université PARIS DIDEROT PARIS 7

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

MI² Medical Infectious diseases Intensive care unit

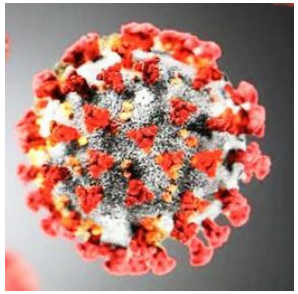
Covid-19 en réanimation qu'a-t-on appris?

IAME UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution

Liens d'intérêt

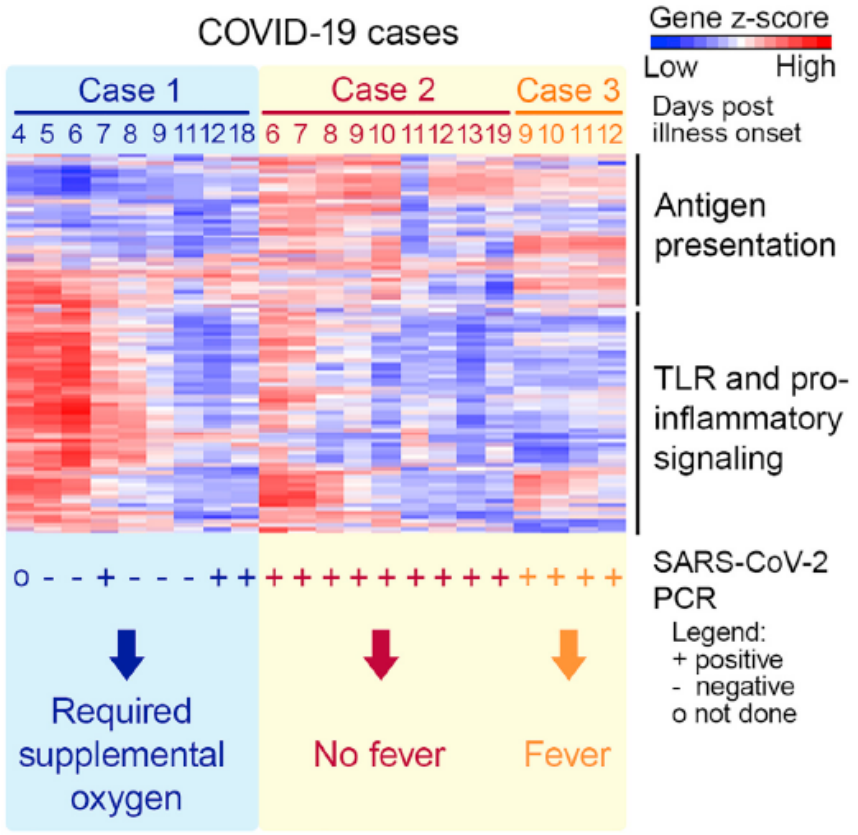
- En rapport avec les firmes commercialisant les immunomodulateurs:
  - Aucun
- En rapport avec le covid-19
  - Aucun
- Académique:
  - Participant au comité de rédaction du HCSP
  - PI Covidicus
- En rapport avec les antibiotiques:
  - MSD, Pfizer, Gilead, Shionoghi, Bayer Pharma, Nabriva, Menarini, Medimmune, Biomerieux, Thermofischer

To sumarize



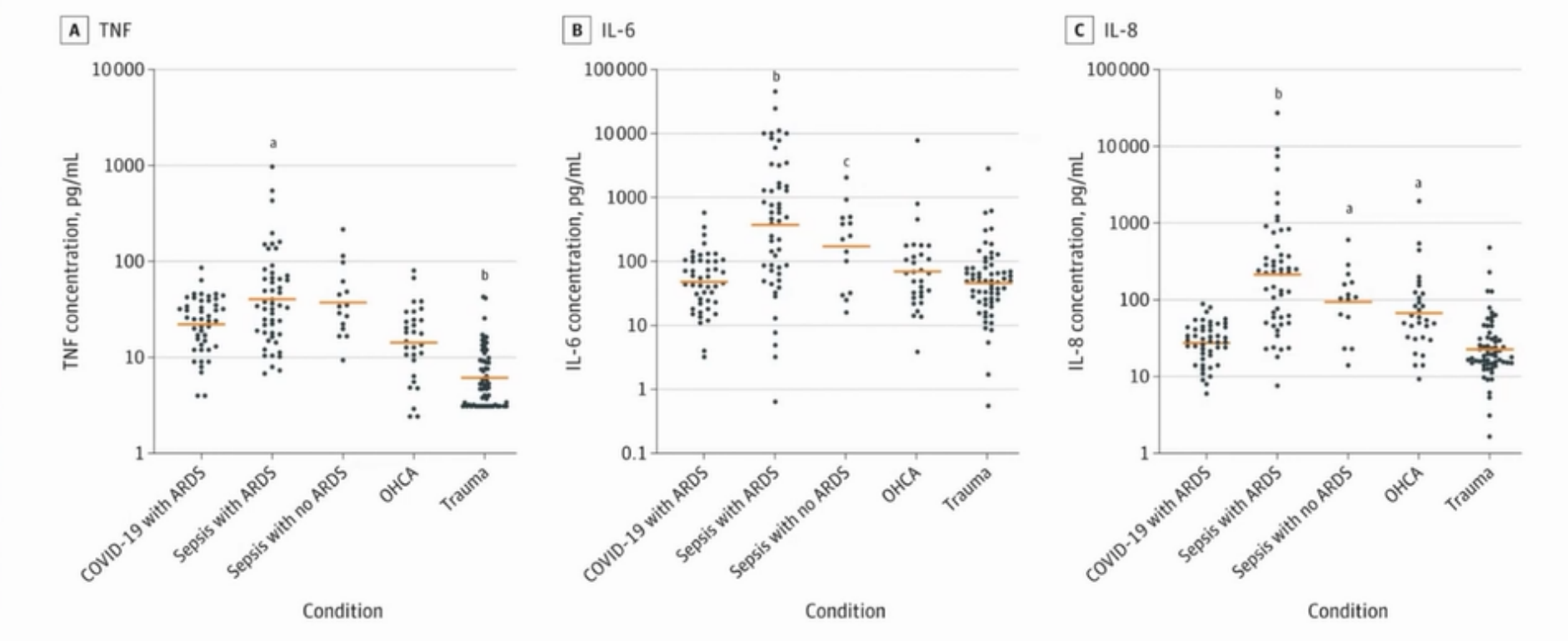
- Immunoprotective response
  - Early interferon responses
  - Leukocytes activation (CD8)
  - Plasmablast response
  - Antibody responses
- Pathologic immune response
  - Altered antiviral IFN responses
  - Cytokine excess
  - T lymphocyte exhaustion

A dynamic process



Ong et al., 2020, Cell Host & Microbe 27, 879–882

Inflammation systémique? Oui un peu? Mais ça dépend…



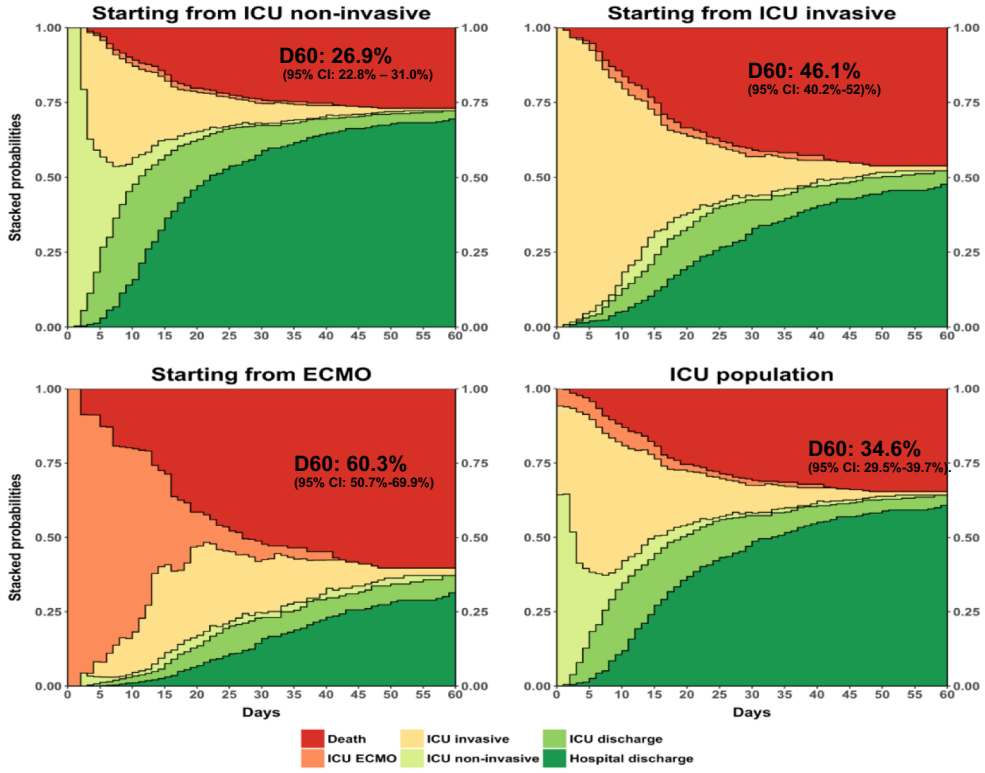
Kox et al – JAMA . 2020 Sep 3;324(15):1565-1567.

EPIDEMIOLOGIE / PRONOSTIC

Non parametric estimates:

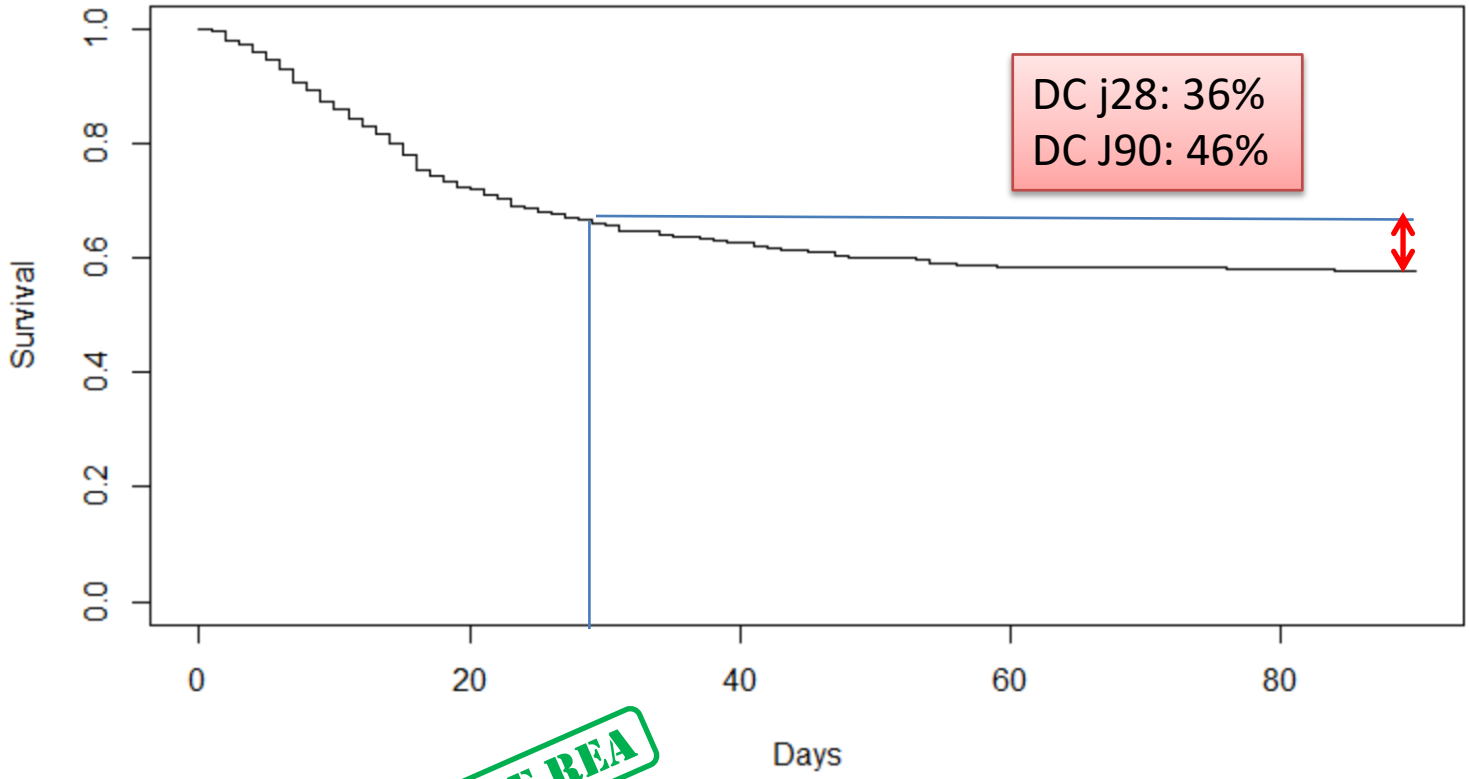
Stacked plots of predicted probability of state occupancy according to initial state

<u>Initial state on admission</u>
Non invasive oxygenation: 254 (64.3%)
Invasive ventilation 118 (30.9%)
ECMO 23 (5.8%)



Ursino M et al - J. Clin. Med. ***2021, 10, 544. https://doi.org/10.3390/jcm10030544***

Base Outcomerea



OUTCOME REA

N=950 (ajustée sur la proportion de VMI

LA RECHERCHE PENDANT UNE PANDEMIE?

Coronavirus : diagnostiquons et traitons ! Premiers résultats pour la chloroquine

1 506 926 vues • 16 mars 2020

J'AIME JE N'AIME PAS

Donald J. Trump ✓ @realDonaldTrump · Mar 21

HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....

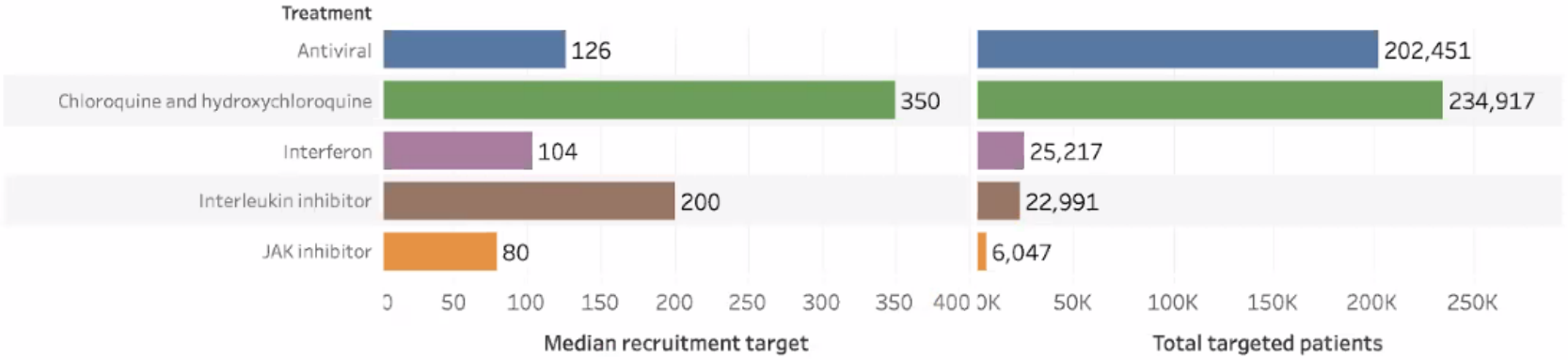
70.5K 102.8K 385.1K

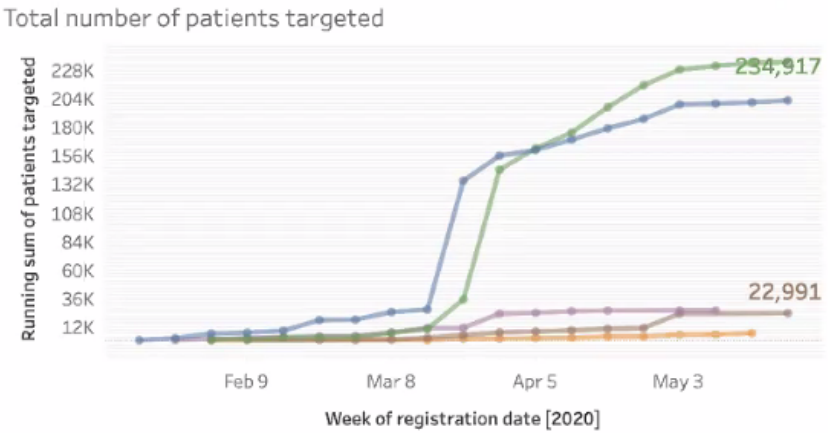
Donald J. Trump ✓
@realDonaldTrump

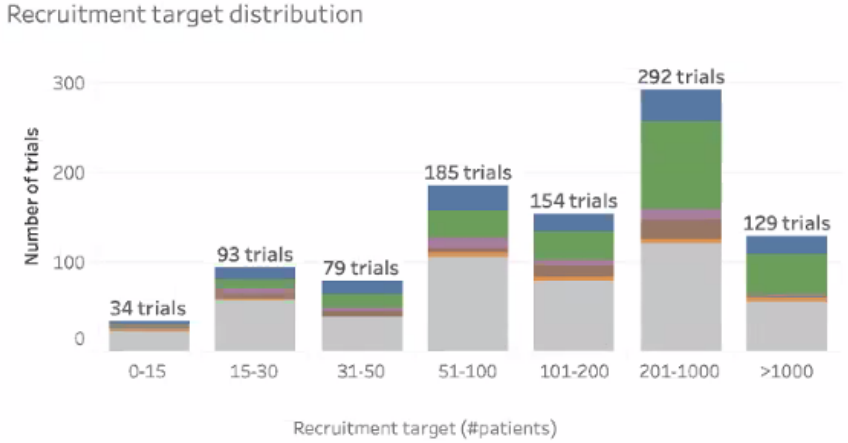
....be put in use IMMEDIATELY. PEOPLE ARE DYING, MOVE FAST, and GOD BLESS EVERYONE! @US_FDA @SteveFDA @CDCgov @DHSgov

10:13 AM · Mar 21, 2020 · Twitter for iPhone

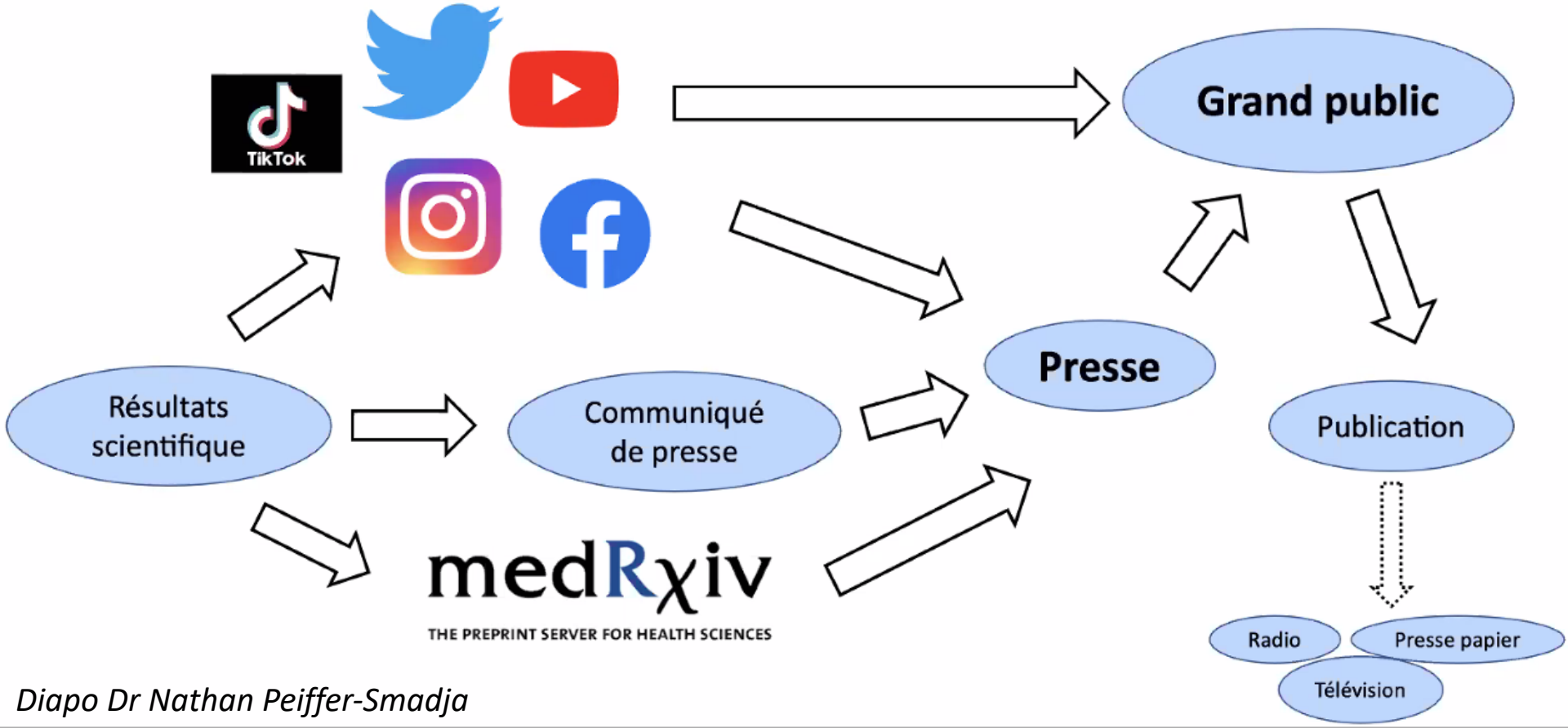
June 2020







Peiffer-Smadja et al. Anticovid, a comprehensive open-access real-time platform of registered clinical studies for COVID-19. *Journal of Antimicrobial Chemotherapy*



Diapo Dr Nathan Peiffer-Smadja

ACADÉMIE NATIONALE DE MÉDECINE

Académie nationale de Pharmacie

INSTITUT DE FRANCE
Académie des sciences

« En définitive, la vitesse et la précipitation de la communication de résultats partiels, non évalués par les pairs, nuisent à la crédibilité de l'essai concerné et à la confiance du public dans les essais thérapeutiques en général. Ils alimentent la critique des médias et portent un mauvais coup à la science. La justification de communiquer un résultat préliminaire avec comme argument de ne pas faire perdre une chance à des patients ultérieurs n'est pas recevable. Les autorisations laxistes ne viennent pas en supplément des autorisations conformes aux impératifs scientifiques. Elles compromettent ces dernières en réduisant leur recrutement et finalement retardent la mise à la disposition de traitements efficaces pour les patients. »

Particularités et limites de la recherche Covid

- Variabilité au cours du temps de :
  - Méthodes diagnostiques
  - Nb de sujets planifié en cours d'étude
  - Critère de jugement? Date de mesure?
    - Scores? Echelles ordinales?
    - Mortalité?
    - Intubation ou dc?
    - Délai de Retour a domicile
  - Choix des bras de rando?
- Standard de soins variable
  - Temps
  - Centre
  - Variants
  - Connaissance de la maladies
  - Résultats des études en cours….

Essais plateforme?

- Avantages:
  - Grosses études, pragmatiques
  - Cadres généraux
    - Master protocol, cahiers, Critères de jugement
  - On peut bouger:
    - Bras et équilibre de la randomisation, produits, SOC, centres, patients …

- Limites:
  - Sponsoring multiple difficile
  - Placebo rare
  - Monitoring incomplet
  - Pas ou peu de safety
  - Même SOC???
  - Témoins au même moment??
  - Choix des bras par centre (ex: remapcap)
  - Choix des bras par patient (recovery, remapcap)
  - Statistiques: Ajustement délicat, difficile à comprendre.

ORGANISATION/ ETHIQUE

REVIEW

How the COVID-19 pandemic will change the future of critical care

Yaseen M. Arabi[1*], Elie Azoulay[2], Hasan M. Al-Dorzi[1], Jason Phua[3], Jorge Salluh[4], Alexandra Binnie[5,6], Carol Hodgson[7,8,9,10], Derek C. Angus[11], Maurizio Cecconi[12,13], Bin Du[14], Rob Fowler[15,16,17], Charles D. Gomersall[18], Peter Horby[19], Nicole P. Juffermans[20], Jozef Kesecioglu[21], Ruth M. Kleinpell[22], Flavia R. Machado[23], Greg S. Martin[24], Geert Meyfroidt[25], Andrew Rhodes[26], Kathryn Rowan[27], Jean-François Timsit[28], Jean-Louis Vincent[29] and Giuseppe Citerio[30,31]

Intensive Care Med. 2021
Mar;47(3):282-291

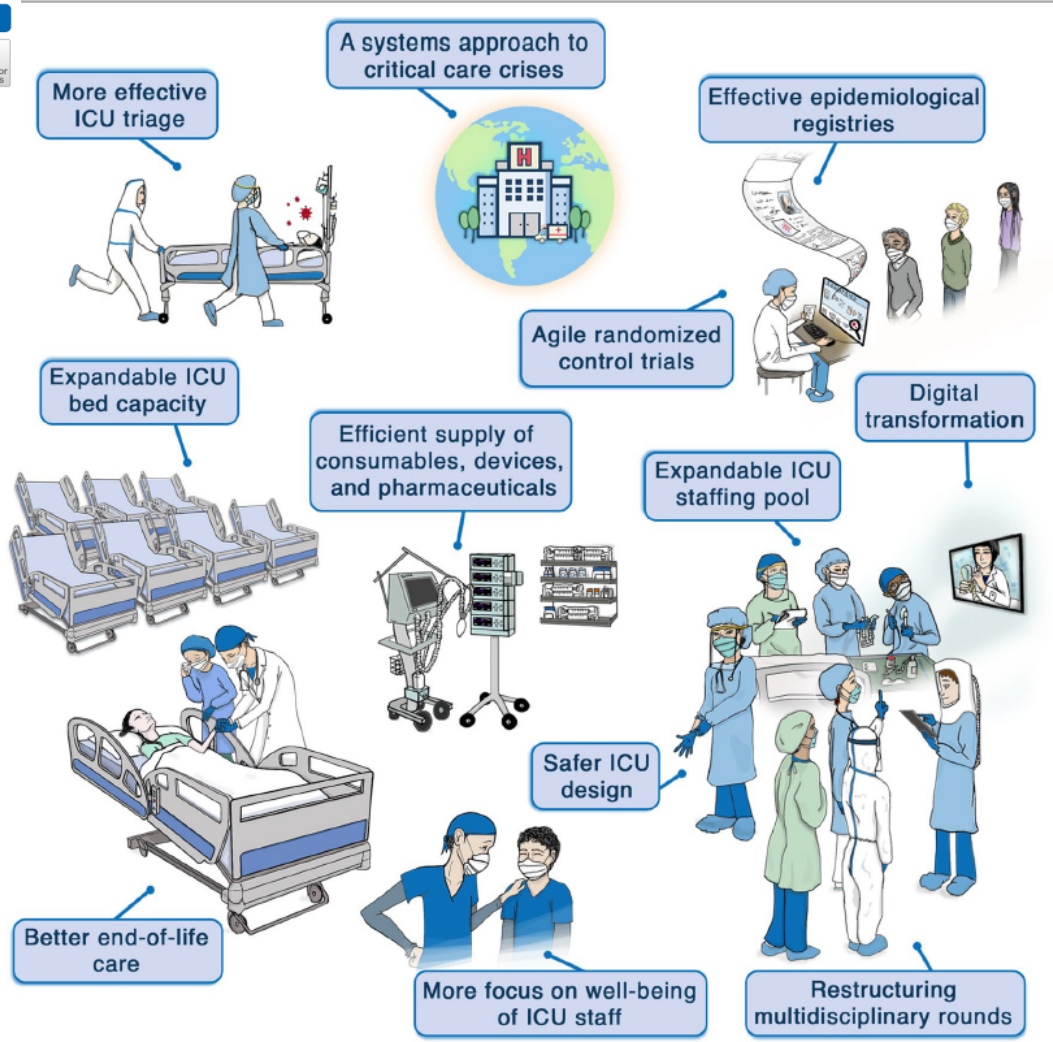


Fig. 1 How the COVID-19 pandemic will shape the future of critical care in the post-COVID-19 era

Covid pandemic:
ICU care outside the wall

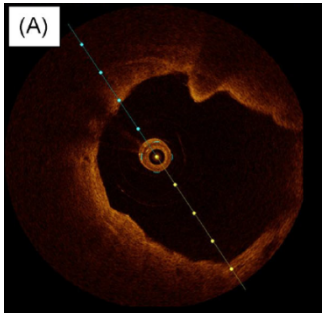
Bichat hospital > 80 ICU beds and > 60 intermediate care beds

ICU in operative rooms
No single rooms
Incredible healthcare workload
(Prone position, extreme body weight)
Heterogeneity of healthcare personnel
Infection control measures not strictly followed?
Inappropriate use of gloves with high risk of cross transmission of MDR/XDR bacterias
Overuse of antimicrobials
Negative airway pressure in the rooms
(Aspergillus/aerosolized pathogens)

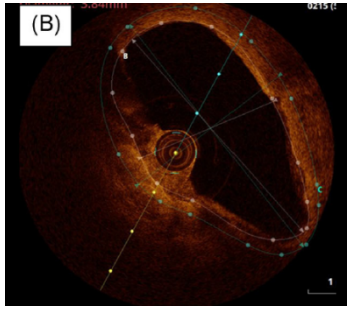
TRAITEMENT SYMPTOMATIQUE

Atelectasis: modification of mucus secretion

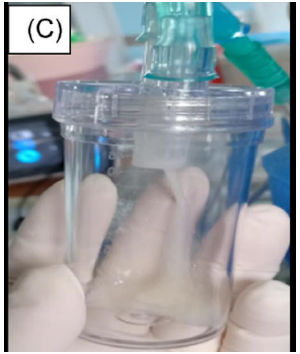
- Airway mucus is an adhesive viscoelastic gel acting as a primary defense layer and facilitates ciliary beating
- Viral infection → mucin overproduction and airway mucus secretion, leading to airway obstruction and disease
- Mucins : increase of both forms
  - Gel-forming, secreted mucins (i.e, MUC5AC)
  - membrane-tethered mucins (i.e. MUC1)4.
  - Modification of the proteomic pathway of airway mucus *Wang Life Sci 2021; Mar 15;269:119046*



Bronchioles: healthy people



Bronchioles: Covid-19



Wenju et al - J Med Virol . 2021 Feb;93(2):582-584
Li et al - Front Immunol . 2021 Sep 28;12:701443

Thrombosis of pulmonary arterioles

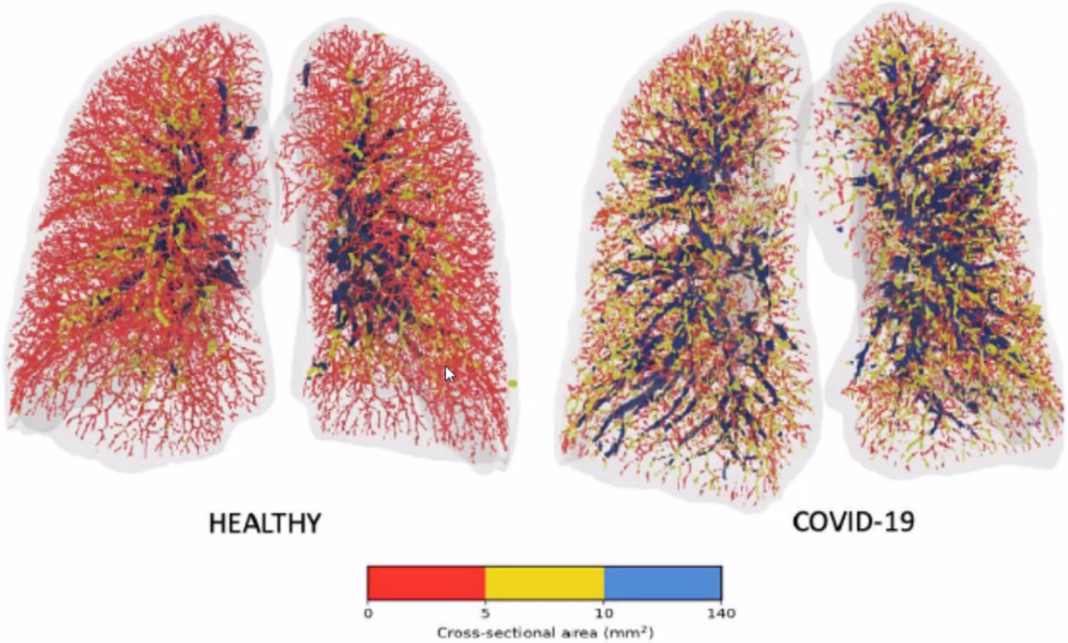


Figure 4: Visual representation of the blood vessels colored according to their size. Red denotes the small vessels, yellow the mid-size vessels and blue the larger vessels.

Lins Acta Radiol 2020

Oxygenation strategies

RECOVERY adaptative platform

RCT comparing oxygen vs CPAP vs HFNO

Center could choose 1:1:1 or only CPAP or HFNO….

Main end-point: tracheal intubation or death at day30

Stopped for efficacy of one arm.

Outcome	Pairwise Treatment Comparisons				Odds Ratio†/Hazard Ratio‡/Mean Difference§ (95% CI)			
	CPAP versus Conventional Oxygen Therapy¶		HFNO versus Conventional Oxygen Therapy‖		CPAP versus Conventional Oxygen Therapy¶		HFNO versus Conventional Oxygen Therapy‖	
					Unadjusted	Adjusted	Unadjusted	Adjusted
	CPAP	Conventional Oxygen Therapy	HFNO	Conventional Oxygen Therapy				
Tracheal Intubation or mortality within 30 days – no./total (%)†	137/377 (36.3)	158/356 (44.4)	184/414 (44.4)	166/368 (45.1)	0.72 (0.53- 0.96)	0.67 (0.48- 0.94)	0.97 (0.73 -1.29)	0.95 (0.69- 1.30)
Intubation within 30 days – no./total (%)†	126/377 (33.4)	147/356 (41.3)	170/414 (41.1)	153/368 (41.6)	0.71 (0.53- 0.96)	0.66 (0.47- 0.93)	0.98 (0.74- 1.30)	0.96 (0.70 - 1.31)
Mortality at 30 days – no./total (%)†	63/378 (16.7)	69/359 (19.2)	78/415 (18.8)	74/370 (20.0)	0.84 (0.58 -1.23)	0.91 (0.59 -1.39)	0.93 (0.65 -1.32)	0.96 (0.64 - 1.45)
Secondary outcomes #								
Tracheal Intubation rate in the study period – no./total (%)†, *	126/377 (33.4)	147/356 (41.3)	169/414 (40.8)	154/368 (41.8)	0.71 (0.53- 0.96)	0.66 (0.47- 0.93)	0.96 (0.72- 1.28)	0.93 (0.68- 1.28)
Admission to critical care – no./total (%)†	205/379 (54.1)	219/356 (61.5)	253/416 (60.8)	214/368 (58.2)	0.74 (0.55- 0.99)	0.69 (0.49- 0.96)	1.12 (0.84- 1.49)	1.06 (0.76-1.47)
Mortality in critical care †	62/204 (30.4)	65/219 (29.7)	72/251 (28.7)	64/214 (29.9)	1.03 (0.68-1.57)	1.13 (0.72- 1.80)	0.94 (0.63-1.41)	1.00 (0.63 -1.56)
Mortality in hospital †	72/364 (19.8)	78/346 (22.5)	88/404 (21.8)	80/359 (22.3)	0.85 (0.59 - 1.22)	0.92 (0.61 -1.37)	0.97 (0.69 -1.37)	1.02 (0.69 -1.50)
Mean length of stay in critical care (SD) – days §	9.5 (15.6)	9.6 (13.6)	10.5 (15.6)	9.5 (14.1)	-0.08 (-2.23, 2.07)	-0.33 (-2.44, 1.78)	1.01 (-1.11, 3.14)	0.69 (-1.37, 2.75)

Perkins et al - medRxiv preprint doi: https://doi.org/10.1101/2021.08.02.21261379

Barotrauma/oxygenation strategies

RECOVERY adaptative platform

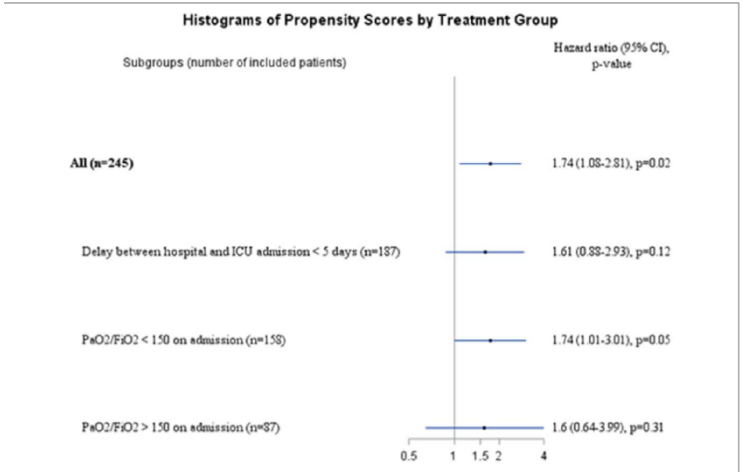
RCT comparing oxygen vs CPAP vs HFNO

	Conventional oxygen therapy (n=475)	CPAP (n=380)	HFNO (n=417)	P-value‖	All participants (n=1272)
Participants with AE/ SAE- n (%)	66 (13.9%)	130 (34.2%)	86 (20.6%)	<0.001	282 (22.2%)
ADVERSE EVENTS **Participants with AE- n (%)**	65 (13.7%)	130 (34.2%)	86 (20.6%)	<0.001	281 (22.1%)
Summary of events- n(%)*					
Interface/therapy Intolerance	1 (0.2%)	22 (5.8%)	3 (0.7%)		26 (2.0%)
Pain	26 (5.5%)	13 (3.4%)	13 (3.1%)	-	52 (4.1%)
Cutaneous pressure sore	14 (2.9%)	32 (8.4%)	14 (3.4%)	-	60 (4.7%)
Claustrophobia	28 (5.9%)	11 (2.9%)	16 (3.8%)	-	55 (4.3%)
Oronasal dryness	9 (1.9%)	25 (6.6%)	25 (6.0%)	-	59 (4.6%)
Respiratory acidosis	4 (0.8%)	4 (1.1%)	11 (2.6%)	-	19 (1.5%)
Haemodynamic instability	29 (6.1%)	43 (11.3%)	36 (8.6%)	-	108 (8.5%)
Aspiration of gastric contents	2 (0.4%)	6 (1.6%)	5 (1.2%)	-	13 (1.0%)
Pneumothorax	11 (2.3%)	7 (1.8%)	8 (1.9%)	-	26 (2.0%)
Pneumomediastinum	5 (1.1%)	12 (3.2%)	3 (0.7%)	-	20 (1.6%)
Anxiety and confusion	0	6 (1.6%)	3 (0.7%)	-	9 (0.7%)
Pulmonary embolism	1 (0.2%)	1 (0.3%)	0	-	2 (0.2%)
Surgical emphysema	0	3 (0.8%)	1 (0.2%)	-	4 (0.3%)
Haemoptysis	0	1 (0.3%)	1 (0.2%)	-	2 (0.2%)
Other†	1 (0.2%)	5 (1.3%)	8 (1.9%)	-	14 (1.1%)

Perkins et al - medRxiv preprint doi: https://doi.org/10.1101/2021.08.02.21261379

IPTW adjusted impact of early IMV
Outcome of patients who failed the no-IMV strategy

	Early IMV (n=134)	Late IMV (n=54)	No IMV (n=96)	P-value*
Outcomes				
Bacteremia	33 (24.63)	10 (18.52)	1 (1.04)	<0.01
HAP-VAP	58 (43.28)	18 (33.33)	7 (7.29)	<0.01
Any Nosocomial infections	74 (55.22)	21 (38.89)	11 (11.46)	<0.01
VFD	1 [0 ; 3]	4 [2 ; 7]	6 [4 ; 8.5]	<0.01
OSFD	0 [0 ; 1]	0 [0 ; 1]	0 [0 ; 1]	0.73
ICU LOS	15 [10 ; 22]	16 [11 ; 22]	6 [4 ; 8.5]	<0.01
ICU Mortality	55 (41.04)	24 (44.44)	7 (7.29)	<0.01
Mortality at day 60	57 (42.54)	25 (46.3)	9 (9.38)	<0.01



Final IPTW Cox model at day 60: HR_w=1.82, CI 95%, 1.16 to 2.86, p<0.01

Not too early? But…when late is too late??

Dupuis C et al - Crit Care Explor. 2021 Jan 22;3(1):e0329.

Thrombosis

Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study

*Lionel Piroth, Jonathan Cottenet, Anne-Sophie Mariet, Philippe Bonniaud, Mathieu Blot, *Pascale Tubert-Bitter, *Catherine Quantin*

	COVID-19 (n=89 530)	2018–19 seasonal influenza (n=45 819)	p value
Acute respiratory failure	24 317 (27·2%)	7977 (17·4%)	<0·0001
Pulmonary embolism	3086 (3·4%)	412 (0·9%)	<0·0001
Venous thrombosis (including pulmonary embolism)	4367 (4·9%)	766 (1·7%)	<0·0001
Median (IQR) stay in ICU among ICU-deceased patients, days	10 (3–21)	5 (2–9)	<0·0001
In-hospital death among patients in ICU with mechanical ventilation	3312/10 430 (31·8%)	780/3004 (26·0%)	<0·0001
In-hospital death among non-ventilated patients in ICU	477/2773 (17·2%)	81/1496 (5·4%)	<0·0001

Data are n (%) or n/N (%) unless otherwise indicated. ICU=intensive care unit. Data are for patients who were hospitalised for COVID-19 between March 1 and April 30, 2020, and for patients who were hospitalised for seasonal influenza between Dec 1, 2018, and Feb 28, 2019.

Table 2: Main outcomes of patients hospitalised in France for COVID-19 or seasonal influenza

Venous thrombosis without PE 1319 (1.5%) 354 (0.8%) X 1.9

X 3.8

Piroth L et al -Lancet Respir Med. 2021;9(3):251-259.

Prophylaxis or curative anticoagulant therapy? ICU data

Research

JAMA | Original Investigation

Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit
The INSPIRATION Randomized Clinical Trial

INSPIRATION Investigators

- 600 ICU patients
- UH or LMWH

Outcome	No. (%) Intermediate dose (n = 276)	Standard dose (n = 286)	*P* value
Primary outcome			
Composite of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality[a]	126 (45.7)	126 (44.1)	.70
Secondary outcomes			
All-cause mortality	119 (43.1)	117 (40.9)	.50
Adjudicated venous thromboembolism	9 (3.3)	10 (3.5)	.87
Ventilator-free days, median (IQR)[b]	30 (3 to 30)	30 (1 to 30)	.50[c]

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

- 1098 Pts/ adaptative platform
- Local protocols
- Early stop for futility

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)	Probability of Futility	Probability of Inferiority
	median no. (IQR)		%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	99.9	95.0
	no. of patients/total no. (%)			
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	—	87.2

Pulmonary Co-infections

- **Is rare**
  - Viral 10%, fungal 4%, bacterial 8 %
    - *Musuuza JS et al-PLoS One. 2021 May 6;16(5):e0251170*
  - *4 time less that influenzae ARDS*
    - *Rouze A et al - Am J Respir Crit Care Med. 2021 May 26. doi: 10.1164/rccm.202101-0030OC*

- ***Considerable overuse of antibacterial agents***
  - *37% before hosp admission, 85% during hospital stay, Less than 10% with relevant microbiological informations.*
    - *Russel (ISARIC) - Lancet Microbe 2021 Published Online June 2, 2021*
  - *Increase the risk of superinfection*
    - *Carolina Garcia-Vidal, Clin Microbiol Infect 2020;*
  - *Reducing AB use is feasible and safe*
    - *Pettit et al. BMC Infectious Diseases (2021) 21:516*

- **Is difficult to diagnose**
- COVID-19 patients presents with **same clinical features as bacterial pneumonia**
  - Hypoxia
  - Fever
  - Radiographic infiltrates
- **Traditional biomarkers are high**
  - Leucocytosis
  - PCT >0.5
  - are not clearly associated with bacterial co-infections
- **Traditional biomarkers may be artificially masked** by imunosupressive agents
  - Corticosteroids
  - IL-6 recepteur antagonists
- **Need for rapid diagnostic test** for identifying patients who may benefit from antibacterial agents.

Superinfection is common and difficult to treat

- High incidence
  - Altered immunity
  - Pulmonary infarction
  - Very long duration of MV, paralytic agents
  - Ecmo
  - Altered nosocomial infection prevention
  - Immunosupressive agents
- Difficult to treat
  - Delayed diagnosis
  - Frequent complications
    - Abscess, empyema
    - Relapse, recurrence
  - PD alterations
    - Glomerular hyperfiltration
    - Altered lung penetration
    - Poor immune respiratory functions

→ Individualized therapy

ANTIVIRAL AGENTS

Open access Original research
BMJ Open

Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis

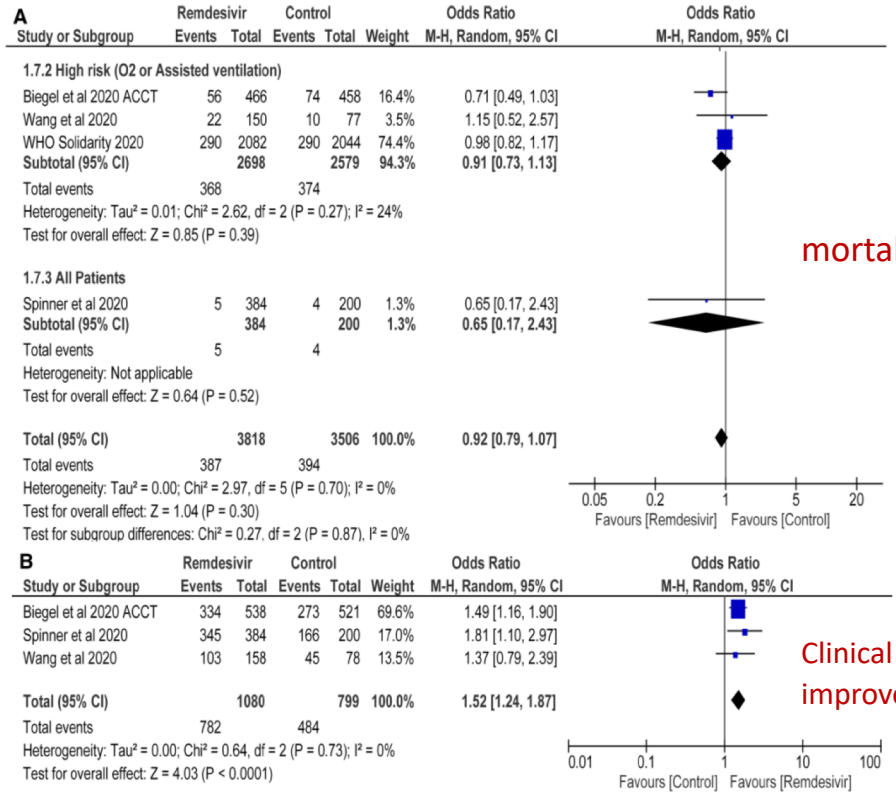
Surjit Singh ,[1] Daisy Khera,[2] Ankita Chugh,[3] Pushpinder Singh Khera,[4] Vinay Kumar Chugh[3]

Meta-analysis

Strengths and limitations of this study

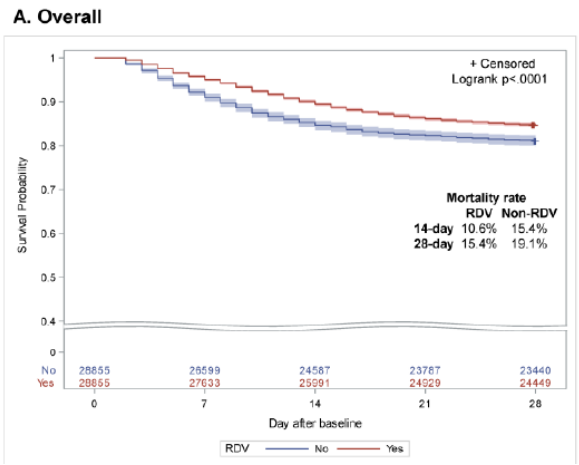
- Four randomised controlled trials (RCTs) were included in our analysis with total sample size of 7324 patients.
- Risk of bias (ROB) of RCTs was done using Cochrane ROB-2 scale.
- ROB-2 showed low ROB for WHO Solidarity trial and Wang *et al* and high ROB for Beigel *et al* and Spinner *et al*
- GRADE was applied and overall evidence suggested no mortality benefit with remdesivir (moderate quality evidence).
- Cost–benefit analysis revealed higher cost with no mortality benefit.

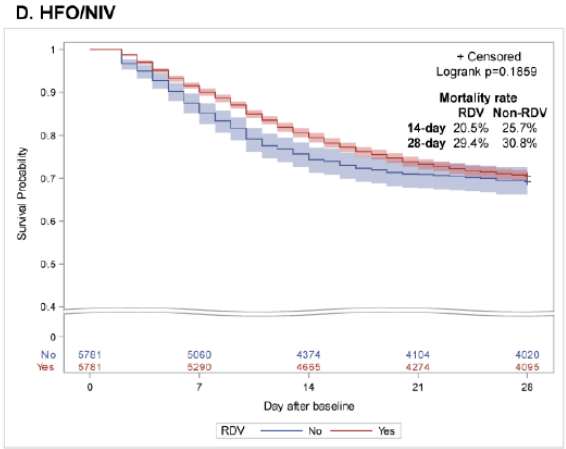
$2345 / 5 days…

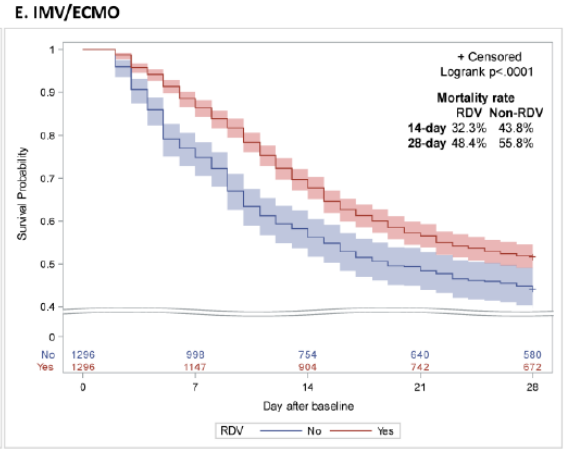


Remdesivir treatment: databases US

- Premier database
- PS matched cohort
- 28,855 RDV patients matched to 16,687 unique non-RDV patients







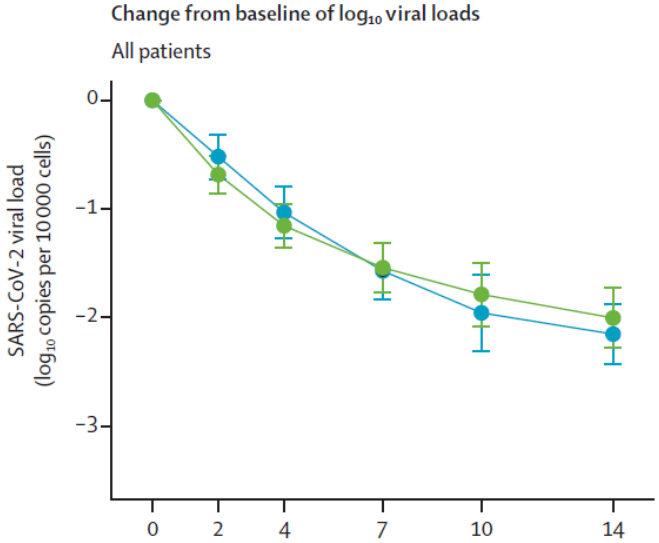
Mozaffari E et al – Clinical infect Dis Oct 1st 2021

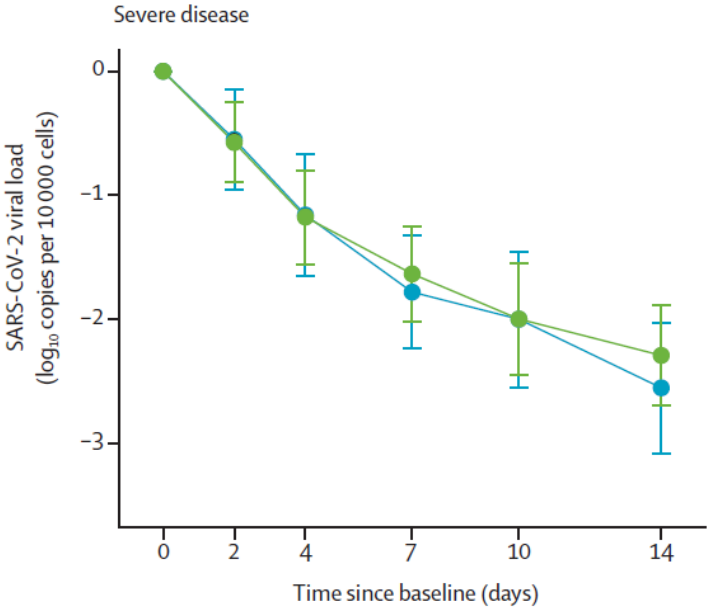
Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Lancet Infect Dis 2021
Published Online September 14, 2021
https://doi.org/10.1016/S1473-3099(21)00485-0

Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet*, France Mentré*, and the DisCoVeRy Study Group

Phase 3, open-label, adaptive, multicentre, RCT (48 sites in Europe); 4 and then 2 arms





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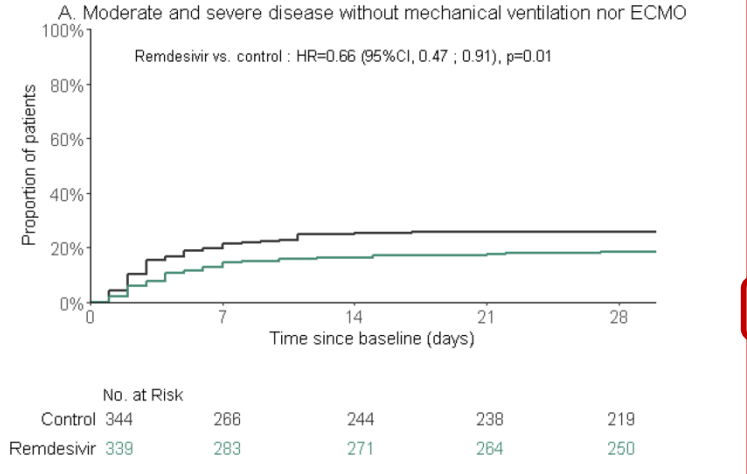


	Overall (n=832)		Moderate COVID-19 (n=504)		Severe COVID-19 (n=328)		Remdesivir vs control, effect measure (95% CI); p value
	Remdesivir group (n=414)	Control group (n=418)	Remdesivir group (n=253)	Control group (n=251)	Remdesivir group (n=161)	Control group (n=167)	
7-point ordinal scale at day 15	..	..	..	..	..	..	OR 0·98 (0·77 to 1·25); p=0·85
7-point ordinal scale at day 29	..	..	..	..	..	..	OR 1·11 (0·87 to 1·42); p=0·39
7: death	34 (8%)	38 (9%)	15 (6%)	15 (6%)	19 (12%)	23 (14%)	..
New mechanical ventilation, ECMO, or death within 29 days*	60/339 (18%)	87/344 (25%)	35/253 (14%)	40/251 (16%)	25/86 (29%)	47/93 (51%)	HR 0·66 (0·47 to 0·91); p=0·010
Oxygenation-free days until day 29	17 (2 to 22)	17 (0 to 23)	21 (14 to 24)	21 (11 to 25)	10 (0 to 17)	5 (0 to 18)	LSMD 0·35 (−0·90 to 1·60); p=0·59
Ventilator-free days until day 29	29 (20 to 29)	29 (16 to 29)	29 (29 to 29)	29 (29 to 29)	21 (6 to 29)	17 (2 to 29)	LSMD 1·08 (−0·15 to 2·30); p=0·080
Death within 28 days	34 (8%)	37 (9%)	15 (6%)	15 (6%)	19 (12%)	22 (13%)	OR 0·93 (0·57 to 1·52); p=0·77

ATUc Traitement Précoce

Ac monoclonaux

ATUc « Sous Oxygène »

Asymptomatique

Symptomatique ≤ 5 jours

Ne nécessitant pas oxygène du fait COVID-19
(Pas de nécessité de sérologie, sont éligibles séronégatifs ou séropositifs)

Casirivimab + imdevimab
1200 mg/1200 mg

Sans limite de durée de symptômes

Oxygénothérapie non invasive
(incluant OHD+ / optiflow)
Séronégatifs (Anti-S < 30 BUA/mL)

Casirivimab + imdevimab
4000 mg/4000 mg

Âge supérieur à 80 ans

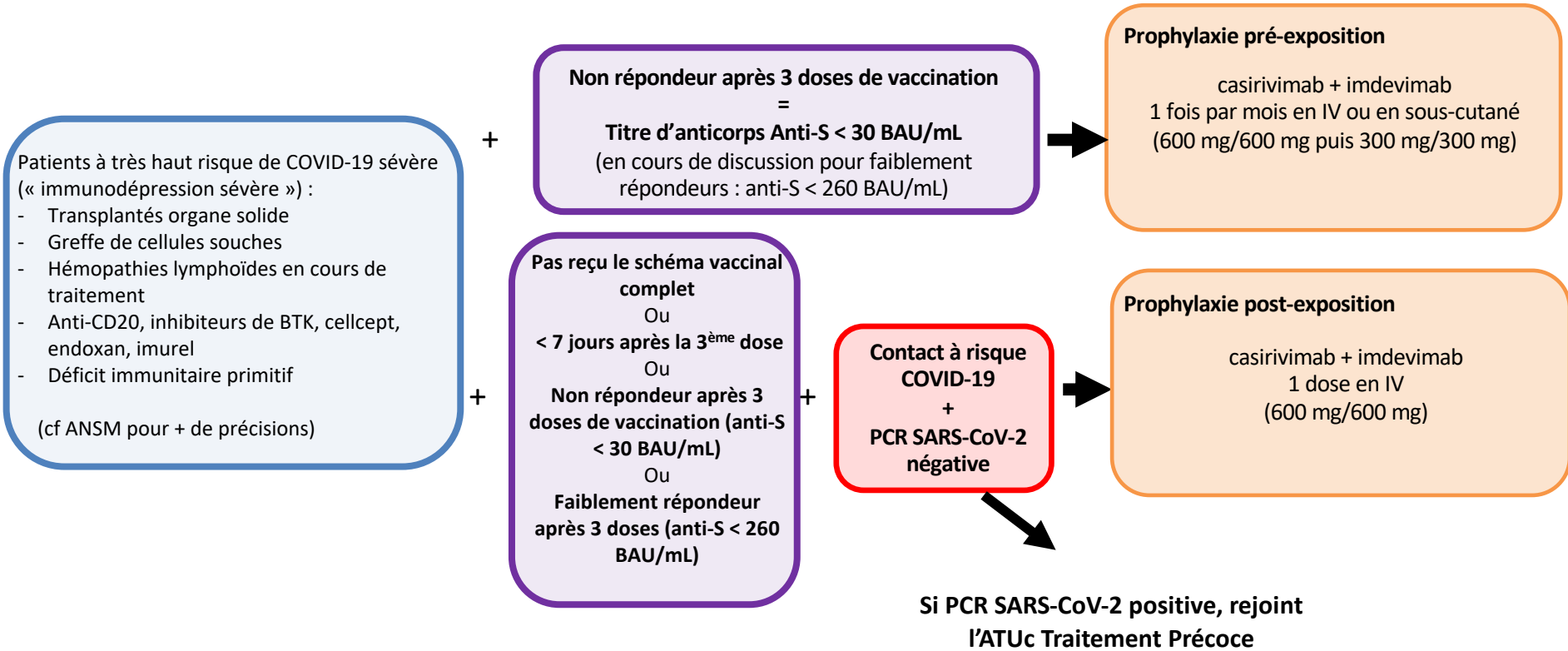
Patients avec comorbidités à risque de complications

- Obésité (IMC >30)
- BPCO et insuffisance respiratoire chronique
- Hypertension artérielle compliquée
- Insuffisance cardiaque
- Diabète (de type 1 et de type 2)
- Insuffisance rénale chronique
- Trisomie 21
- Autres pathologies rares (FSMR)

Patients immunodéprimés

- Chimiothérapie en cours
- Transplantation d'organe solide
- Allogreffe de cellules souches hématopoïétiques
- Maladie rénale avec DFG.< 30 mL/min ou dialyse
- Lupus systémique ou vascularite avec traitement immunosuppresseur
- Traitement par corticoïdes > 10 mg/jour pendant ≥ 2 semaines
- Traitement immunosuppresseur incluant rituximab
- Infection VIH non contrôlée ou stade SIDA

ATUc Prophylaxie



MERCK

At the Interim A
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Merck Plans to S

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On Nov. 30, the advisory committee will meet to discuss the available data supporting the use of molnupiravir to treat mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who have tested positive for COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

"The FDA is evaluating the safety and effectiveness data submitted by Merck and Ridgeback in their emergency use authorization request for molnupiravir, a new oral treatment for high-risk individuals with a newly diagnosed COVID-19 infection. We believe that, in this instance, a public discussion of these data with the agency's advisory committee will help ensure clear understanding of the scientific data and information that the FDA is evaluating to make a decision about whether to authorize this treatment for emergency use," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research.

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, 2021

simple

Ce comprimé réduirait de 50% le risque d'hospitalisation ou de mort du Covid-19. Le laboratoire américain va demander «dès que possible» une autorisation d'utilisation d'urgence aux Etats-Unis.

MERCK

Traitement contre le Covid-19 : quatre choses à savoir sur le molnupiravir, dont la France a commandé 50 000 doses

Le Royaume-Uni est devenu le premier pays à autoriser ce traitement, jeudi.

franceinfo
France Télévisions

Le Télégr

Pilules anti-covid de
risques d'effets se

RÉSERVÉ AUX ABONNÉS

et efficace contre le

La pandémie de Covid-19 en France dossier

Ce comprimé réduirait de 50% le risque d'hospitalisation ou de mort du Covid-19.
va demander «dès que possible» une autorisation d'utilisation d'urgence aux Etats-Unis.

MERCK

At the Interim Analysis, 7.3 Percent of Patients Who Receive[d] ugh Day 29,
Compared With 14.1 Percent of Placebo-Treated P

FUTURA SANTÉ

Merck Plans to Seek Eme

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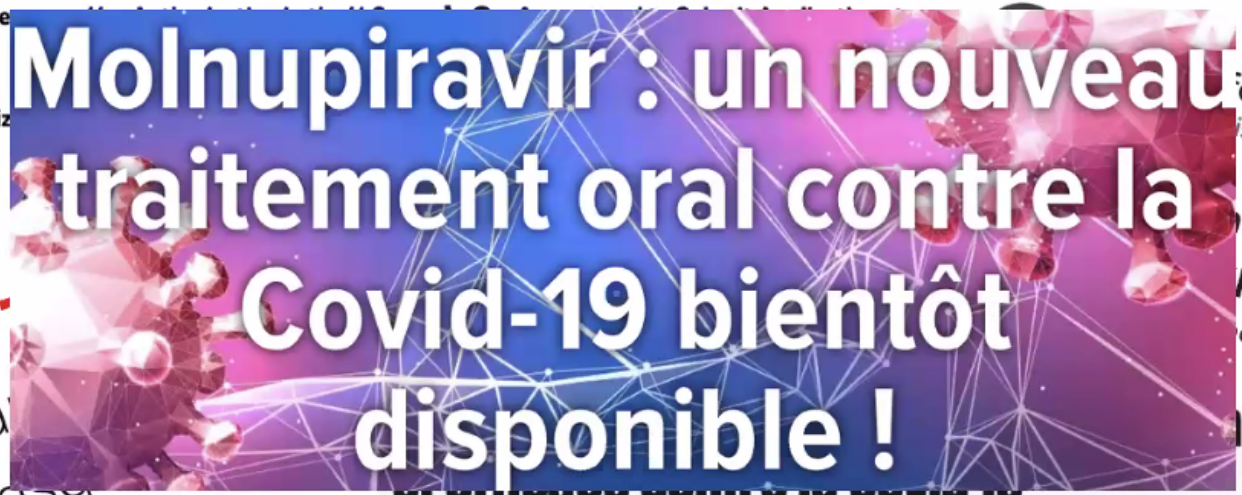

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La pandémie de Covid-19 en France dossier

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MERCK

At the Interim Analys
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Merck Plans to Ser

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franceinfo
France Télévisions

Covid-19 : après le molnupiravir, quels sont les autres traitements qui pourraient être bientôt disponibles ?

Outre le molnupiravir, antiviral élaboré par le laboratoire Merck, cinq traitements sont en cours d'élaboration.

Le
Pilules a
ris

Covid
disponible :

simple

La pandémie de Covid-19 en France dossier

Ce comprimé réduirait de 50% le risque d'hospitalisation ou de mort du Covid-19. Le laboratoire américain va demander «dès que possible» une autorisation d'utilisation d'urgence aux Etats-Unis.

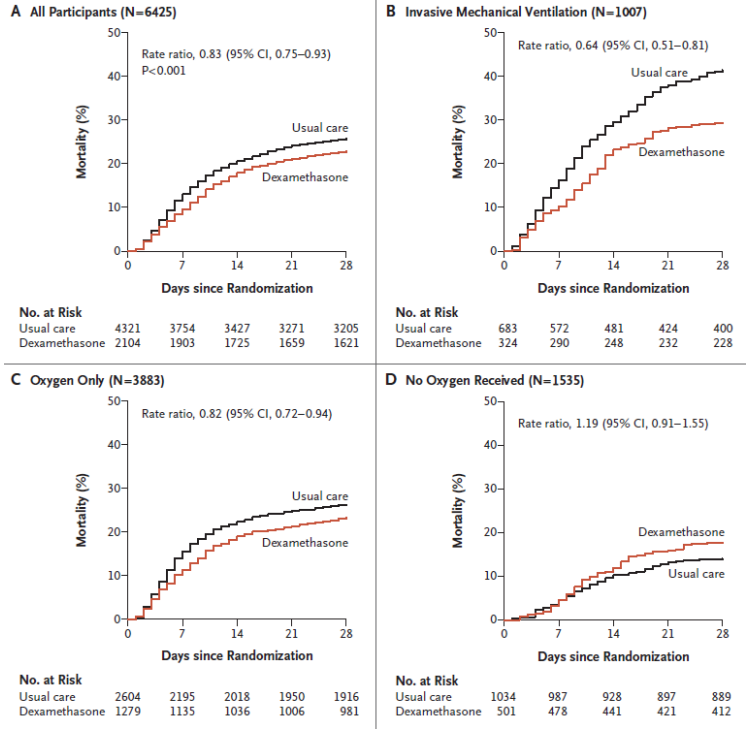
PFIZER'S NOVEL COVID-19 ORAL ANTIVIRAL TREATMENT CANDIDATE REDUCED RISK OF HOSPITALIZATION OR DEATH BY 89% IN INTERIM ANALYSIS OF PHASE 2/3 EPIC-HR STUDY

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced its investigational novel COVID-19 oral antiviral candidate,PAXLOVID™, significantly reduced hospitalization and death, based on an interim analysis of the Phase 2/3 EPIC-HR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, **who are at high risk of progressing to severe illness**. The scheduled interim analysis showed an **89% reduction in risk of COVID-19-related hospitalization or death** from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); **0.8% of patients** who received PAXLOVID™ were **hospitalized** through Day 28 following randomization (3/389 hospitalized with no deaths), **compared to 7.0%** of patients who received placebo and were hospitalized or died (**27/385 hospitalized with 7 subsequent deaths, …**p<0.0001). Similar reductions in COVID-19-related hospitalization or death were observed in **patients treated within five days** of symptom onset; **1.0% of patients** who received PAXLOVID™ were hospitalized through Day 28 following randomization (**6/607 hospitalized**, with no deaths), **compared to 6.7%** of patients who received a placebo (**41/612 hospitalized with 10 subsequent deaths…**p<0.0001). In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 (1.6%) deaths in patients who received placebo.

At the recommendation of an independent Data Monitoring Committee and in consultation with the **U.S. Food and Drug Administration (FDA), Pfizer will cease further enrollment** into the study due to the overwhelming efficacy demonstrated in these results and plans to submit the data as part of its ongoing rolling submission to the U.S. FDA for Emergency Use Authorization (EUA) as soon as possible.

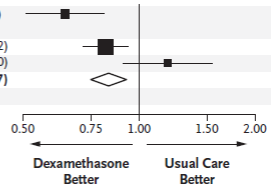
CORTICOIDES

lame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution
université PARIS DIDEROT PARIS 7



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



ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Pittfalls

Non blinded

SOC not established not monitored

Post hoc analyses

Follow up 90%

Protocol violation > 10%

Primary end point only no other data except SUSAR on safety

Randomization not stratified by center

Overmortality of the control group ?

Long-term prognosis?

Remaining questions

Individualization

Dose
Duration

Adverse events

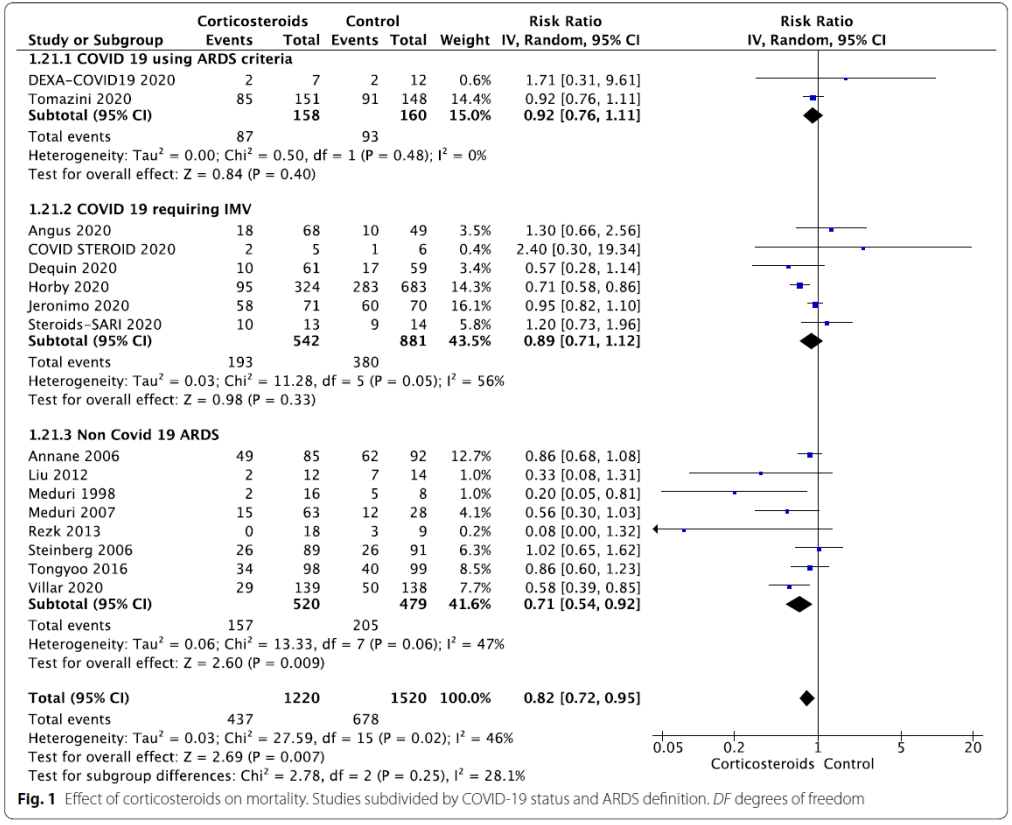
Viral sheeding?

SYSTEMATIC REVIEW

Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis

Dipayan Chaudhuri[1,2], Kiyoka Sasaki[1], Aram Karkar[1], Sameer Sharif[1], Kimberly Lew, Paul Alexander[2], Zhikang Ye[2], Luis Enrique Colunga Lozano[2], Marie Warrer Munch[4], Lawrence Mbuagbaw[2,6], Waleed Alhazzani[1,2], Stephen M. Pastores[7], John Marshall[8], Djillali Annane[10], Gianfranco Umberto Meduri[11] and Bram Rochwerg[1,2,12*]

- Similar impact
  - Covid
  - ARDS definitions
  - Dose
  - Type
  - Placebo
- Longer course of corticosteroids (over 7 days) had higher rates of survival compared to a shorter course.



Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.21.1 COVID 19 using ARDS criteria						
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]
Subtotal (95% CI)		**158**		**160**	**15.0%**	**0.92 [0.76, 1.11]**
Total events	87		93			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.21.2 COVID 19 requiring IMV						
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]
Subtotal (95% CI)		**542**		**881**	**43.5%**	**0.89 [0.71, 1.12]**
Total events	193		380			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 11.28$, df = 5 (P = 0.05); $I^2 = 56\%$						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.21.3 Non Covid 19 ARDS						
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]
Subtotal (95% CI)		**520**		**479**	**41.6%**	**0.71 [0.54, 0.92]**
Total events	157		205			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 13.33$, df = 7 (P = 0.06); $I^2 = 47\%$						
Test for overall effect: Z = 2.60 (P = 0.009)						
Total (95% CI)		**1220**		**1520**	**100.0%**	**0.82 [0.72, 0.95]**
Total events	437		678			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 27.59$, df = 15 (P = 0.02); $I^2 = 46\%$						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: $Chi^2 = 2.78$, df = 2 (P = 0.25), $I^2 = 28.1\%$						

Risk Ratio IV, Random, 95% CI

0.05 0.2 1 5 20

Corticosteroids Control

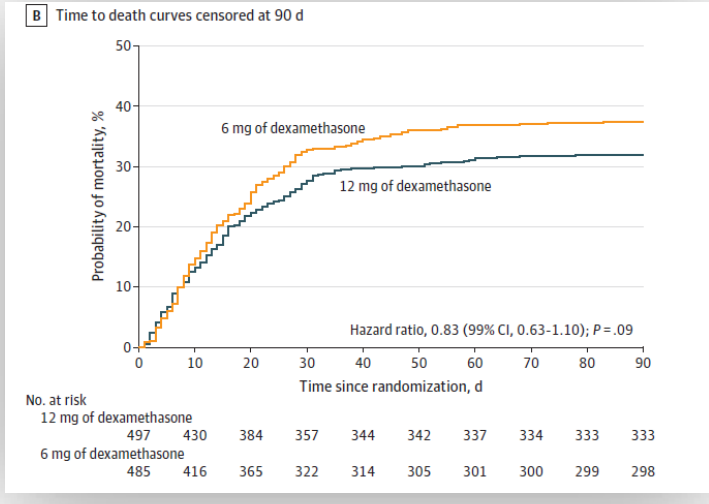
Fig. 1 Effect of corticosteroids on mortality. Studies subdivided by COVID-19 status and ARDS definition. *DF* degrees of freedom

Intensive Care Med (2021) 47:521–537
https://doi.org/10.1007/s00134-021-06394-2

DXM 6 vs 12mg

Characteristic	12 mg of dexamethasone (n = 497)	6 mg of dexamethasone (n = 485)
Country of enrollment, No. (%)		
Denmark	251 (51)	234 (48)
India	182 (37)	187 (39)
Sweden	40 (8)	39 (8)
Switzerland	24 (5)	25 (5)
Age, median (IQR), y	65 (56-74)	64 (54-72)
Weight, median (IQR), kg	80 (68-96)	80 (68-95)
Limitations in the use of life support or CPR at randomization, No. (%)	30 (6)	25 (5)
Time from onset of symptoms to hospitalization, median (IQR), d	(n = 465) 7 (4-9)	(n = 467) 7 (4-10)
Time from hospitalization to randomization, median (IQR), d	2 (1-3)	2 (1-3)
Place of enrollment, No. (%)		
Intensive care unit	389 (78)	393 (81)
Hospital ward	66 (13)	54 (11)
Emergency department	22 (4)	21 (4)
Intermediate care unit	20 (4)	17 (4)
Type of oxygen supplementation		
Nasal cannula or open mask, No. (%)	272 (55)	258 (53)
Flow rate, median (IQR), L/min	22 (15-40)	24 (15-40)
Noninvasive ventilation or continuous positive airway pressure, No. (%)	118 (24)	128 (26)
Invasive mechanical ventilation, No. (%)	107 (22)	99 (20)
Therapies in use at randomization[c]		
Dexamethasone, median (IQR), d	1 (1-2)	1 (1-3)
Antiviral agents	312 (63)	318 (66)
Remdesivir	307 (62)	310 (64)
Vasopressors or inotropes	81 (16)	68 (14)
Anti-inflammatory agents	58 (12)	57 (12)
IL-6 receptor antagonists	52 (11)	47 (10)
Janus kinase inhibitors	8 (2)	7 (1)
Other	9 (2)	10 (2)
Kidney replacement therapy	11 (2)	14 (3)

Outcome[a]	12 mg of dexamethasone (n = 491)	6 mg of dexamethasone (n = 480)	Adjusted mean difference (95% CI)[b]	P value
Primary outcome				
No. of days alive without life support at 28 d, median (IQR)[c]	22.0 (6.0 to 28.0)	20.5 (4.0 to 28.0)	1.3 (0 to 2.6)	.07[d]



*COVID-STEROID2 - JAMA. doi:10.1001/jama.2021.18295*Oct 21, 2021.

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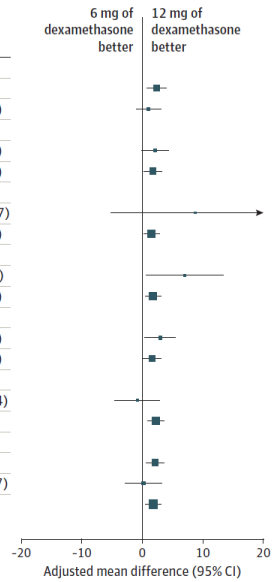
Primary outcome				
No. of days alive without life support at 28 d, median (IQR)[c]	22.0 (6.0 to 28.0)	20.5 (4.0 to 28.0)	1.3 (0 to 2.6)	.07[d]

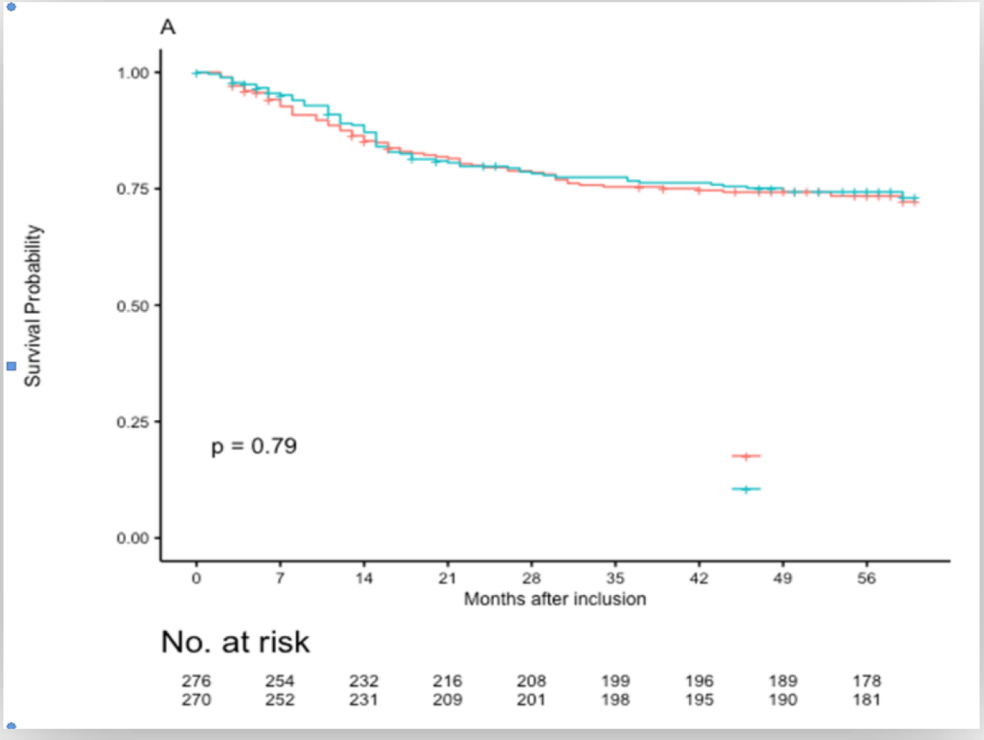
Subgroup	Days alive without life support by dexamethasone dose, median (IQR) 12 mg	6 mg	Adjusted mean difference (95% CI)[a]	*P* value for heterogeneity
Enrollment geographic region				
Europe	22.0 (7.0 to 28.0) (n = 298)	20.0 (4.0 to 28.0) (n = 315)	1.8 (0.2 to 3.4)	.57
India	28.0 (4.8 to 28.0) (n = 187)	25.0 (5.0 to 28.0) (n = 182)	0.5 (-1.7 to 2.6)	
Age, y				
≥70	12.0 (3.0 to 28.0) (n = 167)	8.0 (3.0 to 28.0) (n = 167)	1.6 (-0.7 to 4.0)	.83
<70	26.0 (9.0 to 28.0) (n = 318)	25.0 (5.0 to 28.0) (n = 330)	1.2 (-0.4 to 2.8)	
Chronic use of systemic glucocorticoids at baseline				
Yes	22.0 (6.0 to 28.0) (n = 16)	5.0 (0.8 to 8.0) (n = 13)	8.4 (-5.9 to 22.7)	.53
No	22.0 (6.0 to 28.0) (n = 469)	21.5 (4.0 to 28.0) (n = 484)	1.0 (-0.3 to 2.3)	
Limitations in care[b]				
Yes	9.0 (3.3 to 28.0) (n = 25)	6.0 (3.0 to 28.0) (n = 30)	6.6 (0.1 to 13.1)	.11
No	22.0 (7.0 to 28.0) (n = 460)	22.0 (5.0 to 28.0) (n = 467)	1.2 (-0.1 to 2.5)	
Required invasive mechanical ventilation				
Yes	9.0 (0 to 21.0) (n = 99)	2.5 (0 to 15.0) (n = 107)	2.4 (-0.2 to 5.0)	.44
No	28.0 (9.0 to 28.0) (n = 386)	28.0 (6.0 to 28.0) (n = 390)	1.1 (-0.5 to 2.6)	
Prior use of IL-6 receptor antagonists				
Yes	27.0 (9.5 to 28.0) (n = 47)	28.0 (24.0 to 28.0) (n = 52)	-1.4 (-5.3 to 2.4)	.59
No	22.0 (5.0 to 28.0) (n = 438)	18.0 (4.0 to 28.0) (n = 445)	1.7 (0.3 to 3.1)	
Prior use of dexamethasone before randomization, d				
0-2	22.0 (4.5 to 28.0) (n = 355)	23.0 (5.0 to 28.0) (n = 384)	1.6 (0.1 to 3.1)	.64
3-4	22.0 (6.8 to 28.0) (n = 130)	19.0 (4.0 to 28.0) (n = 113)	-0.4 (-3.4 to 2.7)	
All patients	22.0 (6.0 to 28.0) (n = 491)	20.5 (4.0 to 28.0) (n = 480)	1.3 (0 to 2.6)	



*COVID-STEROID2 - JAMA. doi:10.1001/jama.2021.18295*Oct 21, 2021.

6 mg (Soc) vs 20 mg

- Covidicus
- N=550
- Double-blind



TOCILIZUMAB

lame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution
université PARIS DIDEROT PARIS 7

Adaptive platform trial:

5 interventions: two IL-6 receptor antagonists, tocilizumab and sarilumab; an IL-1 receptor antagonist, anakinra; and interferon beta-1a; as well as control (no immune modulation).
Investigators at each site selected *a priori* at least two interventions, one of which had to be control,

Tocilizumab 8 mg/kg max 800 mg (92% cases) repeated once (29% cases) if decided.
Sarilumab 400 mg once
Open label

Patients could be randomized in other domains.
CS at random before june 17 (n=80 low dose CS) and then recommended (93.3% LD CS).

Markov chain was used to model final impact of drugs and posterior probabilities calculated
Subgroup analyses on terciles of CRP level.

NEJM Feb 21 - DOI: 10.1056/NEJMoa2100433

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

- **Adult patients with Covid-19, within 24 hours of commencing organ support in ICU**

Interim analysis Oct 9th: 99.75% probability for toci efficacy
OR=1.87 95% credibility interval [1.2-2.76]

Stop at Nov 19th 2020 2046 patients (366 Toci; 48 sari; 412 control); 113 centres, 6 countries
1928 patients enrolled
1293 in the immunomodulation domain

IMV: 30%
Vasopressor 30%
CS 92%

NEJM Feb 21 - DOI: 10.1056/NEJMoa2100433

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

The primary analysis used data from all the patients enrolled in the trial who met coronavirus disease 2019 (Covid-19) severe state criteria and who underwent randomization within at least one domain (1928 patients), with adjustment for age, sex, time period, site, region, domain, intervention eligibility, and intervention assignment.

Secondary analyses were restricted to patients enrolled in the Immune Modulation Therapy domain and any domains that have ceased recruitment (Corticosteroid andCovid-19 Antiviral domains) (1293 patients), with adjustment for age, sex, time period, site, region, domain, intervention eligibility, and intervention assignment.

Definitions of outcomes are provided in the trial protocol.
High OR = favorable

Table 2. Primary and Secondary Outcomes.*

Outcome or Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary outcome			
Organ support–free days			
Median (IQR)	10 (−1 to 16)	11 (0 to 16)	0 (−1 to 15)
Adjusted odds ratio			
Mean	1.65±0.23	1.83±0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control — %	>99.9	99.5	—
Subcomponents of organ support–free days			
In-hospital death — no./total no. (%)	98/350 (28)	10/45 (22)	142/397 (36)
Concurrent with tocilizumab randomization	—	—	127/355 (36)†
Concurrent with sarilumab randomization	—	—	19/63 (30)†
Median no. of days free of organ support in survivors (IQR)	14 (7 to 17)	15 (6 to 17)	13 (4 to 17)
Primary in-hospital survival			
Adjusted odds ratio			
Mean	1.66±0.31	2.25±0.96	1
Median (95% credible interval)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
Primary in-hospital survival			
Adjusted odds ratio			
Mean		1.66±0.31	2.25±0.96
Median (95% credible interval)		1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)
Probability of superiority to control — %		99.6	99.5
Adjusted odds ratio			
Mean	1.67±0.31	2.24±0.94	1
Median (95% credible interval)	1.65 (1.15 to 2.34)	2.00 (1.17 to 4.69)	1
Probability of superiority to control — %	99.6	99.4	—

NEJM Feb 21 - DOI: 10.1056/NEJMoa2100433

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

Total recruited*
n=21550

First randomisation†
Part A: Dexamethasone (n=542)
Lopinivir–ritonavir (n=557)
Hydroxychloroquine (n=383)
Azithromycin (n=2041)
Colchicine (n=3083)
Usual care (n=8107)
Part B: Convalescent plasma (n=5285)
REGN–COV2 (n=2416)
Usual care (n=6301)
Part C: Aspirin (n=4450)
Usual care (n=4594)

Did not proceed to second randomisation
– Potentially eligible but not randomised
– No clinical evidence of progressive COVID 19
– Contraindicated medical history
n=17434 (81%)

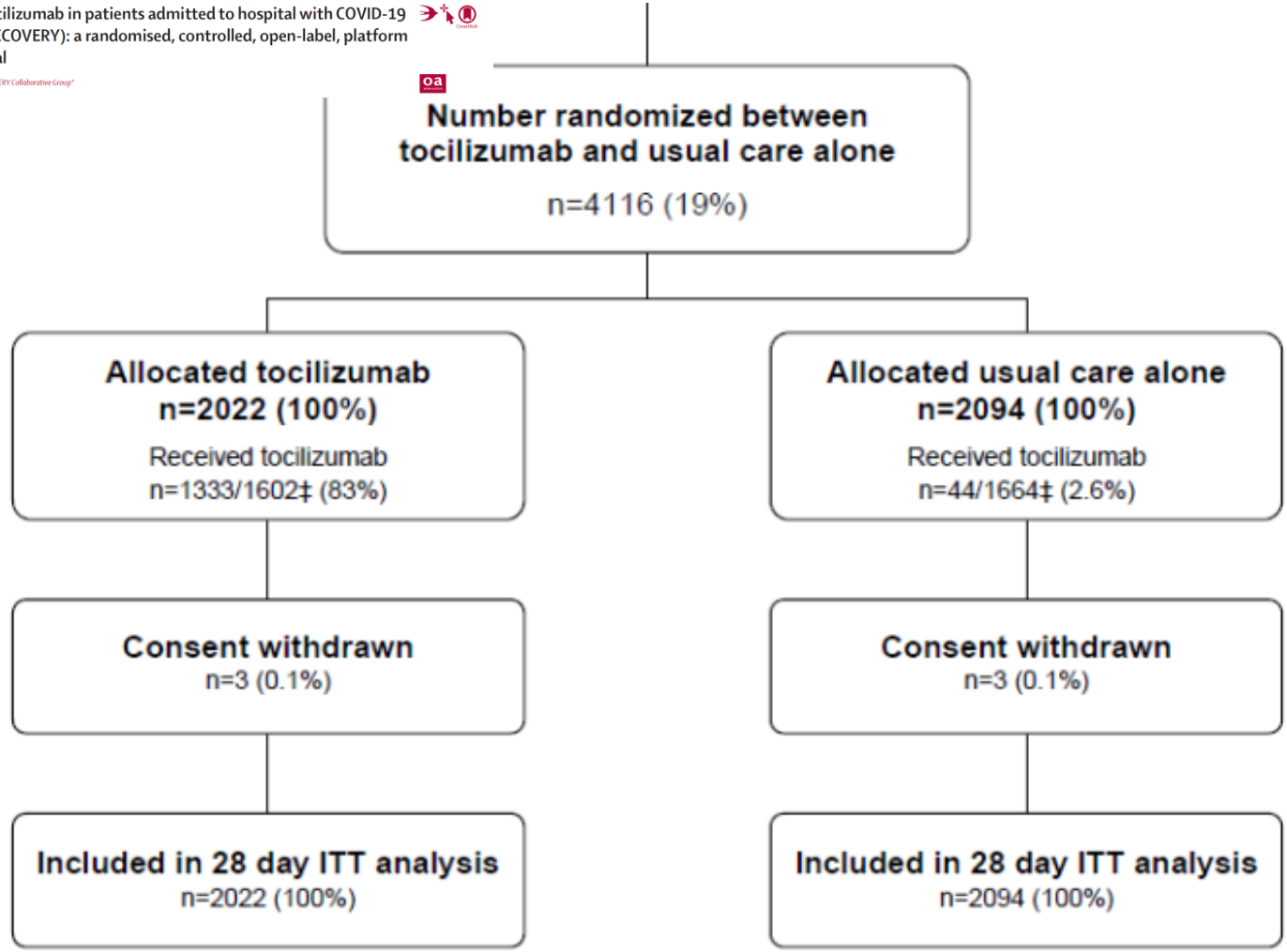
Tocilizumab by intravenous infusion with the dose determined by body weight:

Weight*	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

Number randomized between tocilizumab and usual care alone
n=4116 (19%)

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*



Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

Oxygen saturation <92% on RA or O2

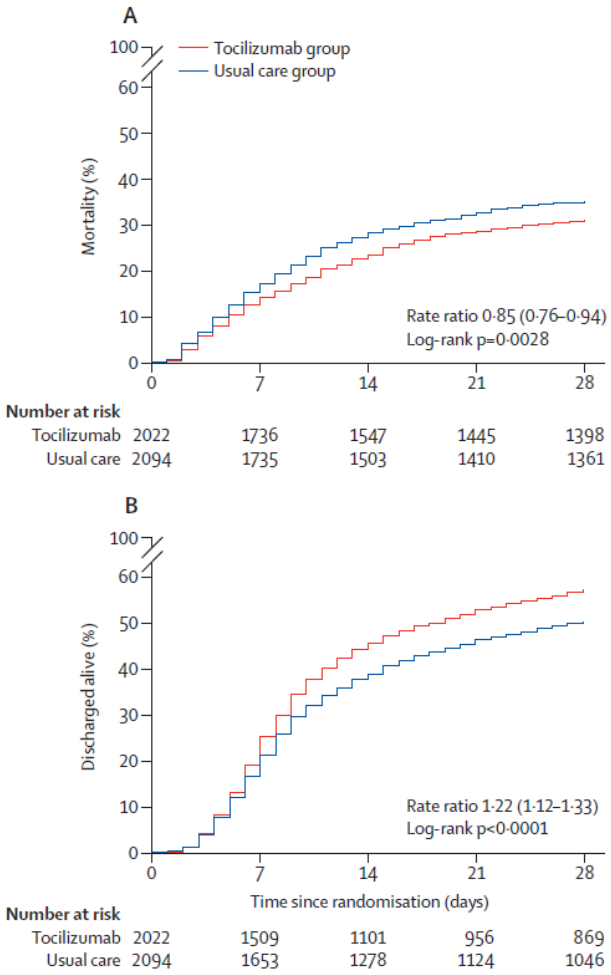
CRP ≥75 mg/L

No other active infection

Oxygen 46%

IMV 13%

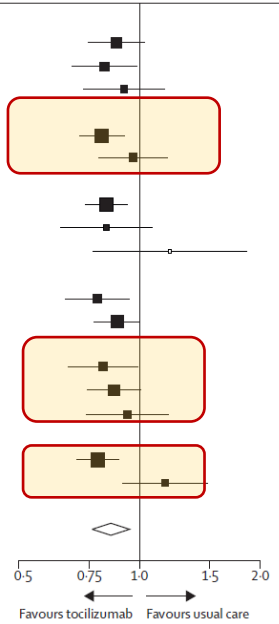
CS 82%



Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

	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- Open label

2- Risk of secondary infection not followed

3- longitudinal assessment of hypoxaemia not collected

4- Only 1837 (91%) of 2022 patients in the tocilizumab group and 1918 (92%) of 2094 patients in the usual care group had data available on study drug receipt.

5- Only 1534/1837 (84%) actually received the drug *(and 44 (3%) of the SOC group received IL6 RA).*

6- day28 mortality? Long term?? (preplanned analyses at 6 months).

*Shruti Gupta, David E Leaf **sgupta21@bwh.harvard.edu***

SYSTEMATIC REVIEW

Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials

Online Table 1: COVID-19 co-interventio? used in interventional and control arms of identified studies

Studies	Antiviral		Glucocorticoids		Convalescent plasma		Hydroxychloroquine	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Gordon (REMAP-CAP)	276/353 (78%)	350/402 (87%)	302/353 (86%)	345/402 (86%)	?	?	?	?
Hermine (CORIMUNO)	7/63 (11%)	16/67 (24%)	21/63 (33%)	41/67 (61%)	?	?	?	?
Horby (RECOVERY)	483/2022 (24%)	541/2094 (26%)	1664/2022 (82%)	1721/2094 (82%)	328/2022 (20%)	364/2094 (22%)	39/2022 (2%)	38/2094 (2%)
Lescure (Sarilumab COVID)	94/332 (28%)	17/84 (20%)	136/332 (41%)	39/84 (46%)	?	?	134/332 (40%)	29/84 (35%)
Rosas (COVACTA)	87/295 (30%)	51/143 (35%)	106/295 (36%)	79/143 (55%)	10/295 (3·4%)	6/143 (4·2%)	?	?
Soin (COVINTOC)	39/91 (43%)	36/88 (41%)	83/91 (91%)	80/88 (91%)	?	?	?	?
Salama (EMPACTA)	196/250 (79%)	101/127 (79%)	138/250 (55%)	86/127 (67%)	?	?	?	?
Salvarani (RCT-TCZ-COVID-19)	?	?	6/60 (10%)	7/63 (11%)	?	?	?	?
Stone (BACC)	53/161 (33%)	24/82 (29%)	18/161 (11%)	5/82 (6%)	?	?	6/161 (4%)	3/82 (4%)
Veiga (TOCIBRAS)	7/67 (10%)	3/62 (5%)	56/67 (87%)	55/62 (89%)	?	?	?	?
Zhao	14/19 (74%)	7/7 (100%)	?	?	?	?	?	?
Totals	1256/3653 (34%)	1146/3156 (36%)	2530/3694 (68%)	2458/3212 (77%)	338/2317 (15%)	370/2237 (17%)	179/2515 (7%)	70/2260 (3%)

Snow et al - Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

SYSTEMATIC REVIEW

Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials

Table 2 Primary, sub-group, secondary, and sensitivity outcome data for included trials

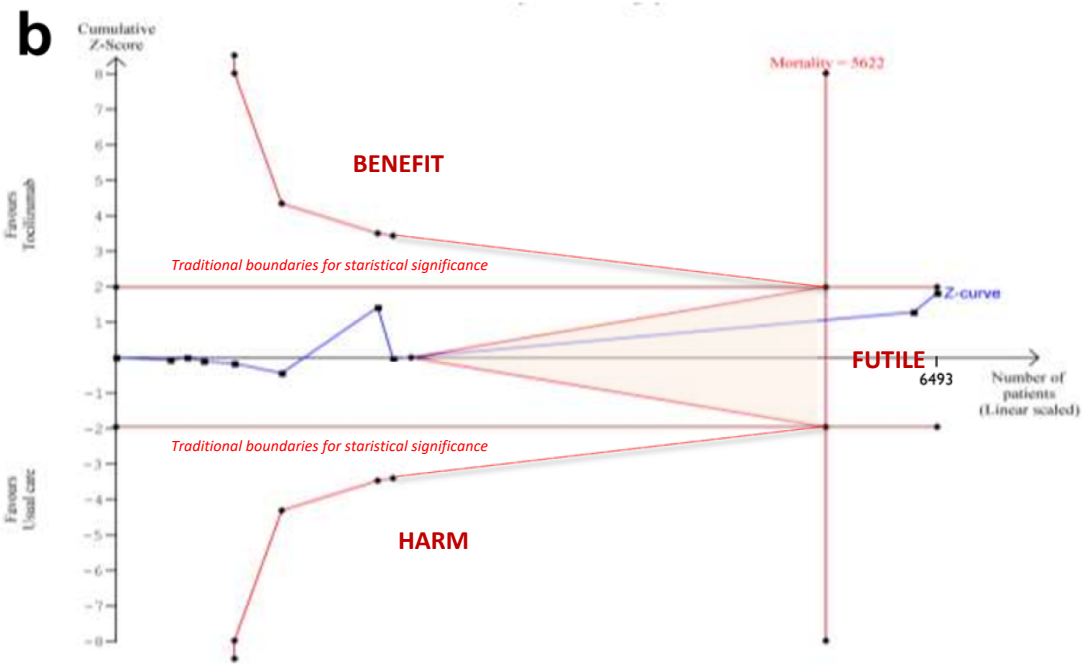
Outcome	References	Intervention group	Control group	Conventional effect estimate (95% CI)	Overall effect	I^2 (%)
Overall mortality	[19–21, 23–28]	821/3358 (24.4%)	909/3135 (29%)	0.87 (0.74–1.01)	$Z = 1.82$ $p = 0.07$	10
ICU patient mortality	[19, 21, 23]	254/732 (34.7%)	297/750 (39.6%)	0.84 (0.65–1.10)	$Z = 1.27$ $p = 0.20$	24
Disease progression						
Mechanical ventilation	[20, 21, 23–26, 28]	152/1742 (8.7%)	152/1454 (10.5%)	0.70 (0.54–0.89)	$Z = 2.86$ $p = 0.004$	0
ICU admission	[20, 23, 26, 28]	118/338 (34.9%)	117/282 (41.5%)	0.73 (0.38–1.39)	$Z = 0.96$ p = 0.34	60
Composite outcome	[18–21, 23–27]	808/2796 (28.9%)	943/2577 (36.6%)	0.72 (0.59–0.89)	$Z = 3.14$ $p = 0.002$	26
Sensitivity analysis						
Combined IL-6 antagonists mortality	[19–28]	861/3738 (23%)	916/3219 (28.5%)	0.86 (0.74–1.01)	$Z = 1.85$ $p = 0.06$	10
Sarilumab mortality	[19, 23]	40/377 (10.6%)	149/481 (31%)	0.72 (0.35–1.51)	$Z = 0.86$ $p = 0.39$	42

NB: random effect models

Snow et al - Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

SYSTEMATIC REVIEW

Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials

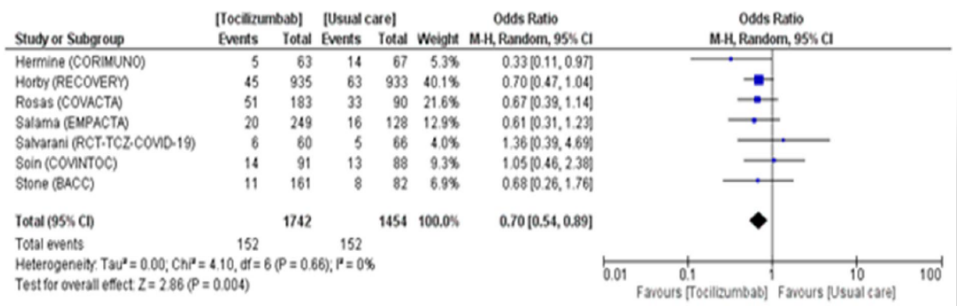


- A diversity-adjusted required information size (RIS) of 5622 was calculated using α = 0.05 (two sided), β = 0.20 (power 80%).
-Relative risk of mortality reduction was 15.7%.
-The cumulative *Z curve crosses neither the conventional nor the TSA boundary for benefit or harm,* but did cross the boundary for futility having exceed the required information size (RIS).

Snow et al - Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

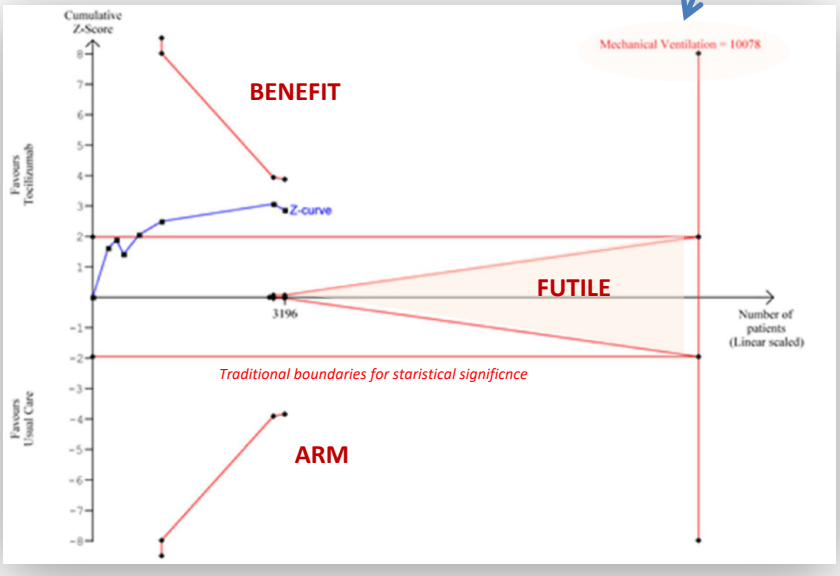
SYSTEMATIC REVIEW

Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials



Need for Mechanical ventilation

Nb needed for firm conclusions



WARNING : Competing risks:

ex: in the RECOVERY trial, which provides the bulk of the data, almost two-thirds of the patients not mechanically ventilated at enrollment who subsequently died did not received ventilation

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Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials

Online Table 2: Adverse events reported in interventional and control arms of identified studies

Complicatio?	Infection		GI and Hepatic disorders		Bleeding events	
	Intervention	Control	Intervention	Control	Intervention	Control
Gordon (REMAP-CAP)	1/353 (0%)	0/402	?	?	5/353 (1%)	4/402 (1%)
Hermine (CORIMUNO)	2/63 (3%)	11/67 (16%)	4/63 (6%)	4/67 (6%)	?	?
Horby (RECOVERY)	?	?	?	?	?	?
Lescure (Sarilumab COVID)	40/332 (12%)	10/84 (12%)	103/332 (31%)	16/84 (19%)	?	?
Rosas (COVACTA)	113/295 (38%)	58/143 (41%)	5/295 (2%)	3/143 (2%)	45/295 (15%)	16/143 (11%)
Soin (COVINTOC)	3/91 (3%)	0/89	1/91 (1%)	0/89	1/91 (1%)	0/89
Salama (EMPACTA)	25/250 (10%)	16/127 (13%)	?	?	?	?
Salvarani (RCT-TCZ-COVID-19)	1/60 (2%)	4/63 (6%)	1/60 (2%)	1/63 (2%)	?	?
Stone (BACC)	13/161 (8%)	14/82 (17%)	14/161 (7%)	7/82 (9%)	0/161	1/82 (1%)
Veiga (TOCIBRAS)	10/65 (15%)	12/64 (19%)	18/67 (27%)	7/62 (11%)	2/67 (3%)	2/62 (3%)
Zhao	?	?	?	?	?	?
Totals	196/1670 (12%)	125/1032 (12%)	146/987 (15%)	38/590 (6%)	53/967 (5%)	23/778 (3%)

Snow et al - Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

SYSTEMATIC REVIEW

Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials

A sensitivity analysis of five trials with low risk of bias [20, 23–26] was performed which included 1314 patients of which 827 (62.9%) were allocated to the treatment arm. Tocilizumab use was not associated with a mortality benefit (12.3% vs. 10.7%; OR 1.09 [0.75–1.57]; $p = 0.65$; $I^2 = 0\%$).

Snow et al - Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

Intensive Care Med (2021) 47:180–187
https://doi.org/10.1007/s00134-021-06346-w

ORIGINAL

COVID-19 increased the risk of ICU-acquired bloodstream infections: a case–cohort study from the multicentric OUTCOMEREA network

Niccolò Buetti[1,11], Stéphane Ruckly[1], Etienne de Montmollin[1,9], Jean Reignier[2], Nicolas Terzi[3,4], Yves Cohen[5,6,7], Shidasp Shiami[8], Claire Dupuis[1,10] and Jean-François Timsit[1,9*]

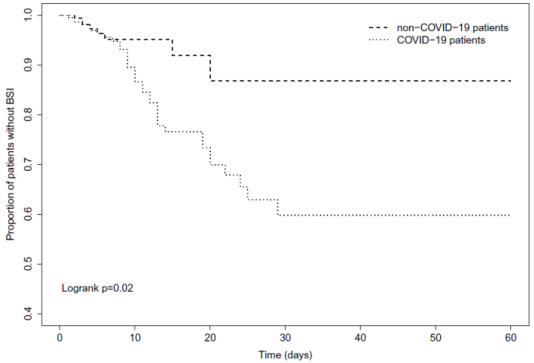


Table 2 Outcomes in the matched population

	Non-COVID-19 (*n* = 235)	COVID-19 (*n* = 235)	*p* value
Length of stay ICU, mean days [IQR]	6 [4; 11]	9 [5; 20]	< 0.0001
ICU-BSI, *n* (%)	8 (3.4)	35 (14.9)	< 0.0001
Time between ICU admission and BSI, median days [IQR]	6.5 [5; 12.5]	12 [9; 16]	0.086§
Mortality day-60, *n* (%)	38 (16.2)	84 (35.7)	< 0.0001
Mortality day-60 among BSIs, *n* (%)	2 (25.0)	25 (71.4)	0.037§

Groups were compared using McNemar, Bowker and Wilcoxon signed rank test, as appropriate

ICU intensive care unit, *BSI* bloodstream infection

§ Wilcoxon or Fisher tests, as appropriate

Fine and Gray model on risk of ICU acquired BSI

- Tocilizumab or anakinra: sHR 3.20, 95% CI 1.31–7.81, p = 0.011)

- Ankinra: sHR 2.54, 95% CI 0.96–6.73, p = 0.061
- **Tocilizumab: sHR 2.87, 95% CI 1.06–7.77, p = 0.038.**

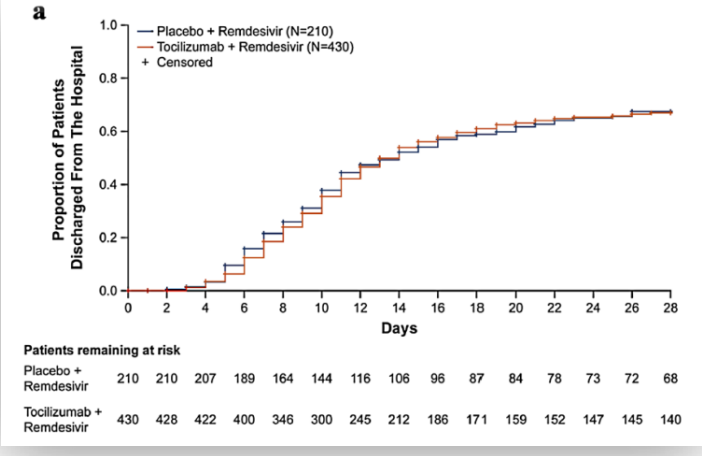
Tocilizumab-remdesivir vs Placebo-remdesivir

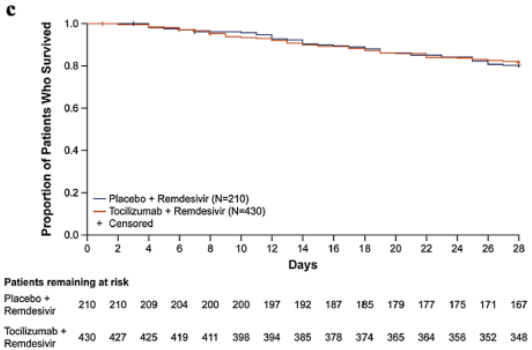
Severe COVID-19 pneumonia requiring > 6 L/min 02

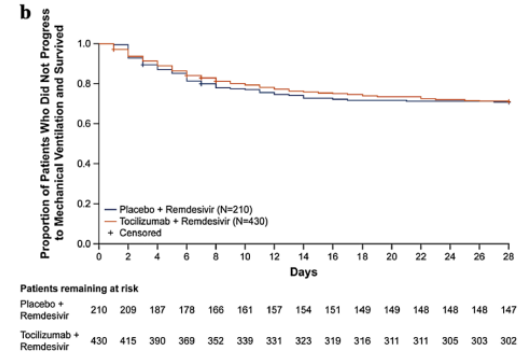
tocilizumab 8 mg/kg or placebo intravenously plus ≤ 10 days of remdesivir.

June 20-Jan 21: n=649

Brazil (*23.7%), Russia*(7.6%), Spain*(2.2%), US(66.6%)*







	Tocilizumab + remdesivir N = 430	Placebo + remdesivir N = 210
Primary outcome		
Time to hospital discharge or "ready for discharge" to day 28, days, median (95% CI)[a]	14 (12–15)	14 (11–16)
P value	*P* = 0.74	
Hazard ratio (95% CI)[b]	0.97 (0.78–1.19)	

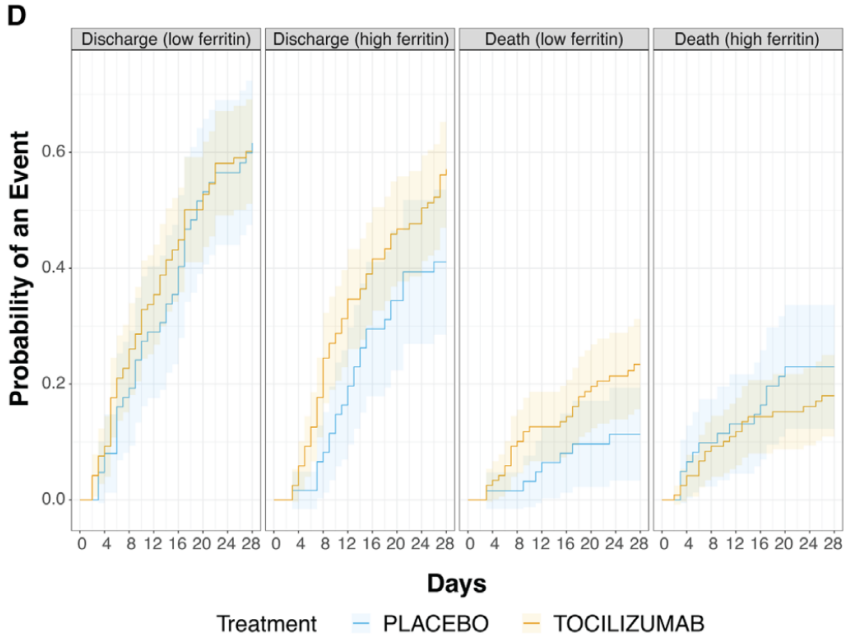
Rosas I et al - Intensive Care Med (2021) 47:1258–1270

CLINICAL INVESTIGATION

OPEN

Prognostic and Predictive Biomarkers in Patients With Coronavirus Disease 2019 Treated With Tocilizumab in a Randomized Controlled Trial

- Covacta trial
- 295 patients Toci/ 142 patients placebo arm
- Modeling in the tocilizumab arm showed a predictive value of ferritin for day 28 clinical outcome of mortality (predictive interaction, *p = 0.03), mechanical ventilation (predictive* interaction, *p = 0.01), and clinical status (predictive interaction, p = 0.02) compared* with placebo.



Arbitrary cutpoint (median): 7.7 pMol/l

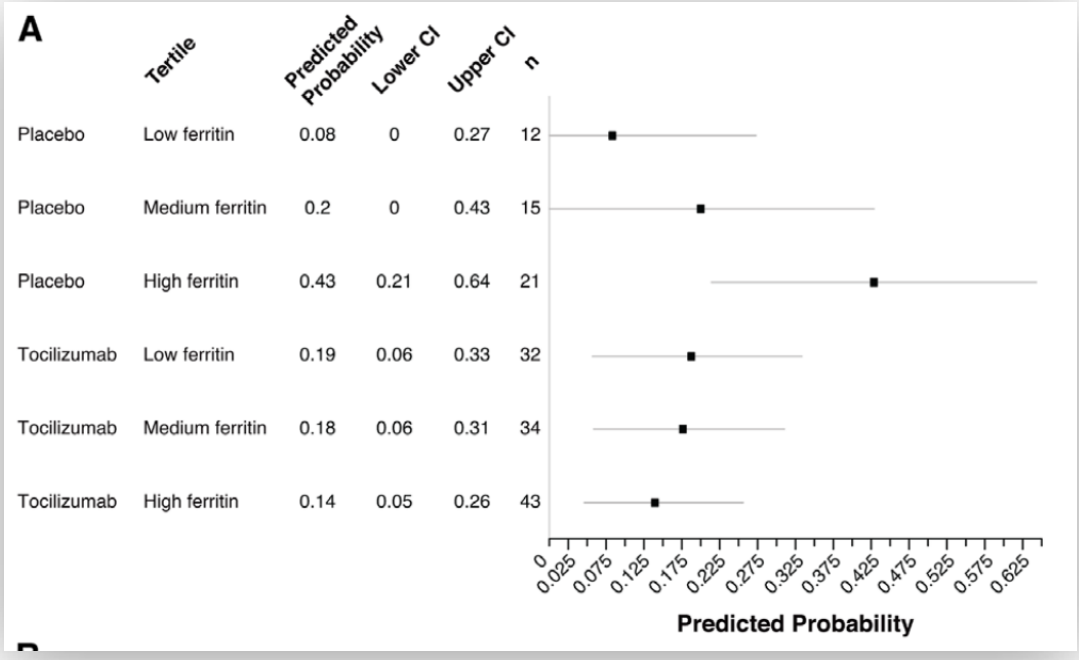
Tom J et al - Crit Care Med . 2021 Oct 12

CLINICAL INVESTIGATION

OPEN

Prognostic and Predictive Biomarkers in Patients With Coronavirus Disease 2019 Treated With Tocilizumab in a Randomized Controlled Trial

Modeling in the tocilizumab arm showed a predictive value of ferritin for day 28 clinical outcome of mortality (predictive interaction, *p = 0.03)*



Low ferritin: 3.63 pmol/L-, 1,480.77 pmol/L
Medium ferritin , 1,480.77 pmol/L -3,150.29 pmol/L,
High ferritin: 3,150.29- 75,299.67 pmol/L

Tom J et al - Crit Care Med . 2021 Oct 12

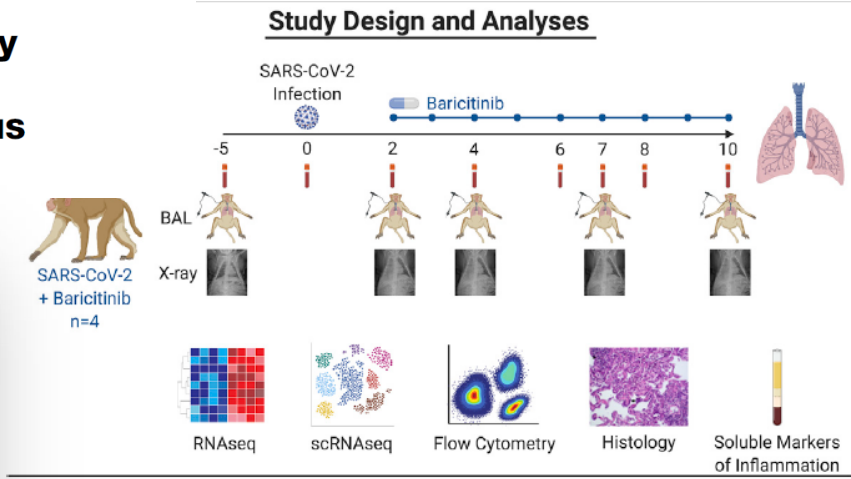

ANAKINRA

ANTI JAK

Cell

Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques

1. SARS-CoV-2-infected RMs mimic signatures of inflammation seen in COVID-19 patients
2. Baricitinib suppresses production of pro inflammatory cytokines in lung macrophages
3. Baricitinib limits recruitment of neutrophils to the lung and NETosis
4. Baricitinib preserves innate antiviral and SARS-CoV-2- specific T cell responses



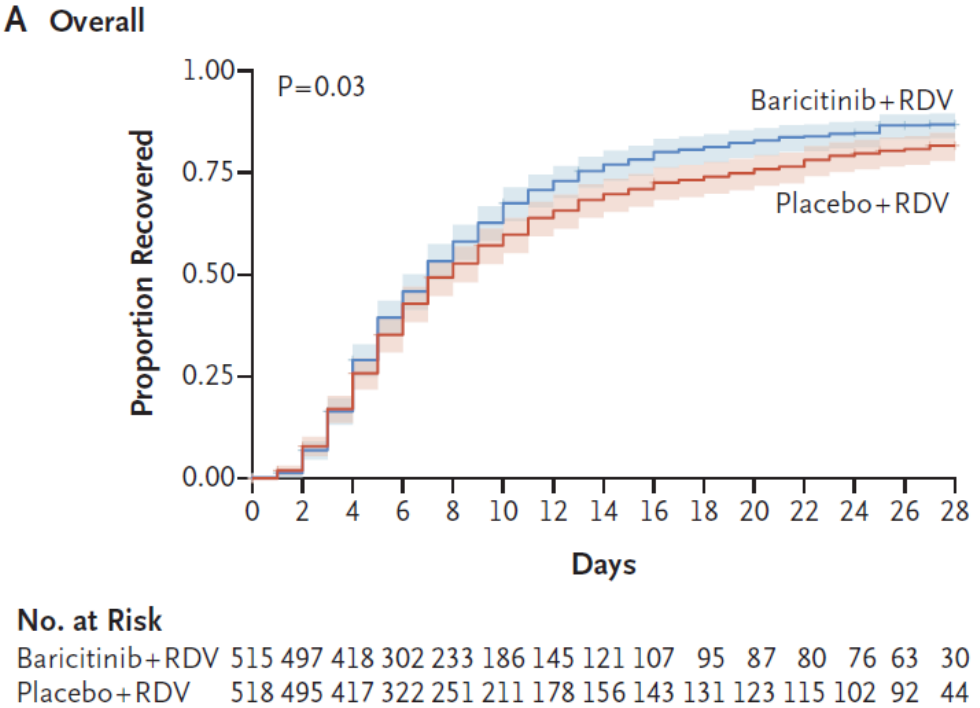
Hoang et al., Cell (2021), https://doi.org/10.1016/j.cell.2020.11.007

ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

- Double blind placebo controlled multicenter
- Ely Lilly + NIH
- Remdesivir IV 200-mg LD and 100-mg/d 10 days or hospital discharge
- Baricitinib 4-mg daily dose (either orally [two 2-mg tablets]or through a nasogastric tube) 14 days
- Primary outcome: Time to recovery

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



Kalil A- N Engl J Med . 2020 Dec 11;NEJMoa2031994. doi: 10.1056/NEJMoa2031994. Online ahead of print.

Baricitinib vs Placebo (RCT)

Marconi et al COV-BARRIER study group

- **Phase 3, double-blind (Ely Lilly)**
- **1525 hospitalized adults**
- **SOC (7% CS)**
- **Baricitinib 4-mg (N=764) or placebo (N=761) for up to 14 days**
- **1ry endpoint; % progression to HFNO, NIV, IV or death by day 28.**
- **2ry: all-cause mortality by day 28.**
- **Participants :**
  - **active Covid-19;**
  - **one inflammatory marker (LDH, CRP, Perritin)**
  - **not intubated at inclusion**

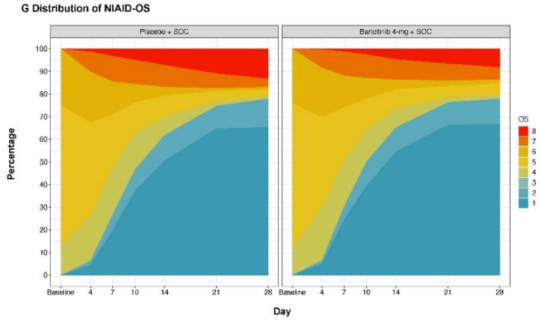
	PB+SOC (n=761)	Baracitinib+SOC (n=764)	Total
Age	57.5 (13.8)	57.8 (14.3)	57.6 (14.1)
Female	288 (37.8)	274 (35.9)	562 (36.9)
BMI	30.6 (6.6)	30.4 (6.4)	30.5 (6.5)
Disease ≥7 days	640/756 (84.7)	625/762 (8Z.0)	1265/1518 (83.3)
4-Hosp no O2	97/756 (12.8)	89/762 (11.7)	186/1518 (12.3)
5-Hosp O2	472/756 (62.4)	490/762 (64.3)	962/1518 (63.4)
6-NIV HFNO	187/756 (24.7)	183/762 (24.0)	370/1518 (24.4)
Remdesivir	147/756 (19.4)	140/762 (18.4)	287/1518 (18.9)
Corticosteroids	592/756 (78.3)	612/762 (80.3)	1204/1518 (79.3)

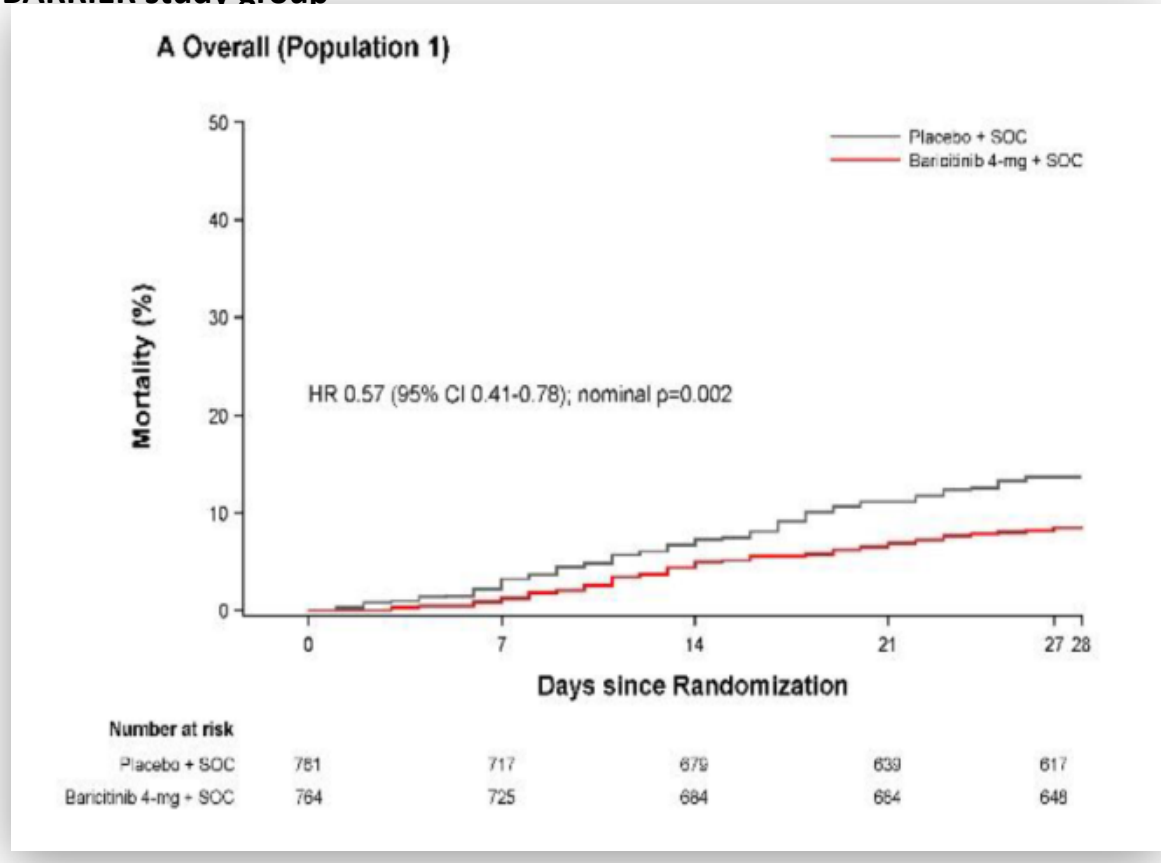
Lancet Respir Med 2021; published online Sep 1. http://dx.doi.org/10.1016/ S2213-2600(21)00331-3.

Baricitinib vs Placebo (RCT)

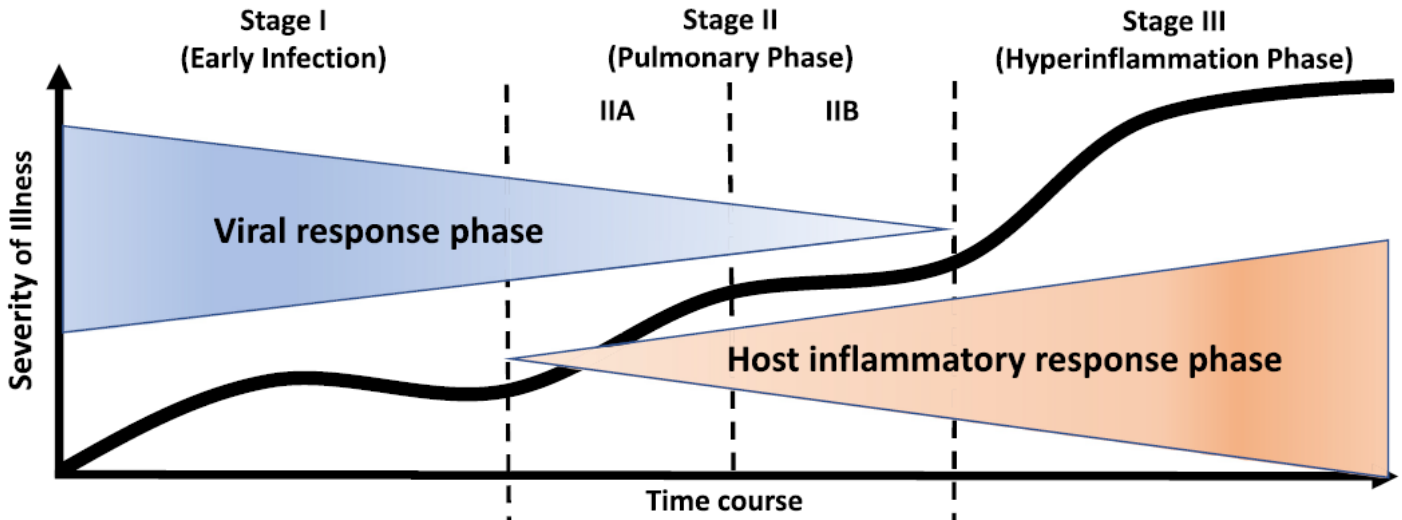
Marconi et al COV-BARRIER study group

Overall, 27.8% of participants receiving baricitinib vs 30.5% receiving placebo progressed (primary endpoint, OR 0.85, 95% CI 0.67-1.08; p=0.18).





Lancet Respir Med 2021; published online Sep 1. http://dx.doi.org/10.1016/ S2213-2600(21)00331-3.



Clinical Symptoms	Mild constitutional symptoms Fever >99.6˚F Dry Cough	Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
Potential Therapies	***Monoclonal Abs*** Remdesivir, [redacted], convalescent plasma transfusions ***Molnupiravir Paxlovid***		
	Redu… (a… *No steroids* …ds)	Careful use of Cortic… IL-1/IL-2/IL-… *Careful use…*	…uman immunoglobulin, …-CSF Inhibitors

Do not harm: oxygenation/ infection prevention and therapies/ toxicities

Siddiqi HK & Mehra MR - J Heart Lung Transplant . 2020 May;39(5):405-407

Vers un traitement personnalisé

Statut immun./ fenêtre temporelle/ degré d'inflammation

Prévention/stratégies anti-virales précoces

- Vaccination
- Ac monoclonaux
- Nouveaux antiviraux
- Pour qui en réa??

Formes précoces?

Charges virales élevée?

Immunodéprimés?

Corticoides

- Pas dans les formes simples
- Probablement bon mais pas pour tout le monde…
- Importantes faiblesses des essais plateformes…

Pour qui?

Dose??

Durée?

Immunomodulation

- Profil inflammatoire variable et changeant
- Résultats discutables
- Négatif pour les patients intubés
- Effets secondaires possibles

Pour qui?

Avec quoi?

Dose??

Durée?