COVID 19: THE CHALLENGING PATHWAY OF SARS-COV-2/COVID-19 MANAGEMENT

Immune modulation

Andrea Calcagno

University of Torino, Italy

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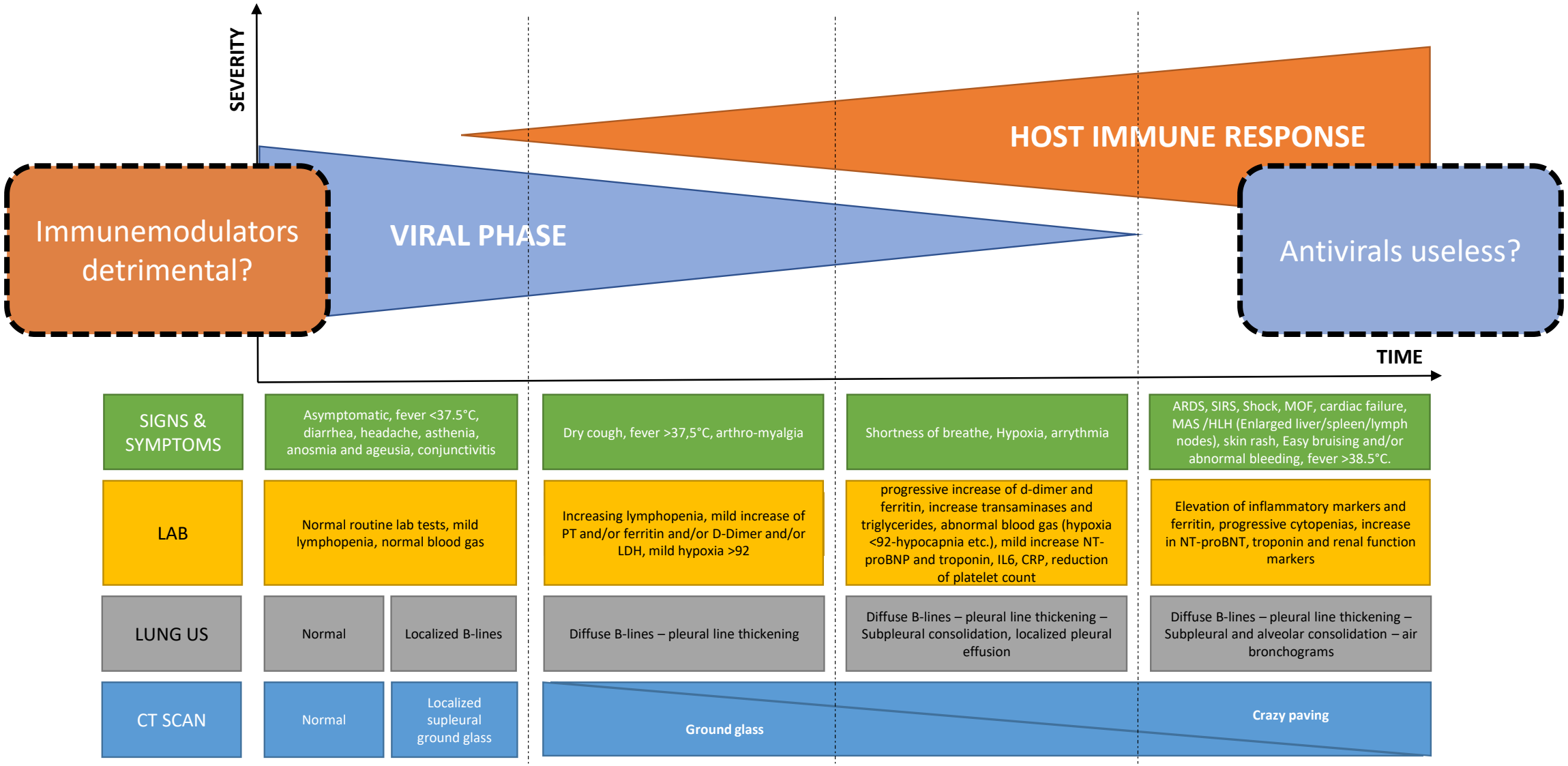
Potential Conflict of Interest

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.



http://www.rheumapainacademy.com/wp-content/uploads/2020/03/Algoritmo-COVID19.pdf

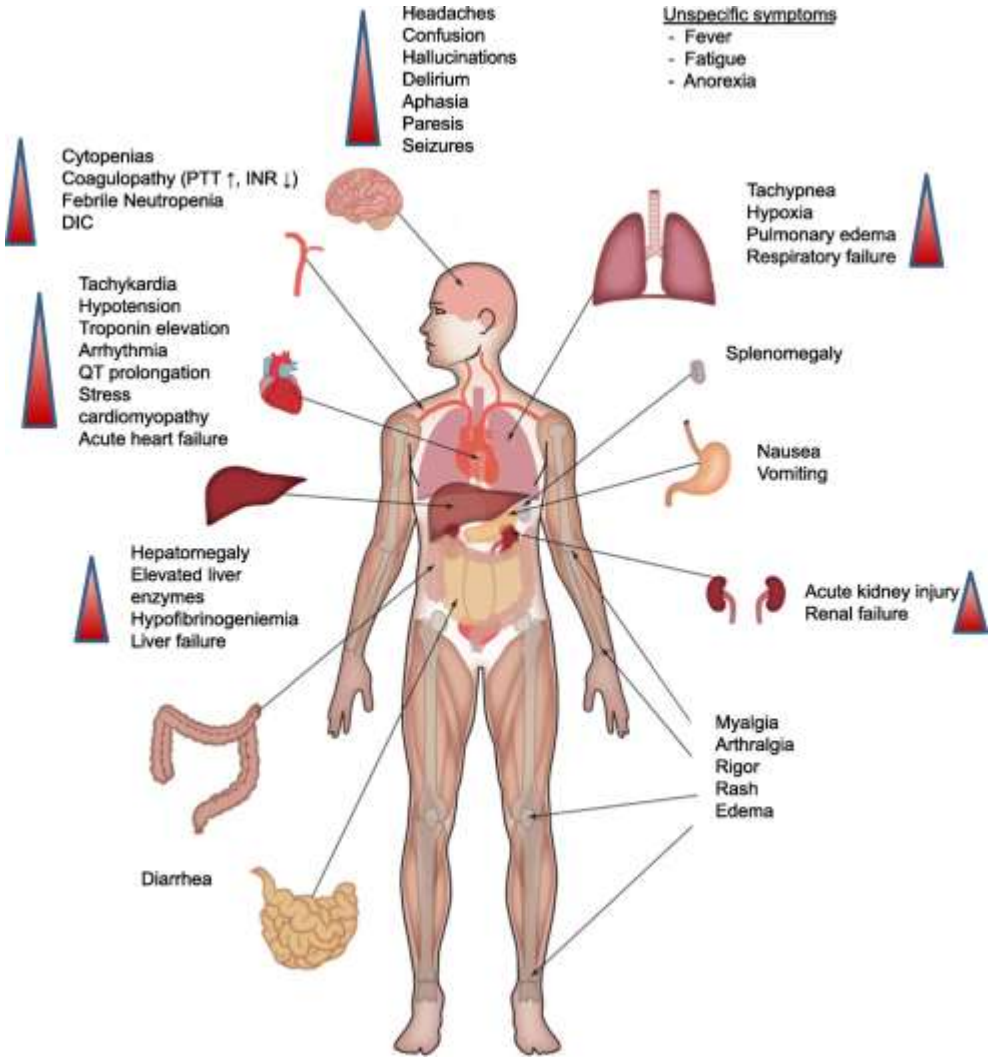
Immune abnormalities

From the point of view of rheumatologists, except for respiratory failure, the critical COVID-19 patients have common features:

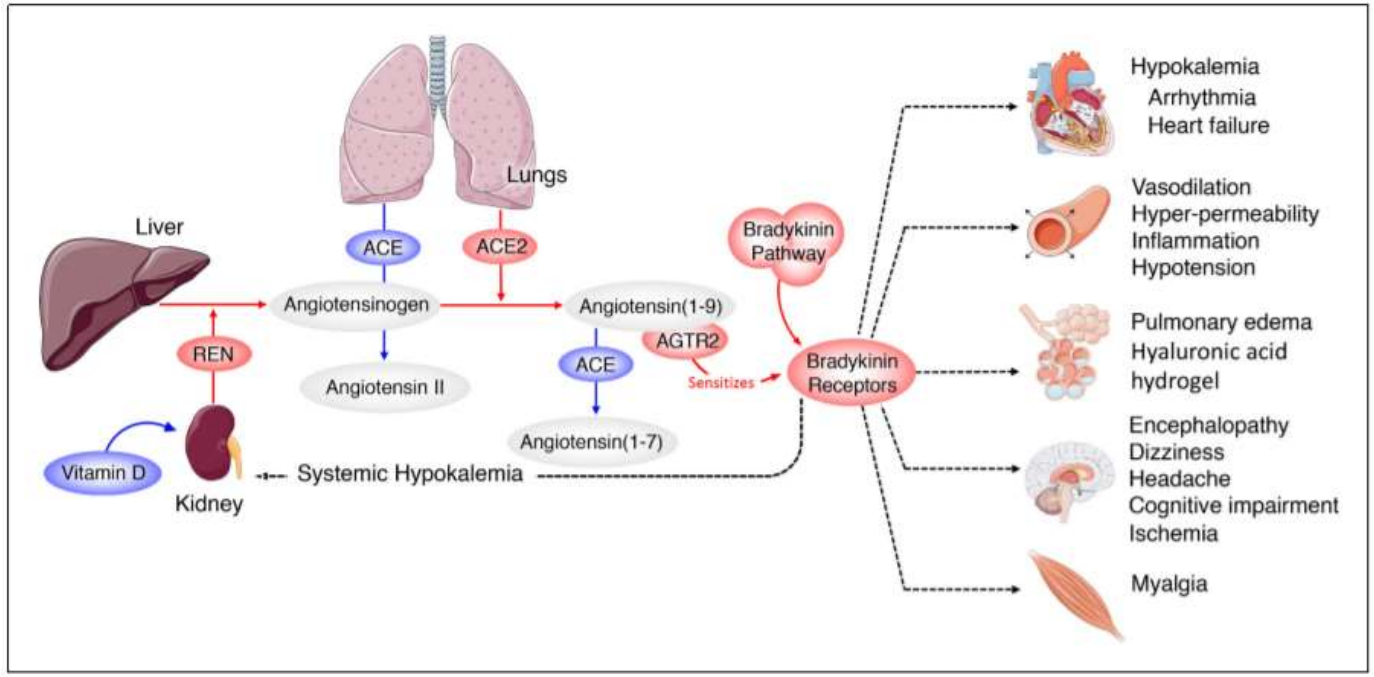
1) sudden deterioration of disease around one to two weeks after onset;
2) much lower level of **lymphocytes**, especially natural killer (NK) cells in peripheral blood;
3) **extremely high inflammatory** parameters, including C reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, IL-8, et al);
4) destroyed immune system revealed by **atrophy of spleen and lymph nodes**, along with reduced lymphocytes in lymphoid organs;
5) the majority of **infiltrated immune cells in lung lesion are monocytes and macrophages**, but minimal lymphocytes infiltration;
6) mimicry of **vasculitis, hypercoagulability and multiple organs damage**.

Zhang W, et al. Clin Imunology 2020

Cytokine release syndrome

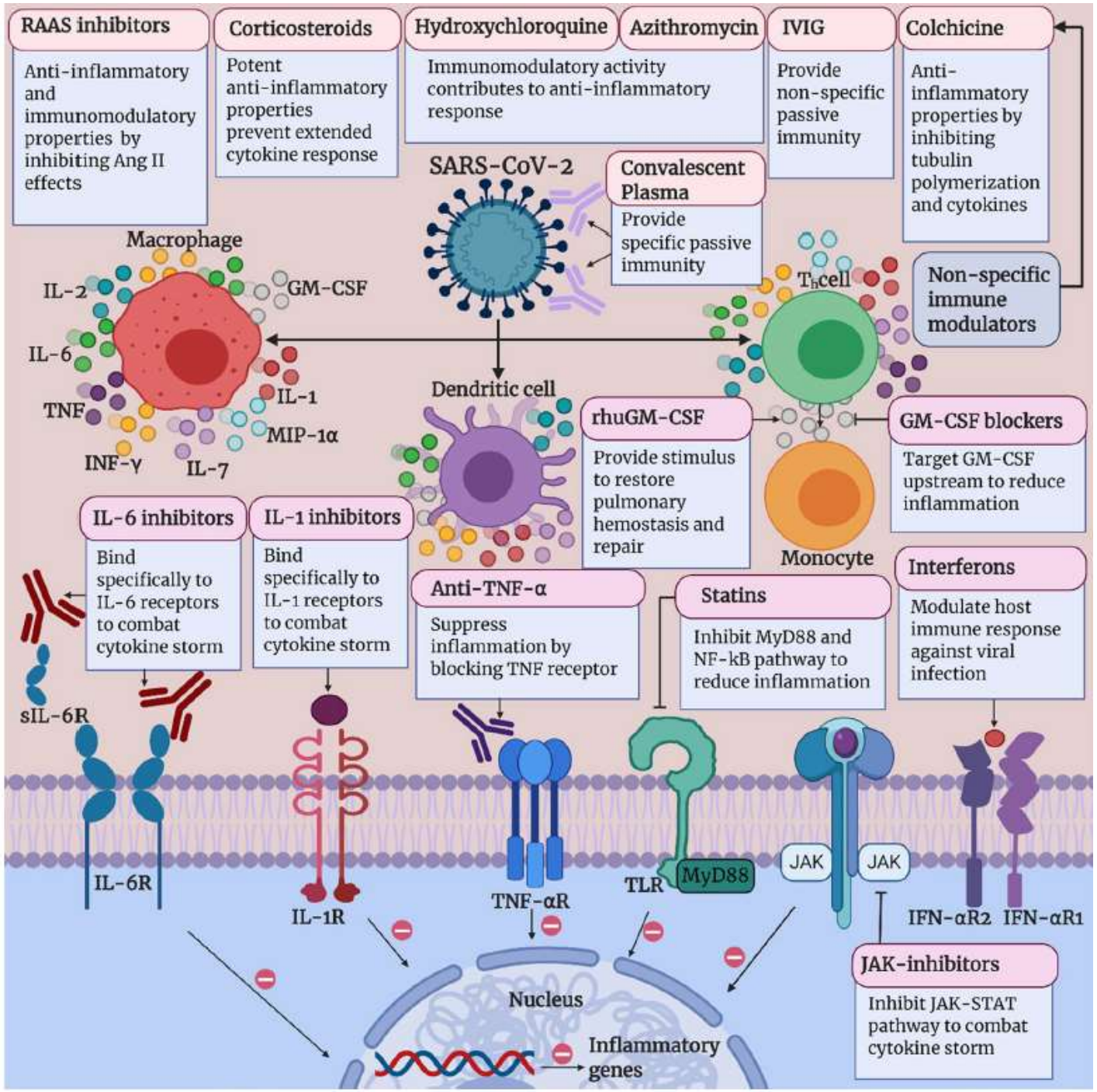


Bradykinin storm syndrome



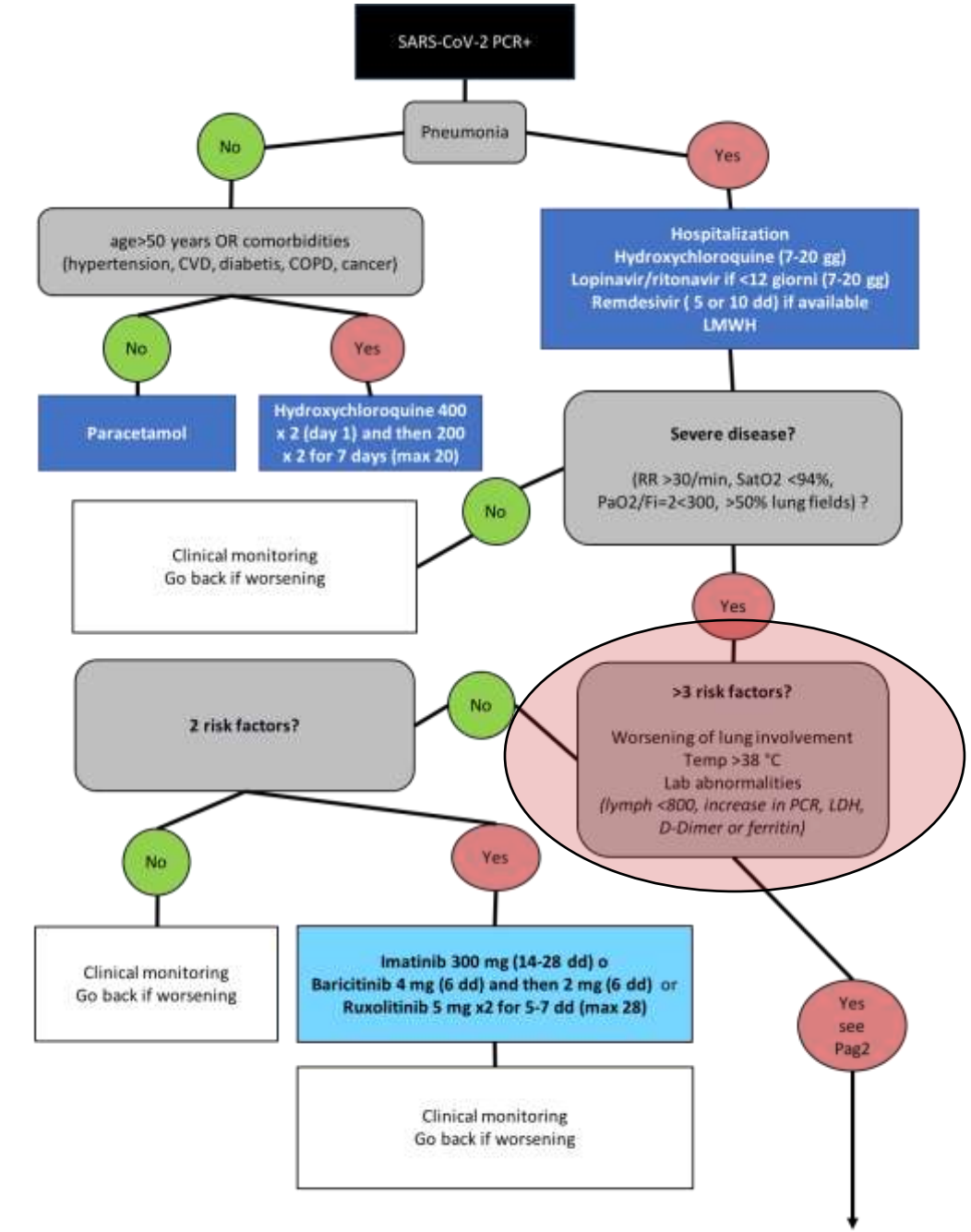
Shimabukuro-Vornhagen A, et al. J Immun Ther Cancer 2018; Garvin MR et al. eLife 2020;9:e59177

therapeutics

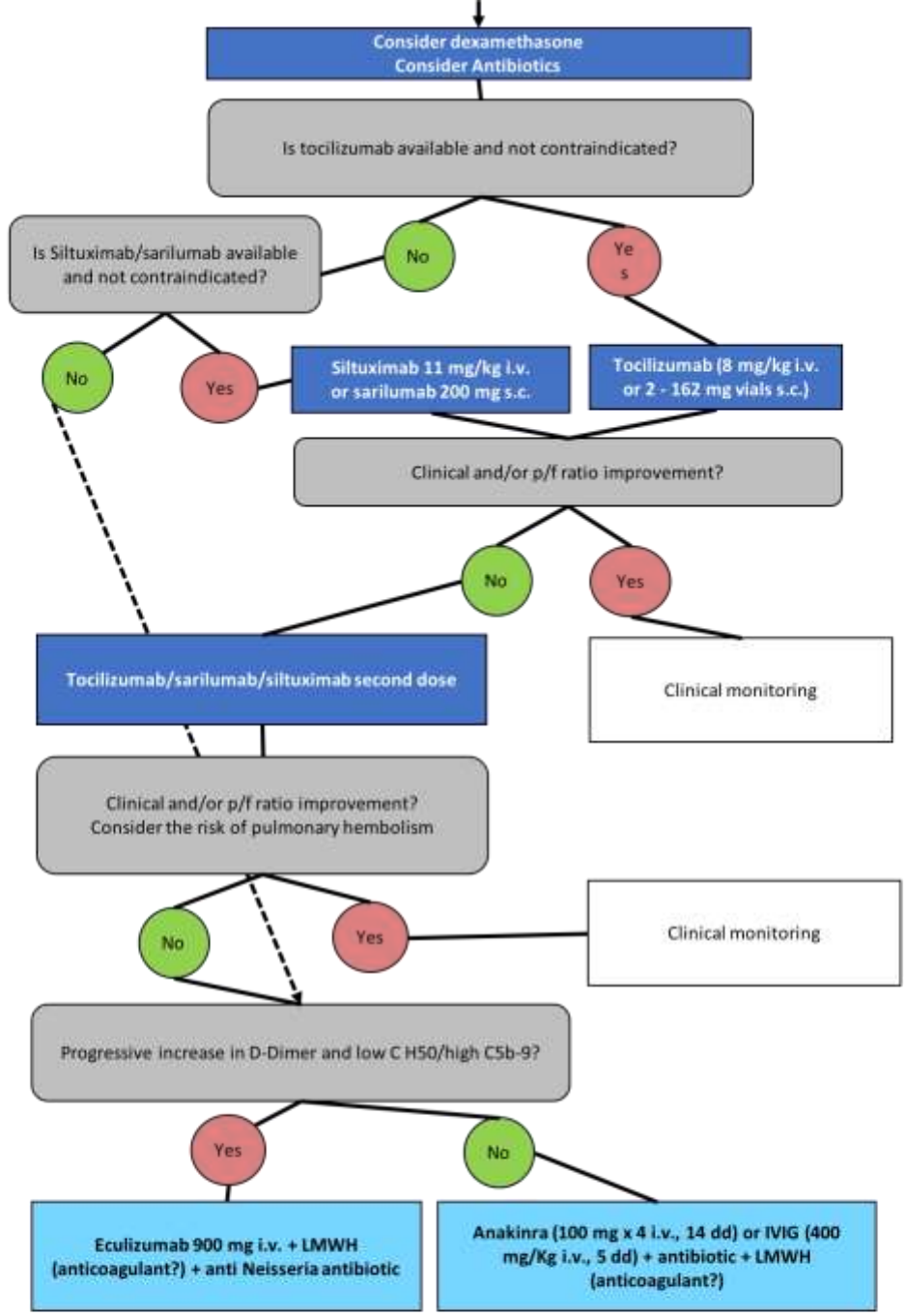


Immune modulators

- Corticosteroids
- Tocilizumab
- Sarilumab
- Siltuximab
- Baricitinib
- Ruxolitinib
- Imatinib
- Thalidomide
- IGIV
- Eculizumab
- Anakinra

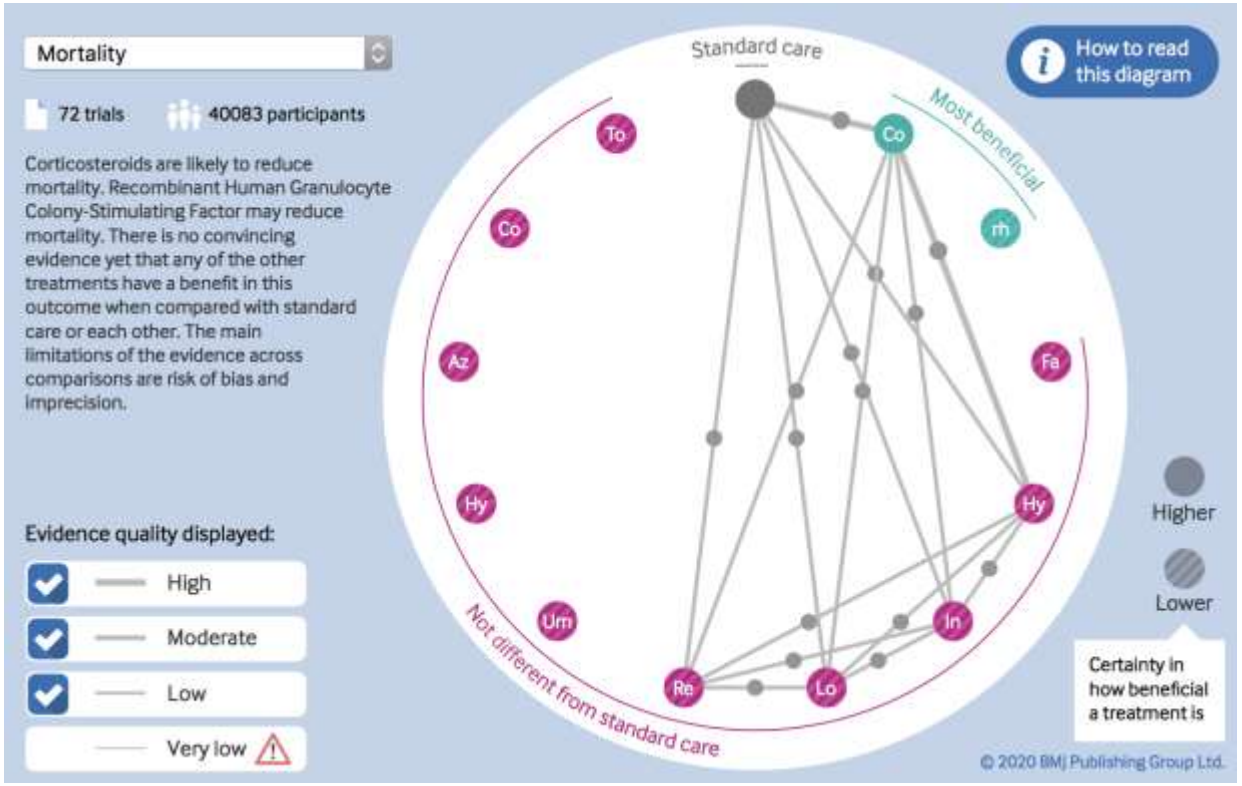


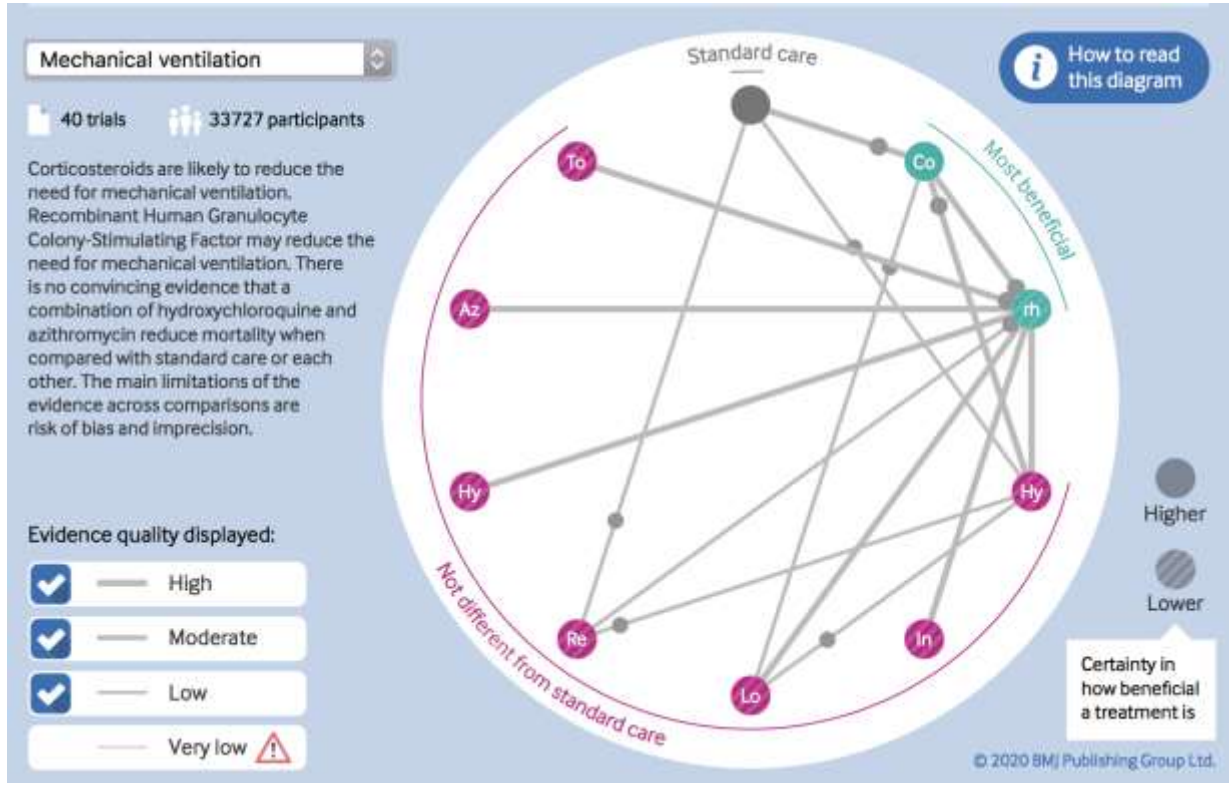
Treatment in light blue boxes are based on expert opinions and patients have to be enrolled in clinical studies



Treatment in light blue boxes are based on expert opinions and patients have to be enrolled in clinical studies

Corticosteroids





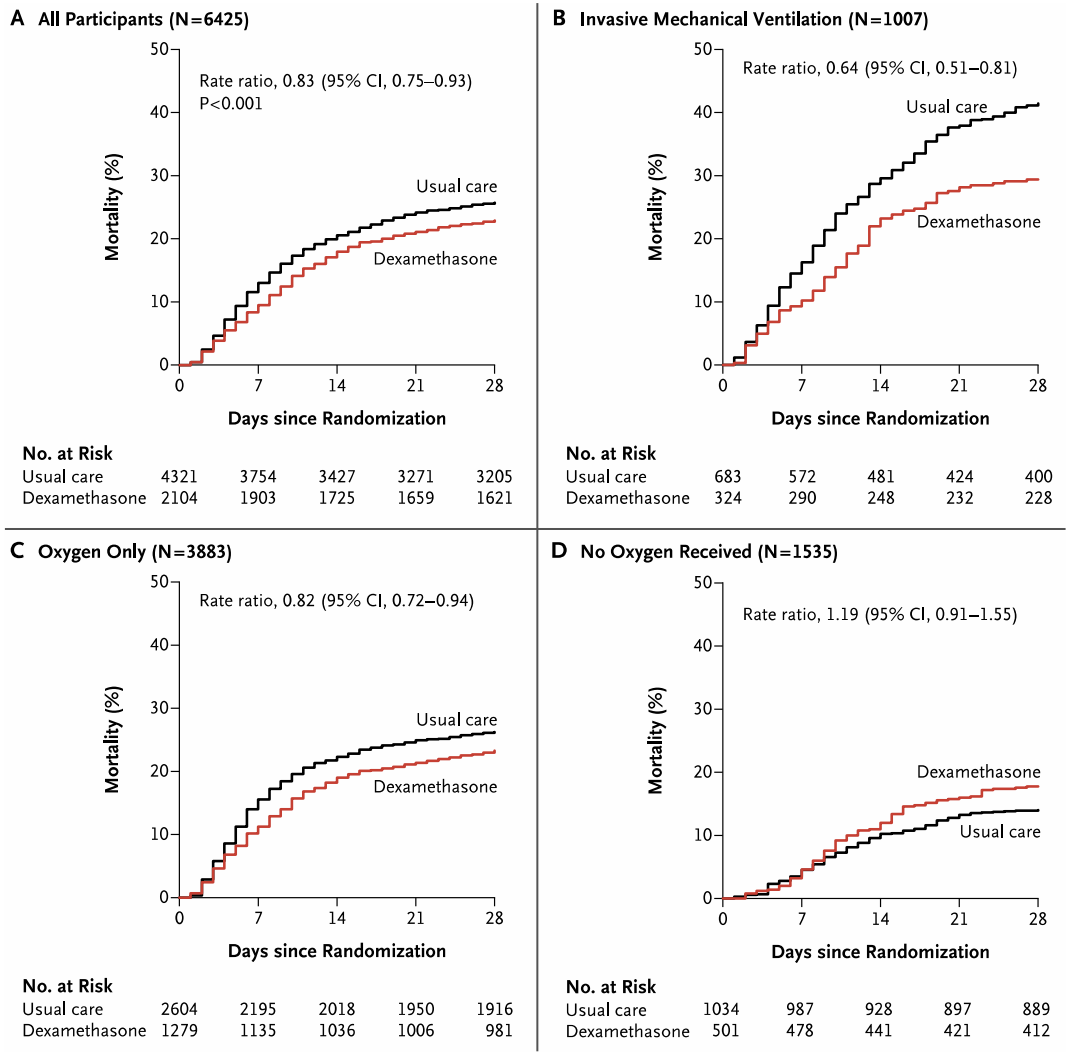
https://www.bmj.com/content/370/bmj.m2980

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

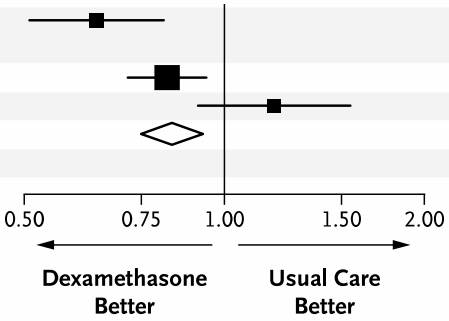


Table 2. Primary and Secondary Outcomes.

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)

Corticosteroids: other RCTs

Early STOP after RECOVERY data

METCOVID (Jeronimo, CID)

194 vs. 199, hospitalized
Methylprednisolone 0.5 mg/Kg x 2 for 5 days
No effect on mortality (Yes in those aged >60)
More insulin needed

CoDex (Tomazini, JAMA)

151 vs. 148, ARDS
Dexamethasone 20 mg (dd 1-5) and 10 mg (dd 6-10)
No effect on mortality but more ventilator-free days
More secondary infections, insulin and Aes

CapeCOVID (Dequin, JAMA)

76 vs. 73, ICU
Hydrocortisone 200 mg for 7 days and then ⇣
No effect on death/persistent respiratory support

REMAP-CAP (JAMA)

137 vs. 146 vs. 101, ICU
Hydrocortisone 50/100 x 4 for 7 dd vs. shock-dependant vs. SOC
Higher probability of improvement (no effect on mortality)

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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)	

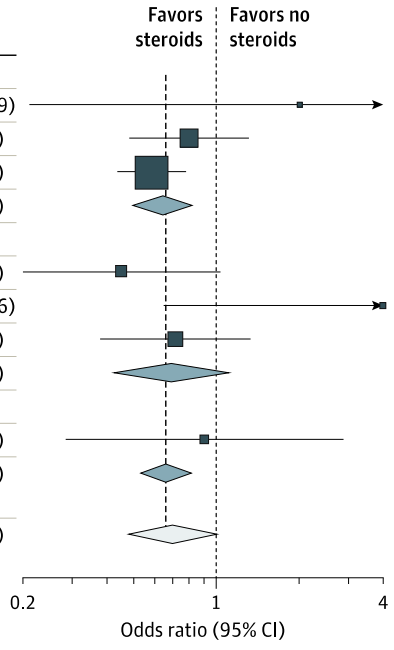
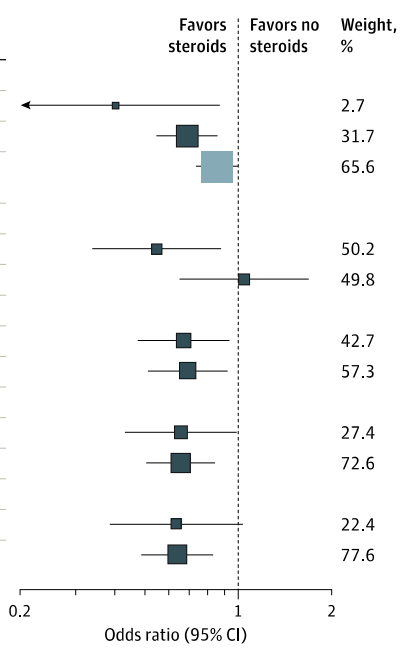


Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization

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

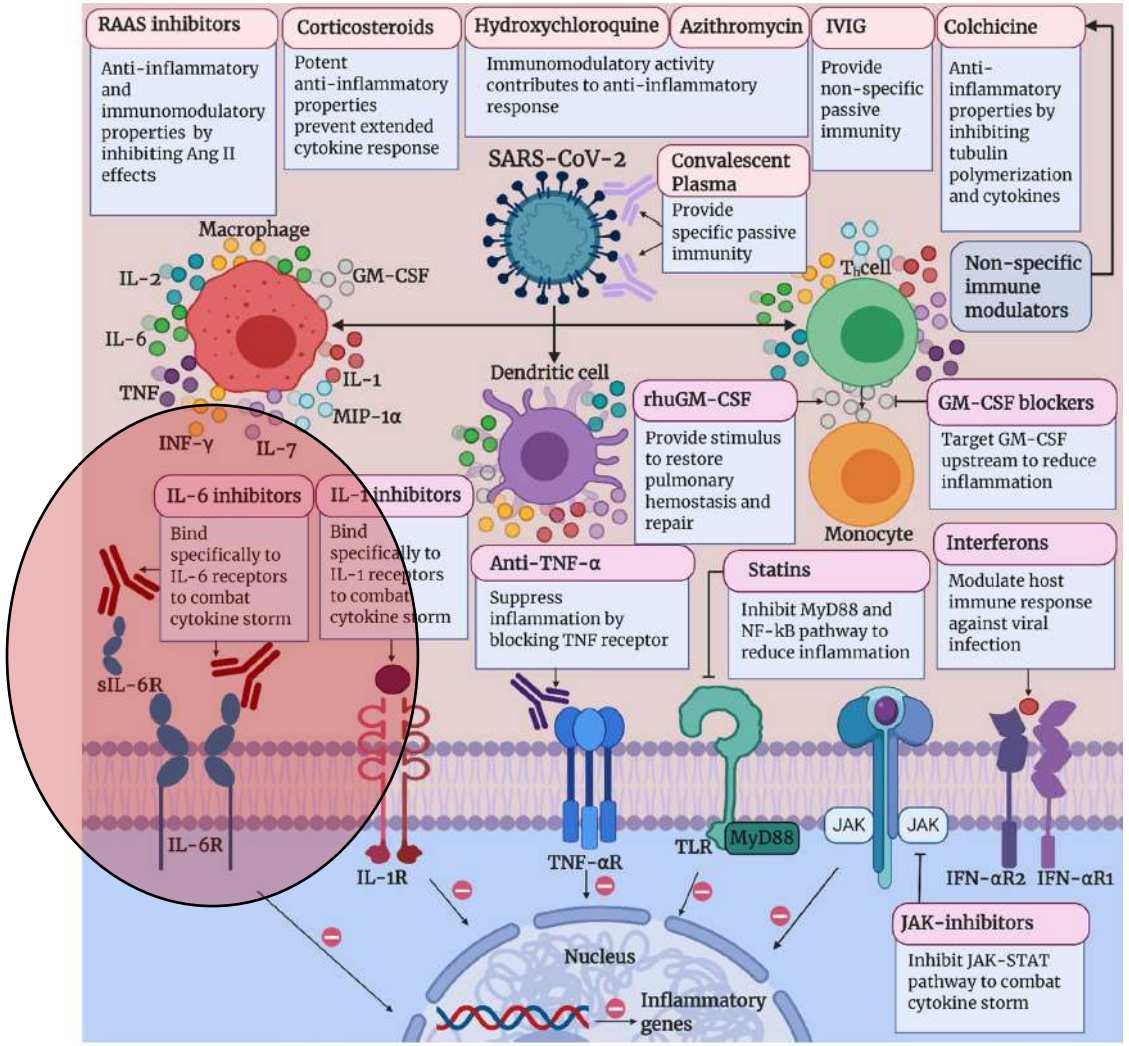


ANTI IL-6/IL-6R medications

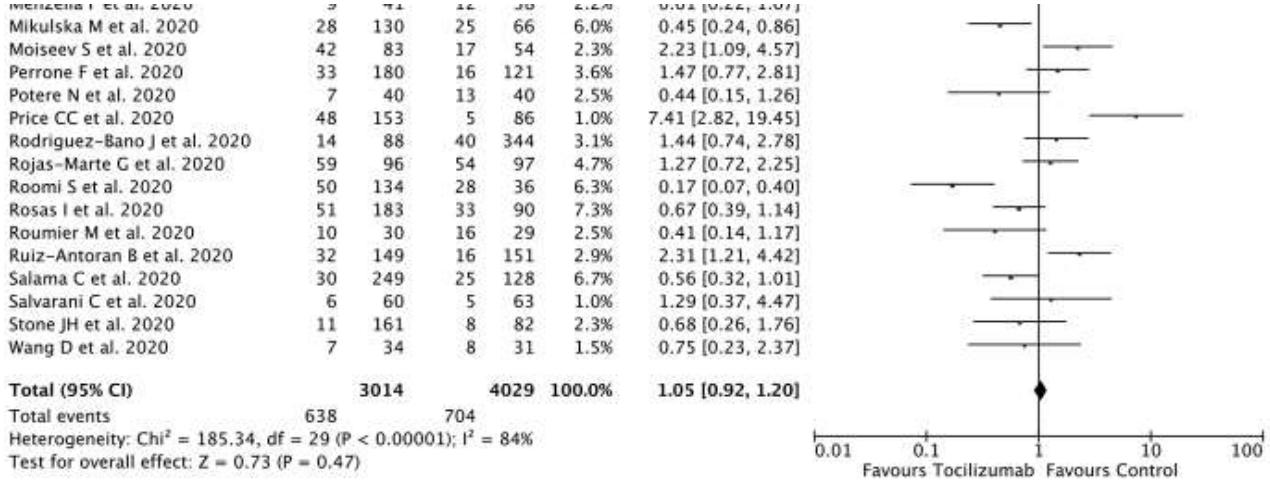
1. **Tocilizumab**
   - Humanized MoA against IL-6R
   - Rheumatoid arthritis and systemic juvenile idiopathic arthritis

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

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

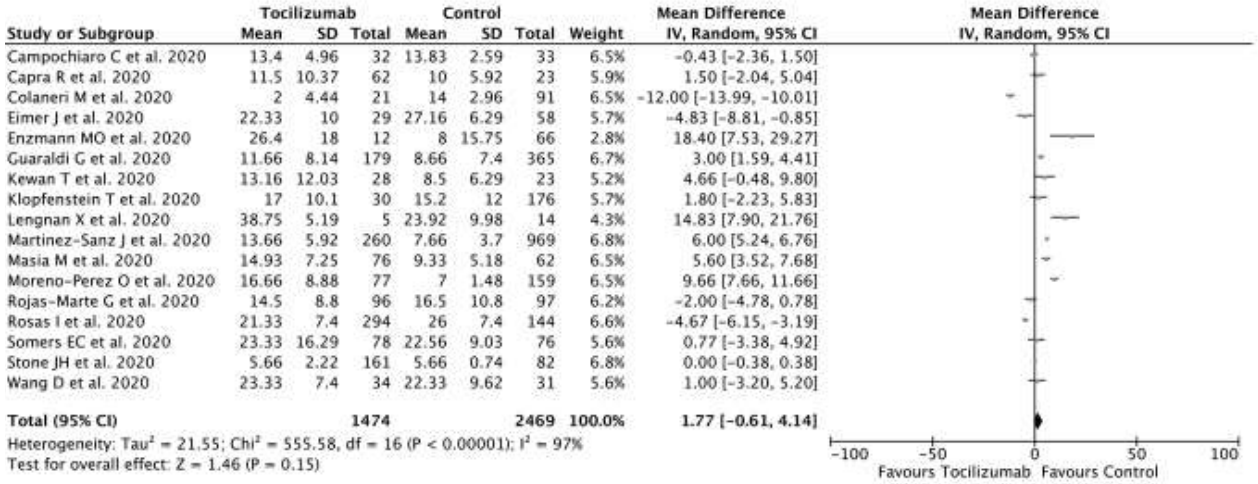


Anti IL-6/IL-6R: observational studies



Study						
Mikulska M et al. 2020	28	130	25	66	6.0%	0.45 [0.24, 0.86]
Moiseev S et al. 2020	42	83	17	54	2.3%	2.23 [1.09, 4.57]
Perrone F et al. 2020	33	180	16	121	3.6%	1.47 [0.77, 2.81]
Potere N et al. 2020	7	40	13	40	2.5%	0.44 [0.15, 1.26]
Price CC et al. 2020	48	153	5	86	1.0%	7.41 [2.82, 19.45]
Rodriguez-Bano J et al. 2020	14	88	40	344	3.1%	1.44 [0.74, 2.78]
Rojas-Marte G et al. 2020	59	96	54	97	4.7%	1.27 [0.72, 2.25]
Roomi S et al. 2020	50	134	28	36	6.3%	0.17 [0.07, 0.40]
Rosas I et al. 2020	51	183	33	90	7.3%	0.67 [0.39, 1.14]
Roumier M et al. 2020	10	30	16	29	2.5%	0.41 [0.14, 1.17]
Ruiz-Antoran B et al. 2020	32	149	16	151	2.9%	2.31 [1.21, 4.42]
Salama C et al. 2020	30	249	25	128	6.7%	0.56 [0.32, 1.01]
Salvarani C et al. 2020	6	60	5	63	1.0%	1.29 [0.37, 4.47]
Stone JH et al. 2020	11	161	8	82	2.3%	0.68 [0.26, 1.76]
Wang D et al. 2020	7	34	8	31	1.5%	0.75 [0.23, 2.37]
Total (95% CI)		**3014**		**4029**	**100.0%**	**1.05 [0.92, 1.20]**
Total events	638		704			

Heterogeneity: $Chi^2 = 185.34$, df = 29 ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: Z = 0.73 (P = 0.47)



Study or Subgroup	Tocilizumab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Campochiaro C et al. 2020	13.4	4.96	32	13.83	2.59	33	6.5%	-0.43 [-2.36, 1.50]
Capra R et al. 2020	11.5	10.37	62	10	5.92	23	5.9%	1.50 [-2.04, 5.04]
Colaneri M et al. 2020	2	4.44	21	14	2.96	91	6.5%	-12.00 [-13.99, -10.01]
Eimer J et al. 2020	22.33	10	29	27.16	6.29	58	5.7%	-4.83 [-8.81, -0.85]
Enzmann MO et al. 2020	26.4	18	12	8	15.75	66	2.8%	18.40 [7.53, 29.27]
Guaraldi G et al. 2020	11.66	8.14	179	8.66	7.4	365	6.7%	3.00 [1.59, 4.41]
Kewan T et al. 2020	13.16	12.03	28	8.5	6.29	23	5.2%	4.66 [-0.48, 9.80]
Klopfenstein T et al. 2020	17	10.1	30	15.2	12	176	5.7%	1.80 [-2.23, 5.83]
Lengnan X et al. 2020	38.75	5.19	5	23.92	9.98	14	4.3%	14.83 [7.90, 21.76]
Martinez-Sanz J et al. 2020	13.66	5.92	260	7.66	3.7	969	6.8%	6.00 [5.24, 6.76]
Masia M et al. 2020	14.93	7.25	76	9.33	5.18	62	6.5%	5.60 [3.52, 7.68]
Moreno-Perez O et al. 2020	16.66	8.88	77	7	1.48	159	6.5%	9.66 [7.66, 11.66]
Rojas-Marte G et al. 2020	14.5	8.8	96	16.5	10.8	97	6.2%	-2.00 [-4.78, 0.78]
Rosas I et al. 2020	21.33	7.4	294	26	7.4	144	6.6%	-4.67 [-6.15, -3.19]
Somers EC et al. 2020	23.33	16.29	78	22.56	9.03	76	5.6%	0.77 [-3.38, 4.92]
Stone JH et al. 2020	5.66	2.22	161	5.66	0.74	82	6.8%	0.00 [-0.38, 0.38]
Wang D et al. 2020	23.33	7.4	34	22.33	9.62	31	5.6%	1.00 [-3.20, 5.20]
Total (95% CI)			**1474**			**2469**	**100.0%**	**1.77 [-0.61, 4.14]**

Heterogeneity: $Tau^2 = 21.55$; $Chi^2 = 555.58$, df = 16 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: Z = 1.46 (P = 0.15)

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

High heterogeneity in doses, timing, inclusion criteria

Author	n	Age	Dose	Design	Additional treatment	Inclusion Criteria	Findings
Mastroian	12	58	324 mg sc (1 or 2)	Retr Obs	ATB, LPV, HCQ	Severe	Improvement in clinical signs and CT scan
Kewan	28/23	62	400 mg iv	Retr Obs	STER, HCQ, AZITR	Severe, LAB	Shorter time on vasopressors
Potere	6/10	55	324 mg sc	Retr Obs	-	LAB	No clinical progression (0 vs. 50%)
Roomi	32/144	65	?	Retr Obs	-	Hosp	No effect
Pettit	74/74	66	400 mg iv	Retr Obs	-	Severe, LAB 70% ICU	Higher mortality and late infections rates
Ip	134/547	?	400 mg iv	Retr Obs	-	ICU	Lower mortality (HR 0.76)
Klopfeinst	30/176	75	8 mg/kg iv (2?)	Retr Obs	-	Severe, LAB	Lower mortality or IMV
Mikulska	29/196	64	8 mg/kg iv (2?)	Retr Obs	STER, LMWH, ATB	Rx, Hosp	Lower mortality (+/- STER, HR 0.41)
Rivera	21/238	-	-	Retr Obs	LMWH, ster	-	Lower mortality (HR 0.37)
De Rossi	90/158	63	400 iv/324 sc	Retr Obs	LPV/HCQ	Severe	Lower mortality (HR 0.06)
Guaraldi	179/544	64	8 mg/kg iv (2) 324 mg sc (1)	Retr Obs	-	ARDS	Lower mortality (HR 0.38)
Biran	210/764	68	400 iv (1 or 2)	Retr Obs	Ster 46%, HCQ 95%	ICU	Lower mortality (HR 0.61-0.71)

Mastroianni A, et al. eClinMed 2020; Kewan T, et al. eClinMed 2020; Potere N, et al. Int J Inf Dis 2020; Roomi S, et al. J Med Intern Res 2020; Pettit MN, et al. JMV 2020; Klopfeinstein T, et al. Int J ID 2020; Ip A, et al. PlosOne 2020; Mikulska M, et al. PlosOne 2020; Rivera-Izauierdo, et al. Med Clin 2020; De Rossi N, et al. e Clin Med 2020; Guaraldi G, et al. Lancet Rheum 2020; Biran N, et al. Lancet Rheum 2020

Pulmonol. 2020;xxx(xx):xxx–xxx

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review

A. Cortegiani[a,*], M. Ippolito[a], M. Greco[b,c], V. Granone[b,c], A. Protti[b,c], C. Gregoretti[a,d], A. Giarratano[a], S. Einav[e], M. Cecconi[b,c]

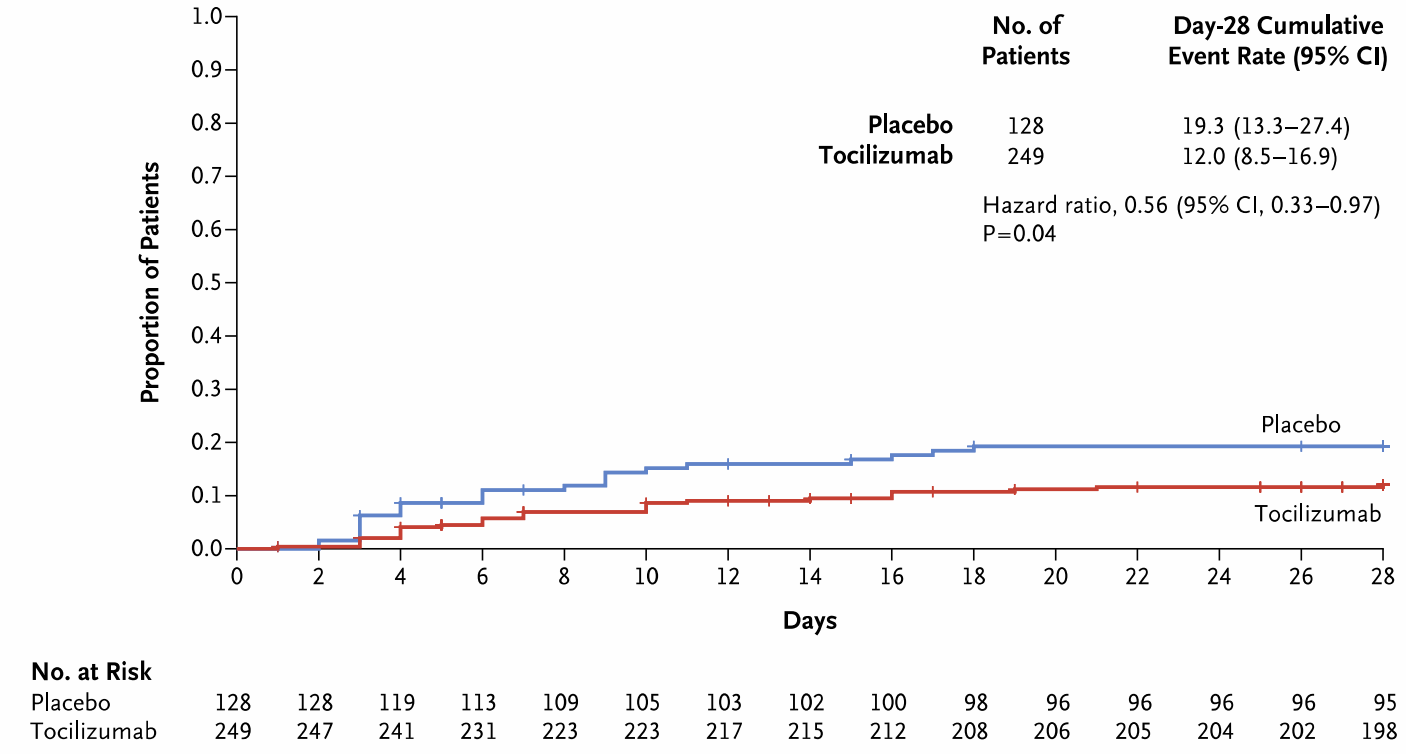
- Although many of the patients included in these studies had severe or critical disease and many were admitted to ICUs, **drawing conclusions from the findings of these studies is a leap of faith, given that most had small sample sizes and high or moderate risk of bias, mostly due to confounding.**
- The identified studies also varied in dosing (single or double), and drug availability issues emerged in some centres, which may have influenced both sample sizes and study designs.
- Regarding the timing of drug administration, that could therefore potentially determine treatment outcomes, a pre-print study evaluated the effect of early vs late administration of the drug on the outcomes, but the association remains unclear and understudied. The authors found that for each addi- tional day of delay from the admission to tocilizumab administration, the odds of receiving mechanical ventilation independently increase by 21% (95% CI: [1.08, 1.38], p = 0.002).
- Clinical studies on patients with COVID-19 have also evoked some safety concerns. The risk of secondary infection complications is unclear.

Petrak R, et al. Tocilizumab as a therapeutic agent for critically Ill patients infected with SARS-CoV-2. medRxiv. 2020

Tocilizumab: RCTs (COVACTA)

- Iv Tocilizumab vs. Placebo plus SOC, randomised, double-blind, placebo-controlled phase III study, n=450
- Hospitalised adult patients with severe COVID-19 associated pneumonia
  - **Primary endpoint: 7-category ordinal scale clinical status**
    - **not met → (p=0.36; odds ratio [95% CI] = 1.19 [0.81, 1.76]**
  - No difference in mortality 19.7% vs. 19.4% →difference 0.3% [-7.6%, 8.2%], p=0.9410
  - Time to hospital discharge shorter in patients on toci (20 vs. 28 days, p=0.0370);
  - The difference in ventilator-free days was not statistically significant (22 vs. 16.5 days, p=0.3202);
  - Similar rates of infections (38.3% vs. 40.6%) and serious infections (21.0% vs. 25.9%).

Tocilizumab: RCTs (EMPACTA)



Salama C, et al. NEJM 2021

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

Carlos Salama, M.D., Jian Han, Ph.D., Linda Yau, Ph.D., William G. Reiss, Pharm.D., Benjamin Kramer, M.D., Jeffrey D. Neidhart, M.D., Gerard J. Criner, M.D., Emma Kaplan-Lewis, M.D., Rachel Baden, M.D., Lavannya Pandit, M.D., Miriam L. Cameron, M.D., Julia Garcia-Diaz, M.D., Victoria Chávez, M.D., Martha Mekebeb-Reuter, M.D., Ferdinando Lima de Menezes, M.D., Reena Shah, F.R.C.P., Maria F. González-Lara, M.D., Beverly Assman, M.S., Jamie Freedman, M.D., Ph.D., and Shalini V. Mohan, M.D.

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) pneumonia is often associated with hyperinflammation. Despite the disproportionate incidence of Covid-19 among underserved and racial and ethnic minority populations, the safety and efficacy of the anti–interleukin-6 receptor antibody tocilizumab in patients from these populations who are hospitalized with Covid-19 pneumonia are unclear.

METHODS

We randomly assigned (in a 2:1 ratio) patients hospitalized with Covid-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either tocilizumab (8 mg per kilogram of body weight intravenously) or placebo. Site selection was focused on the inclusion of sites enrolling high-risk and minority populations. The primary outcome was mechanical ventilation or death by day 28.

RESULTS

A total of 389 patients underwent randomization, and the modified intention-to-treat population included 249 patients in the tocilizumab group and 128 patients in the placebo group; 56.0% were Hispanic or Latino, 14.9% were Black, 12.7% were American Indian or Alaska Native, 12.7% were non-Hispanic White, and 3.7% were of other or unknown race or ethnic group. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% confidence interval [CI], 8.5 to 16.9) in the tocilizumab group and 19.3% (95% CI, 13.3 to 27.4) in the placebo group (hazard ratio for mechanical ventilation or death, 0.56; 95% CI, 0.33 to 0.97; P=0.04 by the log-rank test). Clinical failure as assessed in a time-to-event analysis favored tocilizumab over placebo (hazard ratio, 0.55; 95% CI, 0.33 to 0.93). Death from any cause by day 28 occurred in 10.4% of the patients in the tocilizumab group and 8.6% of those in the placebo group (weighted difference, 2.0 percentage points; 95% CI, –5.2 to 7.8). In the safety population, serious adverse events occurred in 38 of 250 patients (15.2%) in the tocilizumab group and 25 of 127 patients (19.7%) in the placebo group.

CONCLUSIONS

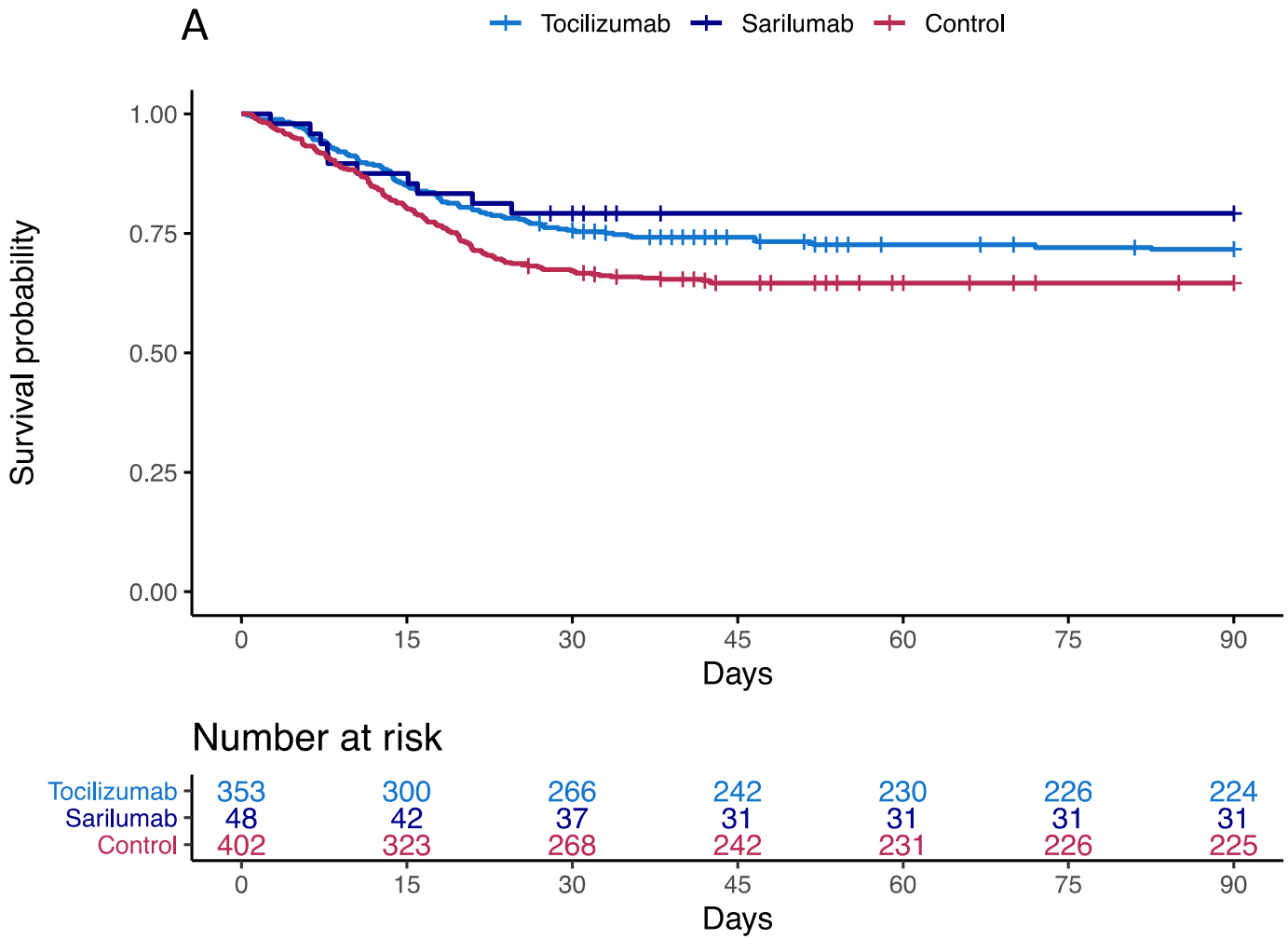
In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. No new safety signals were identified. (Funded by Genentech; EMPACTA ClinicalTrials.gov number, NCT04372186.)

Waiting for RECOVERY data on tocilizumab…

REMAP-CAP pre-print data

Adult within 24 hours of commencing organ support in ICU randomized to tocilizumab (8mg/kg) or sarilumab (400mg) or SOC.

- Median organ support-free days were 10 (-1, 16), 11 (IQR 0, 16) and 0 (IQR -1, 15) for tocilizumab, sarilumab and control, respectively.
- Relative to control, median adjusted odds ratios were 1.64 (1.25, 2.14) for tocilizumab and 1.76 (1.17, 2.91) for sarilumab, yielding >99.9% and 99.5% posterior probabilities of superiority compared with control.
- Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control.



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 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

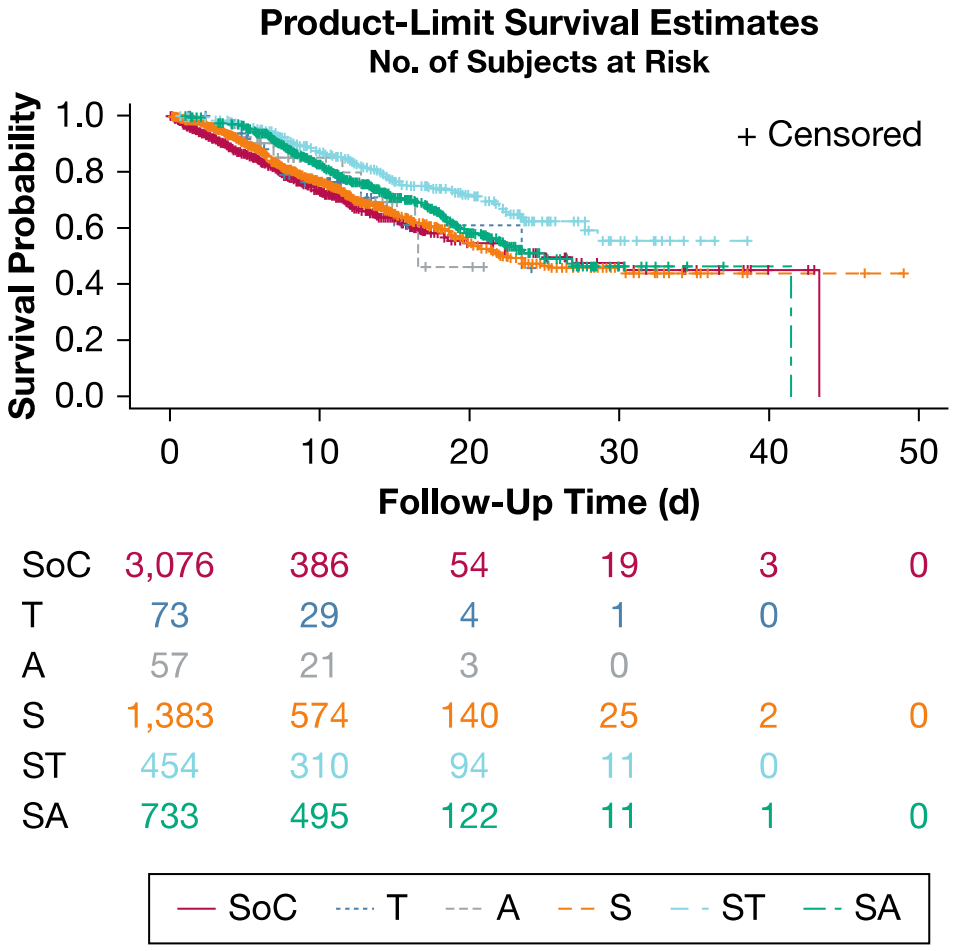
Guaraldi G, et al. Lancet Rheumatol 2020

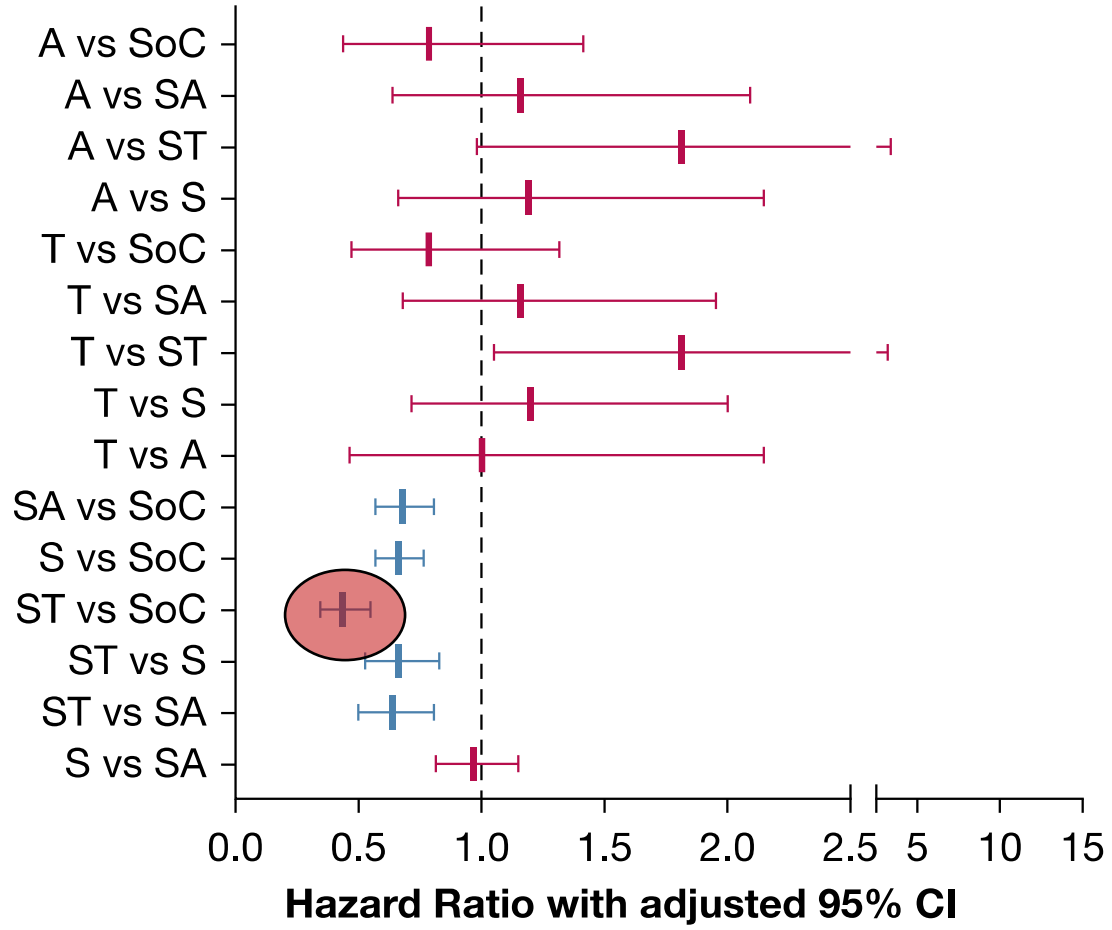
- Mono or combination therapy?

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

Narain S, et al. Chest 2020

Corticosteroids plus tocilizumab?



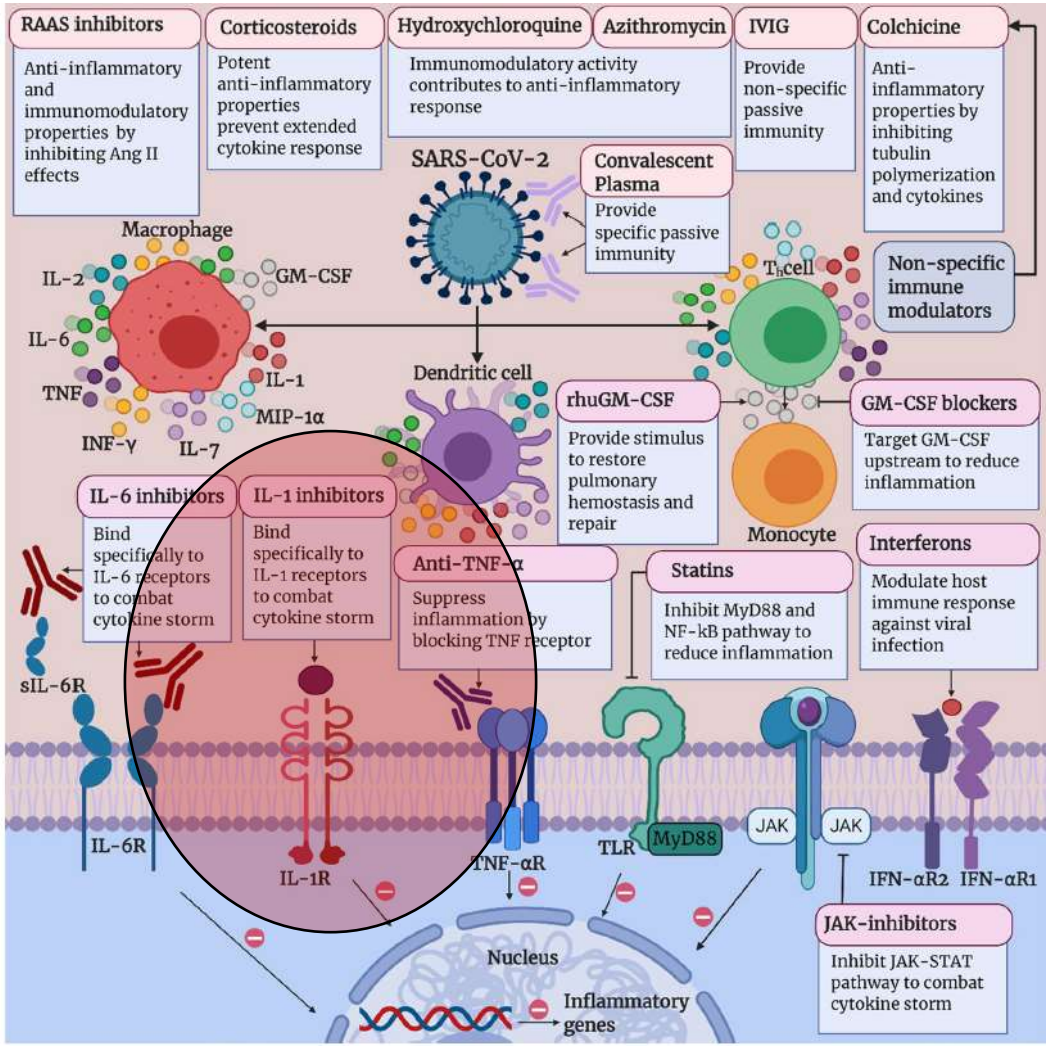


Narain S, et al. Chest 2020

Anti IL-1R medications

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

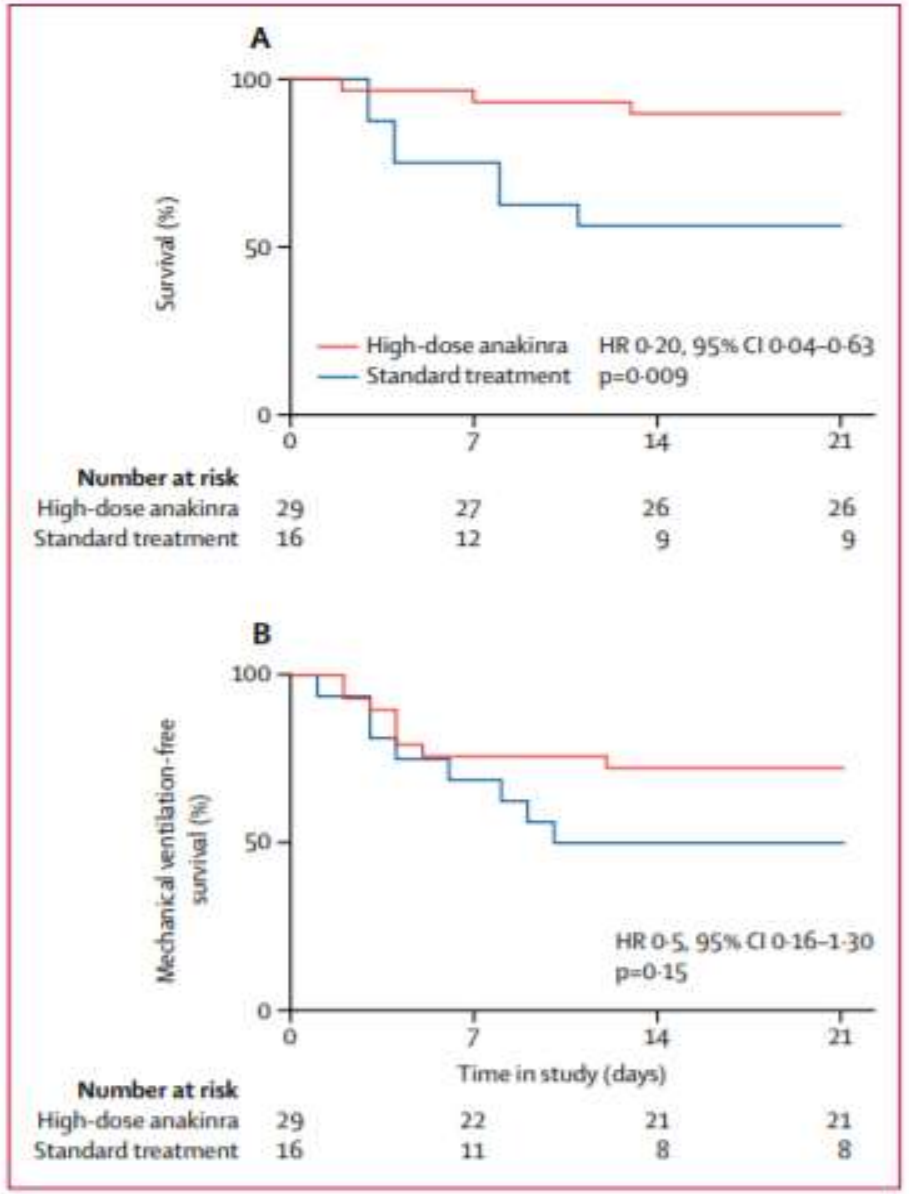
- **Canakinumab**
  - Human anti IL-1Beta
  - systemic juvenile idiopathic arthritis
  - Still's disease
  - cryopyrin-associated periodic syndrome



Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

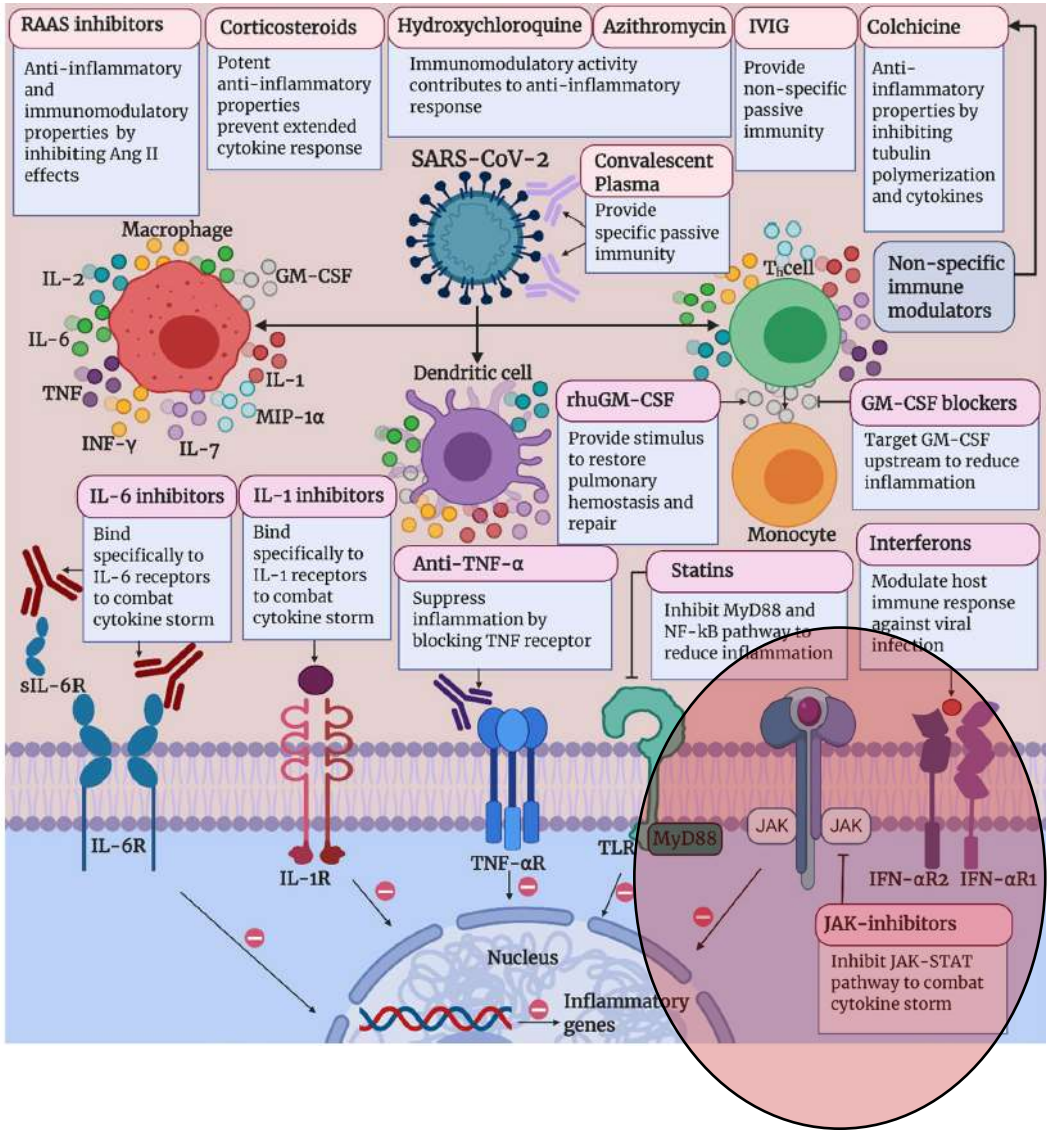
Giulio Cavalli, Giacomo De Luca, Corrado Campochiaro, Emanuel Della-Torre, Marco Ripa, Diana Canetti, Chiara Oltolini, Barbara Castiglioni, Chiara Tassan Din, Nicola Boffini, Alessandro Tomelleri, Nicola Farina, Annalisa Ruggeri, Patrizia Rovere-Querini, Giuseppe Di Lucca, Sabina Martinenghi, Raffaella Scotti, Moreno Tresoldi, Fabio Ciceri, Giovanni Landoni, Alberto Zangrillo, Paolo Scarpellini, Lorenzo Dagna

- Retrospective, 29 vs. 16 pts
- Moderate-to-severe ARDS, and **hyperinflammation** (defined as serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both) who were managed with non-invasive ventilation outside of the ICU
- Standard treatment vs. additional treatment with anakinra
  - 5 mg/kg x 2 intravenously [high dose]
  - or 100 x 2 subcutaneously [low dose] protracted until sustained benefit

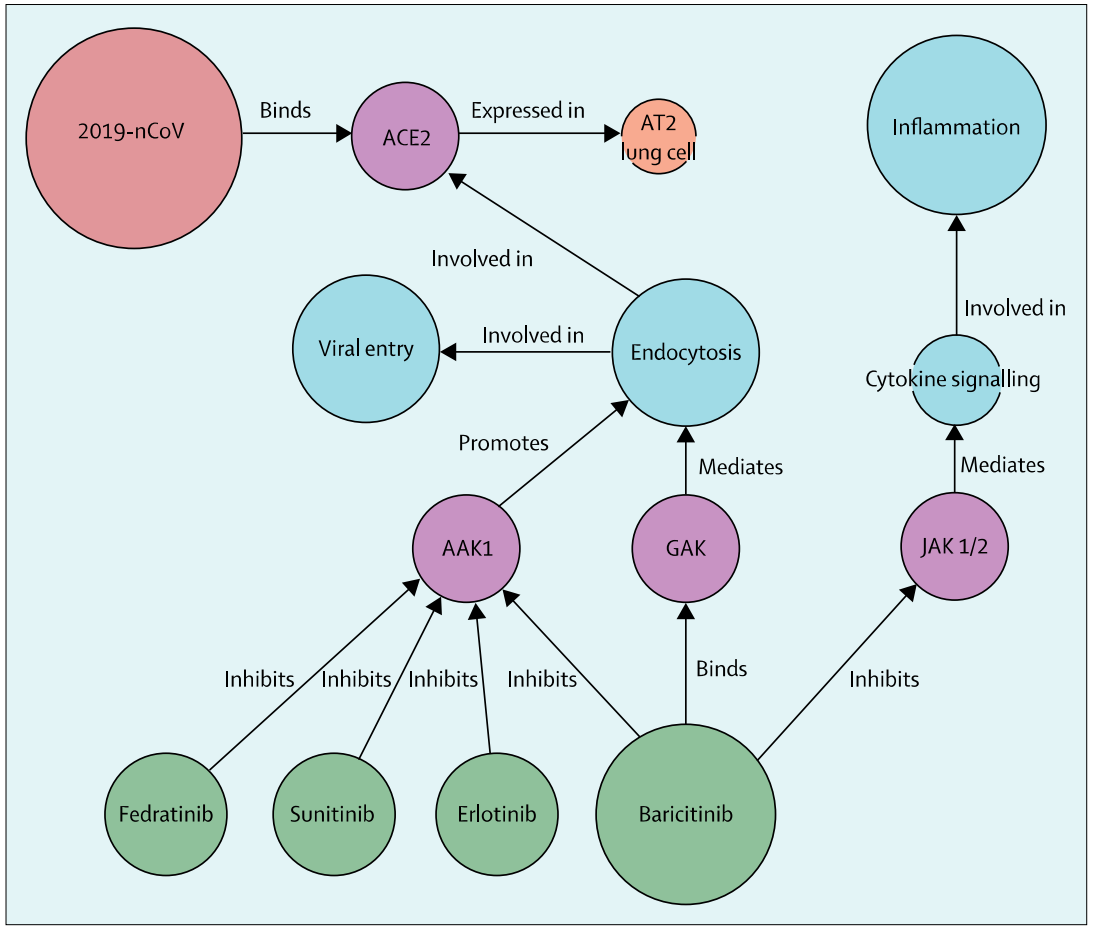


JAnus Kinase 1-2 (JAK1/JAK2) inhibitors

- **Baricitinib**
  - JAK/JAK2 inhibitor
  - Rheumatoid arthritis
- **Ruxolitinib**
  - JAK1/JAK2 inhibitor
  - Myelofibrosis
  - Polycythemia vera
  - GVHD



Baricitinib: theoretically



Baricitinib as potential treatment for 2019-nCoV acute respiratory disease

Richardson P, et al. Lancet 2020

Baricitinib RCT

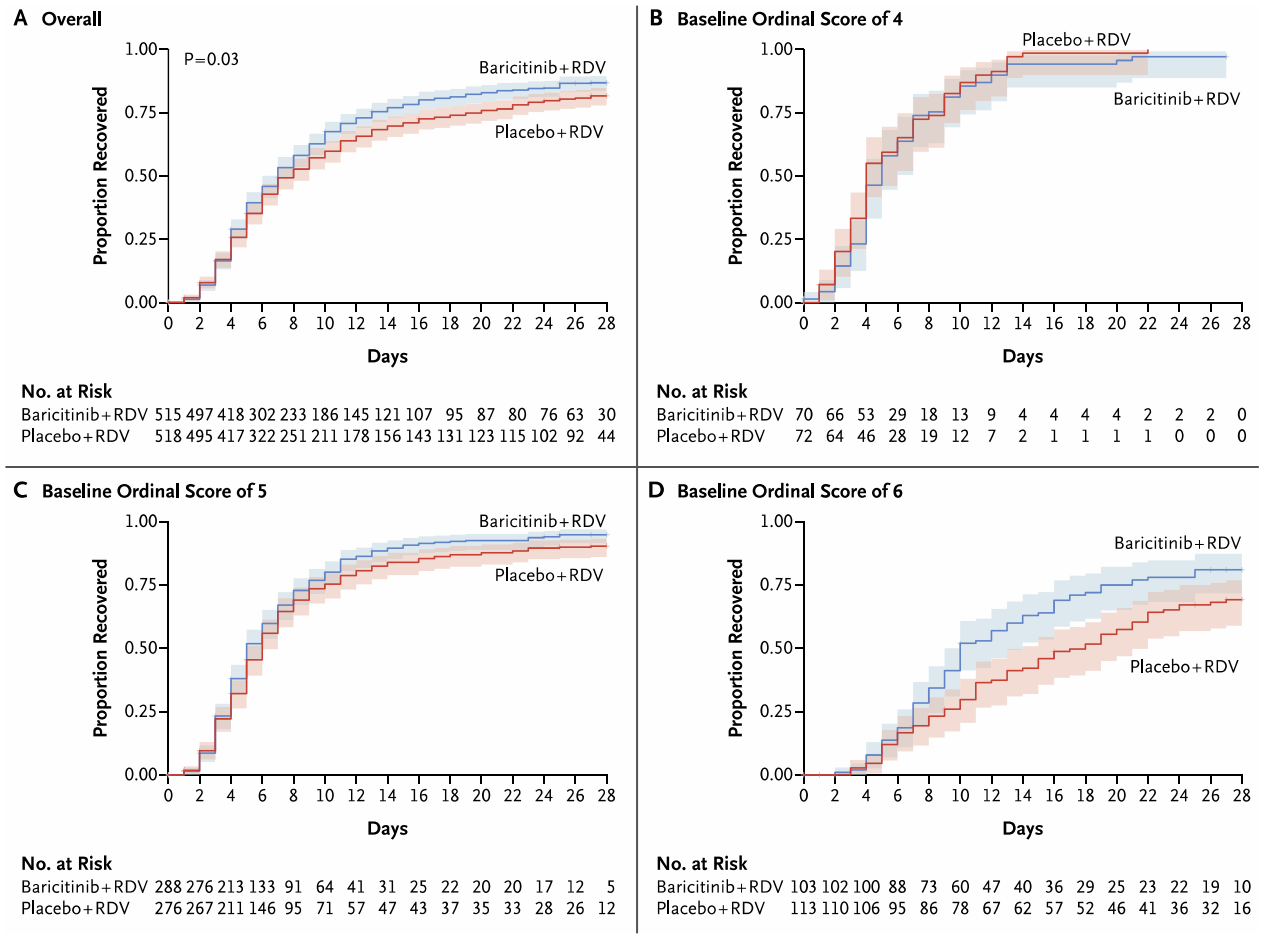
- Double-blind, randomized, placebo-controlled trial
- Baricitinib (4 mg, ≤14 days) plus remdesivir (≤10 days) in hospitalized adults
- 515 vs. 518 to control
  - Time to recovery 7 vs. 8 days (P=0.03)
  - 30% higher odds of improvement in clinical status at day 15
  - Patients receiving high-flow oxygen or NIV at enrollment had a time to recovery of 10 vs. 18 days
  - 28-day mortality was 5.1% vs. 7.8%
  - SAEs 16.0% vs. 21.0% (P=0.03)
  - New infections 5.9% vs. 11.2% (P=0.003).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

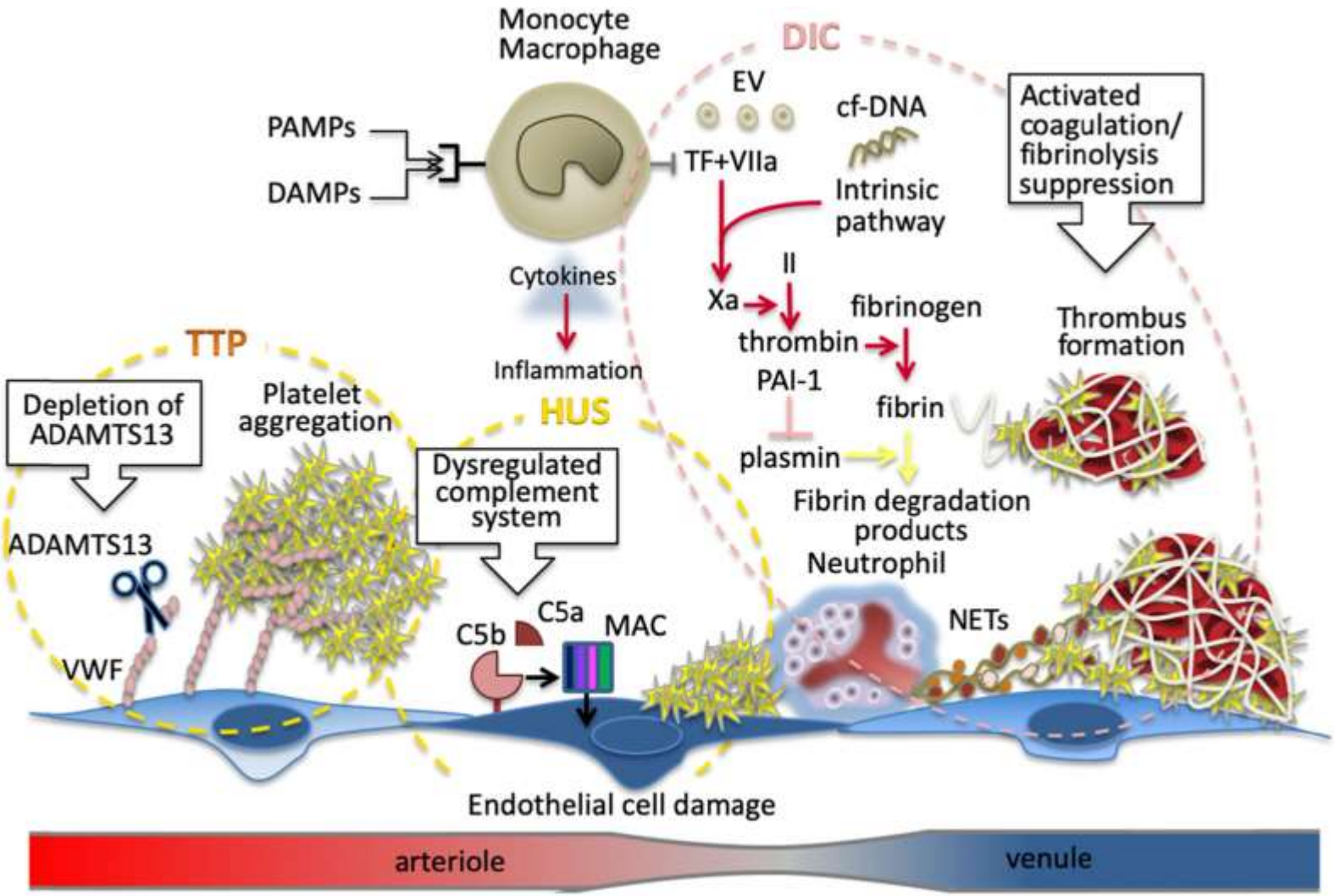
Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan,



Kalil AC, et al. NEJM 2020

Coagulation, complement and ADMATS13 and COVID-19



Potentially improved survival in patients treated with anticoagulants

- Tang N, et al. J Thromb Haemost 2020;
- Paranjipe I, et al. JACC 2020;
- Ayerbe L, et al. J Thromb and Thrombolysis 2020

Iba T, et al. Critical Care 2020

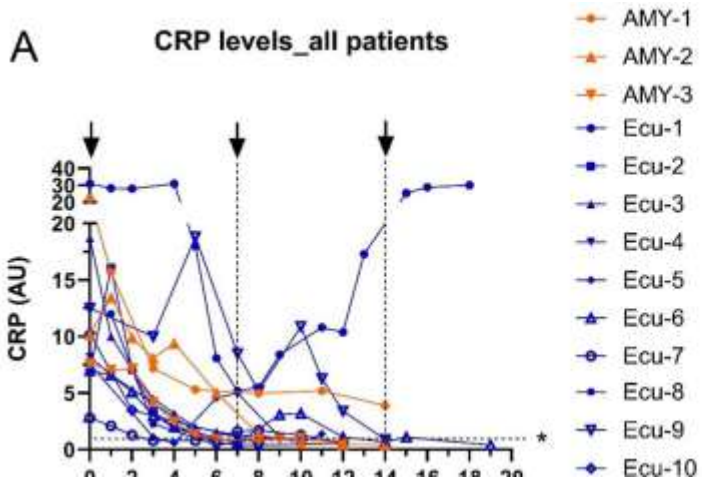
Clinical Immunology 220 (2020) 108598

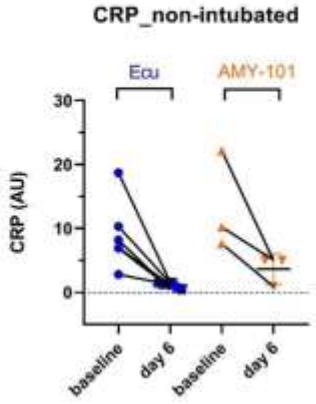
Contents lists available at ScienceDirect

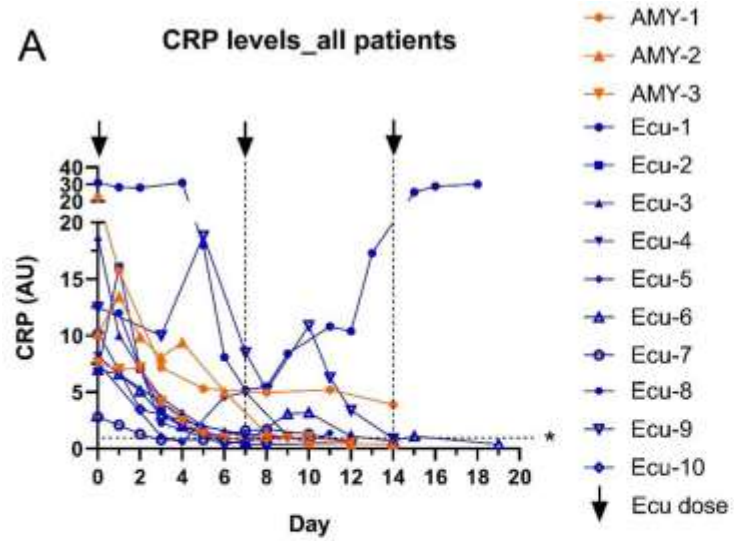
Clinical Immunology

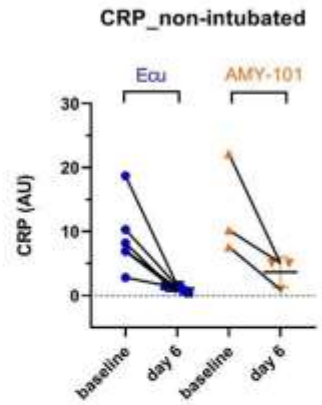
journal homepage: www.elsevier.com/locate/yclim

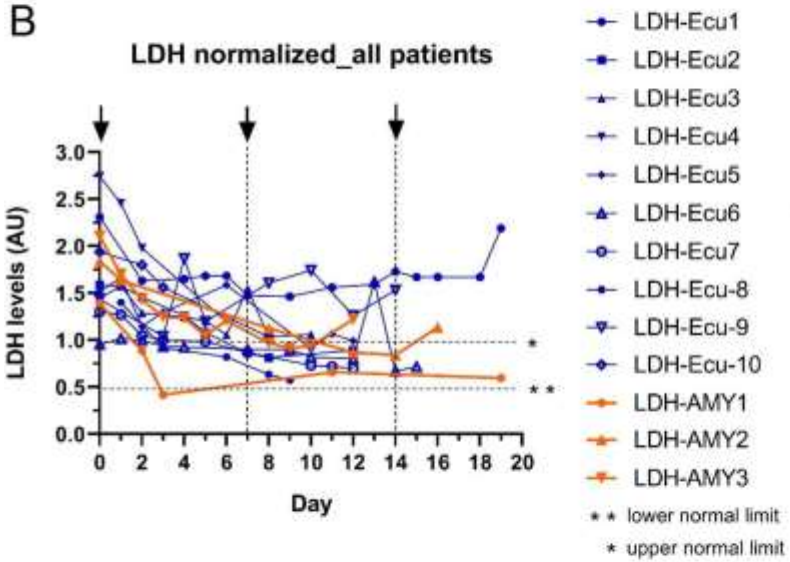
Complement C3 vs C5 inhibition in severe COVID-19: Early clinical findings reveal differential biological efficacy

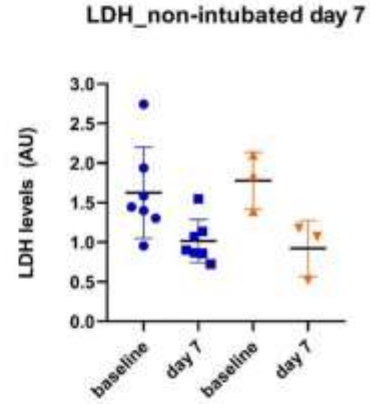












Other treatments

Eculizumab
Inhibits cleavage of C5 into C5a (proinflammatory) and C5b (C5b-9 pro-thrombotic)

Case reports/case series
Ravulizumab study ongoing

Emapalumab
MoAb anti IFN-gamma

Ongoing study prematurely stopped

Ruxolitinib
JAK/JAK2 inhibitor

Several positive case series
No effect in a small RCT (Cao et al.), no effect in RUXCOVID trial (18.12.2020 press release)

IVIG

Case reports/case series
Positive results of a small RCT
(Gharebaghi et al., 30 vs. 29, mortality 20% vs. 48.3%, p=0.025)

Thalidomide
Immunomodulatory, anti-inflamatory, antiangiogenic properties (TNF-alpha)

Case reports/case series

Imatinib
Tyrosin kinase inhibitor

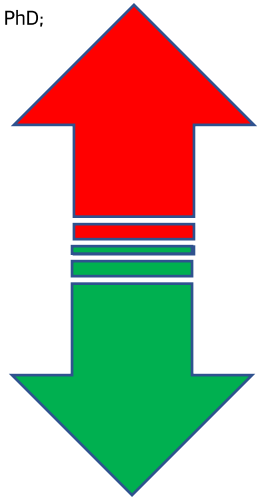
Case reports
RCT ongoing

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zheng, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Heng Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yongpei Yu, PhD; Yong Guo, PhD; Xiaoxiong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD, PhD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; E. Deng, MS; Xuejun Zhang, MS; Chenyue Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD



IMMUNOPATHOLOGY AND INFECTIOUS DISEASES

Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Check for updates

Eric Salazar,*† Paul A. Christensen,* Edward A. Graviss,*‡ Duc T. Nguyen,‡ Brian Castillo,* Jian Chen,* Bevin V. Lopez,§ Todd N. Eagar,*† Xin Yi,*† Picheng Zhao,* John Rogers,* Ahmed Shehabeldin,* David Joseph,* Christopher Leveque,* Randall J. Olsen,*†‡ David W. Bernard,*† Jimmy Gollihar,¶ and James M. Musser*†‡

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

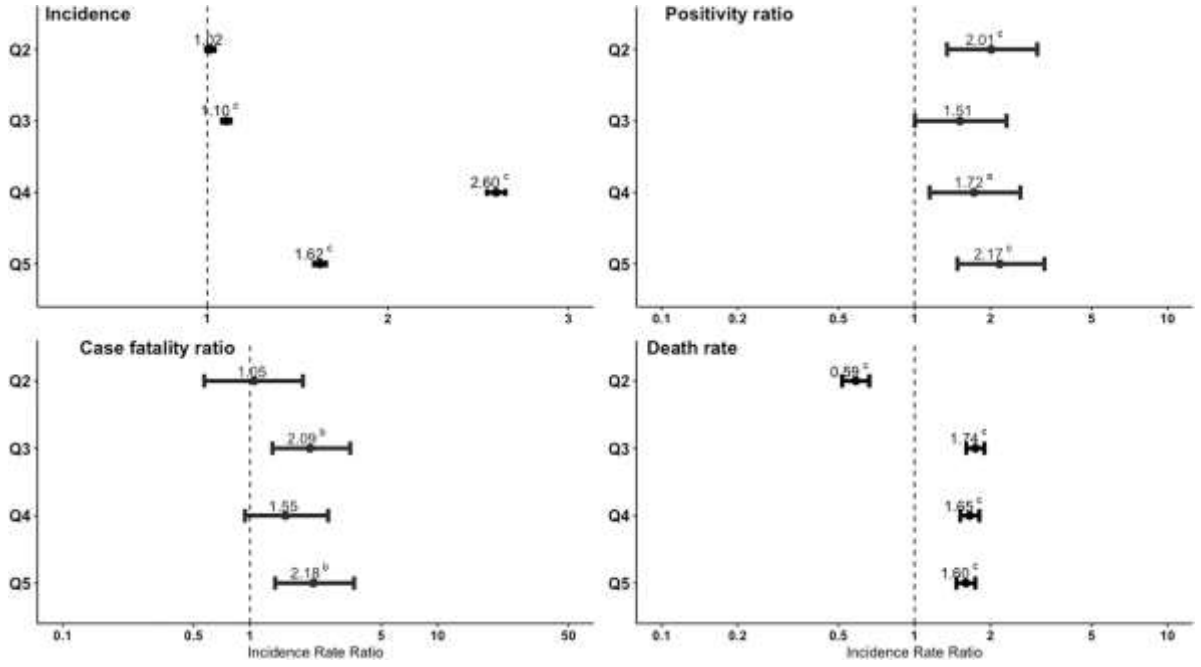
ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

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 reported better outcomes in treated patients



"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]

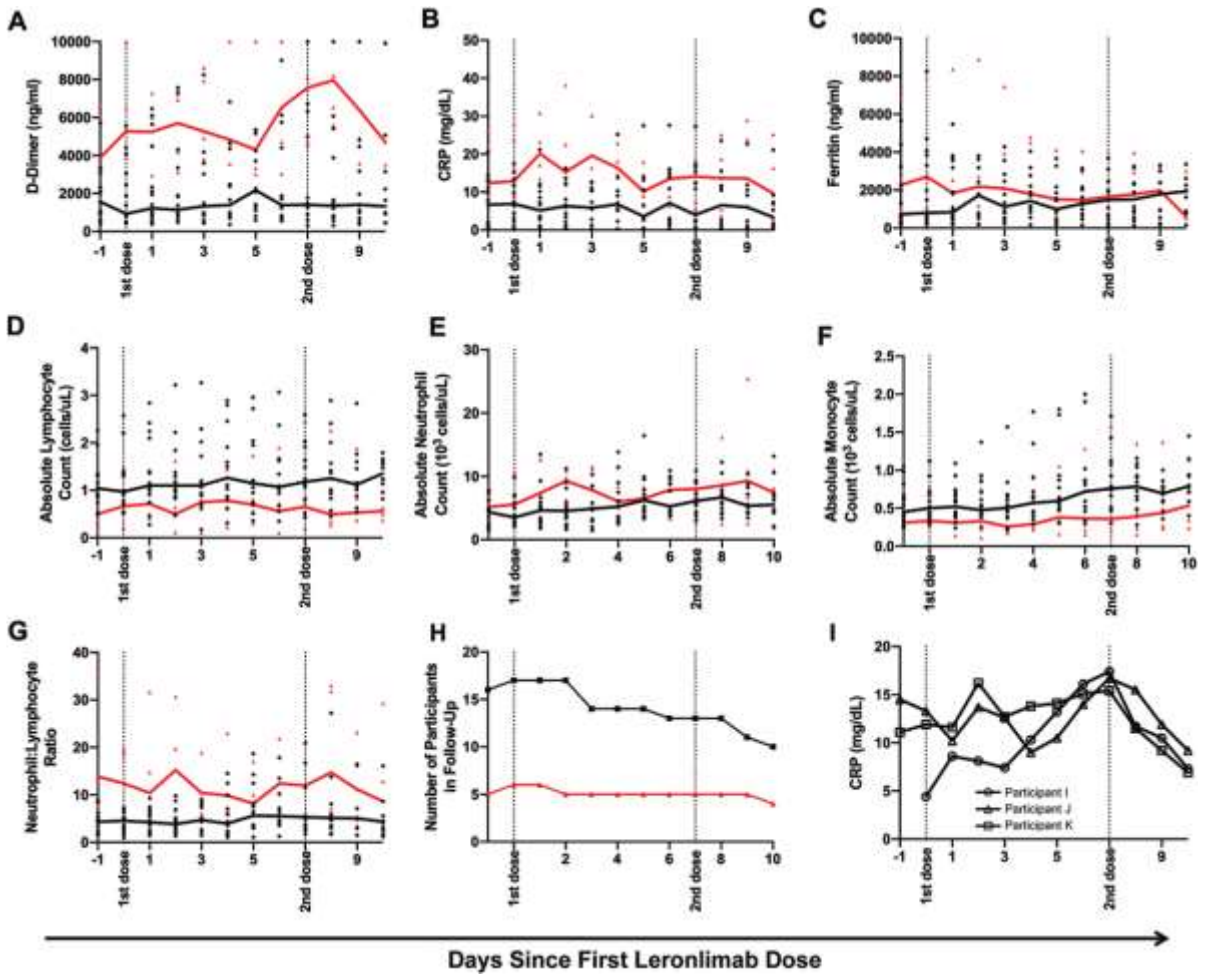
Mariani J, et al. Health Security; Entrenas Castillo M, et al. Journal of Steroid Biochemistry and Molecular Biology 203 (2020)

Clinical Infectious Diseases

MAJOR ARTICLE

Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Patients Who Received Compassionate-Use Leronlimab

Bryant Yang,[1] Jennifer A. Fulcher,[1,2] Jenny Ahn,[3] Marlene Berro,[3] David Goodman-Meza,[1] Kush Dhody,[4] Jonah B. Sacha,[5] Arash Naeim,[3] and Otto O. Yang[1,6]

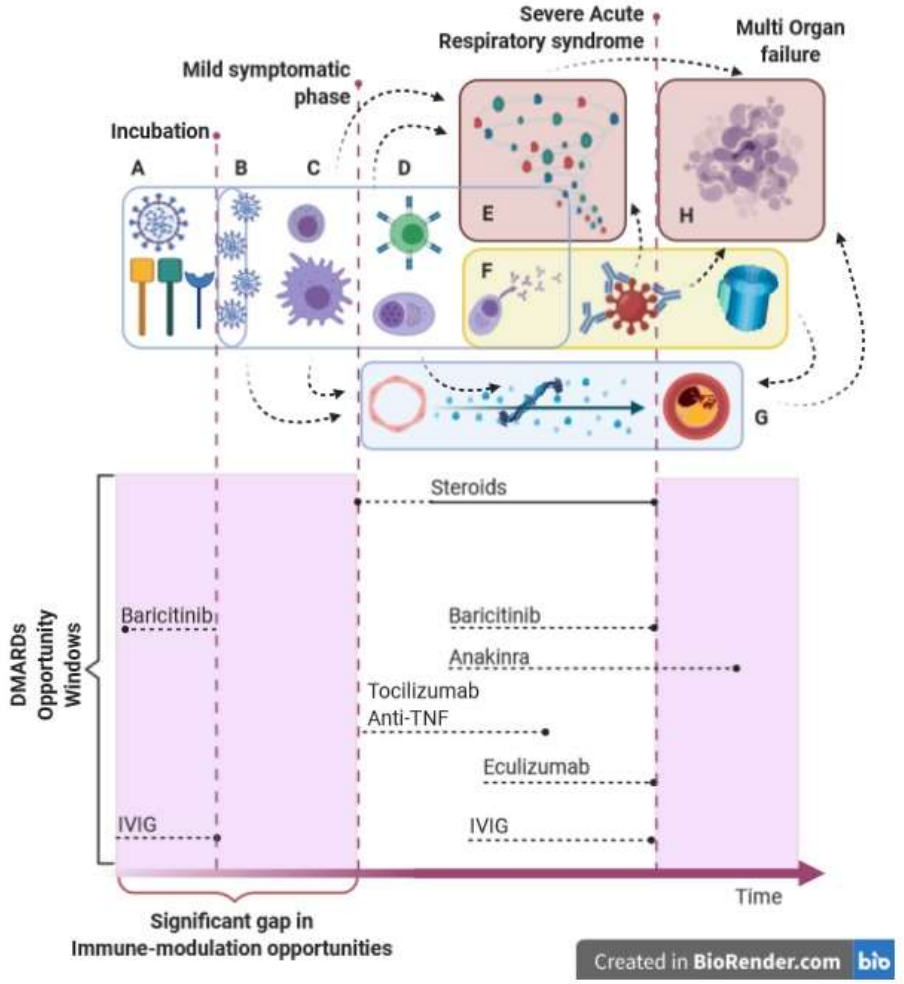


Issues to consider when evaluating potential therapeutics for COVID-19

1. Targets in SARS-CoV-2 life cycle

2. Stage and severity of disease

3. Measured endpoint
    1. Mortality
    2. Clinical improvement
    3. Time to negative NP PCR



Additional issues to consider when evaluating potential therapeutics for COVID-19 beyond timing, dose/route, mechanism, DDIs, tolerability, measured outcomes, patients' immunity…

Systemic vs. Lung targeting vs. Central Nervous System

CNS involvement in COVID-19

- Neurological symptoms very common in patients with critical disease (>40%)
- CSF SARS-CoV-2 found in a minority of patients (1/4 in encephalitis)
- Several clinical pictures reported including:
  - **Encephalopathy**
  - **Guillain-Barré**
  - **Acute cerebrovascular disease (stroke in 2–6% of hospitalized patients)**
  - **CNS vasculitis**

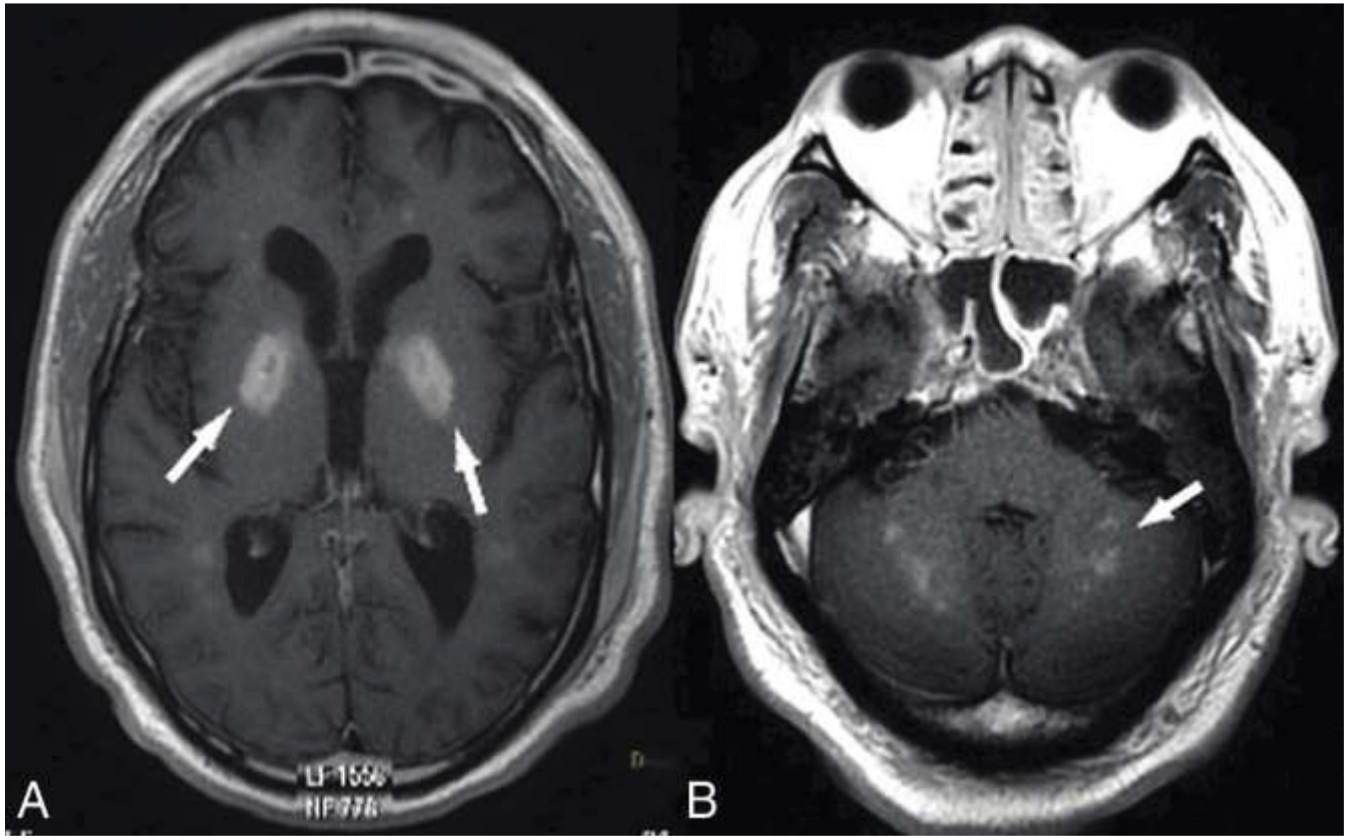
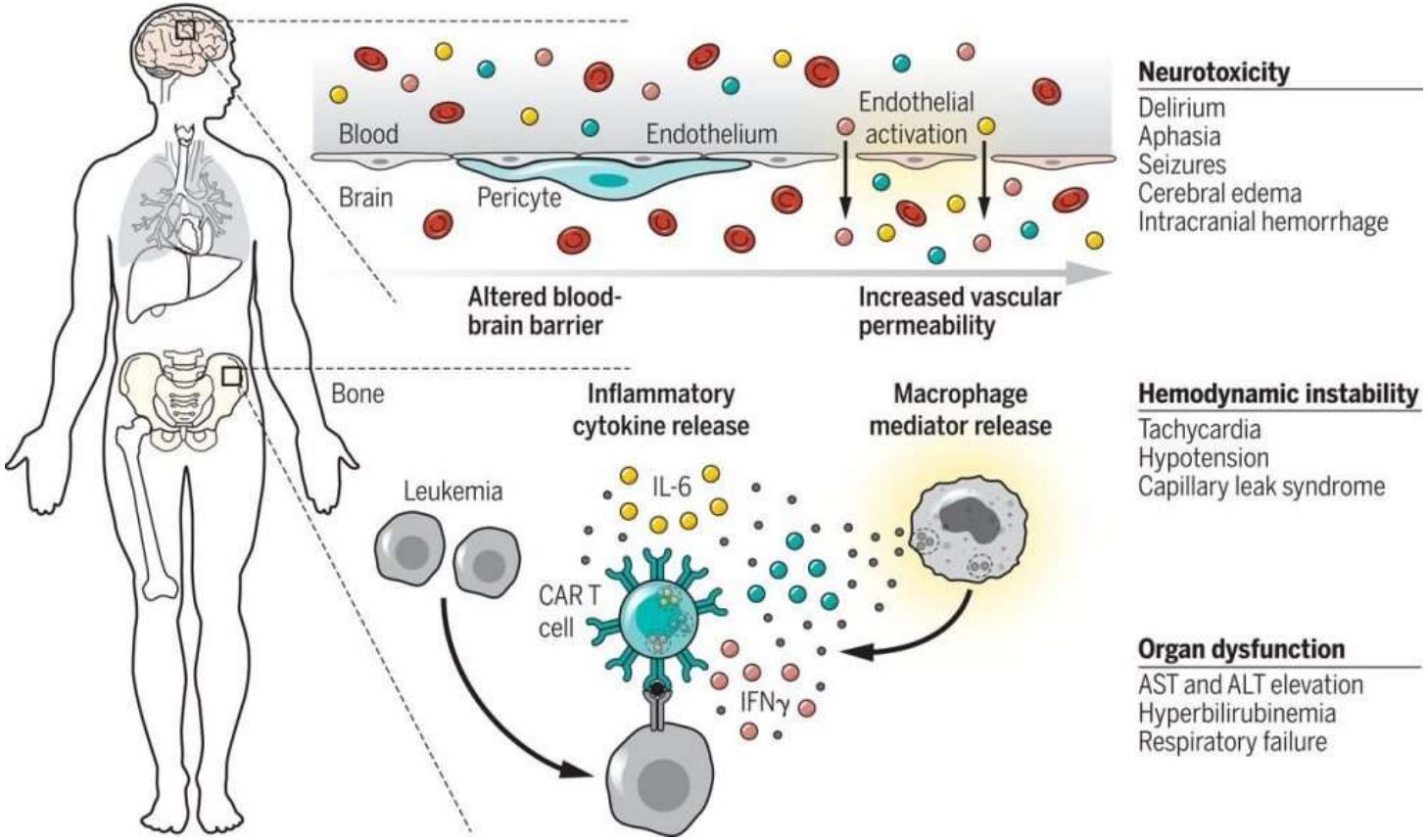


FIG 5. Patchy/punctate postcontrast enhancement pattern with consistent small vessel involvement. Postcontrast T1 MR imaging shows intense patchy enhancement of all lesions, in particular the globus pallidus bilaterally (*A*, *white arrows*), with a punctuate pattern in the middle cerebellar peduncles and cerebellar hemispheres (*B*, *arrow*).

Ellul MA, et al. Lancet Neurology 2020; Hanafi R, et al. AJNR 2020

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

Conclusions

- Immune modulation is a key treatment in patients with severe COVID-19
- Appropriate treatment dose, duration and timing is still under study
- Corticosteroids are the only drugs so far that were associated with improved survival
- IL-6/IL-6R compounds have positive results in observational studies but unclear benefit in randomized controlled trials
- Baricitinib data seem promising but need confirmatory studies with different comparator drugs
- Other treatments need to be verified in robust RCTs
- CNS involvement may benefit for higher corticosteroid doses (direct IL-6 blockade)

Acknowledgements

Medici e infermieri dell'Amedeo di Savoia. In primo piano il professor Giovanni Di Perri e il direttore Paolo Mussano