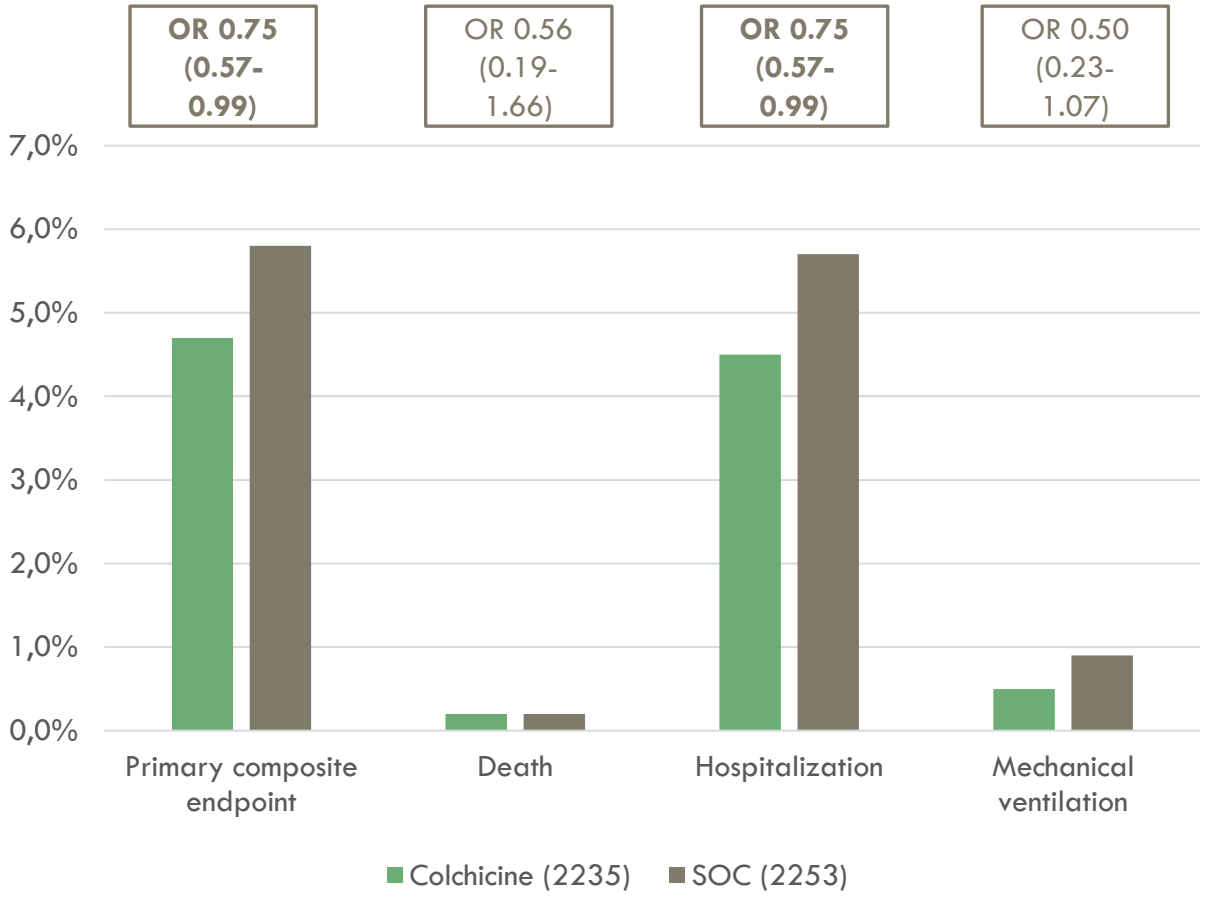
Hospitalization



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lopes(2020)	-0.582	0.345	0.119	-1.259	0.095	-1.685	0.092
Deftereos(2020)	0.120	0.196	0.038	-0.263	0.503	0.613	0.540
Scarsi(2020)	0.552	0.126	0.016	0.305	0.799	4.375	0.000
	0.338	0.101	0.010	0.140	0.537	3.337	0.001

Golpour M, et al. International Journal of Immunopathology and Pharmacology 2021

COLCHICINE HOSPITALIZED VS. OUTPATIENT?



Articles

Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial

*Jean-Claude Tardif, Nadia Bouabdallaoui, Philippe L L'Allier, Daniel Gaudet, Binita Shah, Michael H Pillinger, Jose Lopez-Sendon, Protasio da Luz, Lucie Verret, Sylvia Audet, Jocelyn Dupuis, André Denault, Martin Pelletier, Philippe A Tessier, Sarah Samson, Denis Fortin, Jean-Daniel Tardif, David Busseuil, Elisabeth Goulet, Chantal Lacoste, Anick Dubois, Avni Y Joshi, David D Waters, Priscilla Hsue, Norman E Lepor, Frédéric Lesage, Nicolas Sainturet, Eve Roy-Clavel, Zohar Bassevitch, Andreas Orfanos, Gabriela Stamatescu, Jean C Grégoire, Lambert Busque, Christian Lavallée, Pierre-Olivier Hétu, Jean-Sébastien Paquette, Spyridon G Deftereos, Sylvie Levesque, Marième Cossette, Anna Nozza, Malorie Chabot-Blanchet, Marie-Pierre Dubé, Marie-Claude Guertin, Guy Boivin, for the COLCORONA Investigators**

Summary

Background Evidence suggests a role for excessive inflammation in COVID-19 complications. Colchicine is an oral anti-inflammatory medication beneficial in gout, pericarditis, and coronary disease. We aimed to investigate the effect of colchicine on the composite of COVID-19-related death or hospital admission.

Methods The present study is a phase 3, randomised, double-blind, adaptive, placebo-controlled, multicentre trial. The study was done in Brazil, Canada, Greece, South Africa, Spain, and the USA, and was led by the Montreal Heart Institute. Patients with COVID-19 diagnosed by PCR testing or clinical criteria who were not being treated in hospital were eligible if they were at least 40 years old and had at least one high-risk characteristic. The randomisation list was computer-generated by an unmasked biostatistician, and masked randomisation was centralised and done electronically through an automated interactive web-response system. The allocation sequence was unstratified and used a 1:1 ratio with a blocking schema and block sizes of six. Patients were randomly assigned to receive orally administered colchicine (0·5 mg twice per day for 3 days and then once per day for 27 days thereafter) or matching placebo. The primary efficacy endpoint was the composite of death or hospital admission for COVID-19. Vital status at the end of the study was available for 97·9% of patients. The analyses were done according to the intention-to-treat principle. The COLCORONA trial is registered with ClinicalTrials.gov (NCT04322682) and is now closed to new participants.

Findings Trial enrolment began in March 23, 2020, and was completed in Dec 22, 2020. A total of 4488 patients (53·9% women; median age 54·0 years, IQR 47·0–61·0) were enrolled and 2235 patients were randomly assigned to colchicine and 2253 to placebo. The primary endpoint occurred in 104 (4·7%) of 2235 patients in the colchicine group and 131 (5·8%) of 2253 patients in the placebo group (odds ratio [OR] 0·79, 95·1% CI 0·61–1·03; p=0·081). Among the 4159 patients with PCR-confirmed COVID-19, the primary endpoint occurred in 96 (4·6%) of 2075 patients in the colchicine group and 126 (6·0%) of 2084 patients in the placebo group (OR 0·75, 0·57–0·99; p=0·042). Serious adverse events were reported in 108 (4·9%) of 2195 patients in the colchicine group and 139 (6·3%) of 2217 patients in the placebo group (p=0·051); pneumonia occurred in 63 (2·9%) of 2195 patients in the colchicine group and 92 (4·1%) of 2217 patients in the placebo group (p=0·021). Diarrhoea was reported in 300 (13·7%) of 2195 patients in the colchicine group and 161 (7·3%) of 2217 patients in the placebo group (p<0·0001).

Interpretation In community-treated patients including those without a mandatory diagnostic test, the effect of colchicine on COVID-19-related clinical events was not statistically significant. Among patients with PCR-confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospital admission than placebo. Given the absence of orally administered therapies to prevent COVID-19 complications in community-treated patients and the benefit of colchicine in patients with PCR-proven COVID-19, this safe and inexpensive anti-inflammatory agent could be considered for use in those at risk of complications. Notwithstanding these considerations, replication in other studies of PCR-positive community-treated patients is recommended.

Funding The Government of Quebec, the Bill & Melinda Gates Foundation, the National Heart, Lung, and Blood Institute of the US National Institutes of Health, the Montreal Heart Institute Foundation, the NYU Grossman School of Medicine, the Rudin Family Foundation, and philanthropist Sophie Desmarais.

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Lancet Respir Med 2021

Published Online May 27, 2021 https://doi.org/10.1016/S2213-2600(21)00222-8

See Online/Comment https://doi.org/10.1016/S2213-2600(21)00225-3

Montreal Heart Institute (Prof J-C Tardif MD, N Bouabdallaoui MD, P L L'Allier MD, L Verret MSc, S Audet MSc, Prof J Dupuis MD, Prof A Denault MD, S Samson BSN, D Fortin BSN, J-D Tardif BSc, D Busseuil PhD, E Goulet RN, C Lacoste DEC, A Dubois PhD, Prof F Lesage PhD, J C Grégoire MD, Prof M-P Dubé PhD), **Ecogene-21** (D Gaudet MD), **and Department of Medicine** (D Gaudet), **Université de Montréal, Montreal, QC, Canada; New York University Grossman School of Medicine, New York, NY, USA** (B Shah MD, Prof M H Pillinger MD); **H La Paz, IdiPaz, UAM, Cibec-CV, Madrid, Spain** (Prof J Lopez-Sendon MD); **Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brasil** (Prof P da Luz MD); **Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, QC, Canada** (M Pelletier PhD, P A Tessier PhD, G Boivin MD); **Mayo Clinic, Rochester, MN, USA** (Prof A Y Joshi MD); **San Francisco General Hospital, San Francisco, CA, USA** (Prof D D Waters MD, Prof P Hsue MD); **Cedars-Sinai Heart Institute, Geffen School of Medicine-UCLA, Los Angeles, CA, USA** (Prof N E Lepor MD); **Montréal Health Innovations Coordinating Center, Montreal,**

*Members listed in the appendix

VITAMIN D

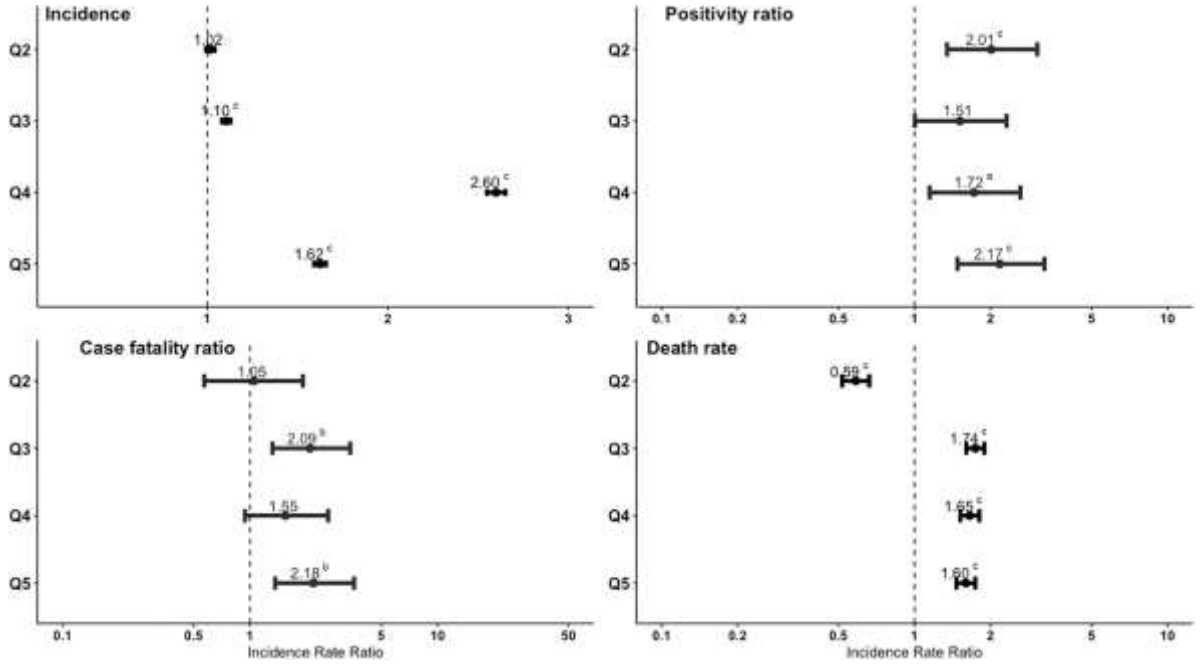
Several observations of lower levels in patients with COVID-19 and even lower with severe forms

Immune-modulatory properties

Supported by a network-based analysis (*Ahmed F, Front Immun*)

Involved in bradykinin storm cascade

One small interventional study (**calcifediol**)reported better outcomes in treated patients; another one was retracted after concerns about randomization



"Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study"

Marta Entrenas Castillo [a], Luis Manuel Entrenas Costa [a,*], José Manuel Vaquero Barrios [a], Juan Francisco Alcalá Díaz [b], José López Miranda [b], Roger Bouillon [c], José Manuel Quesada Gomez [d]

Mariani J, et al. Health Security; Entrenas Castillo M, et al. Journal of Steroid Biochemistry and Molecular Biology 203 (2020)

JAMA | Original Investigation

Effect of a Single High Dose of Vitamin D_3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19
A Randomized Clinical Trial

Igor H. Murai, PhD; Alan L. Fernandes, PhD; Lucas P. Sales, MSc; Ana J. Pinto, BSc; Karla F. Goessler, PhD; Camila S. C. Duran, MD; Carla B. R. Silva, MD; André S. Franco, MD; Marina B. Macedo, MD, MSc; Henrique H. H. Dalmolin, MD; Janaina Baggio, MD; Guilherme G. M. Balbi, MD; Bruna Z. Reis, PhD; Leila Antonangelo, MD, PhD; Valeria F. Caparbo, PhD; Bruno Gualano, PhD; Rosa M. R. Pereira, MD, PhD

Editorial page 1047
Supplemental content

IMPORTANCE The efficacy of vitamin D_3 supplementation in coronavirus disease 2019 (COVID-19) remains unclear.

OBJECTIVE To investigate the effect of a single high dose of vitamin D_3 on hospital length of stay in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, double-blind, randomized, placebo-controlled trial conducted in 2 sites in Sao Paulo, Brazil. The study included 240 hospitalized patients with COVID-19 who were moderately to severely ill at the time of enrollment from June 2, 2020, to August 27, 2020. The final follow-up was on October 7, 2020.

INTERVENTIONS Patients were randomly assigned to receive a single oral dose of 200 000 IU of vitamin D_3 (n = 120) or placebo (n = 120).

MAIN OUTCOMES AND MEASURES The primary outcome was length of stay, defined as the time from the date of randomization to hospital discharge. Prespecified secondary outcomes included mortality during hospitalization; the number of patients admitted to the intensive care unit; the number of patients who required mechanical ventilation and the duration of mechanical ventilation; and serum levels of 25-hydroxyvitamin D, total calcium, creatinine, and C-reactive protein.

RESULTS Of 240 randomized patients, 237 were included in the primary analysis (mean [SD] age, 56.2 [14.4] years; 104 [43.9%] women; mean [SD] baseline 25-hydroxyvitamin D level, 20.9 [9.2] ng/mL). Median (interquartile range) length of stay was not significantly different between the vitamin D_3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank P = .59; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; P = .62). The difference between the vitamin D_3 group and the placebo group was not significant for in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, −4.1% to 9.2%]; P = .43), admission to the intensive care unit (16.0% vs 21.2%; difference, −5.2% [95% CI, −15.1% to 4.7%]; P = .30), or need for mechanical ventilation (7.6% vs 14.4%; difference, −6.8% [95% CI, −15.1% to 1.2%]; P = .09). Mean serum levels of 25-hydroxyvitamin D significantly increased after a single dose of vitamin D_3 vs placebo (44.4 ng/mL vs 19.8 ng/mL; difference, 24.1 ng/mL [95% CI, 19.5-28.7]; P < .001). There were no adverse events, but an episode of vomiting was associated with the intervention.

CONCLUSIONS AND RELEVANCE Among hospitalized patients with COVID-19, a single high dose of vitamin D_3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04449718

JAMA. 2021;325(11):1053-1060. doi:10.1001/jama.2020.26848
Published online February 17, 2021.

Author Affiliations: Author affiliations are listed at the end of this article.

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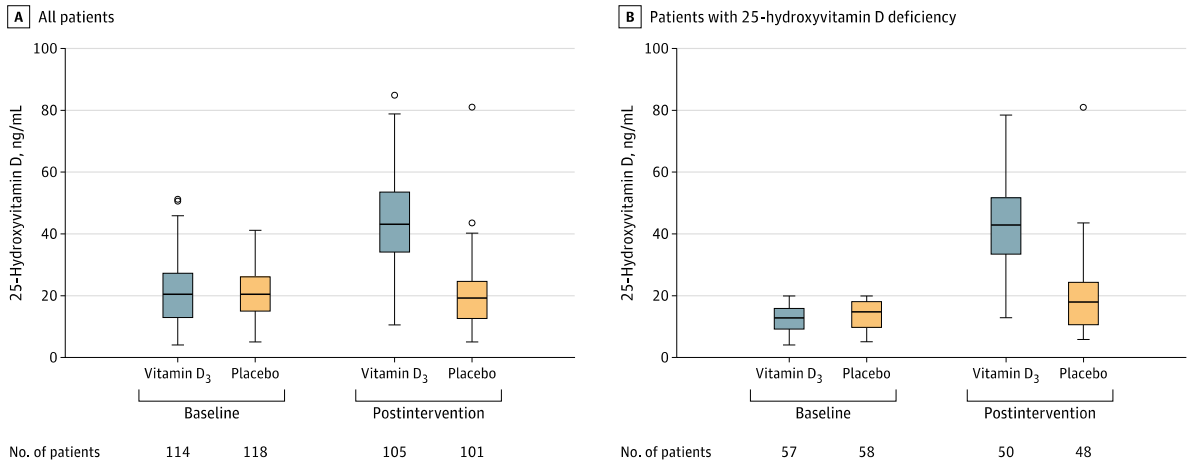

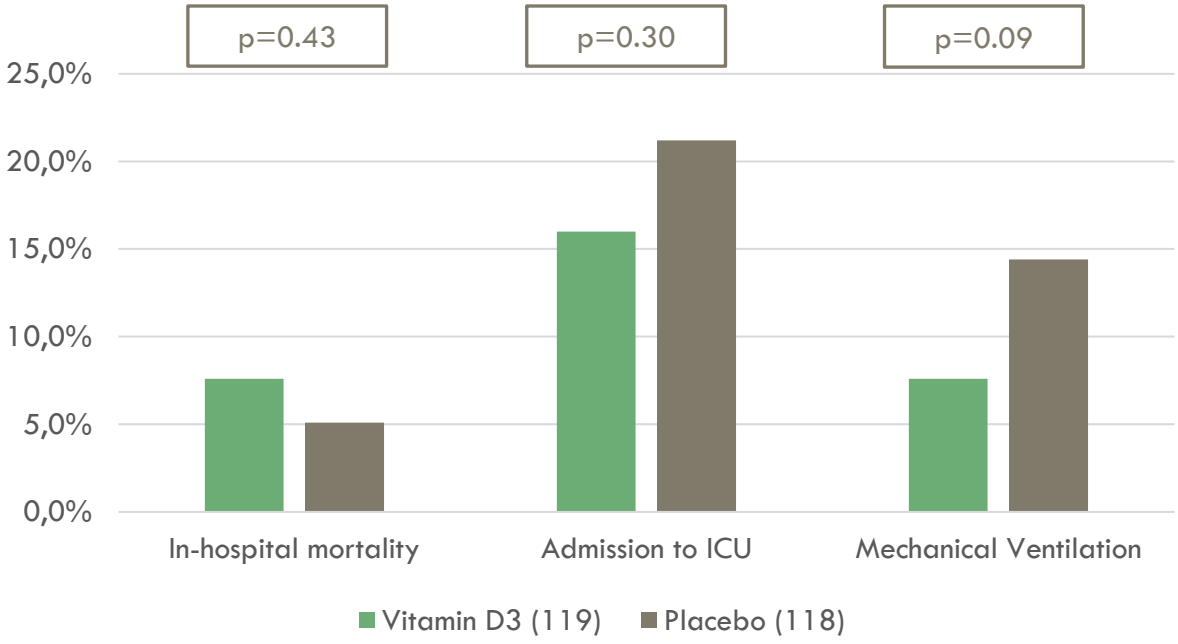

Murai IH, et al. JAMA 2021

scientific reports

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OPEN

Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease

Maheshwar Lakkireddy[1], Srikanth Goud Gadiga[2], R. D. Malathi[2], Madhu Latha Karra[1]✉, I. S. S. V. Prasad Murthy Raju[2], Ragini[2], Sangeetha Chinapaka[2], K. S. S. Sai Baba[1] & Manohar Kandakatla[1]

COVID 19 is known to cause immune dysregulation and vitamin D is a known immunomodulator. This study aims to objectively investigate the impact of Pulse D therapy in reducing the inflammatory markers of COVID-19. Consented COVID-19 patients with hypovitaminosis D were evaluated for inflammatory markers (N/L ratio, CRP, LDH, IL6, Ferritin) along with vitamin D on 0th day and 9th/11th day as per their respective BMI category. Subjects were randomised into VD and NVD groups. VD group received Pulse D therapy (targeted daily supplementation of 60,000 IUs of vitamin D for 8 or 10 days depending upon their BMI) in addition to the standard treatment. NVD group received standard treatment alone. Differences in the variables between the two groups were analysed for statistical significance. Eighty seven out of one hundred and thirty subjects have completed the study (VD:44, NVD:43). Vitamin D level has increased from 16 ± 6 ng/ml to 89 ± 32 ng/ml after Pulse D therapy in VD group and highly significant ($p < 0.01$) reduction of all the measured inflammatory markers was noted. Reduction of markers in NVD group was insignificant ($p > 0.05$). The difference in the reduction of markers between the groups (NVD vs VD) was highly significant ($p < 0.01$). Therapeutic improvement in vitamin D to 80–100 ng/ml has significantly reduced the inflammatory markers associated with COVID-19 without any side effects. Hence, adjunctive Pulse D therapy can be added safely to the existing treatment protocols of COVID-19 for improved outcomes.

COVID-19 pandemic caused by SARS-CoV-2 virus has created an unprecedented hardship in the recent times[1,2]. Serious consequences of COVID-19 were attributed to the immune dysregulation leading to the enhanced production of pro inflammatory mediators (cytokine storm)[3–7]. In the absence of a specific vaccine or a treatment, strategies to minimize the effects of COVID-19 have become extremely important. Recent observational studies have reported that the patients with higher levels of serum vitamin D (vit.D) had less severe symptoms and vice versa and have postulated the usefulness of vit.D in prevention and treatment of COVID-19[3,8–12]. The beneficial effects of vit.D in COVID-19 were attributed to be mediated through its multiple actions on the immune system. Vit.D is known to enhance the production of various anti-microbial peptides by the immune cells and vit.D modulates the immune system according to the internal milieu. It reduces the dysregulated production of self-damaging pro-inflammatory cytokines and promotes the expression of anti-inflammatory cytokines by immune cells[13–18]. The dynamic role of vit.D can be of immense value in the context of immune dysfunction observed in COVID-19 patients with cytokine storm and acute respiratory distress syndrome[2–6].

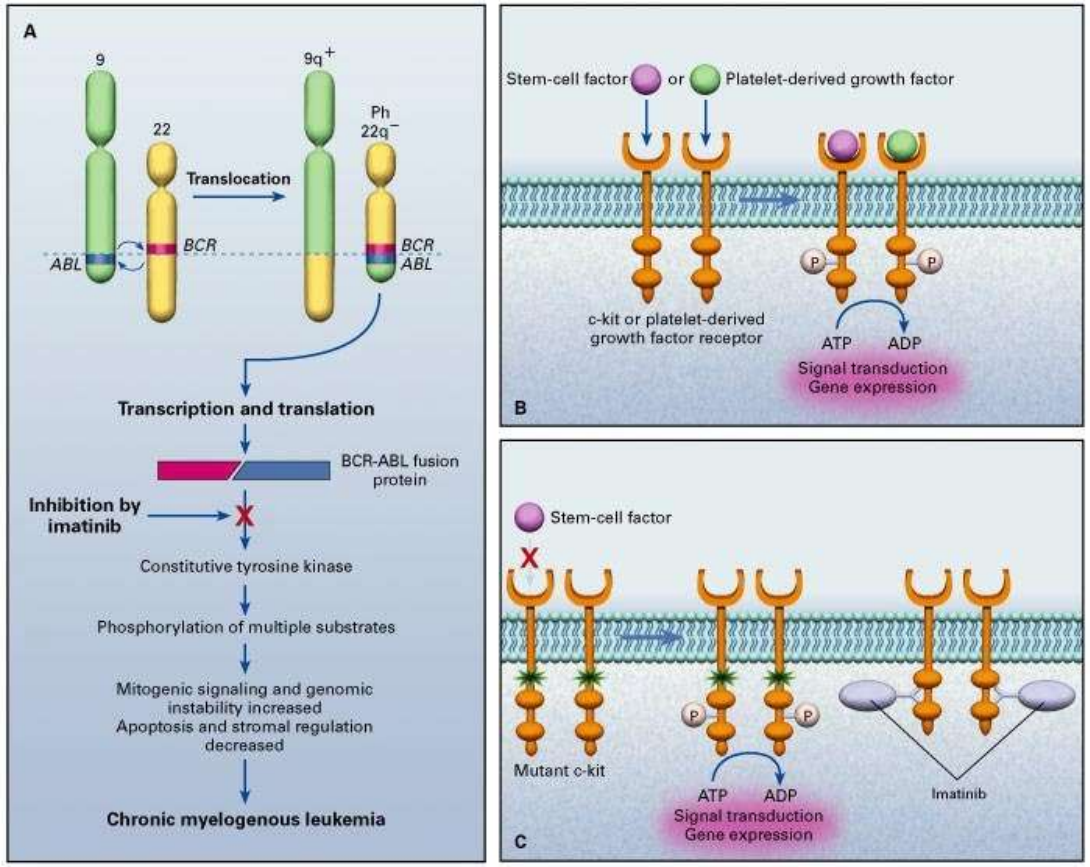
Though the protective immuno-modulatory effects of vit.D were explored in many autoimmune diseases and respiratory tract infections, there is a dearth of information from the randomised clinical trials in COVID-19.

Pulse D therapy is a targeted approach to increase the serum vit.D level by using high dose (60,000 IUs) oral supplementation of vit.D daily for a specific period of time determined by the individual's BMI, initial level of vit.D and the formulation[19].

This study aims to objectively investigate the role of vit.D and the impact of Pulse D therapy in reducing the inflammatory biomarkers of COVID-19.

[1]Department of Orthopaedics/ Biochemistry/ Internal Medicine, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India. [2]Department of General Medicine/ Biochemistry, Gandhi Medical College, Secunderabad, Telangana, India. ✉email: madhu.harini123@gmail.com

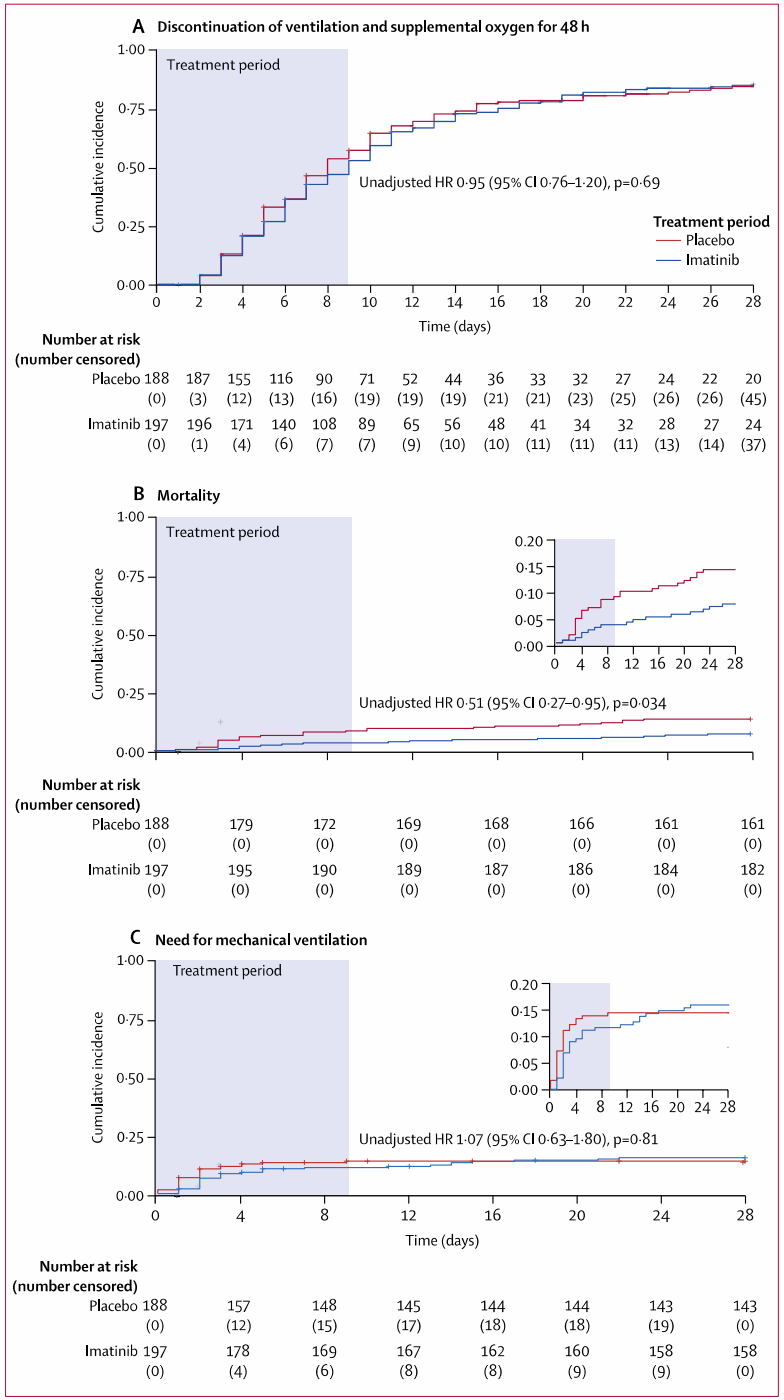
IMATINIB



- BCR–ABL tyrosine-kinase inhibitor
- chronic myeloid leukaemia
  - gastrointestinal stromal tumours
- antiviral properties against other β-coronaviruses in vitro by hindering the early stages of the virus lifecycle.
  - as the upregulation of genes involved in the response against viruses?
- possible immunomodulator capable of reducing pro- inflammatory cytokines, chemokines, and vascular adhesion molecules
- preventing pulmonary endothelial barrier dysfunction observed in some inflammatory conditions, which might lead to a mitigation of pulmonary capillary leak.

IMATINIB

- RCT, Netherlands
- Hospitalised patients (aged ≥18 years) with supplemental Oxygen
- Excluded if:
  - severe pre-existing pulmonary disease
  - pre-existing heart failure
  - undergone active treatment of a haematological or non-haematological malignancy (12 months)
  - receiving concomitant treatment with medication known to strongly interact with imatinib.
- Loading dose of 800 mg on day 0 followed by 400 mg daily on days 1–9, or placebo.
- Imatinib group (n=204) or placebo group (n=196).

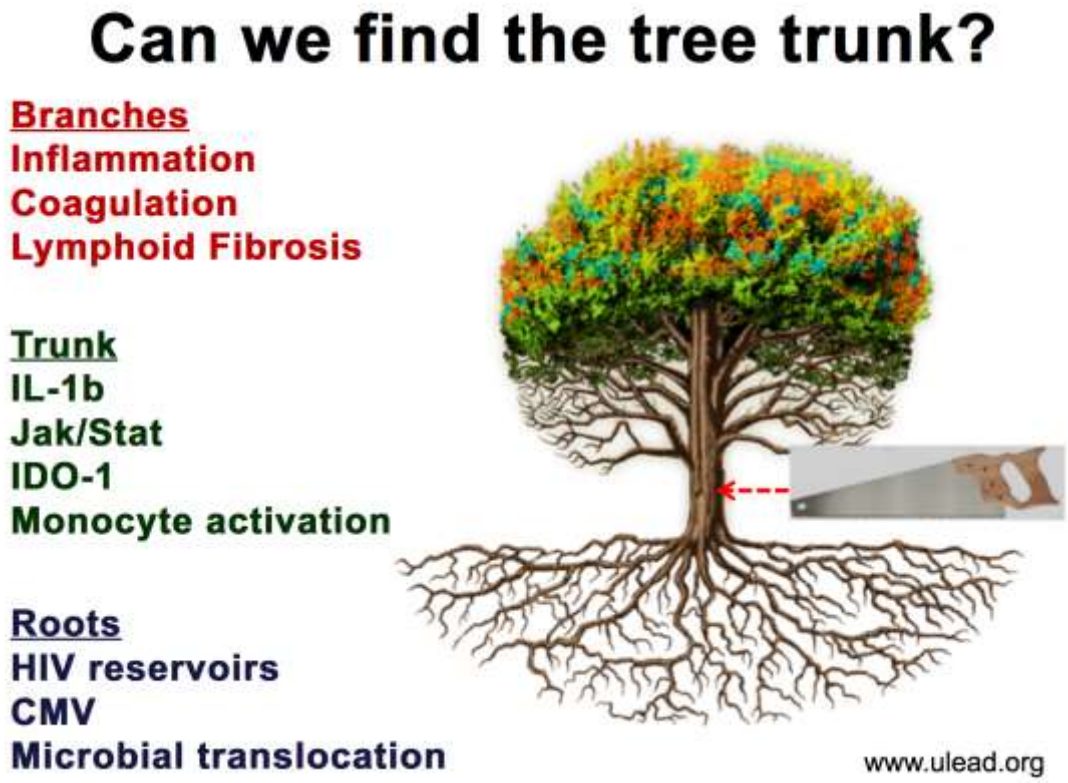


Aman J, et al. Lancet Resp Med 2021

CONCLUSIONS

No magic bullet but probably the combination of timely and tailored interventions according to the risk of progression, phase of disease and extrapulmonary involvement

- Dexamethasone 6 mg 5-10 days
- Tocilizumab 8 mg/Kg (one/two doses?)
- Anakinra in high-risk patients (not on NIV/IV)
- Baricitinib (early? late?)



Peter Hunt, personal communication

CONCLUSIONS

No magic bullet but probably the combination of timely and tailored interventions according to the risk of progression, phase of disease and extrapulmonary involvement

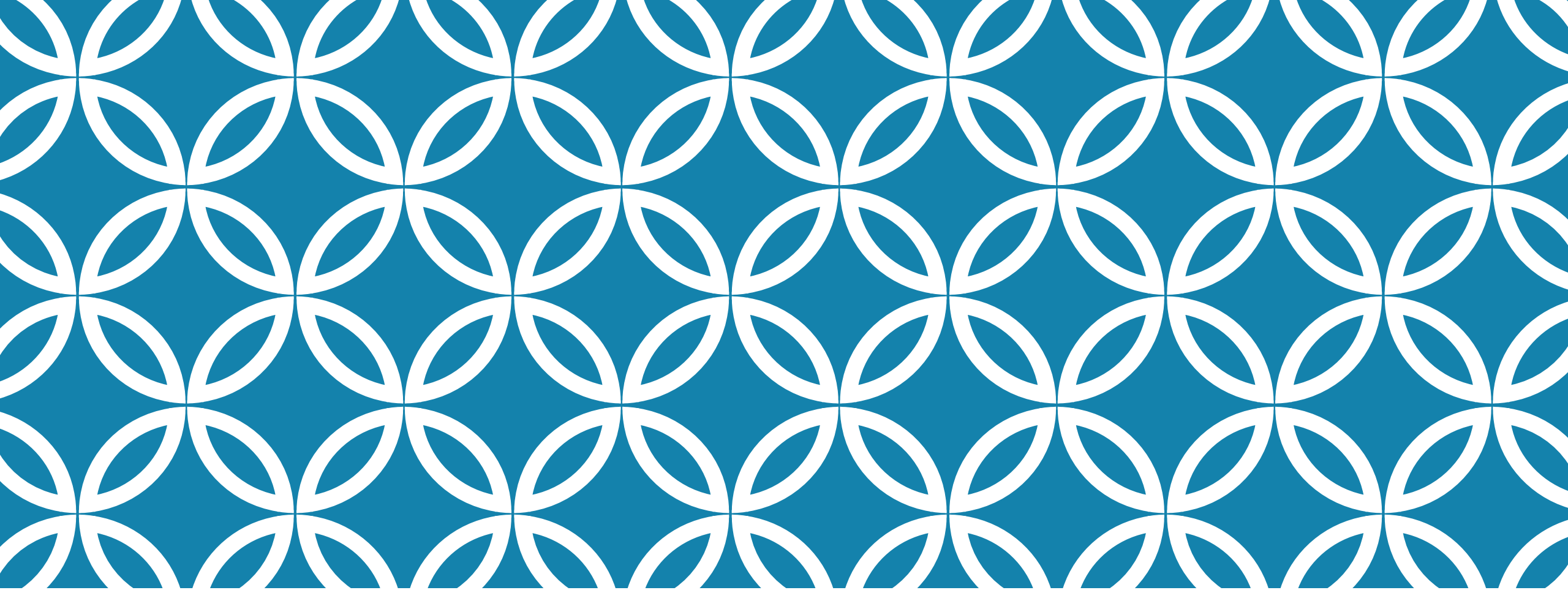
- Dexamethasone 6 mg 5-10 days
- Tocilizumab 8 mg/Kg (one/two doses?)
- Anakinra in high-risk patients (not on NIV/IV)
- Baricitinib (early? late?)

Several ongoing RCTs

Need accurate and careful evaluation of setting, methods and results

Open Questions

- Dose and choice of corticosteroids (vs. dexamethasone 6 mg as SOC)
- Anti-IL6 vs. anti IL-1 vs. JAK-i?
- Are the available data enough to widely use colchicine in outpatients?
- High-dose calcifediol?



THANK YOU FOR YOUR ATTENTION

andrea.calcagno@unito.it