Success and failures of immunomodulators in Covid19

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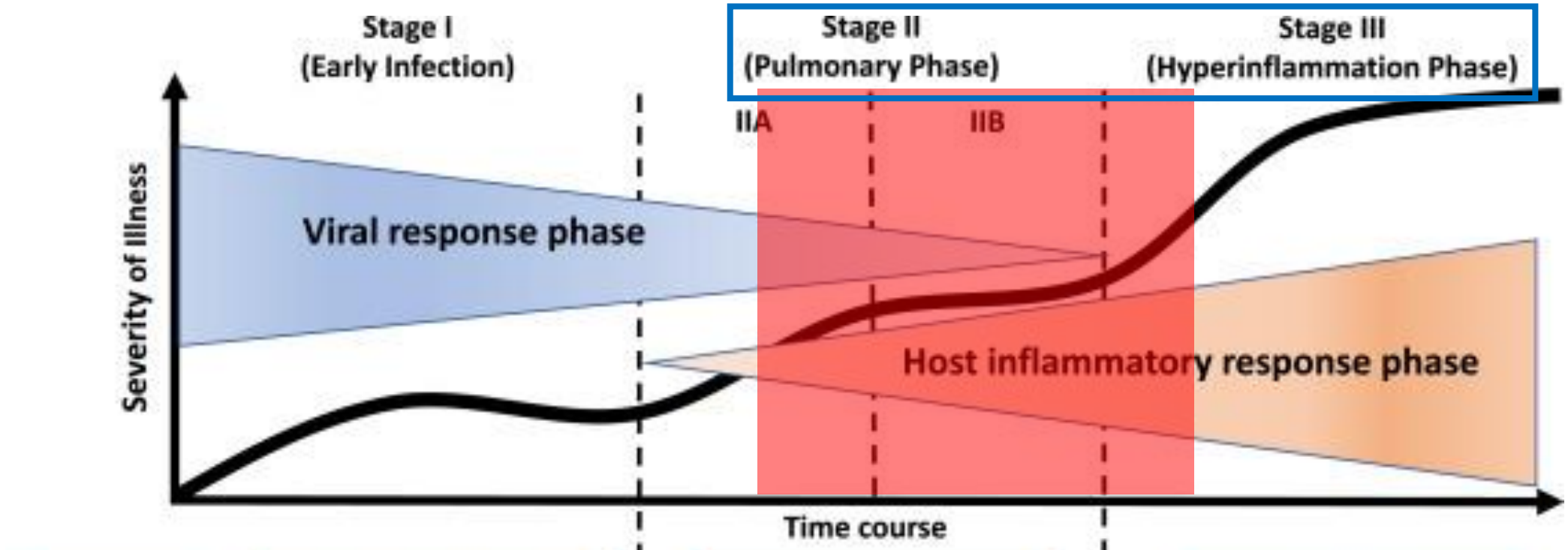
Disclosures

- Honorarium outside COVID-19 from BMS, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, UCB

- Research grant outside COVID-19 from Ose Pharmaceutics

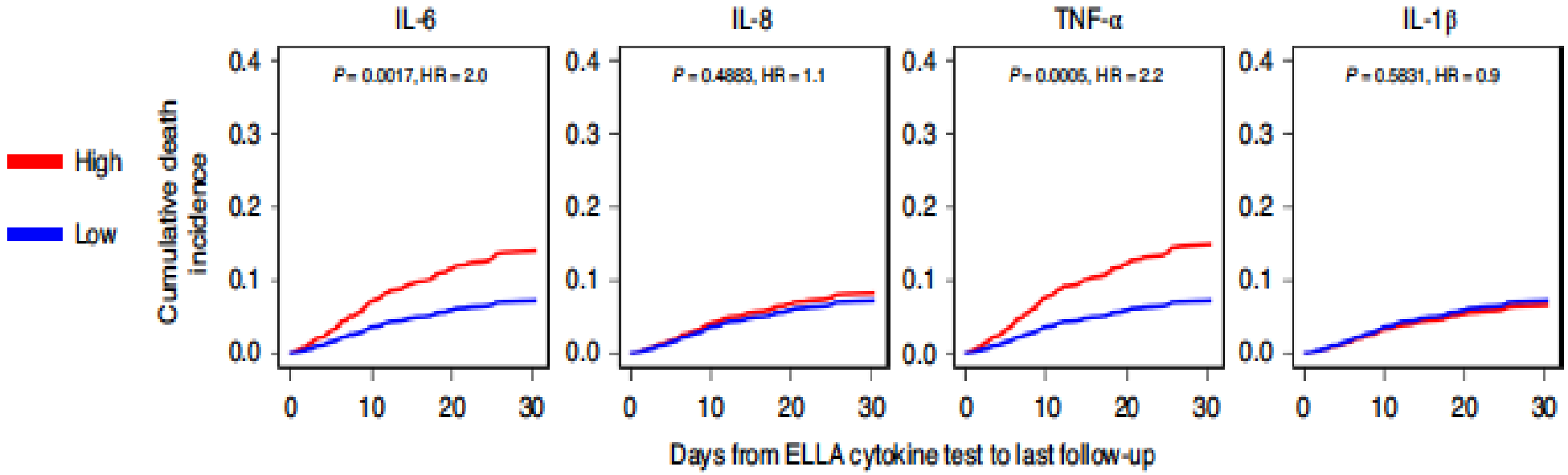
COVID 19 natural history



Clinical Symptoms	Mild constitutional symptoms Fever >99.6˚F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
Potential Therapies	Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions		
	Reduce immunosuppression	Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors	

Baseline serum IL-6 and TNF levels are predictive of survival in COVID-19 infection

After multivariate analysis, adjusted on markers of inflammation, hypoxia and other vital signs, demographics and comorbidities, baseline serum levels of IL-6 and TNF-α independently predicted disease severity and mortality.



Competitive risk model and after adjustment for markers of inflammation, hypoxia and other vital signs, demographics and comorbidities

Del Valle, Nature Medicine, 2020

What immunomodulatory drugs for COVID ?

- **Corticosteroids**
- IL-6 inhibitors
- IL-1 inhibitors
- Jak inhibitors
- Other immunomodulators

Indiquez parmi les situations suivantes, celles dans lesquelles on peut recommander un traitement par dexamethasone

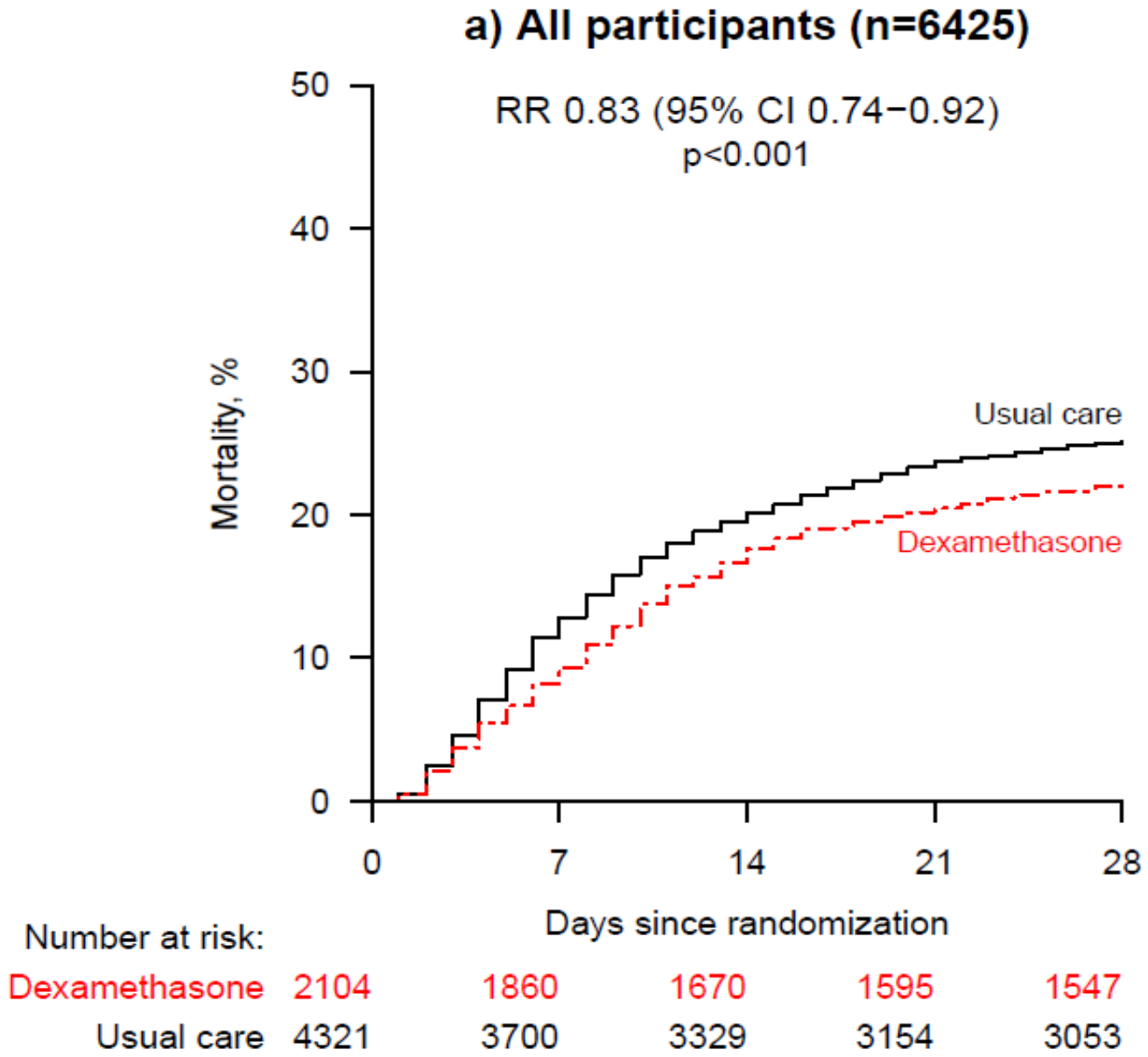
- A. Un patient de 67 ans à domicile avec une infection récente Sars-CoV-2, fièvre à 39, toux, dyspnée modérée et saturation normale

- B. Un patient de 67 ans hospitalisé avec une infection récente Sars-CoV-2, fièvre à 39, toux, dyspnée, nécessitant 4L/mn d'oxygène

- C. Un patient de 67 ans hospitalisé avec une infection récente Sars-CoV-2, fièvre à 39, toux, dyspnée sévère, nécessitant de l'oxygène en optiflow à 50 L/mn

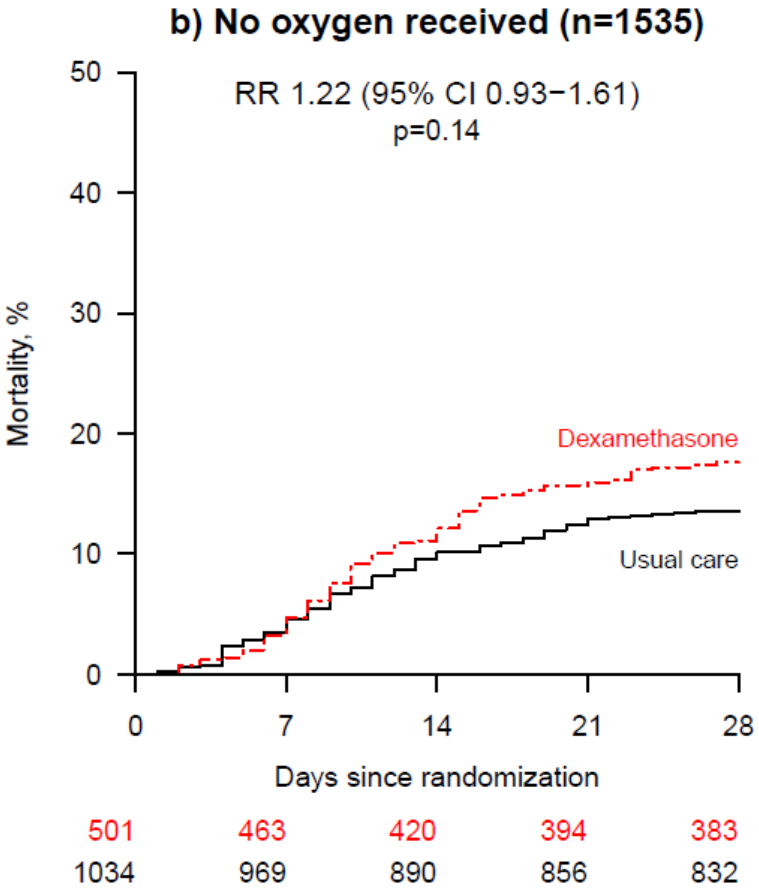
- D. Un patient de 67 ans hospitalisé en réanimation de puis 24 heures avec une infection récente Sars-CoV-2, fièvre à 39, toux, dyspnée, saturation en air ambiant à 85%, necessitant4l/mn d'oxygène

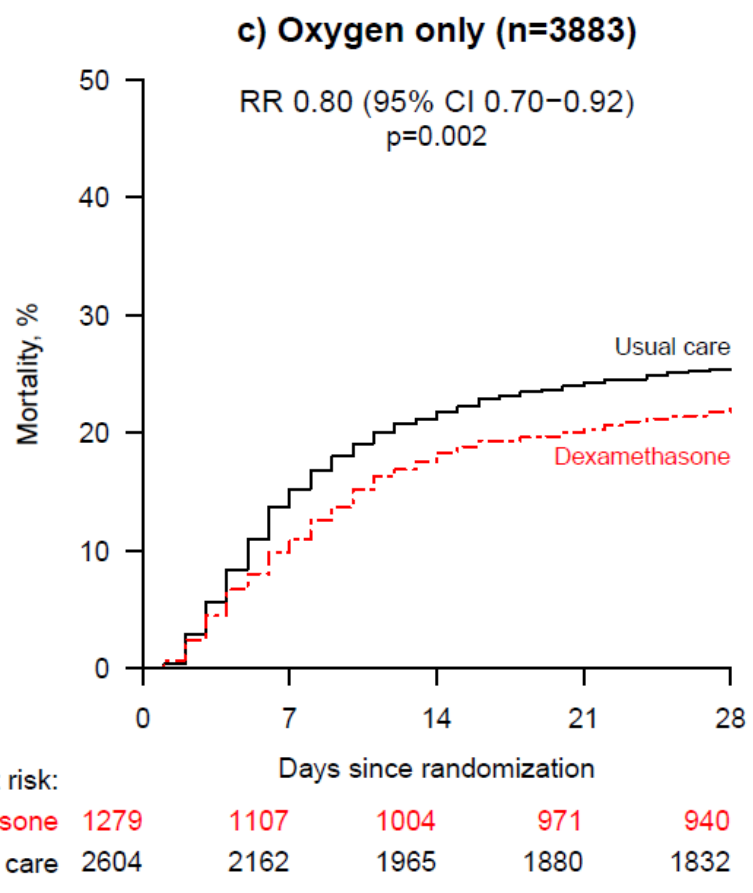
Dexamethasone in RECOVERY: mortality

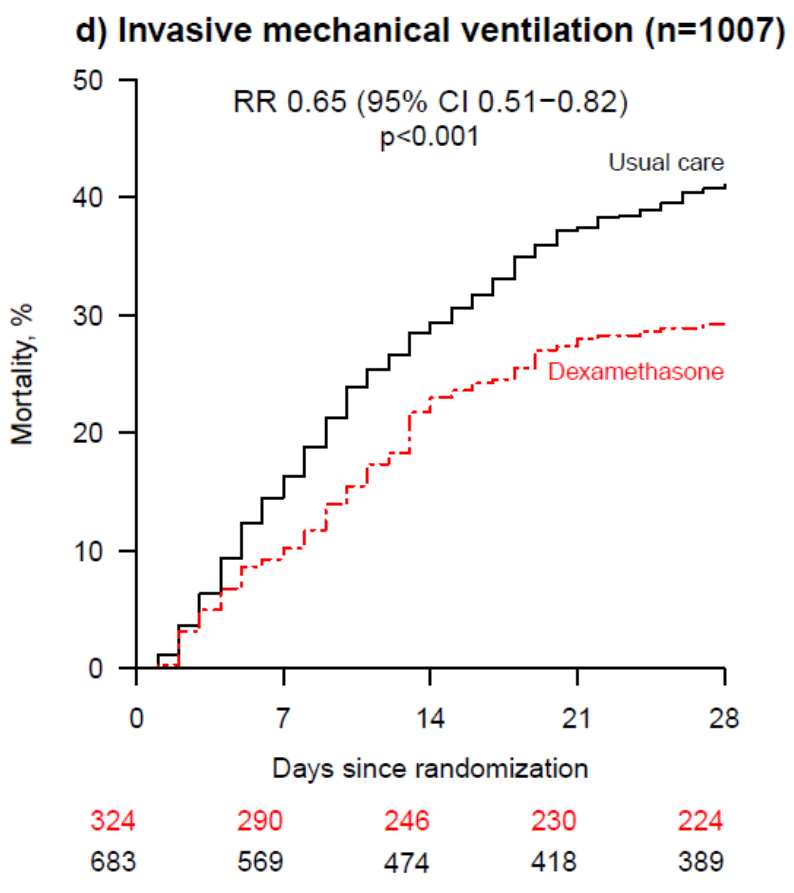


Recovery group. N Engl J Med 2020

Dexamethasone in RECOVERY: mortality





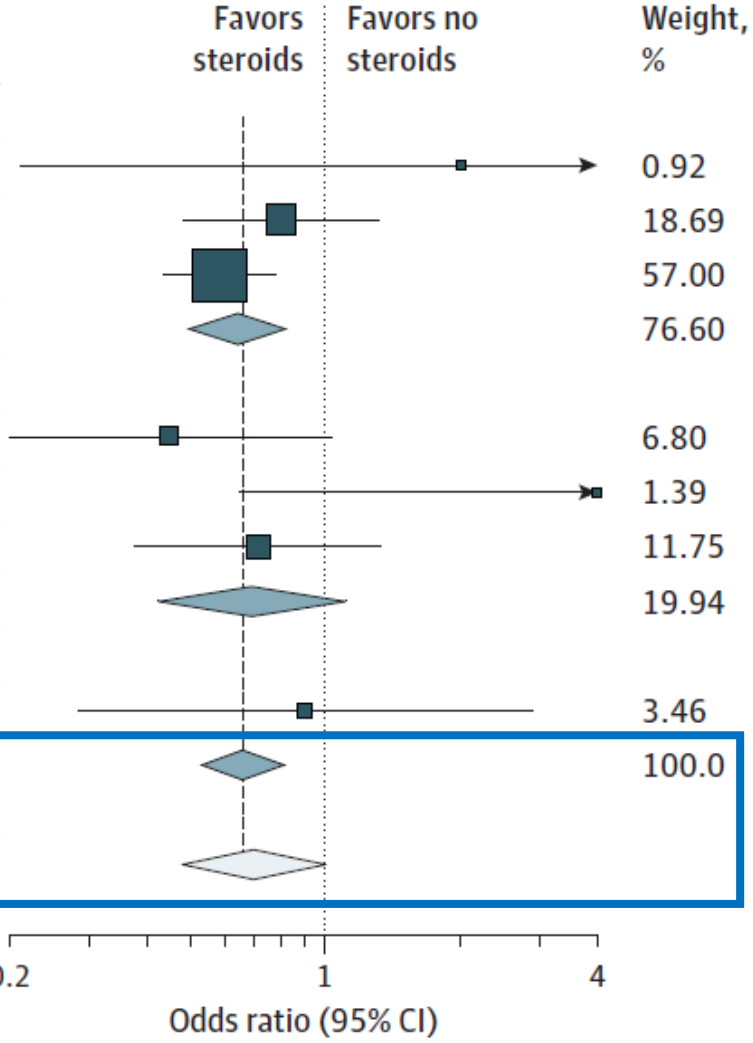


Recovery group. N Engl J Med 2020

Corticosteroids in critically-ill patients: WHO meta-analysis

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		Odds ratio (95% CI)	Weight, %
			Steroids	No steroids		
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) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT)Working Group **JAMA** Published online September 2, 2020

What immunomodulatory drugs for COVID ?

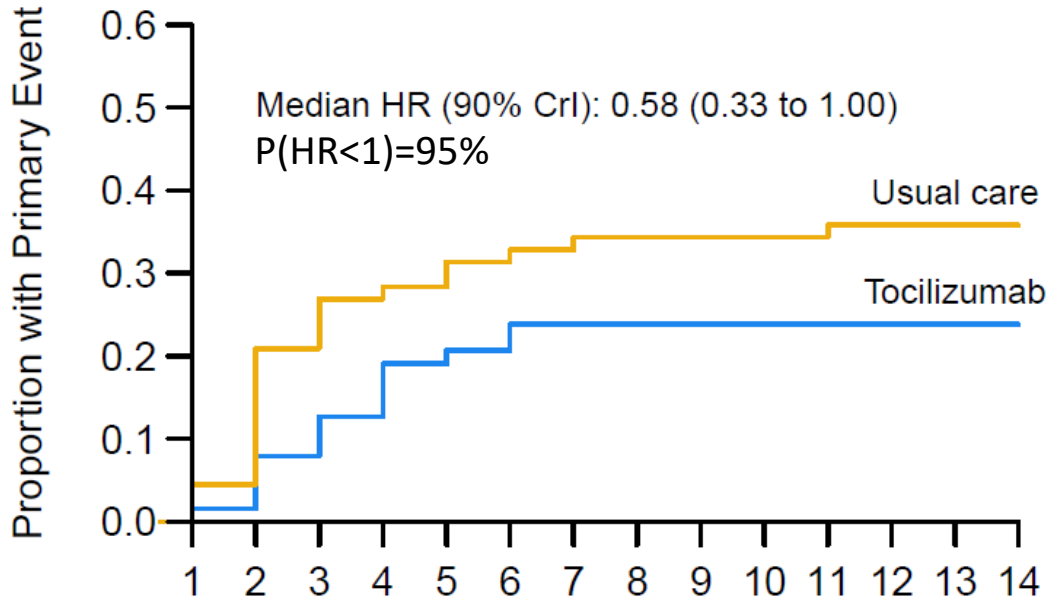
- Corticosteroids
- **IL-6 inhibitors**
- IL-1 inhibitors
- Jak inhibitors
- Other immunomodulators

CORIMUNO-19- TOCI 1

- Patients in WHO class 5 on oxygen: ≥ 3L/min
- Randomization between Usual care (UC) and UC + Tocilizumab (TCZ)
- TCZ given by IV route 8mg/kg D1 followed by 400 mg fixed dose à D3 in case of good tolerance and absence of decrease of oxygen requirement of more than 50%
- 130 patients

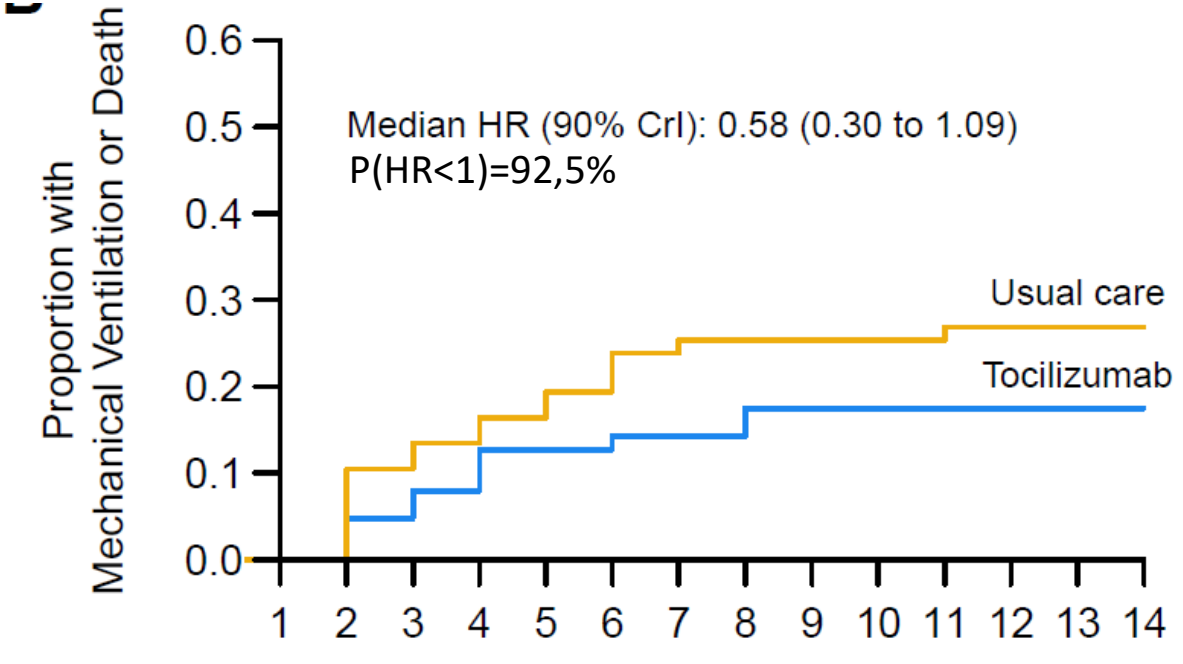
Proportion of patients with occurrence of the primary event at D14

Time to Non-Invasive Ventilation or mechanical ventilation or Death



No. at risk														
Tocilizumab	63	62	58	55	51	50	48	48	48	48	48	48	48	48
Usual care	67	64	53	49	48	46	45	44	44	44	44	43	43	43

Time to mechanical ventilation or Death



No. at risk														
Tocilizumab	63	63	60	58	55	55	54	54	52	52	52	52	52	52
Usual care	67	67	60	58	56	54	51	50	50	50	50	49	49	49

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

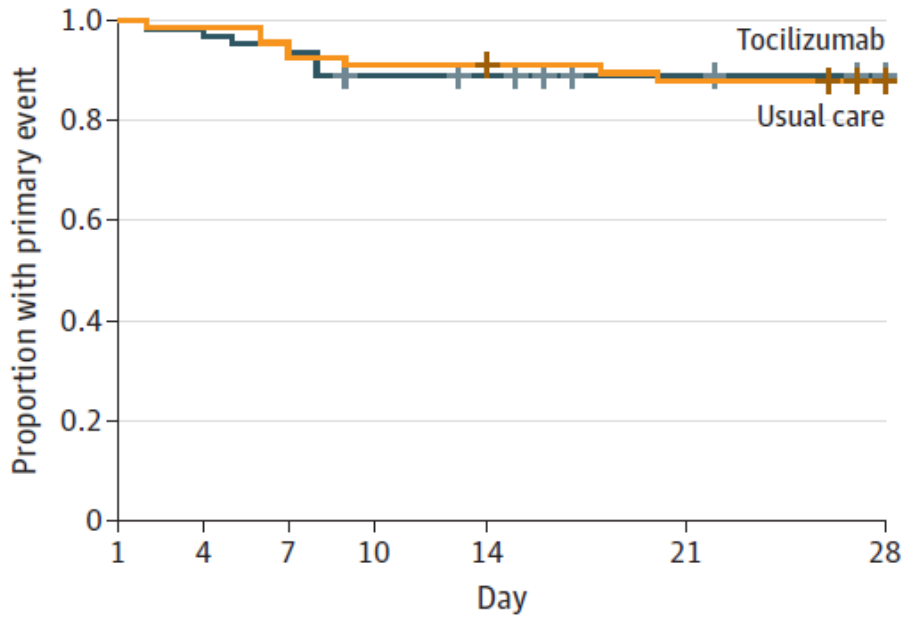
Hermine O, Mariette X and the CORIMUNO-19 group. JAMA Intern Med; 22 Oct 2020

CORIMUNO

CORIMUNO-19- TOCI 1 Overall survival

Overall survival

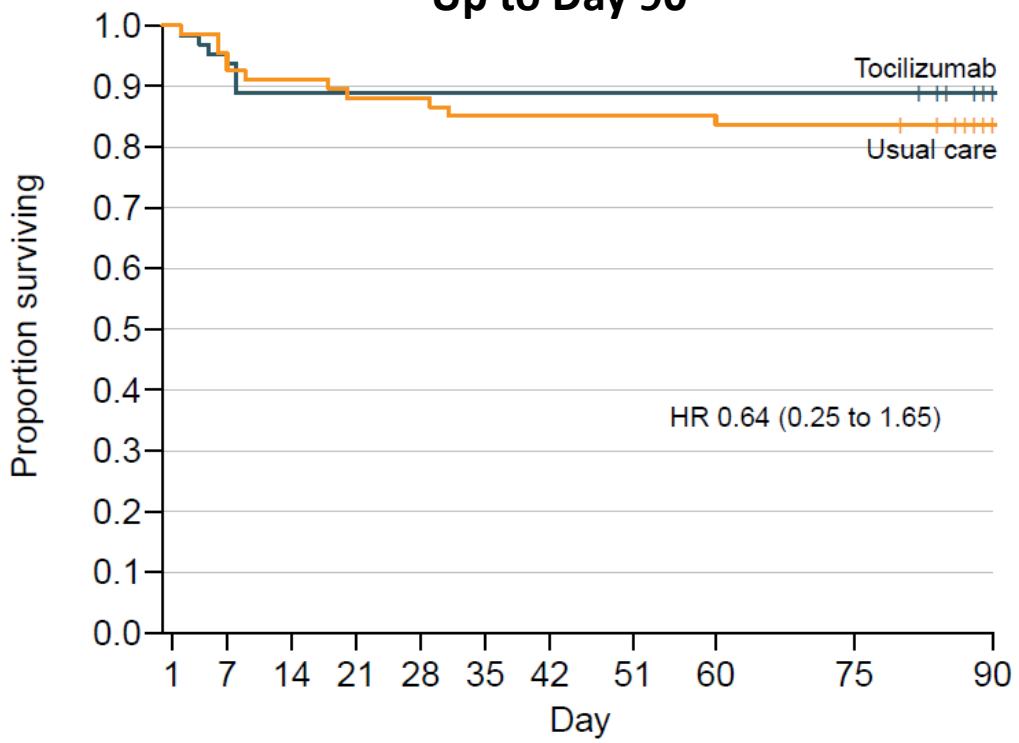
Up to Day 28



No. at risk

Tocilizumab	63	62	60	55	54	50	46
Usual care	67	66	64	61	61	56	50

Up to Day 90



Number at risk

Tocilizumab	63	60	56	56	56	56	56	56	56	56	45
Usual care	67	64	61	59	59	57	57	57	57	56	49

	Tocilizumab (n=63)		UC (n=67)		
	N deaths	OS	N deaths	OS	Adjusted HR (95% CI)
Day 14	7	89%	6	91%	1.19 (0.40 to 3.55)
Day 28	7	89%	8	88%	0.92 (0.33 to 2.53)
Day 90	7	89%	11	82%	0.65 (0.25 to 1.67)

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Mariette X, Hermine O and the CORIMUNO-19 group. JAMA Intern Med; 25 May 2021

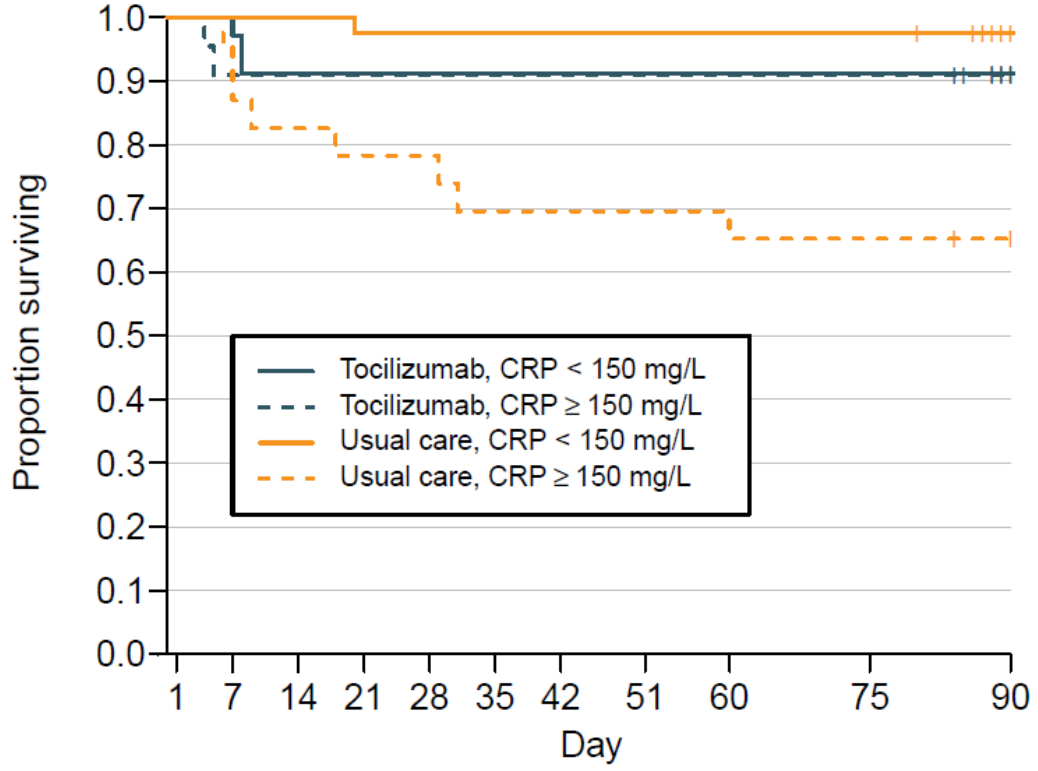
Post-hoc analysis in patients with high CRP>150 mg/L

Primary end-point: Day 14-survival without non invasive or invasive ventilation

A	Tocilizumab n = 63*	Usual care n = 67*	Adjusted HR (95% CI)
CRP > 150 mg/L	4/22, 18%	13/23, 57%	0.18 (0.057 to 0.59)
CRP ≤ 150 mg/L	8/34, 24%	9/40, 23%	0.99 (0.38 to 2.56)
Interaction			*P* = 0.045

Overall survival up to Day 90

B	Tocilizumab n = 63*	Usual care n = 67*	Adjusted HR (95% CI)
CRP > 150 mg/L	2/22, 9%	8/23, 35%	0.18 (0.037 to 0.89)
CRP ≤ 150 mg/L	3/34, 9%	1/40, 2%	NA
Interaction			*P* = 0.015



Number at risk

TCZ, CRP < 150 mg/L	34	34	31	31	31	31	31	31	31	31	27
TCZ, CRP ≥ 150 mg/L	22	20	20	20	20	20	20	20	20	20	14
UC, CRP < 150 mg/L	40	40	40	39	39	39	39	39	39	39	33
UC, CRP ≥ 150 mg/L	23	22	19	18	18	16	16	16	16	15	14

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CORIMUNO-19- TOCI-1 SAFETY

	Tocilizumab (N=63)	SoC (N=67)	P
Adverse events			
- Patients with at least one AE*	28 (44%)	36 (54%)	0.30*
- Patients with multiple AE	16 (25%)	19 (28%)	
- Number of events**	66	86	0.21**
Serious adverse events			
- Patients with at least one SAE***	20 (32%)	29 (43%)	0.21*
- Patients with multiple SAE	5 (8%)	10 (15%)	
- Number of events****	27	57	0.003**
ACFA	0	1	
Anemia	1	4	
Hyperlipasemia	0	1	
Cholestasis	0	2	
Hepatic cytolysis	4	4	

	Tocilizumab (N=63)	SoC (N=67)
Serious adverse events		
Multiple organ failure (death)	0	1 (1)
Pulmonary embolism (death)	0	3 (1)
Fever	2	0
Hyperkaliemia	0	1
Hypoglycemia	0	1
Hypertension	1	0
Acute renal failure	1	2
Arterial ischemia	0	2
Lymphopenia	1	0
Neutropenia	4	0
Pneumothorax	0	1
ARDS (death)	9 (7)	19 (9***)
Bacterial sepsis	2	11
Fungal sepsis	0	2
Viral spsis	0	1
Tetraparesis	0	1
Cough	1	0
Overdosing of TCZ by 10%****	1	0

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Hermine O, Mariette X et al. JAMA Intern Med; 22 Oct 2020

CORIMUNO

No increase rate of serious infections rate all TCZ RCTs

	TCZ	Placebo or UC	
BACC Bay Tocilizumab Trial (US)	8,1%	17,1%	0,03
RCT-TCZ-COVID-19 Study Group (Italy)	1,7%	6,3%	
CORIMUNO-19 (France)	3,1%	16,4%	
EMPACTA (Roche)	5,2%	7,1%	
COVACTA (Roche)	21%	25,9%	
Coalition covid-19 Brazil VI (Brazil)	15%	16%	
REMAP-CAP (International)	2,5%	2,7%	
RECOVERY (UK)	?	?	

RECOVERY

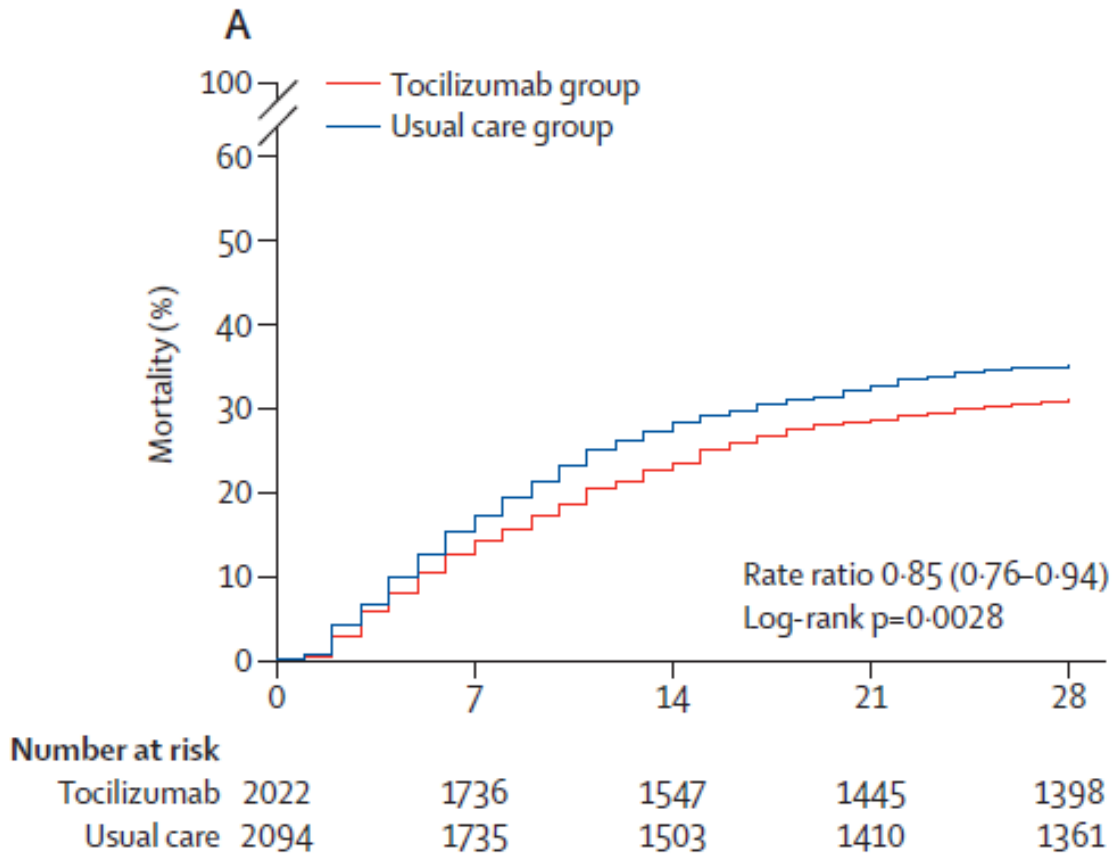
Table 1: Baseline characteristics by randomised allocation

	Tocilizumab (n=2022)	Usual care (n=2094)
Mean (SD) Age, years	63.3 (13.7)	63.9 (13.6)
≥18 to <70	1332 (66%)	1354 (65%)
≥70 to <80	477 (24%)	480 (23%)
≥80	213 (11%)	260 (12%)
Sex		
Male	1335 (66%)	1437 (69%)
Female*	687 (34%)	657 (31%)
Ethnicity		
White	1356 (67%)	1426 (68%)
Black, Asian, or Minority Ethnic	341 (17%)	357 (17%)
Unknown	325 (16%)	311 (15%)
Number of days since symptom onset	9 (7-13)	10 (7-14)
Number of days since hospitalisation	2 (1-5)	2 (1-5)
Oxygen saturation, %	94 (92-96)	94 (91-95)
Respiratory support at second randomisation		
No ventilator support†	935 (46%)	933 (45%)
Non-invasive ventilation‡	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)
Biochemistry at second randomisation		
Latest C-reactive protein, mg/L	143 (107-203)	144 (106-205)
Ferritin, ng/mL	947 (497-1599)	944 (507-1533)
Creatinine, umol/L	77 (62-98)	77 (62-100)

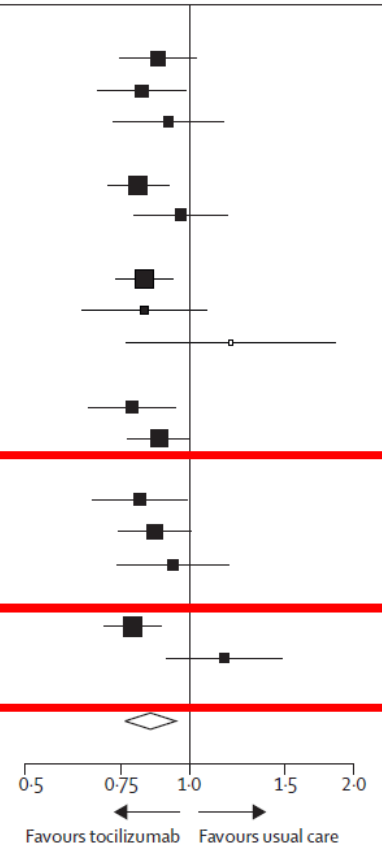
	Tocilizumab (n=2022)	Usual care (n=2094)
Part A allocation		
Usual care	839 (41%)	869 (41%)
Lopinavir/ritonavir	51 (3%)	64 (3%)
Dexamethasone	49 (2%)	45 (2%)
Hydroxychloroquine	37 (2%)	38 (2%)
Azithromycin	197 (10%)	177 (8%)
Use of systemic corticosteroids^		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)
Previous diseases		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease	473 (23%)	484 (23%)
Tuberculosis	3 (<1%)	5 (<1%)
HIV	7 (<1%)	8 (<1%)
Severe liver disease¶	14 (<1%)	10 (<1%)
Severe kidney impairment||	118 (6%)	99 (5%)
Any of the above	1100 (54%)	1163 (56%)

Recovery group. Lancet 2021; 397: 1637-45

RECOVERY 28-day mortality



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



1 saved life for 25 treated patients

Recovery group. Lancet 2021; 397: 1637-45

REMAP-CAP

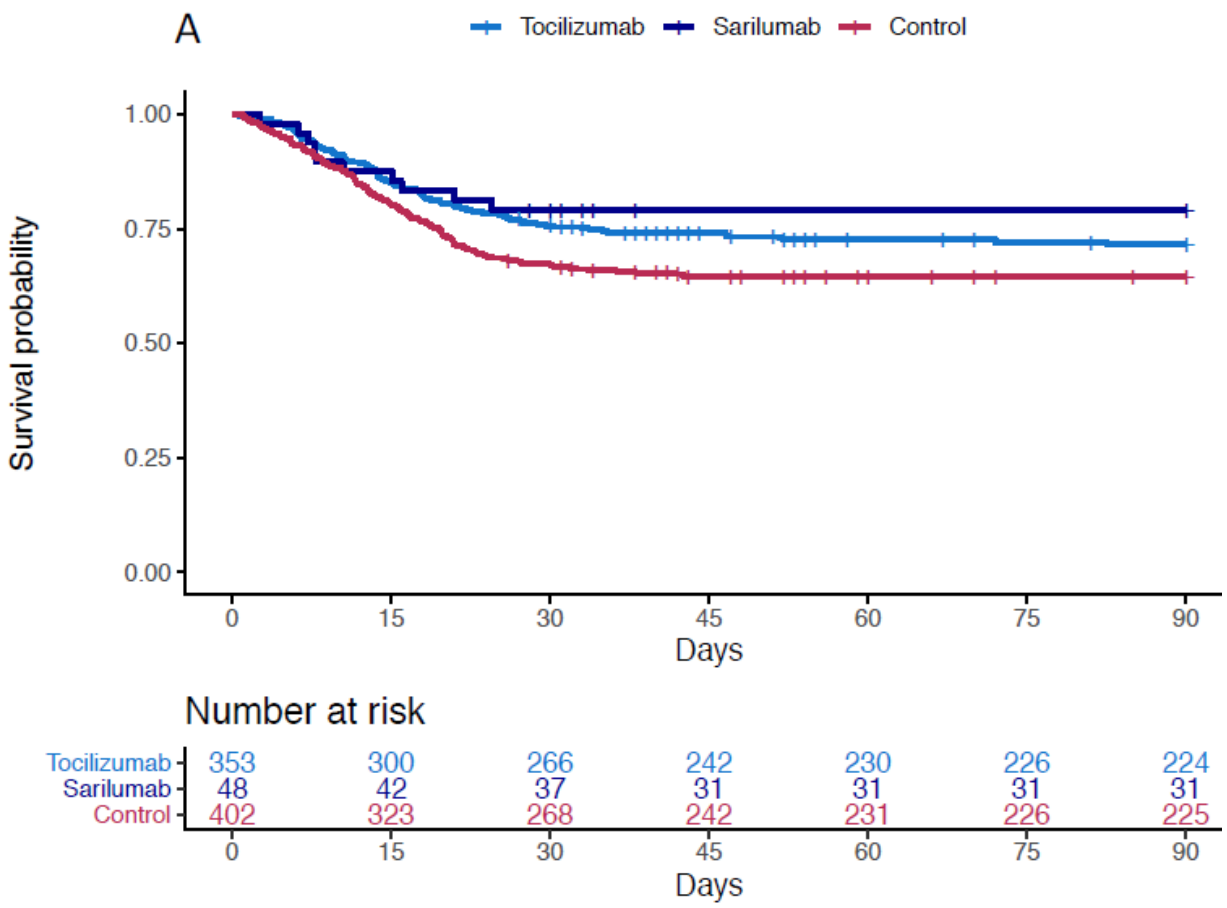
- RCT of TOCI vs usual care
- At the entry in ICU (max: 24 hours)
- 895 patients have been randomized in the Immune Modulation Therapy domain (366 to tocilizumab, 48 to sarilumab, 412 to control and 69 to other interventions within the domain)
- 93% of patients on corticosteroids

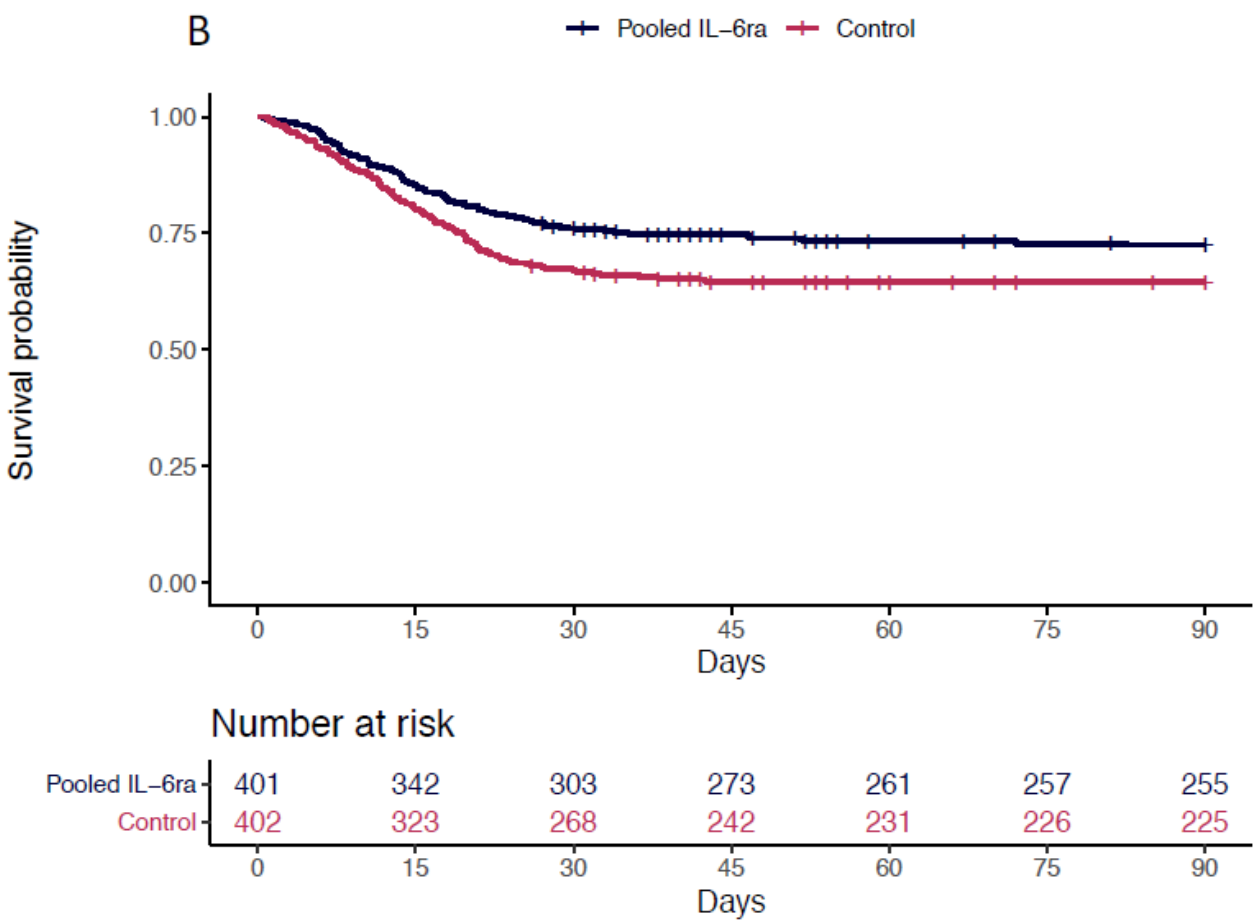
NEJM 25 Feb 2021

Table 1. Baseline Characteristics of the Patients in the Immune Modulation Therapy Domain.*

Characteristic	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)†	All Patients (N=865)‡
Age — yr	61.5±12.5	63.4±13.4	61.1±12.8	61.4±12.7
Male sex — no. (%)	261 (74)	39 (81)	283 (70)	629 (73)
Race or ethnic group — no./total no. (%)§				
White	160/228 (70)	29/39 (74)	206/279 (74)	420/580 (72)
Asian	41/228 (18)	8/39 (21)	47/279 (17)	99/580 (17)
Black	12/228 (5)	1/39 (3)	9/279 (3)	23/580 (4)
Mixed	2/228 (1)	0/39	5/279 (2)	7/580 (1)
Other	13/228 (6)	1/39 (3)	12/279 (4)	31/580 (5)
Body-mass index¶				
Patients evaluated	342	39	377	815
Median (IQR)	30.5 (26.9–34.9)	29.2 (26.0–33.8)	30.9 (27.1–34.9)	30.5 (26.8–34.9)
APACHE II score‖				
Patients evaluated	337	42	381	820
Median (IQR)	13 (8–19)	10 (7–16)	12 (8–18)	12 (8–19)
Confirmed SARS-CoV-2 infection — no./total no. (%)**	284/345 (82)	44/47 (94)	334/394 (85)	715/847 (84)
Median time to enrollment (IQR)				
From hospital admission — days	1.2 (0.8–2.8)	1.4 (0.9–2.8)	1.2 (0.8–2.8)	1.2 (0.8–2.8)
From ICU admission — hr	13.1 (6.6–19.0)	16.0 (11.4–20.8)	14.0 (6.8–19.5)	13.6 (6.6–19.4)
Acute respiratory support — no./total no. (%)				
None or supplemental oxygen only	1/353 (<1)	0/48	2/402 (<1)	3/865 (<1)
High-flow nasal cannulae	101/353 (29)	17/48 (35)	110/402 (27)	249/865 (29)
Noninvasive ventilation only	147/353 (42)	23/48 (48)	169/402 (42)	359/865 (42)
Invasive mechanical ventilation	104/353 (29)	8/48 (17)	121/402 (30)	254/865 (29)
Vasopressor support — no./total no. (%)	63/353 (18)	4/48 (8)	79/402 (20)	163/865 (19)
Pao_2:Fio_2				
Patients evaluated	335	35	354	780
Median (IQR)	115 (89–162)	126 (99–157)	118 (89–169)	116.5 (89–165)
Laboratory values††				
C-reactive protein				
Patients evaluated	207	37	244	533
Median (IQR) — μg/ml	150 (85–221)	136 (105–204)	130 (71–208)	136 (79–208)
D-dimer				
Patients evaluated	159	20	172	385
Median (IQR) — ng/ml	832 (461–1763)	828 (355–1435)	1010 (500–2115)	910 (480–1916)

REMAP-CAP 90-day survival rate





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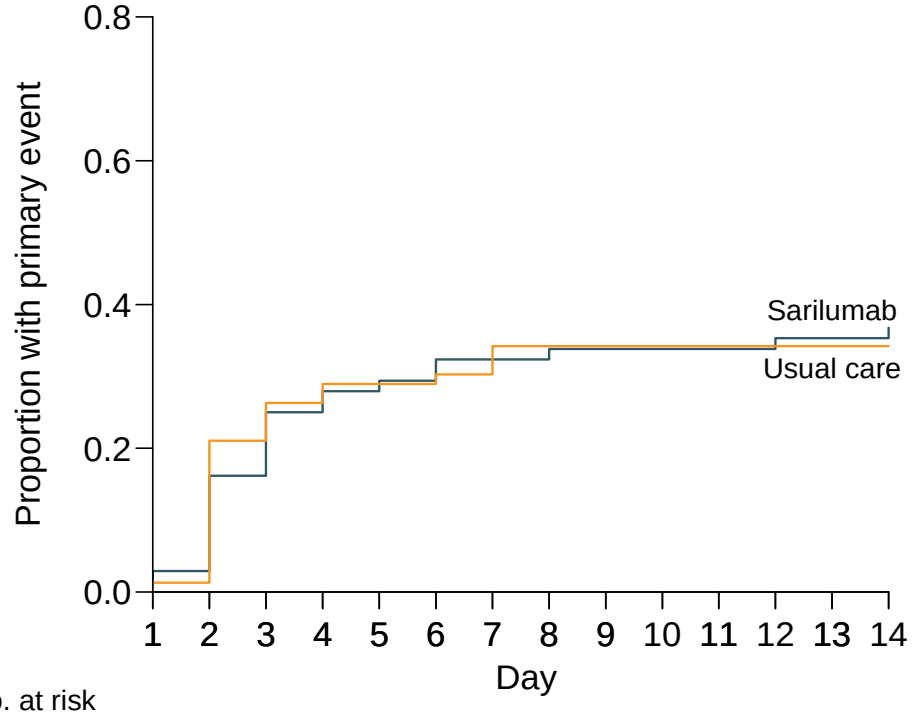
CORIMUNO-19- SARI-1

- Patients in WHO class 5 on oxygen: ≥ 3L/min
- Randomization between Usual care (UC) and UC + Sarilumab (SARI)
- SARI given by IV route 400 mg D1 followed by 400 mg fixed dose à D3 in case of good tolerance and absence of decrease of oxygen requirement of more than 50%
- 144 patients

Proportion of patients with occurrence of the primary event at D14

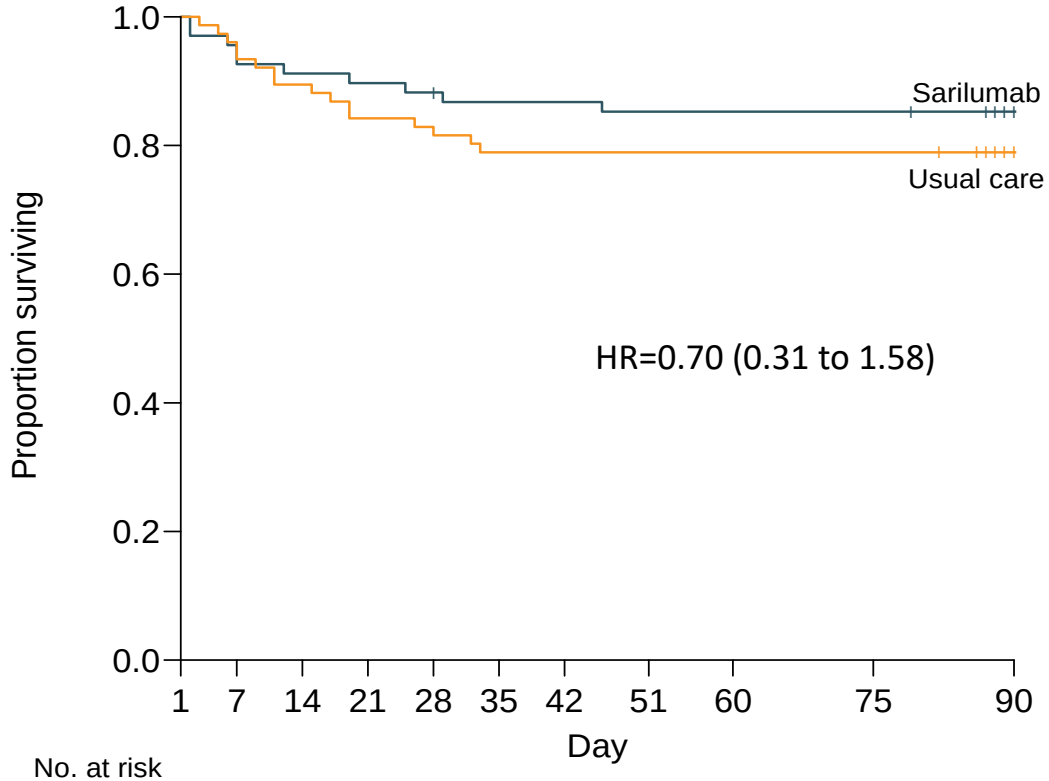
Time to Non-Invasive Ventilation or mechanical ventilation or Death



No. at risk														
Sarilumab	68	66	57	51	49	48	46	46	45	45	45	45	44	44
Usual care	76	75	60	56	54	54	53	50	50	50	50	50	50	50

@14 days: SRL: 37% (24 to 47); UC: 34% (23 to 44)

Time to mechanical ventilation or Death



No. at risk											
Sarilumab	68	65	62	61	60	58	58	57	57	57	42
Usual care	76	73	68	64	63	60	60	60	60	60	40

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

The CORIMUNO-19 group. Lancet Rheumatology 2021, accepted

CORIMUNO

CORIMUNO-19-SARI-1 SAFETY

	Sarilumab (N=68)	UC (N=76)	P
Adverse events			
- Patients with at least one AE*	37 (54%)	33 (43%)	0.24*
- Patients with multiple AE	17 (25%)	11 (14%)	
- Number of events**	77	58	0.023**
Serious adverse events			
- Patients with at least one SAE	27 (40%)	28 (37%)	0.73*
- Patients with multiple SAE	10 (15%)	9 (12%)	
- Number of events	44	40	0.34**
Hepatic cytolysis	6	3	
Multiple organ failure	0	2	
Pulmonary embolism	1	2	
Acute renal failure	1	1	
Neutropenia	5	0	
ARDS	7	11	
Bacterial sepsis	12	7	

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

The CORIMUNO-19 group. Lancet Rheumatology 2021, accepted

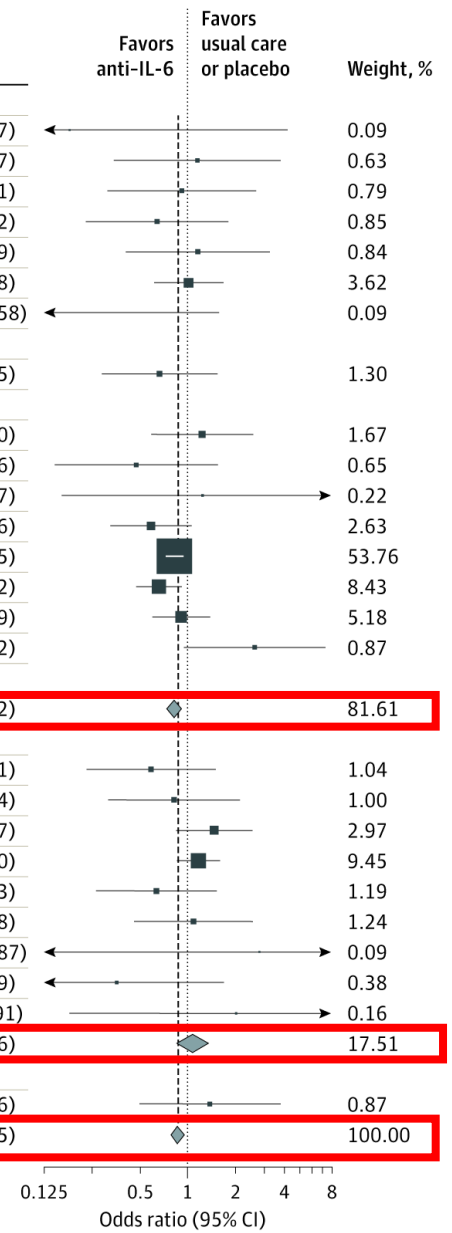
CORIMUNO

Meta-analysis of the 27 anti-IL-6R RCTs made by WHO

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA, July 6, 2021

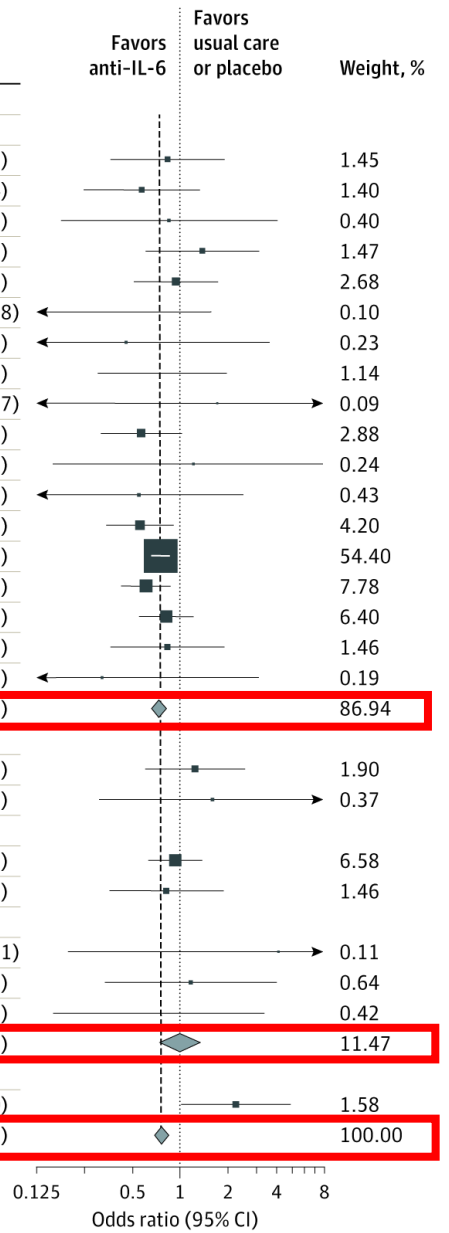
28-day mortality

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



Progression to IMV, ECMO or death

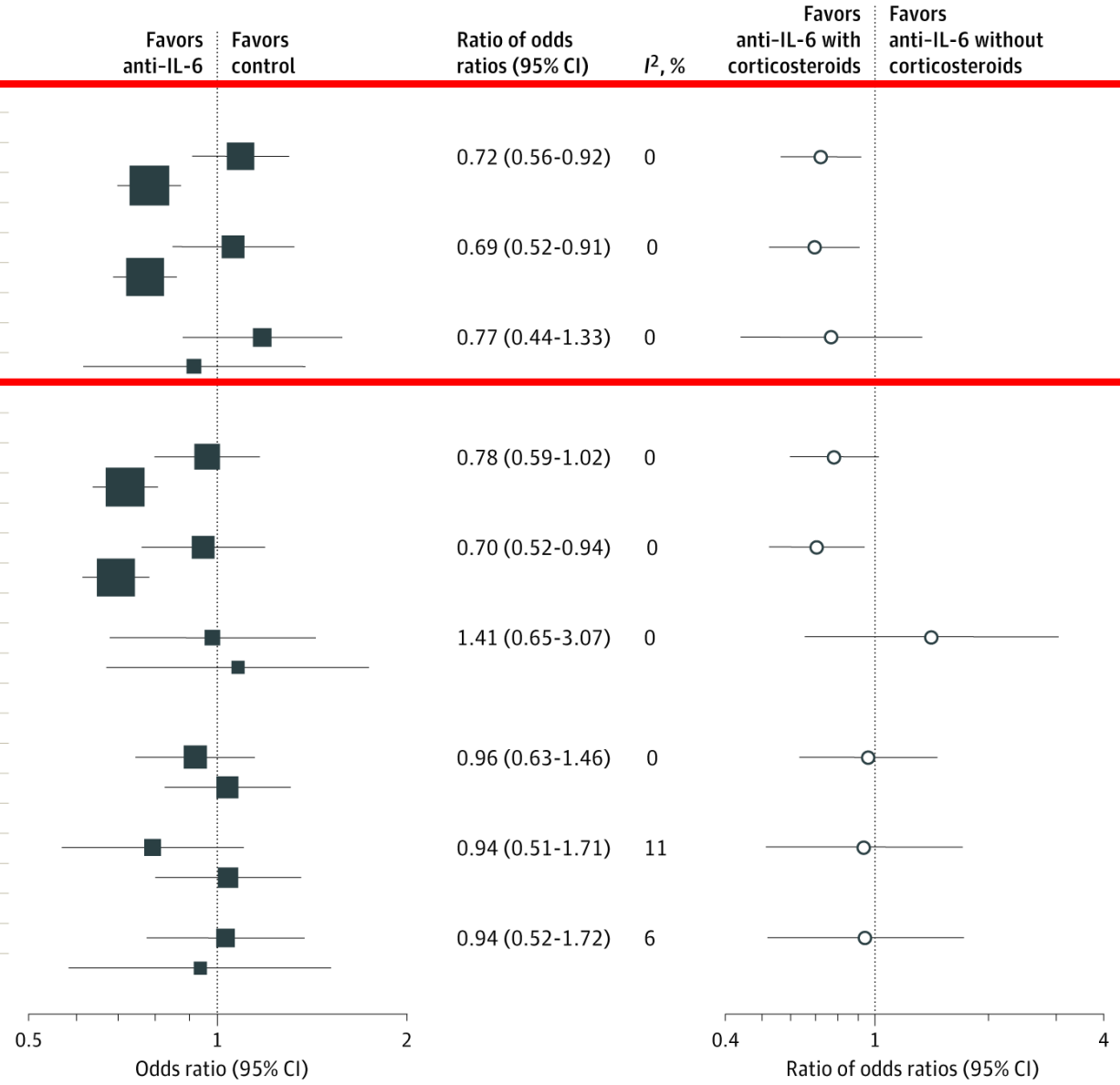
Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	1/1	0/0	NA[a]	
BACC-Bay	10/81	17/161	0.84 (0.37-1.92)	1.45
CORIMUNO-TOCI-1	18/67	11/63	0.58 (0.25-1.34)	1.40
CORIMUNO-TOCI-ICU	6/12	6/13	0.86 (0.18-4.13)	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



Meta-analysis of the 27 anti-IL-6R RCTs made by WHO
Better efficacy it associated with corticosteroids

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA, July 6, 2021

Outcome and treatment	I^2, %	No. of events/total patients: Control	No. of events/total patients: Anti-IL-6	Odds ratio (95% CI)	Ratio of odds ratios (95% CI)	I^2, %	*P* value
28-d mortality							
All anti-IL-6							
No corticosteroid use	0	293/1280	537/2357	1.09 (0.91-1.30)	0.72 (0.56-0.92)	0	.008
Corticosteroid use	0	838/2848	827/3468	0.78 (0.69-0.88)			
Tocilizumab							
No corticosteroid use	0	211/898	254/1192	1.06 (0.85-1.33)	0.69 (0.52-0.91)	0	.008
Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)			
Sarilumab							
No corticosteroid use	0	83/384	283/1134	1.18 (0.88-1.58)	0.77 (0.44-1.33)	0	.34
Corticosteroid use	0	48/281	124/607	0.92 (0.61-1.38)			
Progression to IMV, ECMO, or death at 28 d							
All anti-IL-6							
No corticosteroid use	0	308/1004	399/1541	0.96 (0.79-1.17)	0.78 (0.59-1.02)	0	.07
Corticosteroid use	0	893/2496	822/2986	0.71 (0.63-0.80)			
Tocilizumab							
No corticosteroid use	0	250/791	266/1016	0.95 (0.76-1.20)	0.70 (0.52-0.94)	0	.02
Corticosteroid use	0	859/2283	729/2518	0.69 (0.61-0. 78)			
Sarilumab							
No corticosteroid use	0	59/214	126/498	0.98 (0.67-1.44)	1.41 (0.65-3.07)	0	.38
Corticosteroid use	0	38/227	75/423	1.08 (0.67-1.75)			
28-d secondary infections[a]							
All anti-IL-6							
No corticosteroid use	3	165/758	434/1820	0.92 (0.74-1.15)	0.96 (0.63-1.46)	0	.85
Corticosteroid use	1	160/798	310/1378	1.04 (0.82-1.31)			
Tocilizumab							
No corticosteroid use	0	86/385	146/659	0.79 (0.57-1.10)	0.94 (0.51-1.71)	11	.83
Corticosteroid use	16	132/573	210/772	1.04 (0.80-1.36)			
Sarilumab							
No corticosteroid use	8	79/373	285/1130	1.03 (0. 77-1.38)	0.94 (0.52-1.72)	6	.85
Corticosteroid use	0	28/225	92/560	0.94 (0.58-1.52)			

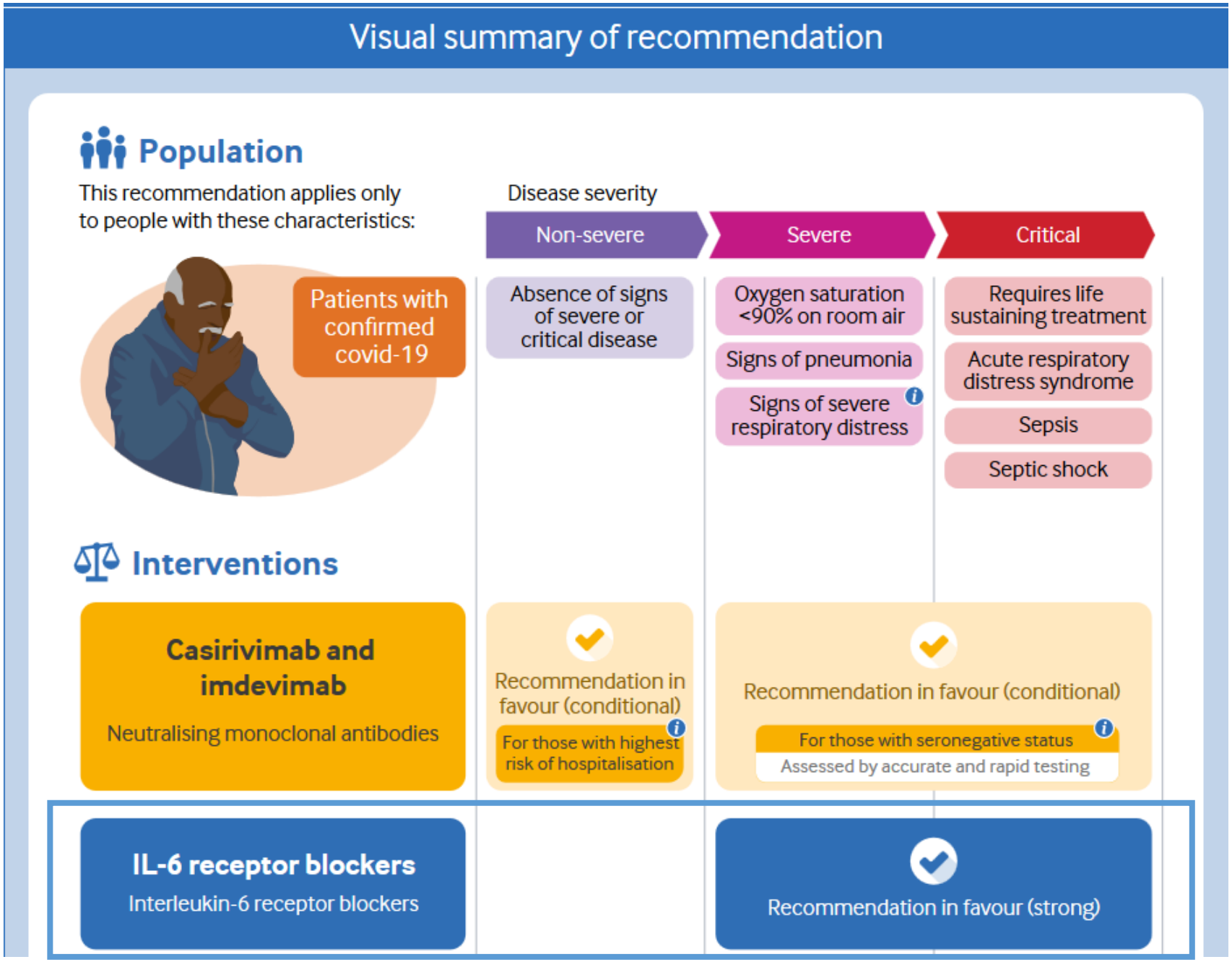


Parmi les médicaments ci-dessous, indiquez ceux qui sont recommandés par l’OMS dans les formes sévères et critiques de COVID-19

- A. Dexamethasone
- B. Baricitinib
- C. Tocilizumab
- D. Sarilumab

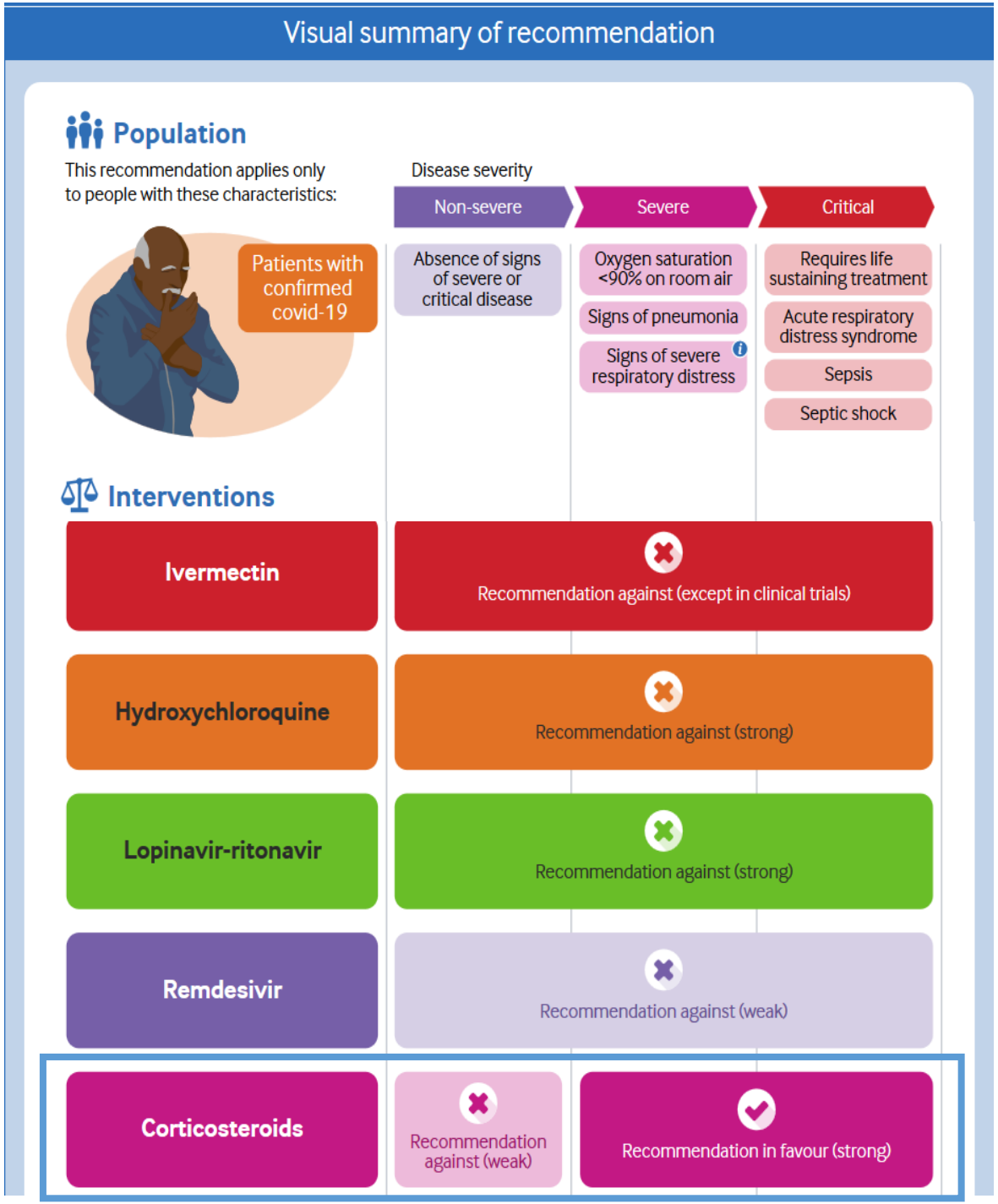
WHO live guidelines

BMJ, July 6, 2021



WHO live guidelines

BMJ, July 6, 2021



What immunomodulatory drugs for COVID ?

- Corticosteroids
- IL-6 inhibitors
- **IL-1 inhibitors**
- Jak inhibitors
- Other immunomodulators

Anakinra: CORIMUNO-19-ANA 1

- Patients in WHO class 5 on oxygen: ≥ 3L/min
- Randomization between Usual care (UC) and UC + Anakinra (ANA)
- Anakinra given by IV route
- 114 patients

All patients			200 mg : **100 mg x2/j**	**100 mg x1/j**	
D1	**D2**	**D3**	Non Responders		
400 mg : **200 mg x2/d**	400 mg : **200 mg x2/d**	400 mg : **200 mg x2dj**			

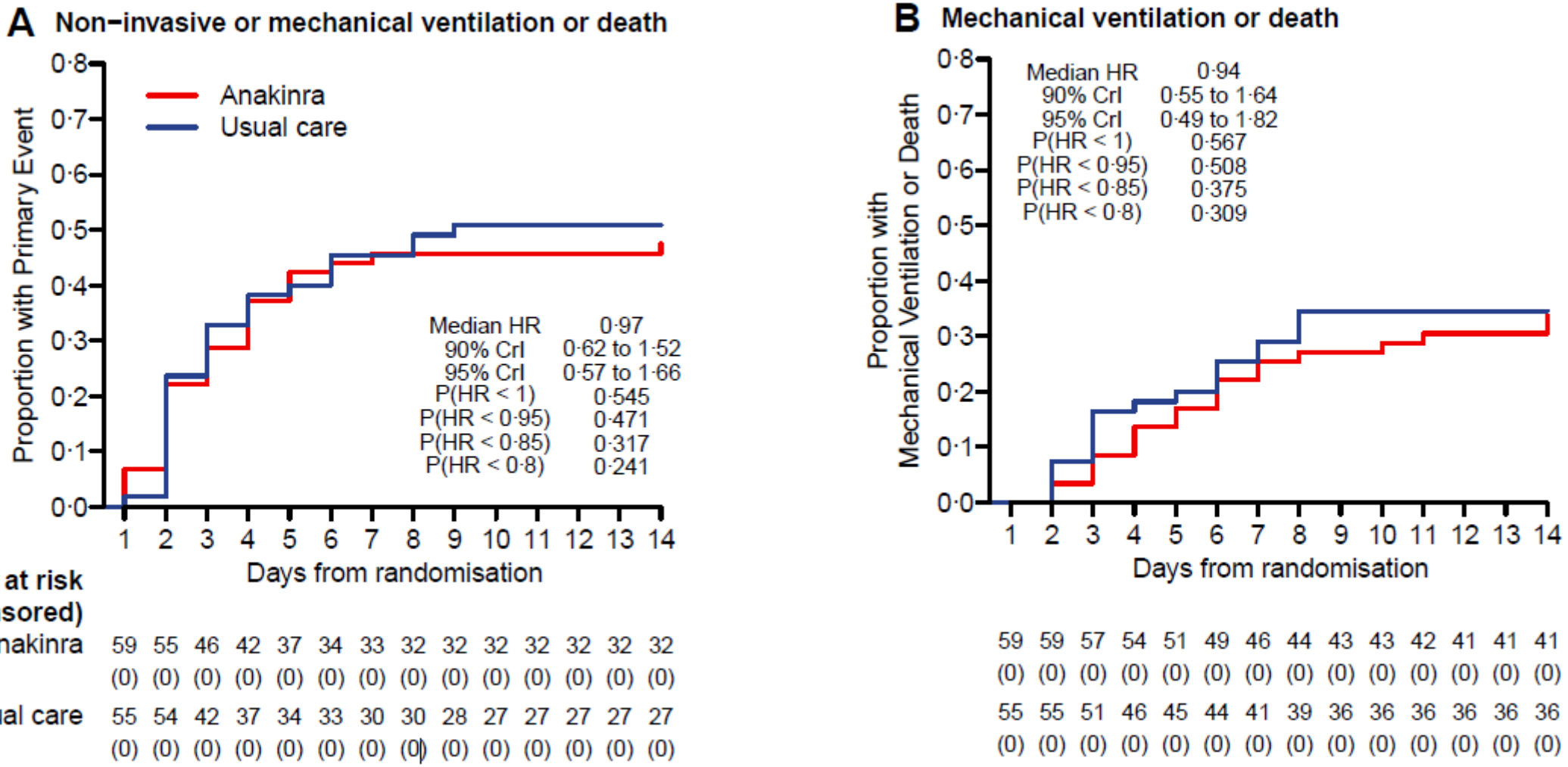
D4	**D5**	**D6**	**D7**	**D8**
400 mg : **200 mg x2/d**	400 mg : **200 mg x2/d**	400 mg : **200 mg x2/d**	200 mg : **100 mg x2/d**	**100 mg x1/d**

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Mariette X, Hermine O, and the CORIMUNO-19 group. Lancet Resp Medicine; 22 Fev 2021

CORIMUNO

Proportion of patients with occurrence of the primary event at D14 ANA-1

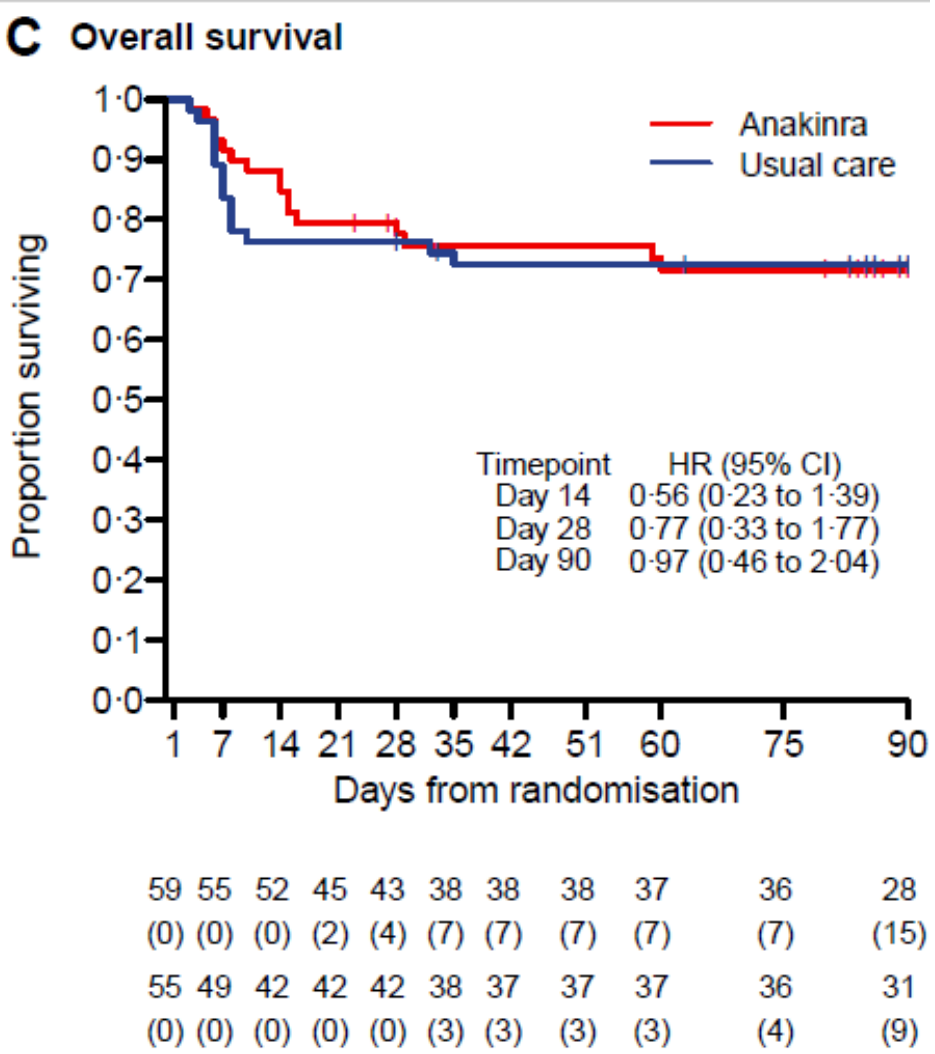


ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Mariette X, Hermine O, and the CORIMUNO-19 group. Lancet Resp Medicine; 22 Fev 2021

CORIMUNO

CORIMUNO-ANA-1. Survival up to D90



Overall survival

	Anakinra (n=59)		UC (n=55)		
	N deaths	OS	N deaths	OS	Adjusted HR (95% CI)
Day 14	9	85%	13	76%	0.56 (0.23 to 1.39)
Day 28	13	78%	13	76%	0.77 (0.33 to 1.77)
Day 90	16	70%	15*	71%	0.96 (0.46 to 2.04)

* One patient died on day 91, and is not counted among the 15.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Mariette X, Hermine O, and the CORIMUNO-19 group. Lancet Resp Medicine; 22 Fev 2021

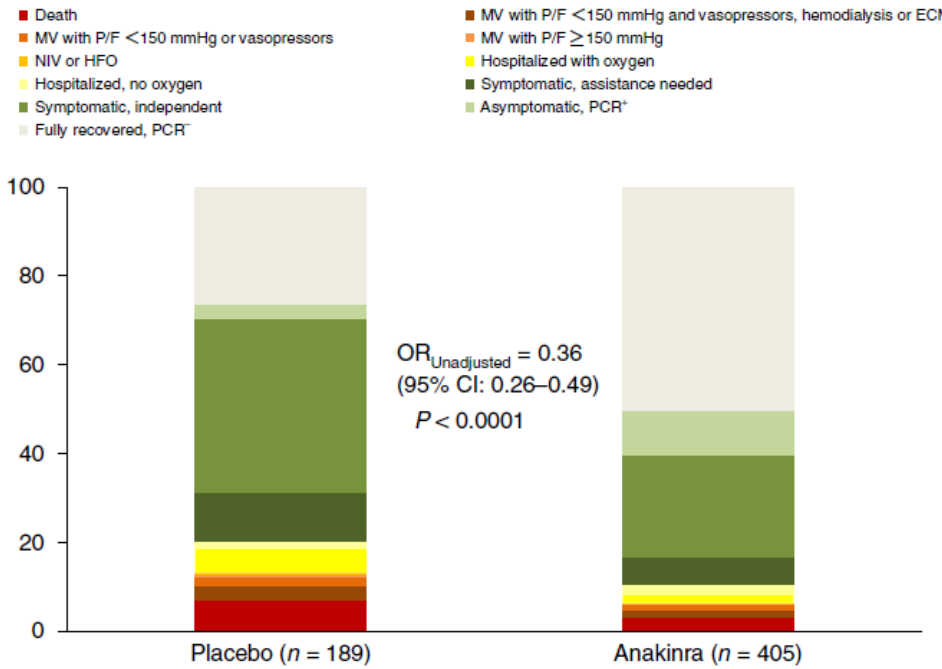
CORIMUNO

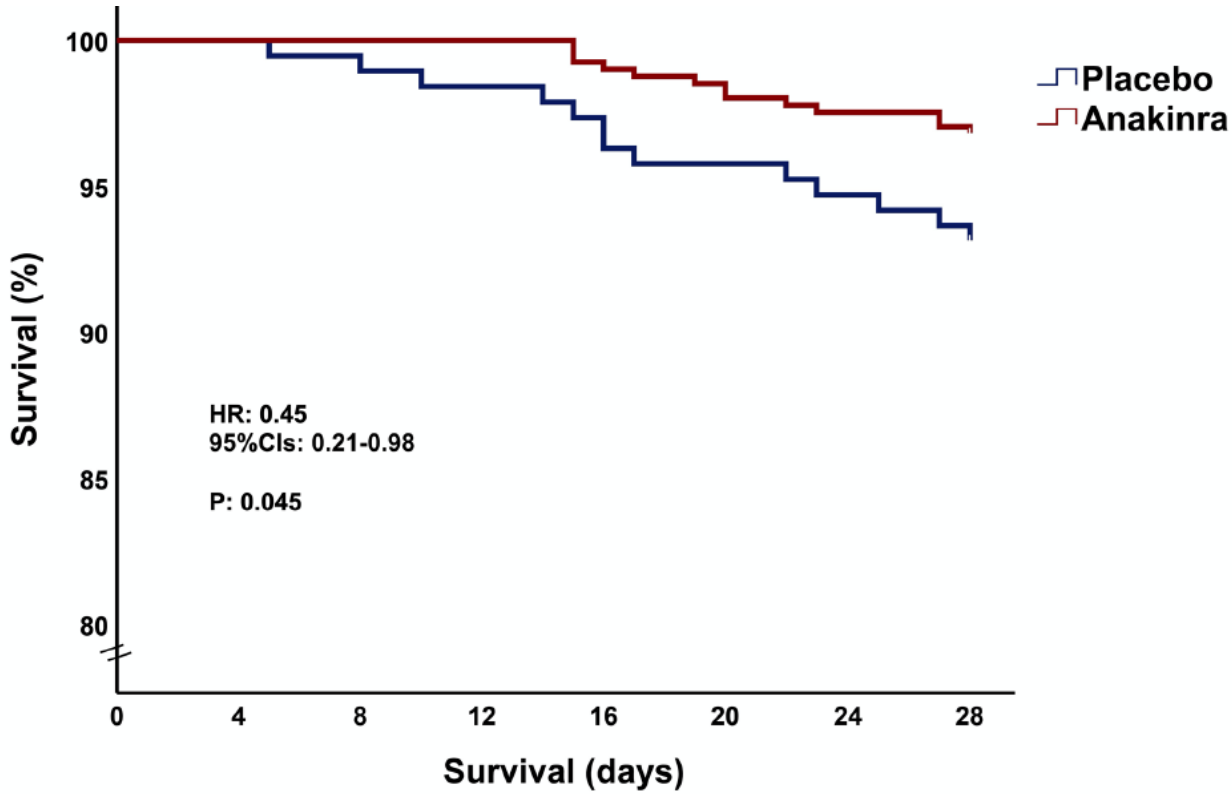
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01499-z
Check for updates

OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

- Patients included if baseline level of suPAR > 6 ng/ml
- Anakinra (100mg/d) or placebo for 7-10 days
- Primary end-point: WHO-CPS at Day28
- At baseline, CRP: 51 mg/L
  - 9 days from symptoms begin
  - 92% on Oxygen, 86% on dexamethasone





Patients at risk (n)

Placebo	189	189	187	186	182	181	179	176
Anakinra	405	405	405	405	401	397	395	392

- Benefit on D28 mortality: 3,2% vs 6,9% HR= 0.45, 95% CI 0.21–0.9)
- Less severe infections with anakinra: 16% vs 8% (p=0,01)

Kyriazopoulou E et al Nature Med on line 03 Sept 2021

What immunomodulatory drugs for COVID ?

- Corticosteroids
- IL-6 inhibitors
- IL-1 inhibitors
- **Jak inhibitors**
- Other immunomodulators

Parmi les affirmations ci-dessous concernant JAK inhibiteurs et COVID, indiquez celles qui sont exactes

- A. Les essais récents ne montrent pas d'intérêt du tofacitinib et du baricitinib dans les formes sévères de COVID-19
- B. Les essais récents ne montrent pas d'intérêt du tofacitinib main un intérêt du baricitinib dans les formes sévères de COVID-19
- C. Les essais récents montrent un intérêt du tofacitinib mais pas d'intérêt du baricitinib dans les formes sévères de COVID-19
- D. Les essais récents montrent un intérêt du tofacitinib et du baricitinib dans les formes sévères de COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

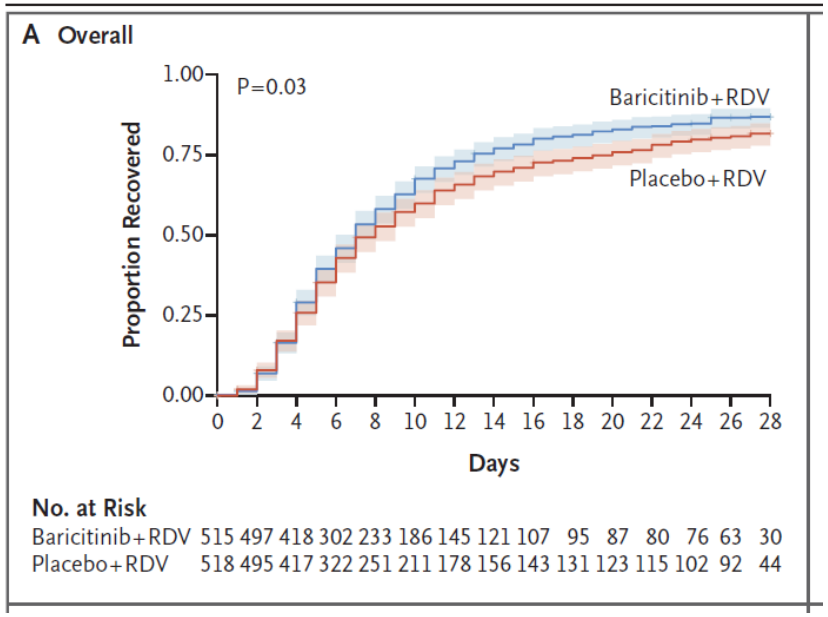
ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

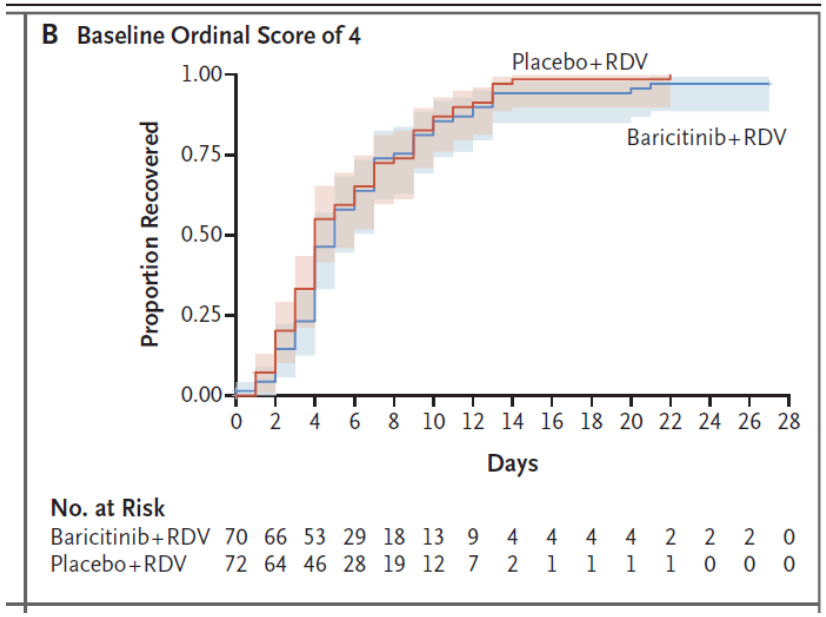
- 1033 hospitalized patients with COVID
- Randomization between remdesevir (< 10 days) and remdesevir + baricitinib (Jak2 inhibitor, < 14 days)
- Primary end-point: Time to hospital discharge
  - Remdesevir: 8 days
  - Remdesevir + baricitinib: 7 days p=0.03
- Day 28 Mortality: 5.1% vs 7.8%, HR=0.65; 95% CI, 0.39 to 1.09

Kalil AC, et al. N Engl J Med. Dec 11, 2020.

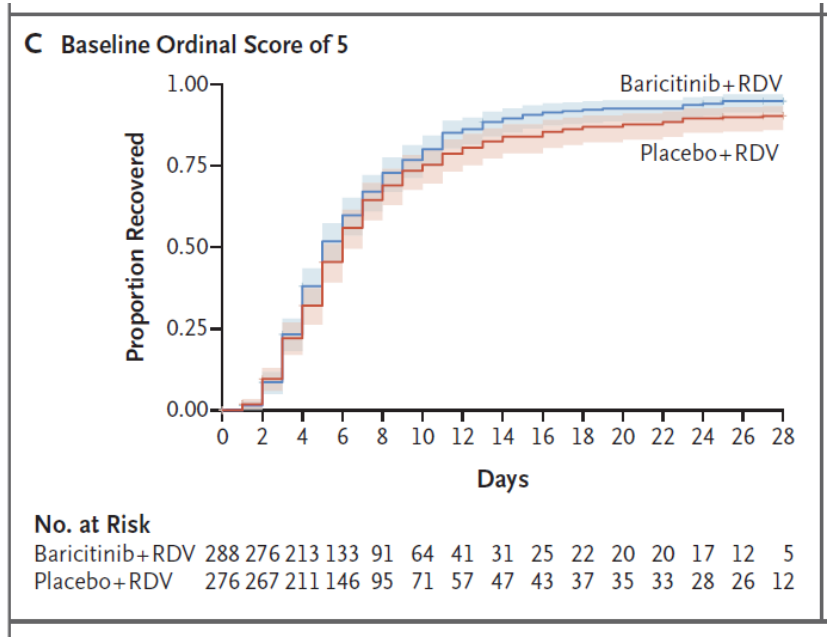
Overall



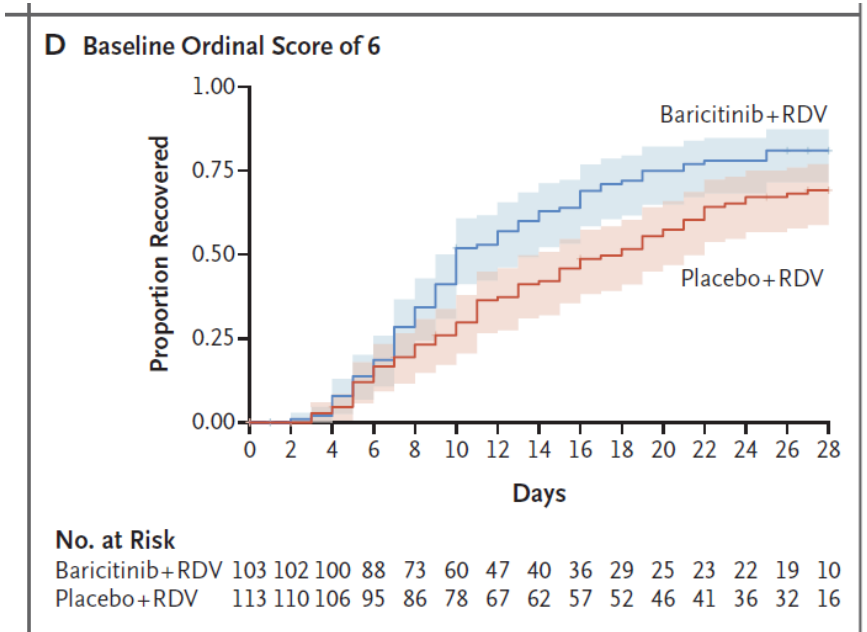
No oxygen



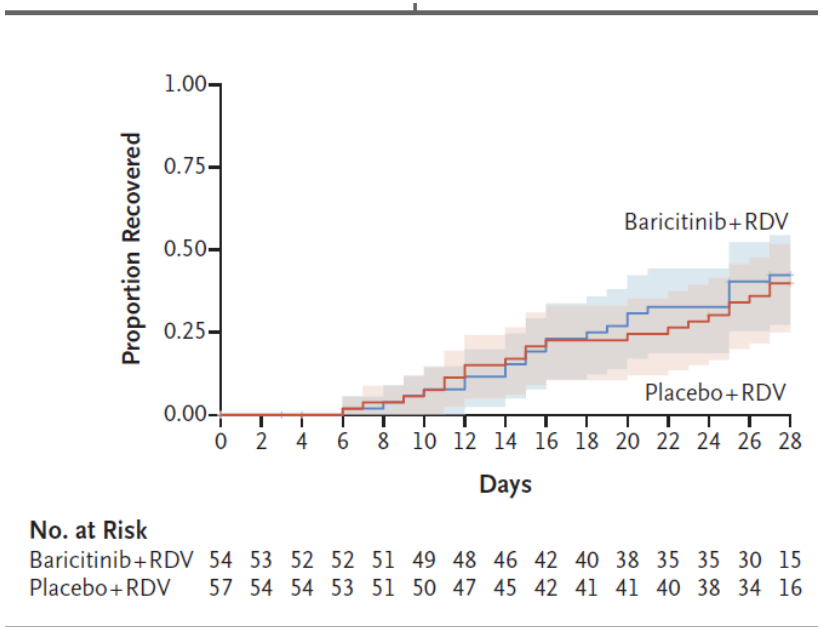
Oxygen



Non-invasive ventilation



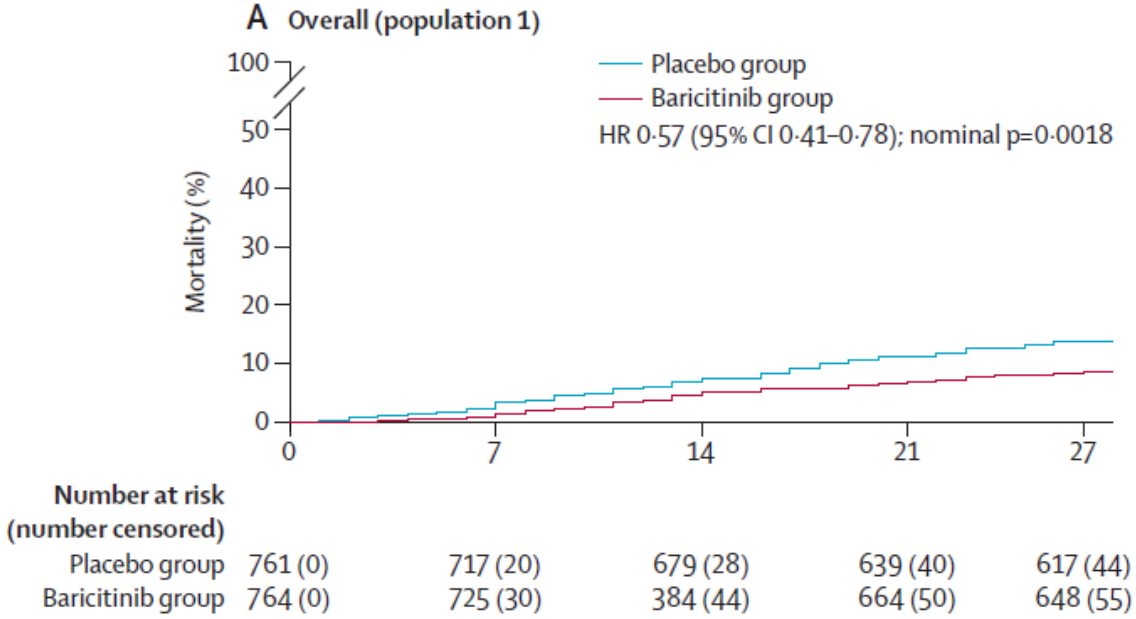
Mechanical ventilation

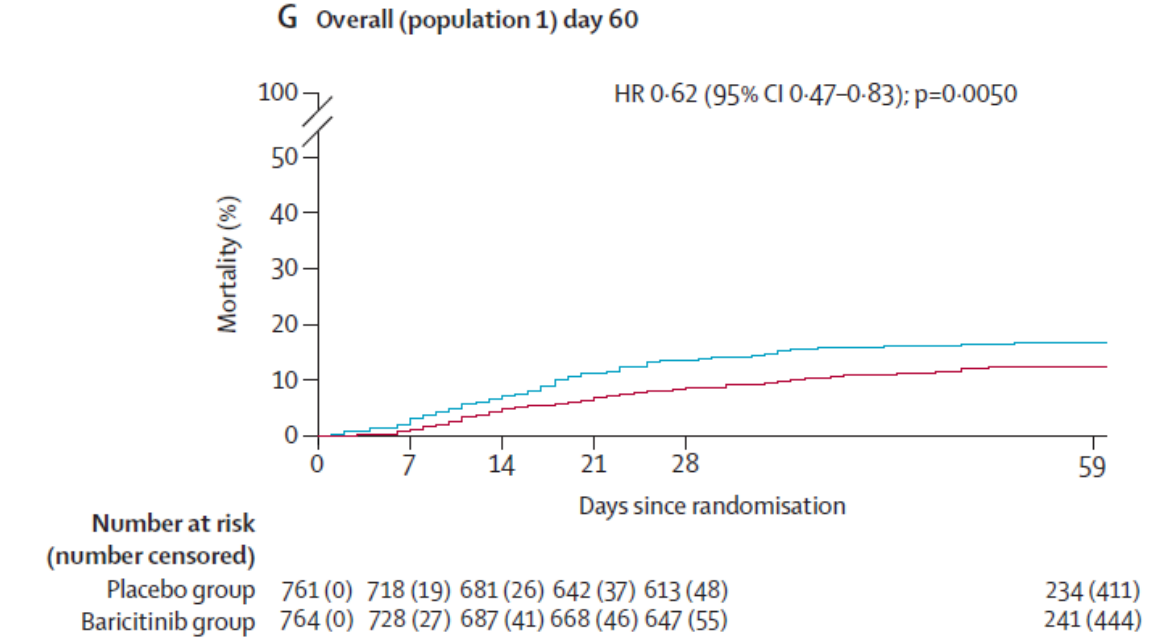


Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

*Vincent C Marconi, Athimalaipet V Ramanan, Stephanie de Bono, Cynthia E Kartman, Venkatesh Krishnan, Ran Liao, Maria Lucia B Piruzeli, Jason D Goldman, Jorge Alatorre-Alexander, Rita de Cassia Pellegrini, Vicente Estrada, Mousumi Som, Anabela Cardoso, Sujatro Chakladar, Brenda Crowe, Paulo Reis, Xin Zhang, David H Adams, E Wesley Ely, on behalf of the COV-BARRIER Study Group**

- Baricitinib (4mg/d) or placebo for 14 days
- At baseline,
  - 12% no Oxygen, 64% on Oxygen, 24% on high flow
  - 80% on corticosteroids (92% on dexamethasone)
  - CRP: 65 mg/L
- Primary end-point: Progression to ventilation or death at Day28 not achieved:
  - OR=0·85 [95% CI 0·67 to 1·08], p=0·18)
- Decrease of 28-day all-cause mortality: 8% vs 13% (HR=0·57 [95% CI 0·41–0·78]; p=0·0018)
- Serious infections (64 [9%] vs 74 [10%]),
- Venous thromboembolic events (20 [3%] vs 19 [3%])





Marconi VC, et al. Lancet Respi Medicine on line. 1 Sept 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia

- Tofacitinib (10mg/twice a day) or placebo for 14 days
- At baseline,
  - 25% no Oxygen, 63% on Oxygen, 13% on high flow
  - 79% on corticosteroids
  - CRP: 65 mg/L
- Primary end-point: Progression to ventilation or death at Day28 achieved:
  - RR=0.63; 95% [CI], 0.41 to 0.97; P = 0.04)
- Non-significant decrease of 28-day all-cause mortality: 2,8% vs 5,5% (HR=0.49; 95% CI, 0.15 to 1.63)
- Serious adverse events: 14,1% vs 12,0%
- Serious infections: 3,5% vs 4,2%

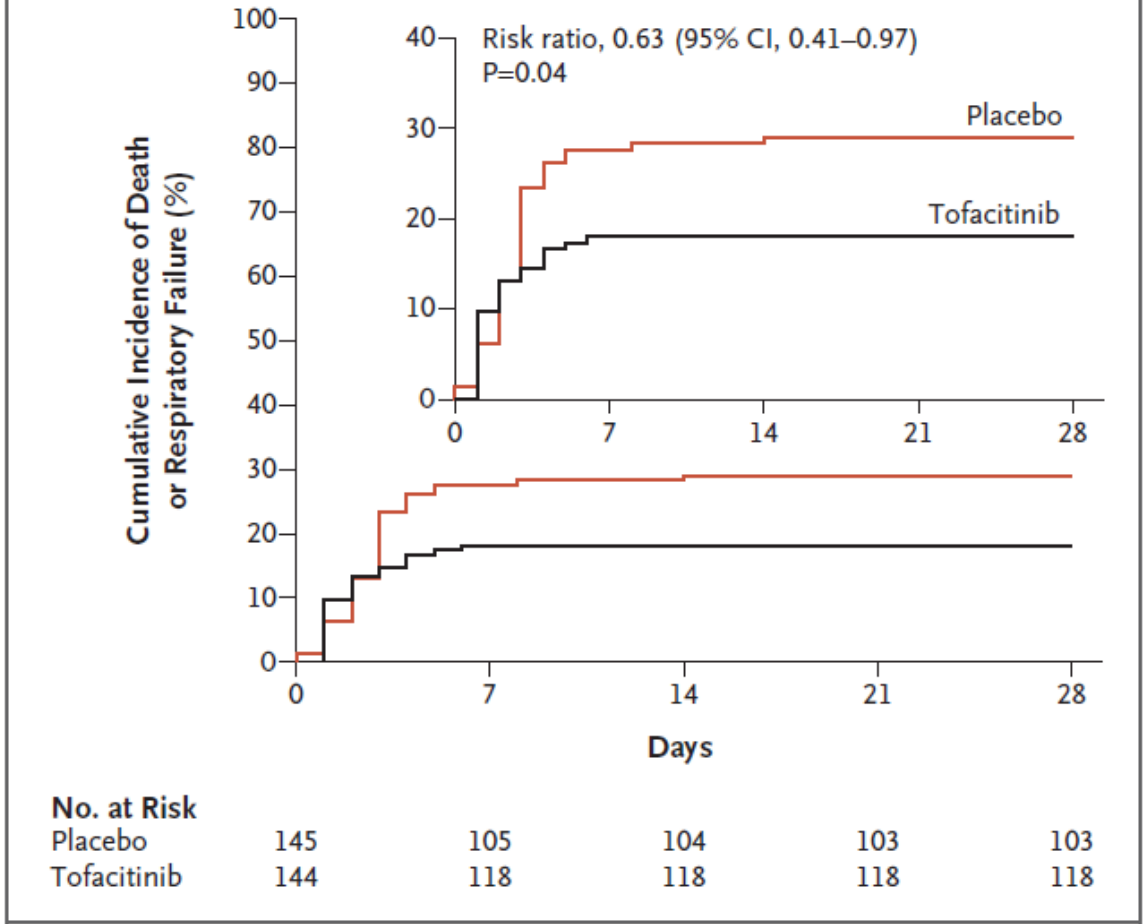


Figure 2. Cumulative Incidence of the Primary Outcome.

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

Guimarães PO, et al. N Engl J Med 2021;385:406-15.

What immunomodulatory drugs for COVID ?

- Corticosteroids
- IL-6 inhibitors
- IL-1 inhibitors
- Jak inhibitors
- **Other immunomodulators**

Parmi les immunothérapies ci-dessous, indiquez celles pour lesquelles il y a des indications suggérant une possible efficacité dans certaines formes de COVID-19

- A. Colchicine
- B. Anti-TNF
- C. Anti-GM-CSF
- D. Secukinumab

Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19

- 4488 non-hospitalized patients
- Randomization between colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for 30 days.
- The primary efficacy endpoint was the composite of death or hospitalization for COVID-19.

Table 2. Rates and Odds Ratios for Major Clinical Outcomes.

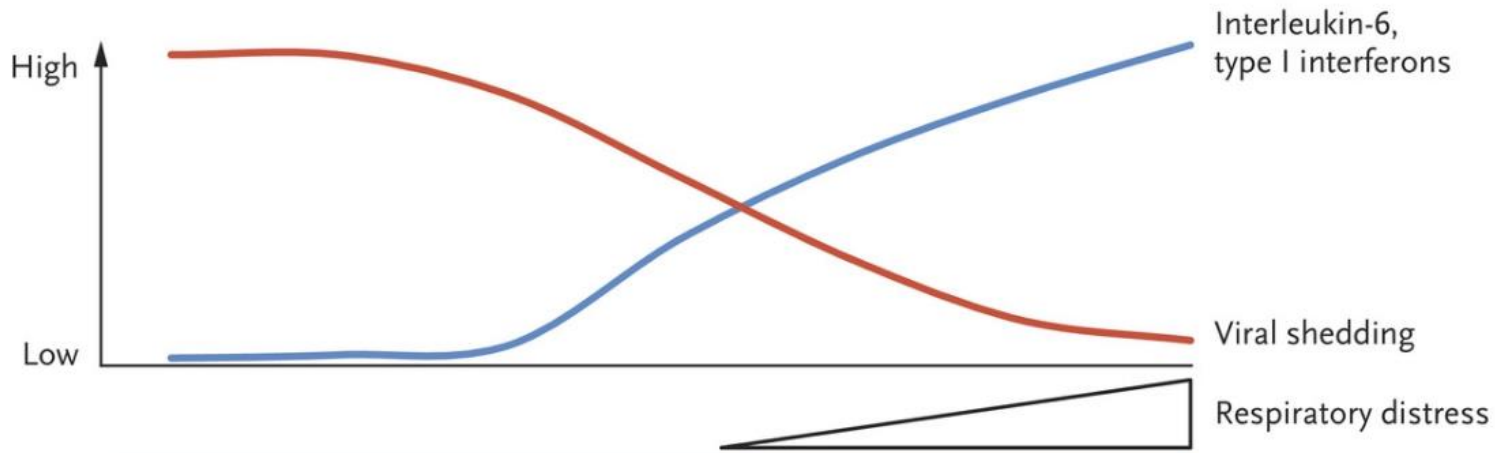
Clinical Outcome	Colchicine	Placebo	Odds Ratio (95% CI)	P Value
ITT population	N=2235	N=2253		
Primary composite endpoint - no. (%)	104 (4.7%)	131 (5.8%)	0.79 (0.61-1.03)	0.08
Components of primary endpoint:				
Death - no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.67)	
Hospitalization for COVID-19 no. (%)	101 (4.5%)	128 (5.7%)	0.79 (0.60-1.03)	
Secondary endpoint:				
Mechanical ventilation - no. (%)	11 (0.5%)	21 (0.9%)	0.53 (0.25-1.09)	
Patients with PCR-proven COVID-19	N=2075	N=2084		
Primary composite endpoint – no. (%)	96 (4.6%)	126 (6.0%)	0.75 (0.57-0.99)	0.04
Components of primary endpoint:				
Death – no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.66)	
Hospitalization for COVID-19 no. (%)	93 (4.5%)	123 (5.9%)	0.75 (0.57-0.99)	

Tardif JC et al. https://doi.org/10.1101/2021.01.26.21250494 doi: medRxiv preprint

What data regarding immunomodulatory drugs for COVID are expected in the next weeks (to date only press releases)?

- Anti-IL17
  - Secukinumab: failed
- Anti-TNF
  - ???
- Anti-GM-CSF
  - Otilimab: failure but sucess over 70 years
  - Mavrilimumab: sucess

Conclusion



Ordinal Scale	1	2	3	4	5	6	7
Drugs with Significant Effects on Covid-19 Mortality in Randomized, Controlled Trials							
Glucocorticoids					Dexamethasone		
Janus kinase inhibitors (with or without glucocorticoids)				Baricitinib, tofacitinib			
Interleukin-6 receptor antagonists (with glucocorticoids)					Tocilizumab		
	Therapeutic Window for Antiviral Agents				**Therapeutic Window for Immunomodulators and Antiinflammatory Agents**		

J. Stebbing and V.M. Lauschke. N Engl J Med 2021;385:463-465

Conclusion

- Immunomodulators should not be given early in COVID infection
- Corticosteroids (dexamethasone 6 to 10 mg/day) should be given in patients requiring oxygen, high flow or mechanical ventilation
- A recent meta-analysis from WHO demonstrates an efficacy of Tocilizumab especially if associated with DXM in patients requiring Oxygen or high flow
- To date probably no room for anakinra
- Probably a room for JAK inhibitors in patients requiring oxygen or high flow ventilation