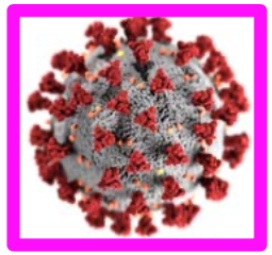
UNIMORE

UNIVERSITÀ DEGLI STUDI DI
MODENA E REGGIO EMILIA

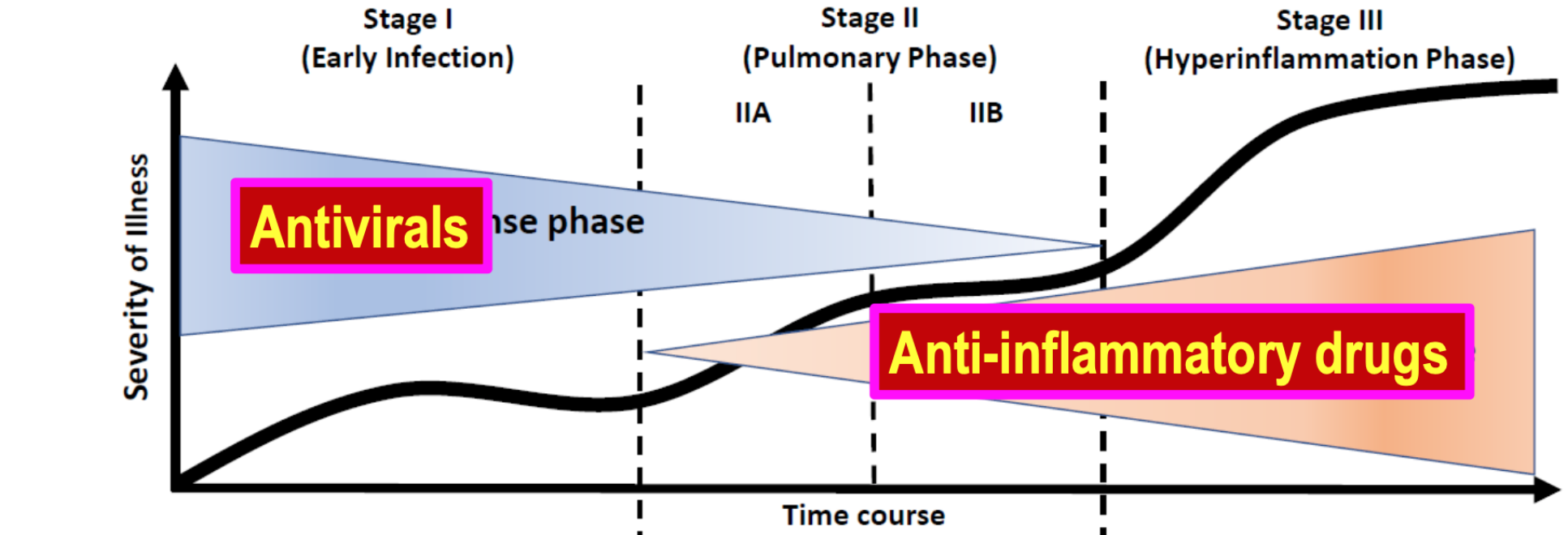
La terapia della fase infiammatoria: ruolo dello steroide e dei farmaci ad azione anticitochinica

Disclosures

Cristina Mussini has served as a paid consultant to Gilead Sciences, Angelini, Abbvie, Janssen, MSD, ViiV Healthcare and received research fundings from Gilead Sciences, Janssen, MSD and ViiV Healthcare.



Classification of COVID-19 Disease Stages



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

Siddiqu HK, Mehra MR. J Heart Lung Transplant. March 25th 2020 doi: 10.1016/j.healun.2020.03.012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

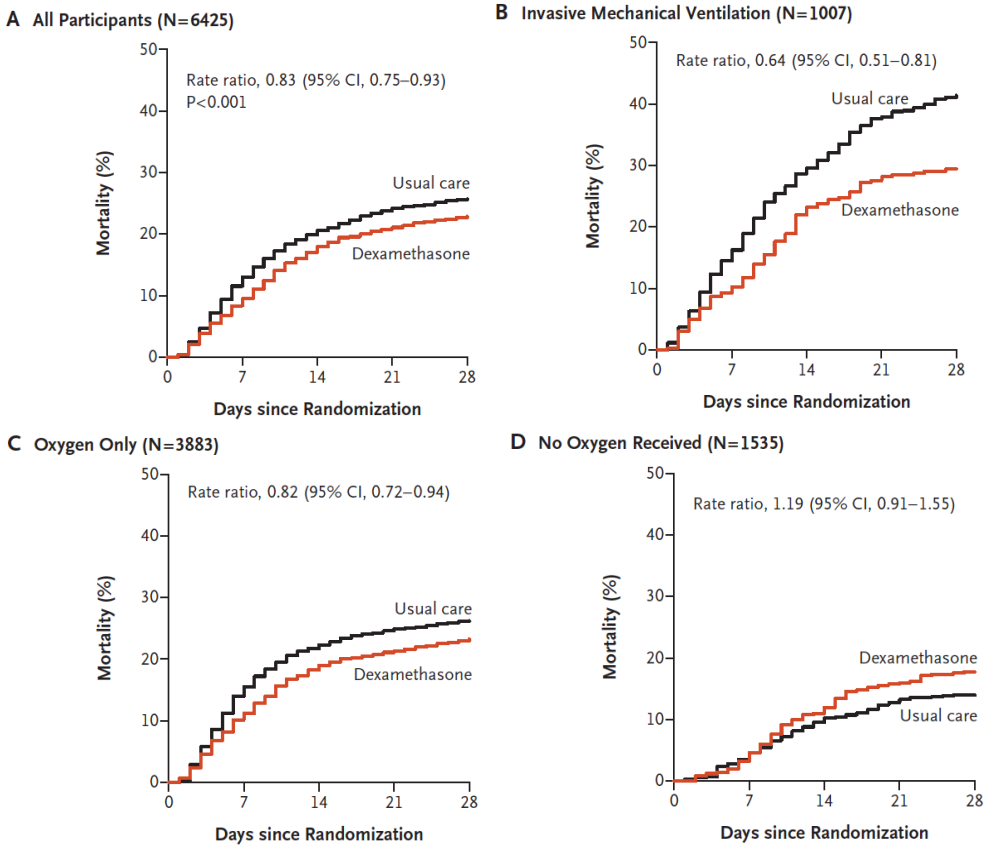
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

In this controlled, open-label trial were assigned to receive dexamethasone (2104) receive usual care (4321).

Oral or intravenous dexamethasone (at a dose of 6 mg once daily) was used for up to 10 days or to receive usual care alone.

The use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ven- tilation or oxygen alone at randomization but not among those receiving no respiratory support.



N Engl J Med. 2020 Jul 17:NEJMoa2021436.

Original article

Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicentre study

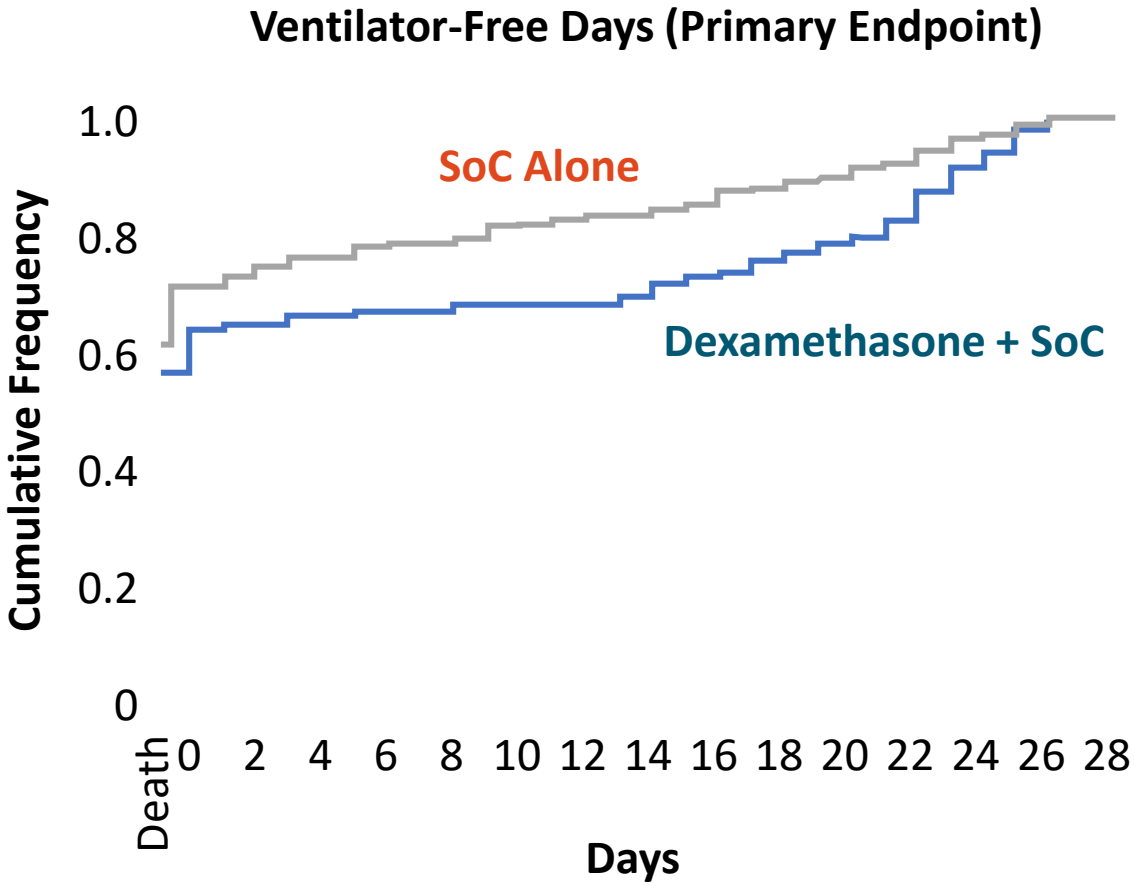
Michele Bartoletti [1, *, †], Lorenzo Marconi [4, †], Luigia Scudeller [7, †], Livia Pancaldi [1], Sara Tedeschi [1], Maddalena Giannella [1], Matteo Rinaldi [1], Linda Bussini [1], Ilaria Valentini [5], Anna Filomena Ferravante [5], Antonella Potalivo [6], Elisa Marchionni [4], Giacomo Fornaro [1], Renato Pascale [1], Zeno Pasquini [9, 10], Massimo Puoti [8], Marco Merli [8], Francesco Barchiesi [9, 10], Francesca Volpato [1], Arianna Rubin [1], Annalisa Saracino [11], Tommaso Tonetti [2], Paolo Gaibani [3], Vito Marco Ranieri [2], Pierluigi Viale [1], Francesco Cristini [4], on behalf of the PREDICO Study Group[§]

A B S T R A C T

Objective: To assess the efficacy of corticosteroids in patients with coronavirus disease 2019 (COVID-19).
Methods: A multicentre observational study was performed from 22 February through 30 June 2020. We included consecutive adult patients with severe COVID-19, defined as respiratory rate ≥30 breath per minute, oxygen saturation ≤93% on ambient air or arterial partial pressure of oxygen to fraction of inspired oxygen ≤300 mm Hg. We excluded patients being treated with other immunomodulant drugs, receiving low-dose corticosteroids and receiving corticosteroids 72 hours after admission. The primary endpoint was 30-day mortality from hospital admission. The main exposure variable was corticosteroid therapy at a dose of ≥0.5 mg/kg of prednisone equivalents. It was introduced as binomial covariate in a logistic regression model for the primary endpoint and inverse probability of treatment weighting using the propensity score.
Results: Of 1717 patients with COVID-19 evaluated, 513 were included in the study, and of these, 170 (33%) were treated with corticosteroids. During hospitalization, 166 patients (34%) met the criteria of the primary outcome (60/170, 35% in the corticosteroid group and 106/343, 31% in the noncorticosteroid group). At multivariable analysis corticosteroid treatment was not associated with lower 30-day mortality rate (adjusted odds ratio, 0.59; 95% confidence interval (CI), 0.20–1.74; p 0.33). After inverse probability of treatment weighting, corticosteroids were not associated with lower 30-day mortality (average treatment effect, 0.05; 95% CI, −0.02 to 0.09; p 0.12). However, subgroup analysis revealed that in patients with PO2/FiO2 < 200 mm Hg at admission (135 patients, 52 (38%) treated with corticosteroids), corticosteroid treatment was associated with a lower risk of 30-day mortality (23/52, 44% vs. 45/83, 54%; adjusted odds ratio, 0.20; 95% CI, 0.04–0.90; p 0.036).

CoDex: Dexamethasone to Treat COVID-19–Related ARDS

- Multicenter, randomized, open-label trial in patients with COVID-19 and moderate to severe ARDS
  - Dexamethasone 20 mg/day for 5 days then 10 mg/day for 5 days or until ICU discharge + SOC (n = 151) vs
  - SOC alone (n = 148)
- During first 28 days, mean ventilator-free days:
  - Dexamethasone + SOC: 6.6 (95% CI: 5.0-8.2)
  - SOC alone: 4.0 (95% CI: 2.9-5.4)
  - **Difference: 2.26 (95% CI: 0.2-4.38; *P* = .04)**
- No difference in mortality with dexamethasone + SOC vs SOC alone (56.3% vs 61.5%)



Tomazini. JAMA. 2020;[Epub]. NCT04327401.

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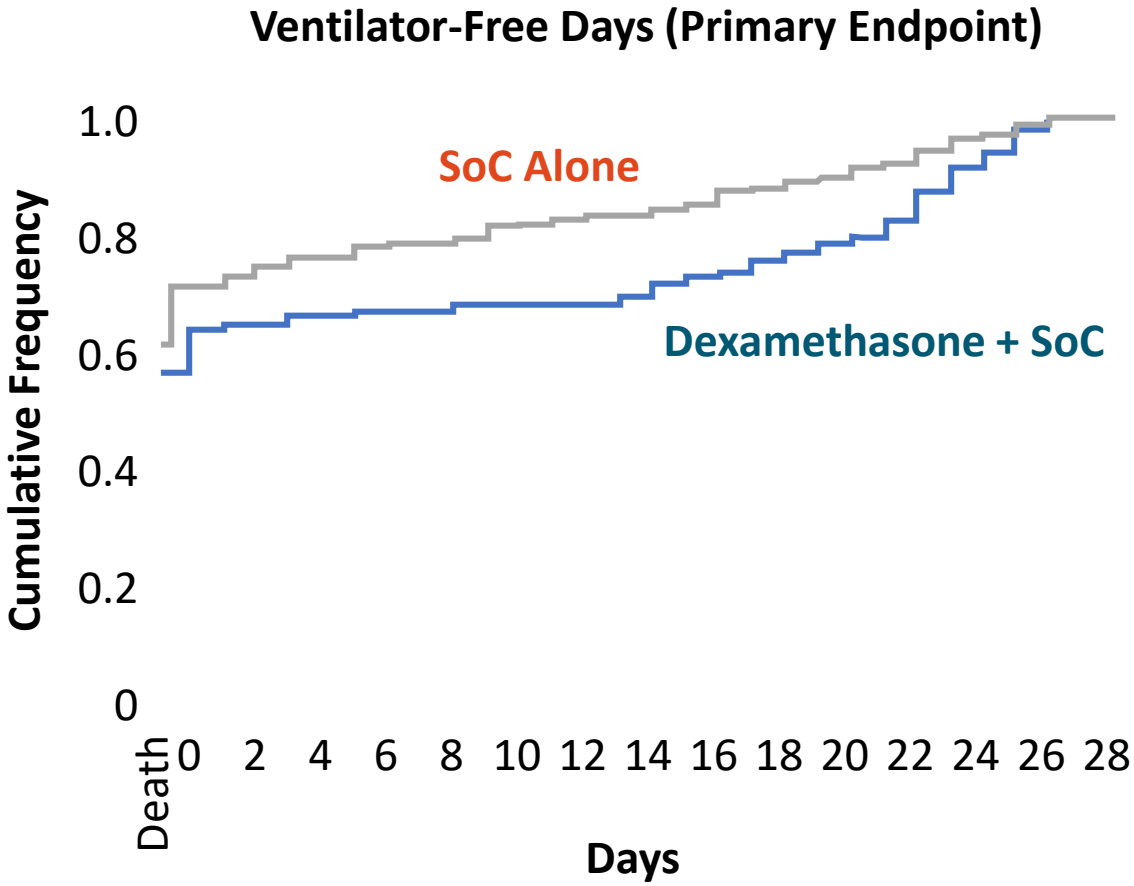


Tomazini. JAMA. 2020;[Epub]. NCT04327401.

High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia

Aikaterini Papamanoli[1] | **Jeanwoo Yoo**[2] | **Prabhjot Grewal**[2] | **William Predun**[2] | **Jessica Hotelling**[2] | **Robin Jacob**[2] | **Azad Mojahedi**[2] | **Hal A. Skopicki**[3] | **Mohamed Mansour**[4] | **Luis A. Marcos**[1] | **Andreas P. Kalogeropoulos**[3]

Methods: Retrospective cohort of consecutive adults with severe COVID-19 pneumonia on high-flow oxygen ($FiO_2 \geq 50\%$) admitted to an academic centre in New York, from 1 March to 15 April 2020. We used inverse probability of treatment weights to estimate the effect of methylprednisolone on clinical outcomes and intensive care resource utilization.

Results: Of 447 patients, 153 (34.2%) received methylprednisolone and 294 (65.8%) received no corticosteroids. At 28 days, 102 patients (22.8%) had died and 115 (25.7%) received mechanical ventilation. In weighted analyses, risk for death or mechanical ventilation was 37% lower with methylprednisolone (hazard ratio 0.63; 95% CI 0.47-0.86; $P = .003$), driven by less frequent mechanical ventilation (subhazard ratio 0.56; 95% CI 0.40-0.79; $P = .001$); mortality did not differ between groups. The methylprednisolone group had 2.8 more ventilator-free days (95% CI 0.5-5.1; $P = .017$) and 2.6 more intensive care-free days (95% CI 0.2-4.9; $P = .033$) during the first 28 days. Complication rates were not higher with methylprednisolone.

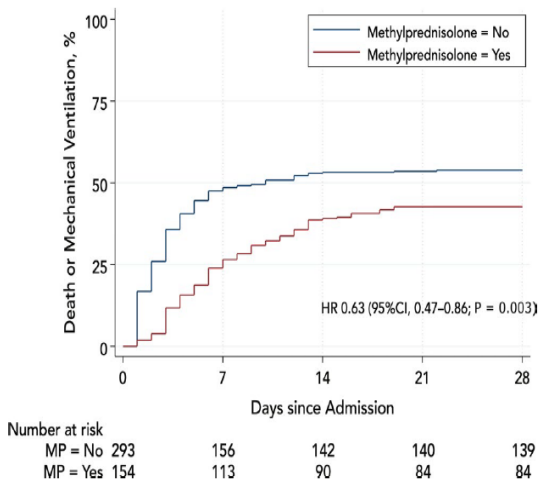


FIGURE 2 Rates of death or mechanical ventilation in methylprednisolone groups weighted by the inverse probability of treatment (propensity score). MP, methylprednisolone

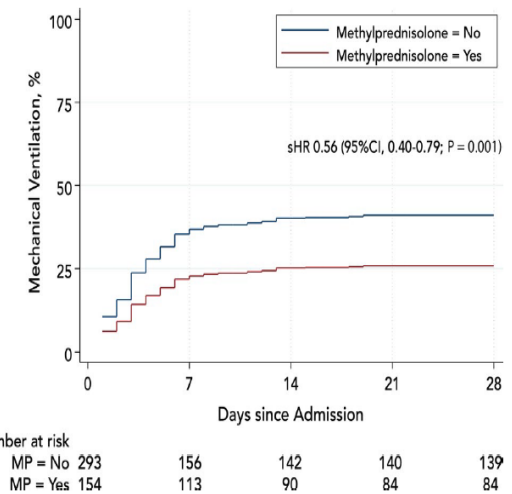
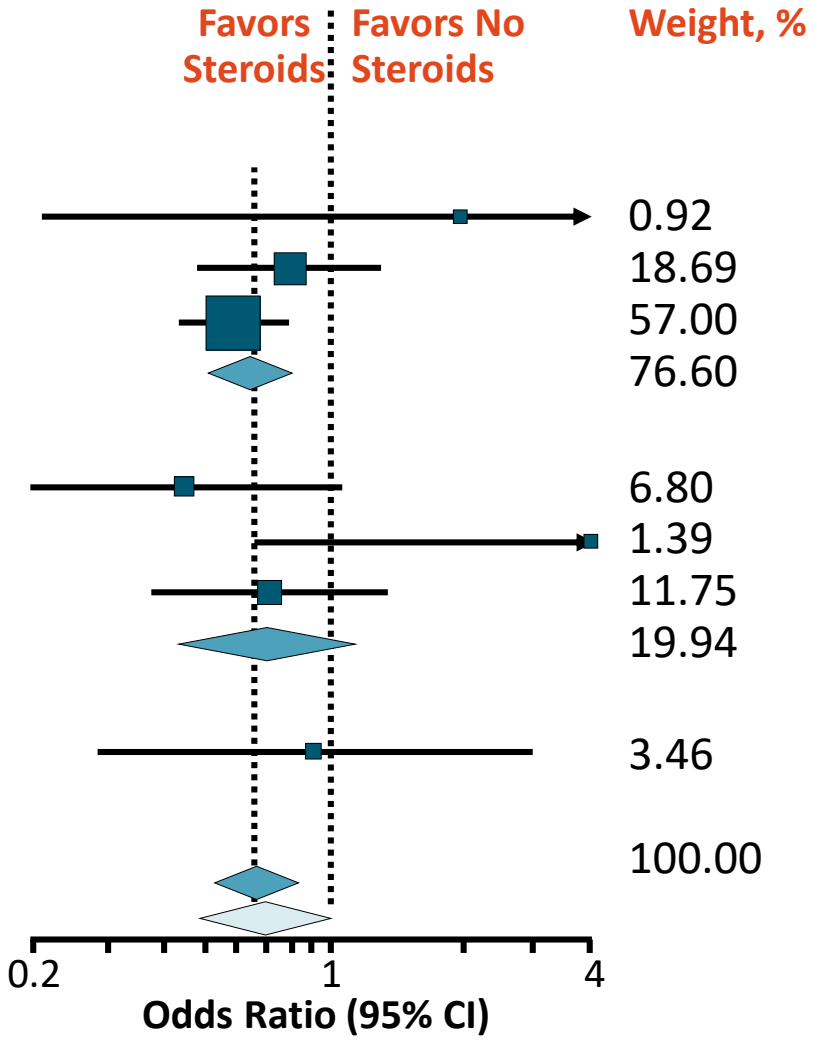


FIGURE 4 Cumulative incidence of mechanical ventilation, accounting for competing mortality, in methylprednisolone groups weighted by the inverse probability of treatment. MP, methylprednisolone

Systemic Corticosteroids and 28-Day All-Cause Mortality in Critically Ill Patients With COVID-19

Drug/Trial	Initial Dose	Deaths/n		Odds Ratio (95% CI)	*P* Value
		Steroids	No Steroids		
Dexamethasone					
DEXA-COVID 19	High: 20 mg/day IV	2/7	2/12	2.00 (0.21-18.69)	
CoDEX	High: 20 mg/day IV	69/128	76/128	0.80 (0.49-1.31)	
RECOVERY	Low: 6 mg/day PO or IV	95/324	283/683	0.59 (0.44-0.78)	
Subgroup fixed effect		166/459	361/823	0.64 (0.50-0.82)	< .001
Hydrocortisone					
CAPE COVID	Low: 200 mg/day IV	11/75	20/73		
COVID STEROID	Low: 200 mg/day IV	6/15	2/14		
REMAP-COVID	Low: 50 mg every 6 hrs IV	26/105	29/92		
Subgroup fixed effect		43/195	51/179	0.69 (0.43-1.12)	.13
Methylprednisolone					
Steroids-SARI	High: 40 mg every 12 hrs IV	13/24	13/23	0.91 (0.29-2.87)	.87
Overall*					
Overall (fixed effects)		222/678	425/1025	0.66 (0.53-0.82)	< .001
Overall (random effects)		222/678	425/1025	0.70 (0.48-1.01)	.053

**P* = .31 for heterogeneity; I^2 = 15.6%.



WHO REACT Working Group. JAMA. 2020;[Epub].

Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes

Judith van Paassen[1], Jeroen S. Vos[1], Eva M. Hoekstra[2], Katinka M. I. Neumann[2], Pauline C. Boot[2] and Sesmu M. Arbous[1,3*]

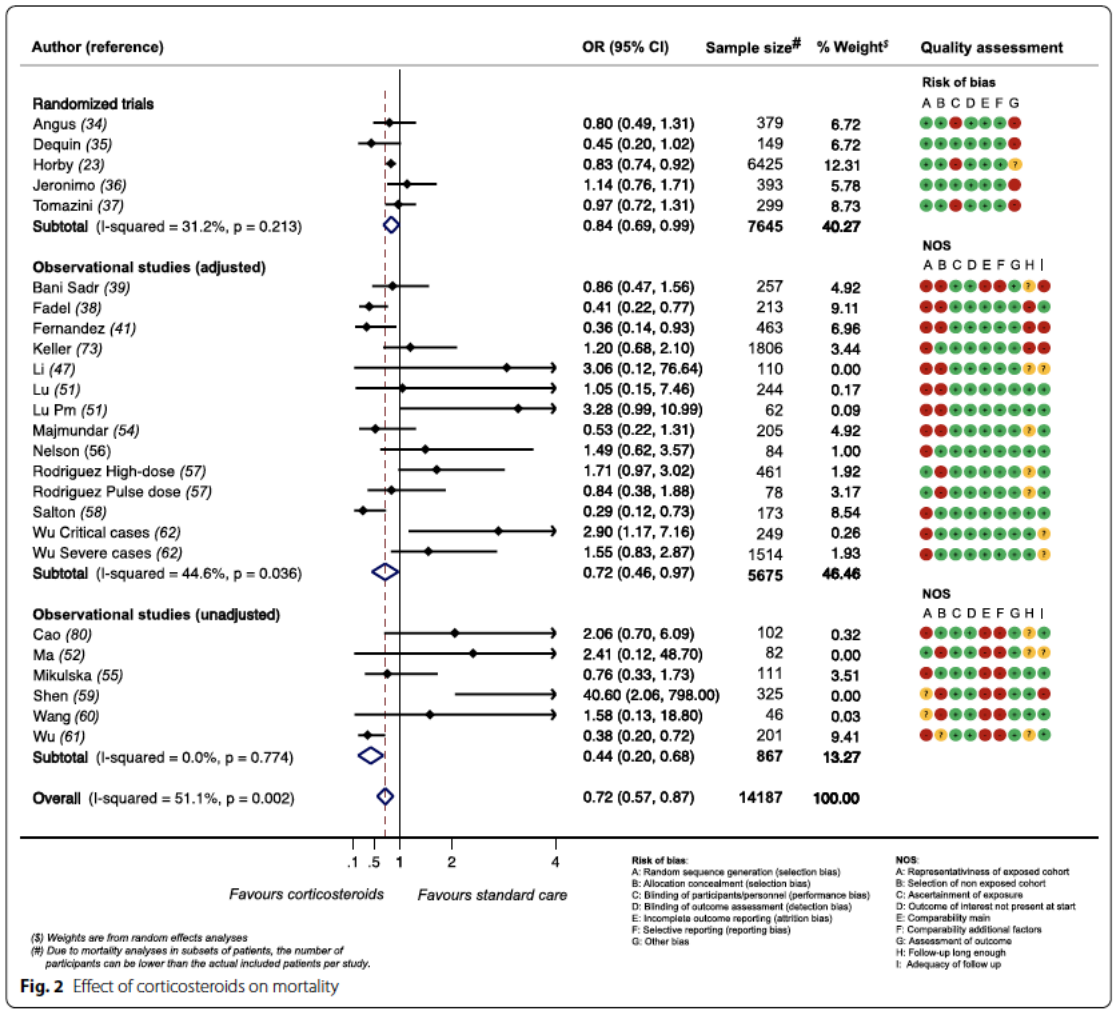


Fig. 2 Effect of corticosteroids on mortality

Abstract

Background: In the current SARS-CoV-2 pandemic, there has been worldwide debate on the use of corticosteroids in COVID-19. In the recent RECOVERY trial, evaluating the effect of dexamethasone, a reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation was shown. Their results have led to considering amendments in guidelines or actually already recommending corticosteroids in COVID-19. However, the effectiveness and safety of corticosteroids still remain uncertain, and reliable data to further shed light on the benefit and harm are needed.

Objectives: The aim of this systematic review and meta-analysis was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

Methods: A systematic literature search of RCTS and observational studies on adult patients was performed across Medline/PubMed, Embase and Web of Science from December 1, 2019, until October 1, 2020, according to the PRISMA guidelines. Primary outcomes were short-term mortality and viral clearance (based on RT-PCR in respiratory specimens). Secondary outcomes were: need for mechanical ventilation, need for other oxygen therapy, length of hospital stay and secondary infections.

Results: Forty-four studies were included, covering 20.197 patients. In twenty-two studies, the effect of corticosteroid use on mortality was quantified. The overall pooled estimate (observational studies and RCTs) showed a significant reduced mortality in the corticosteroid group (OR 0.72 (95%CI 0.57–0.87). Furthermore, viral clearance time ranged from 10 to 29 days in the corticosteroid group and from 8 to 24 days in the standard of care group. Fourteen studies reported a positive effect of corticosteroids on need for and duration of mechanical ventilation. A trend toward more infections and antibiotic use was present.

Conclusions: Our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Corticosteroids, Mortality, Viral clearance, Mechanical ventilation

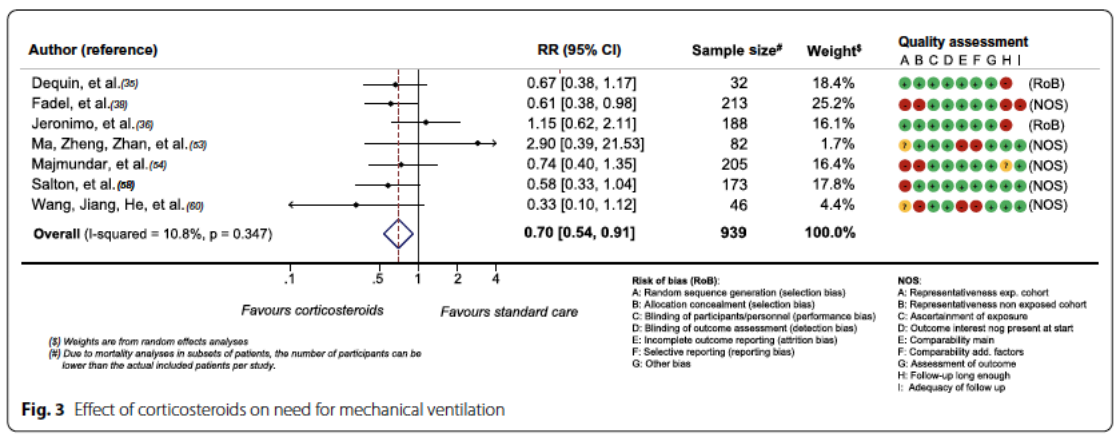


Fig. 3 Effect of corticosteroids on need for mechanical ventilation

Dexamethasone inhibits SARS-CoV-2 spike pseudotyped virus viropexis by binding to ACE2

Yongjing Zhang [a,b], Shiling Hu [a,b], Jue Wang [a,b], Zhuoyin Xue [a,b], Cheng Wang [a,b], Nan Wang [a,b,*]

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ARTICLE INFO

Keywords:
Dexamethasone
SARS-CoV-2
ACE2

ABSTRACT

The SARS-CoV-2 outbreak, began in late 2019, has caused a worldwide pandemic and shows no signs of slowing. Glucocorticoids (GCs), including dexamethasone (DEX), have been widely used as effective anti-inflammatory and immunosuppressant drugs. In this study, seven GCs had no obvious effect on cell viability of angiotensin converting enzyme 2 (ACE2) high expressed HEK293T cells when concentrations were under 10 μM. Molecular docking results revealed that DEX occupied with active binding site of ACE2 of SARS-CoV-2 spike protein. Surface plasmon resonance (SPR) results showed that K_D value between DEX and ACE2 was (9.03 ± 0.78) e−6 M. Cell membrane chromatography (CMC) results uncovered that DEX had a chromatographic retention. DEX was found out to inhibiting the viropexis into ACE2^h cells using SARS-CoV-2 spike pseudotyped virus. Therefore, DEX inhibits the entrance of SARS-CoV-2 spike pseudotyped virus into cell by binding to ACE2.

COVID-19 treatment options

ANTIVIRAL THERAPY	Mechanism of action and rationale
Hydroxychloroquine	- Blockade of viral entry - Immunomodulatory effects
Remdesevir	RNA polymerase inhibitor
Lopinavir/ritonavir	Protease inhibitor
Darunavir/cobicistat	Protease inhibitor
Umifenovir	Blocks the fusion between S protein and ACE-2 receptor
Favipiravir	RNA polymerase inhibitor
IMMUNE ACTIVE THERAPY	**Mechanism of action and rationale**
Tocilizumab	IL-6 receptor inhibitor
Sarilumab	IL-6 receptor inhibitor
Siltuximab	IL-6 blocker
Anakinra	IL-1 receptor inhibitor
Baricitinib	Janus kinase inhibitor
OTHERS	**Mechanism of action and rationale**
Convalescent plasma therapy	convalescent plasma collected from recovered individuals

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

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

Summary

Background Mortality of patients with coronavirus disease 2019 (COVID-19), acute respiratory distress syndrome (ARDS), and systemic inflammation is high. In areas of pandemic outbreak, the number of patients can exceed maximum capacity of intensive care units (ICUs), and, thus, these individuals often receive non-invasive ventilation outside of the ICU. Effective treatments for this population are needed urgently. Anakinra is a recombinant interleukin-1 receptor antagonist that might be beneficial in this patient population.

Methods We conducted a retrospective cohort study at the San Raffaele Hospital in Milan, Italy. We included consecutive patients (aged ≥18 years) with COVID-19, moderate-to-severe ARDS, and hyperinflammation (defined as serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both) who were managed with non-invasive ventilation outside of the ICU and who received standard treatment of 200 mg hydroxychloroquine twice a day orally and 400 mg lopinavir with 100 mg ritonavir twice a day orally. We compared survival, mechanical ventilation-free survival, changes in C-reactive protein, respiratory function, and clinical status in a cohort of patients who received additional treatment with anakinra (either 5 mg/kg twice a day intravenously [high dose] or 100 mg twice a day subcutaneously [low dose]) with a retrospective cohort of patients who did not receive anakinra (referred to as the standard treatment group). All outcomes were assessed at 21 days. This study is part of the COVID-19 Biobank study, which is registered with ClinicalTrials.gov, NCT04318366.

Findings Between March 17 and March 27, 2020, 29 patients received high-dose intravenous anakinra, non-invasive ventilation, and standard treatment. Between March 10 and March 17, 2020, 16 patients received non-invasive ventilation and standard treatment only and comprised the comparison group for this study. A further seven patients received low-dose subcutaneous anakinra in addition to non-invasive ventilation and standard treatment; however, anakinra treatment was interrupted after 7 days because of a paucity of effects on serum C-reactive protein and clinical status. At 21 days, treatment with high-dose anakinra was associated with reductions in serum C-reactive protein and progressive improvements in respiratory function in 21 (72%) of 29 patients; five (17%) patients were on mechanical ventilation and three (10%) died. In the standard treatment group, eight (50%) of 16 patients showed respiratory improvement at 21 days; one (6%) patient was on mechanical ventilation and seven (44%) died. At 21 days, survival was 90% in the high-dose anakinra group and 56% in the standard treatment group (p=0·009). Mechanical ventilation-free survival was 72% in the anakinra group versus 50% in the standard treatment group (p=0·15). Bacteraemia occurred in

The ANSM (French National Agency for Medicines and Health Products Safety) has issued a public communication regarding the suspension of inclusions of all clinical trials assessing use of anakinra in indication of treatment of Covid-19 in France.

Intermediate analysis of ANACONDA-COVID19 (sponsor : CHRU of Tours, regional university hospital center) showed an early excess mortality in the group of patients treated by anakinra and standard of care versus patients treated with standard of care alone. Role of anakinra could not be excluded as no information was available to explain the difference between the groups at the time of the report. Therefore, CHRU of Tours suspended inclusions in ANACONDA-COVID-19 trial. Inclusions in other trials with anakinra in Covid-19 indication in France were also suspended. They were already suspended or did not start yet.

Regarding CORIMUNO-19_ANA trial, inclusions in group 1 were already suspended on 28-Apr-2020 and last inclusion in group 2 was performed on 04-Jun-2020.
The ANSM contacted us regarding of on number of deaths occurring in this trial, and asked for the DSMB's opinion. We have planned to discuss this during our next meeting on November 24th. It is planned that Raphael will provide analysis on survival for « ANA » for this meeting.

Kind regards,
Stephany

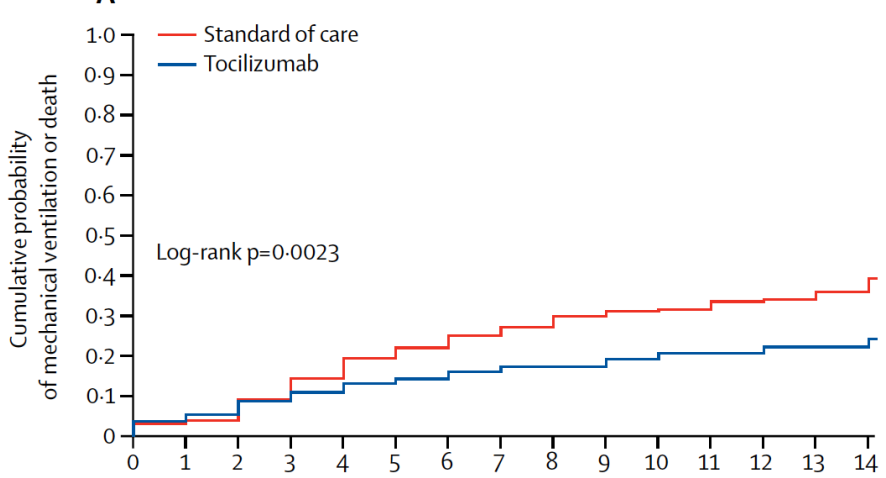
Tocilizumab

- **Interleukin 6 inhibitor;** binds specifically to both soluble and membrane bound IL-6 receptors
- Widely used in rheumatology
- Limited clinical experience in COVID-19 pneumonia
- **Dosage:**
  - IV: 8 mg/kg; 800 mg maximum dose, two doses 12 hours apart
  - SC: 162 mg single shot in two sites
- Potential reactivation of latent TB or HBV infection

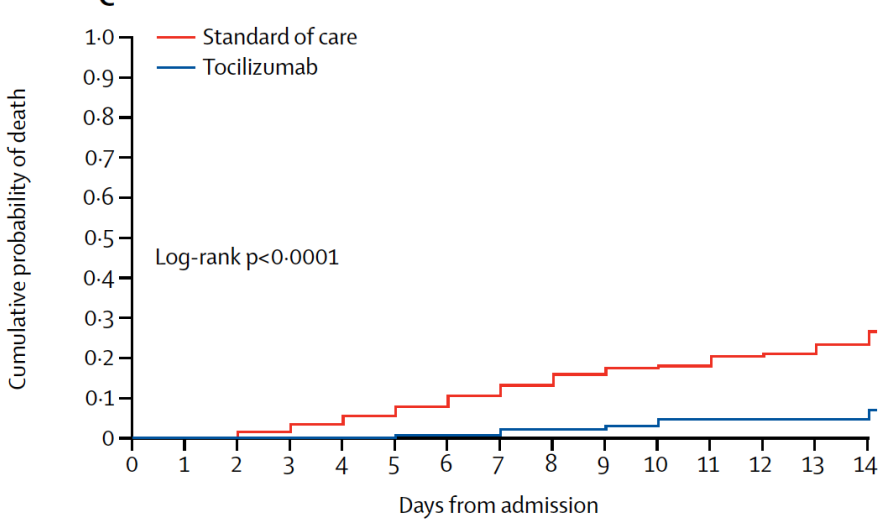
Tocilizumab in patients with severe COVID-19: a retrospective cohort study

Giovanni Guaraldi, Marianna Meschiari*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbì, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonello Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini*

The aim of this multicentre cohort study was to assess the role of tocilizumab in reducing the risk of invasive mechanical ventilation and/or death in patients with severe COVID-19 pneumonia who received standard of care (SoC) treatment.



39% reduction in risk



62% reduction in risk

Implications of all the available evidence

Tocilizumab, regardless of IV or SC administration may be capable of reducing invasive mechanical ventilation or death in severe COVID-19 pneumonia.

Guaraldi G. et al. 2020. Lancet Rheumatology

Clinical Infectious Diseases IDSA hivma

ACCEPTED MANUSCRIPT

Two fatal cases of acute liver failure due to HSV-1 infection in COVID-19 patients following immunomodulatory therapies FREE

Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy

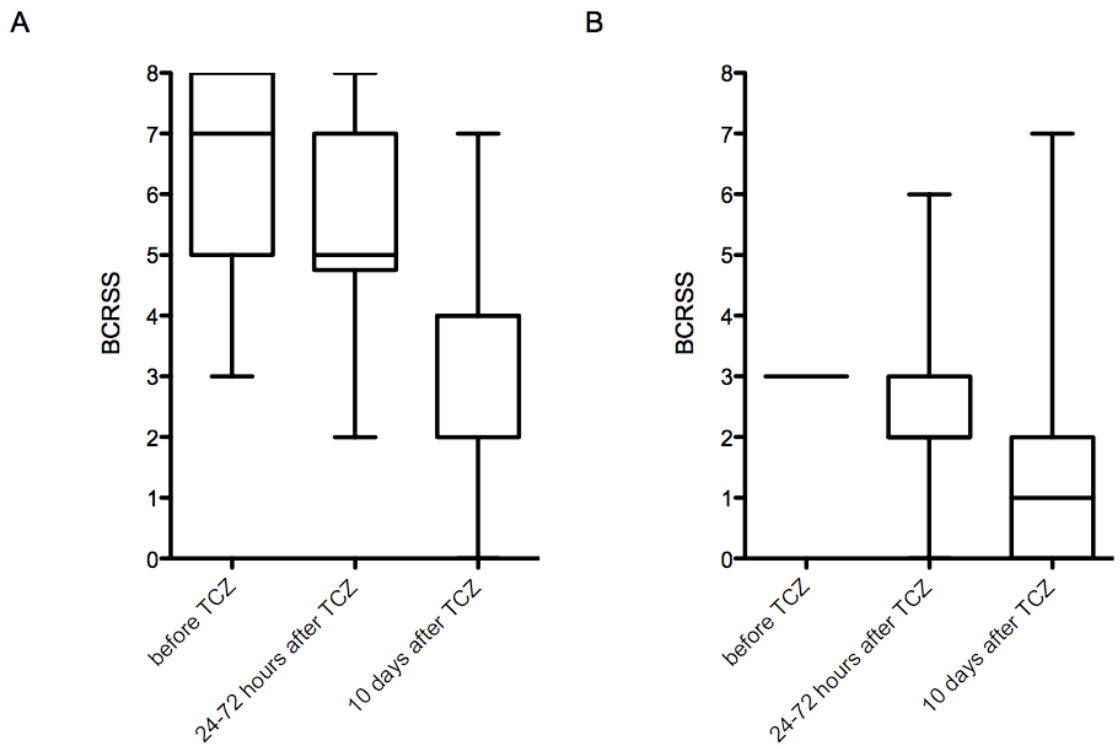


Fig. 2. Brescia COVID-19 Respiratory Severity Scale (BCRSS) trend over time after Tocilizumab administration in patients treated in the ICU (panel A) and in the general ward (panel B).

Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia

ROCHE Press release 29/7/20

- **COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality**
- **The study is the first global, randomised, double-blind, placebo-controlled phase III trial investigating Actemra/RoActemra in this setting**
- **Roche remains committed to continuing the Actemra/RoActemra clinical trial programme in COVID-19 to further explore Actemra/RoActemra in other treatment settings, including in combination with an antiviral**

JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia

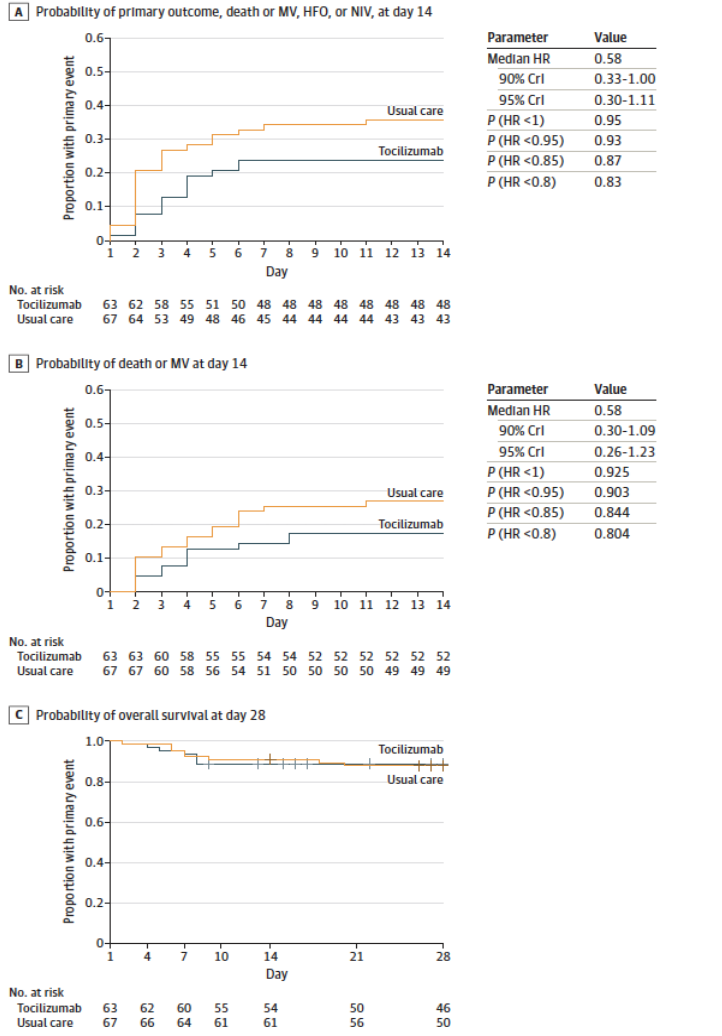
A Randomized Clinical Trial

Olivier Hermine, MD, PhD; Xavier Mariette, MD, PhD; Pierre-Louis Tharaux, MD, PhD; Matthieu Resche-Rigon, MD, PhD; Raphaël Porcher, PhD; Philippe Ravaud, MD, PhD; for the CORIMUNO-19 Collaborative Group

Table 1. Patient Characteristics at Baseline

Characteristic	No.	Tocilizumab, No./No. (%)	No.	UC, No./No. (%)
No.		63		67
Age, median (IQR), y		64.0 (57.1-74.3)		63.3 (57.1-72.3)
Male		44/63 (70)		44/67 (66)
Female		19/63 (30)		23/67 (34)
Weight, median (IQR), kg		80.0 (70.0-90.0)	55	78.0 (70.0-90.0)
BMI,[a] median (IQR)	46	27.9 (23.3-30.8)	46	27.4 (24.5-31.3)
WHO-CPS score (0-10) = 5		63/63 (100)		67/67 (100)
rRT-PCR–confirmed SARS-CoV-2 infection		56/63 (89)		61/67 (90)
Temperature, median (IQR), °C		37.3 (36.8-38.2)		37.9 (37.0-38.6)
Respiratory rate, median (IQR), bpm	56	24.0 (22.0-30.0)	57	26.0 (24.0-30.0)
Flow, median (IQR), L/min		5.0 (3.0-8.0)		5.0 (3.0-6.0)
SpO_2, median (IQR), %		95.0 (93.0-96.0)		95.0 (93.0-97.0)
Time from symptoms onset to randomization, median (IQR), d	62	10 (7-13)	66	10 (8-13)
Time from hospital admission to randomization, median (IQR), d	63	1 (1-4)	67	1 (1-2)
Coexisting conditions				
Chronic cardiac disease		20/61 (33)		20/67 (30.0)
Diabetes		20/61 (33)		23/67 (34)
Chronic kidney disease (stage 1 to 3) or dialysis		5/61 (8)		13/67 (19)
Asthma		5/61 (8)		3/67 (5)
Chronic pulmonary disease (not asthma)		3/61 (5)		3/67 (5)
Active malignant neoplasm		4/61 (7)		5/67 (8)
Smoking				
No		55/61 (90)		62/67 (93)
Current		1/61 (2)		2/67 (3)
Former		5/61 (8)		3/67 (4)
Laboratory values, median (IQR)				
CRP, mg/L	56	119.5 (74.5-219.5)	63	127.0 (84.0-171.0)
D-Dimer, µg/L	50	869 (524-1380)	50	1250 (780-1812)
Neutrophil count, G/L	60	4.9 (3.9-7.5)	63	5.1 (3.4-6.6)
Lymphocyte count, G/L	60	1.0 (0.7-1.4)	60	1.1 (0.6-1.2)
Lymphocytes to neutrophils ratio	48	0.2 (0.1-0.3)	40	0.2 (0.1-0.3)
Hemoglobin, g/dL	62	12.8 (11.9-13.8)	65	12.3 (10.9-13.4)
Platelet count, g/L	62	230 (187-324)	65	226 (163-286)
ALT/SGPT, IU/L	57	40.0 (30.0-67.0)	62	35.0 (22.0-55.0)
AST/SGOT, IU/L	58	50.0 (34.0-66.0)	62	55.0 (36.0-74.0)
Albumin, g/L	43	30.0 (27.0-36.0)	42	32.2 (28.0-36.0)
Creatinine, µmol/L	61	71.0 (56.0-87.0)	64	75.0 (59.5-119.5)
Blood urea, mmol/L	62	5.8 (4.4-7.7)	65	5.1 (4.2-8.6)
Ferritin, mg/L	43	1292 (424-2484)	46	1070 (563-1790)
LDH, IU/L	46	401 (313-582)	51	434 (351-558)
CPK, IU/L	42	136.0 (48.0-284.0)	41	105.0 (67.0-236.0)

Figure 2. Occurrence of Primary Outcome Events During Follow-up



Kaplan-Meier cumulative estimates of probability of (A) the primary outcome, death or ventilation support (mechanical ventilation, high-flow or noninvasive ventilation); B, death or mechanical ventilation; (C) overall survival in the tocilizumab arm compared with the usual care arm. In panel A, events occurring on day 1 occurred on the same day as but after randomization. For the primary event and death or mechanical ventilation, data are analyzed in a bayesian framework, and median posterior HR and 90% credible intervals (CrIs) are presented, together with posterior probabilities of achieving specified effects, in the tables on the right. Overall survival was analyzed in a frequentist framework, so these probabilities were not relevant. HFO indicates high-flow oxygen; MV, mechanical ventilation; NIV, noninvasive ventilation.

EMPACTA

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

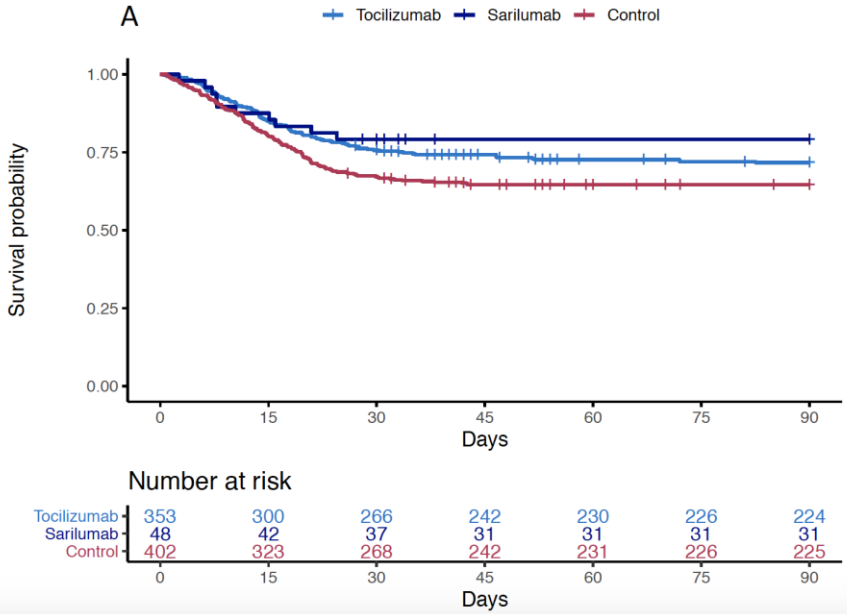
Carlos Salama, M.D., Jian Han, Ph.D., Linda Yau, Ph.D.,

Table 2. Primary and Key Secondary Efficacy Outcomes by Day 28 in the Modified Intention-to-Treat Population.*

Outcome	Tocilizumab (N=249)	Placebo (N=128)	Hazard Ratio (95% CI)	Weighted Difference (95% CI)	P Value†
Primary outcome: mechanical ventilation or death — % (95% CI)‡	12.0 (8.5 to 16.9)	19.3 (13.3 to 27.4)	0.56 (0.33 to 0.97)	NA	0.04
Secondary outcomes					
Median time to hospital discharge or readiness for discharge (95% CI) — days§	6.0 (6.0 to 7.0)	7.5 (7.0 to 9.0)	1.16 (0.91 to 1.48)	NA	
Median time to improvement in clinical status (95% CI) — days§¶	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.15 (0.90 to 1.48)	NA	
Median time to clinical failure (95% CI) — days§	NE	NE	0.55 (0.33 to 0.93)	NA	
Death — no. (% [95% CI])‖	26 (10.4 [7.2 to 14.9])	11 (8.6 [4.9 to 14.7])	NA	2.0 (–5.2 to 7.8)**	

N Engl J Med 2021;384:20-30.

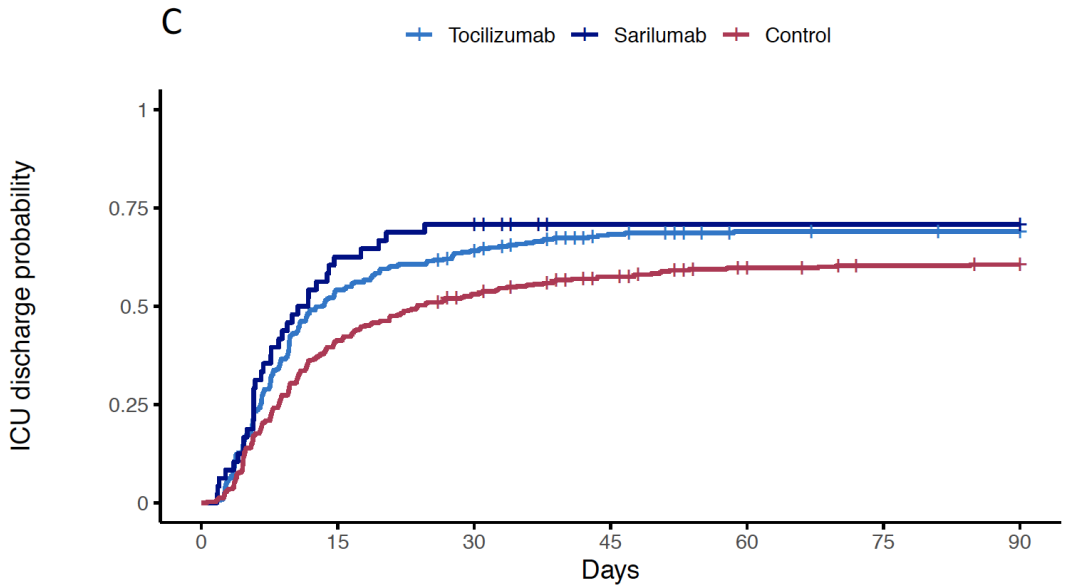
Figure 2



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

The REMAP-CAP Investigators

Figure 2



..and in prevention of cytokine storm?

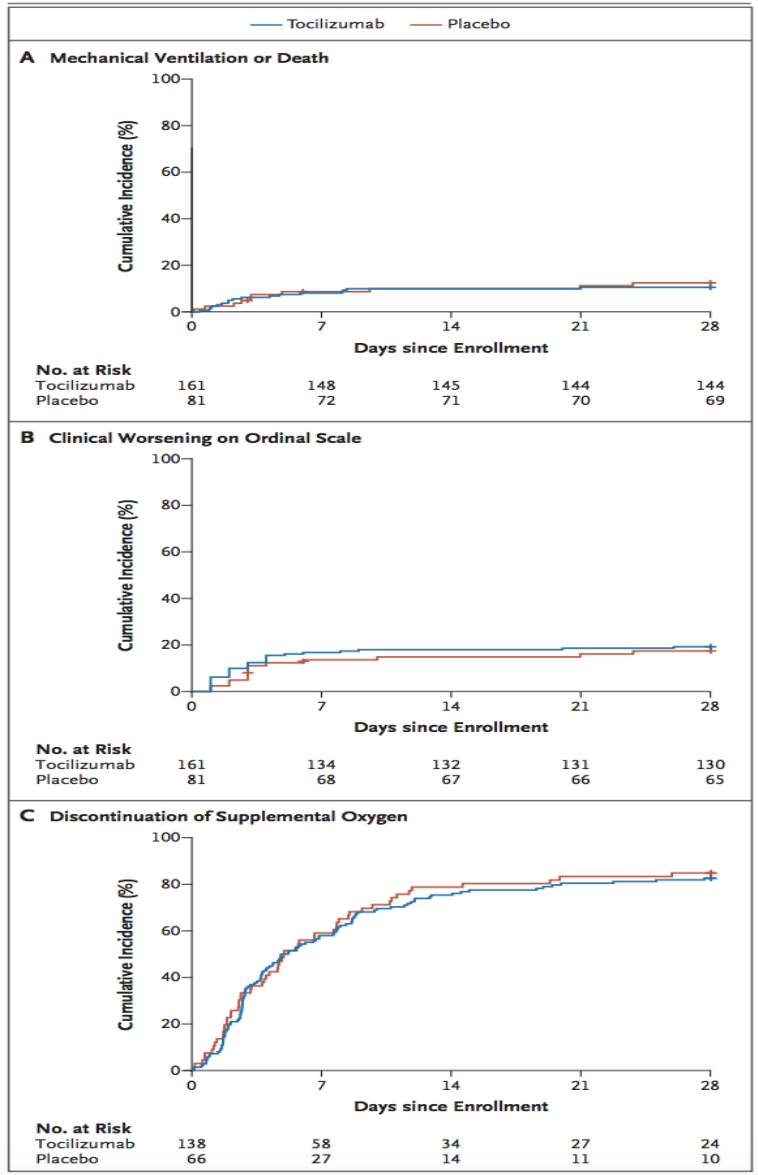
ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen,

Table 1. (Continued)

Characteristic	Tocilizumab (N=161)	Placebo (N=82)	All Patients (N=243)
Ordinal scale score — no. (%)§			
2	23 (14)	15 (18)	38 (16)
3	133 (83)	61 (74)	194 (80)
4	5 (3)	5 (6)	10 (4)
5	0	1 (1)	1 (<1)
Median laboratory values (IQR)¶			
Absolute lymphocyte count — cells/mm^3	1040 (700–1400)	1030 (680–1360)	1030 (700–1400)
C-reactive protein level — mg/liter	116.0 (67.1–190.6)	94.3 (58.4–142.0)	110.0 (64.9–175.3)
Ferritin level — ng/ml	723 (413–1212)	686 (382–1228)	708 (411–1225)
D-Dimer level — ng/ml	857 (536–1695)	980 (500–1739)	884 (527–1730)
Lactate dehydrogenase level — U/liter	351 (287–420)	324 (290–395)	340 (289–413)
Serum interleukin-6 level — pg/ml	23.6 (14.0–49.9)	25.4 (14.6–40.3)	24.4 (14.1–45.5)
Erythrocyte sedimentation rate — mm/hr	61 (42–90)	63 (42–87)	61 (42–88)
Troponin level — ng/liter	8 (6–22)	9 (6–24)	9 (6–22)
NT-proBNP level — pg/ml	110 (50–438)	93 (33–431)	108 (38–437)
Procalcitonin level — ng/ml	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.4)



Patients with a PaO2/FiO2 >250 mmHg

	Unadjusted and adjusted relative hazards of death	
	RH (95% CI)	**p-value**
RH of TCZ vs Soc		
Unadjusted	0.58 (0.29, 1.16)	0.126
Adjusted[1]	0.76 (0.38, 1.53)	0.439
Adjusted[2]	0.84 (0.38, 1.86)	0.672
Adjusted[3]	0.80 (0.40, 1.60)	0.524
Adjusted[4]	0.81 (0.40, 1.62)	0.548
Adjusted[5]	0.95 (0.42, 2.13)	0.896

[1]adjusted for age

[2]adjusted for age and Sofa Score

[3]adjusted for age and Charlston Index

[4]adjusted for sex, age and Charlston Index

[5]adjusted for sex, age, Sofa Score and wave

Patients with a PaO2/FiO2 >200 mmHg

	Unadjusted and adjusted relative hazards of death	
	RH (95% CI)	**p-value**
RH of TCZ vs Soc		
Unadjusted	0.16 (0.08, 0.33)	<.001
Adjusted[1]	0.21 (0.10, 0.42)	<.001
Adjusted[2]	0.19 (0.09, 0.41)	<.001
Adjusted[3]	0.19 (0.09, 0.40)	<.001
Adjusted[4]	0.19 (0.09, 0.38)	<.001
Adjusted[5]	0.17 (0.08, 0.37)	<.001

[1]adjusted for age

[2]adjusted for age and Sofa Score

[3]adjusted for age and Charlston Index

[4]adjusted for sex, age and Charlston Index

[5]adjusted for sex, age, Sofa Score and wave

The NEW ENGLAND JOURNAL of MEDICINE

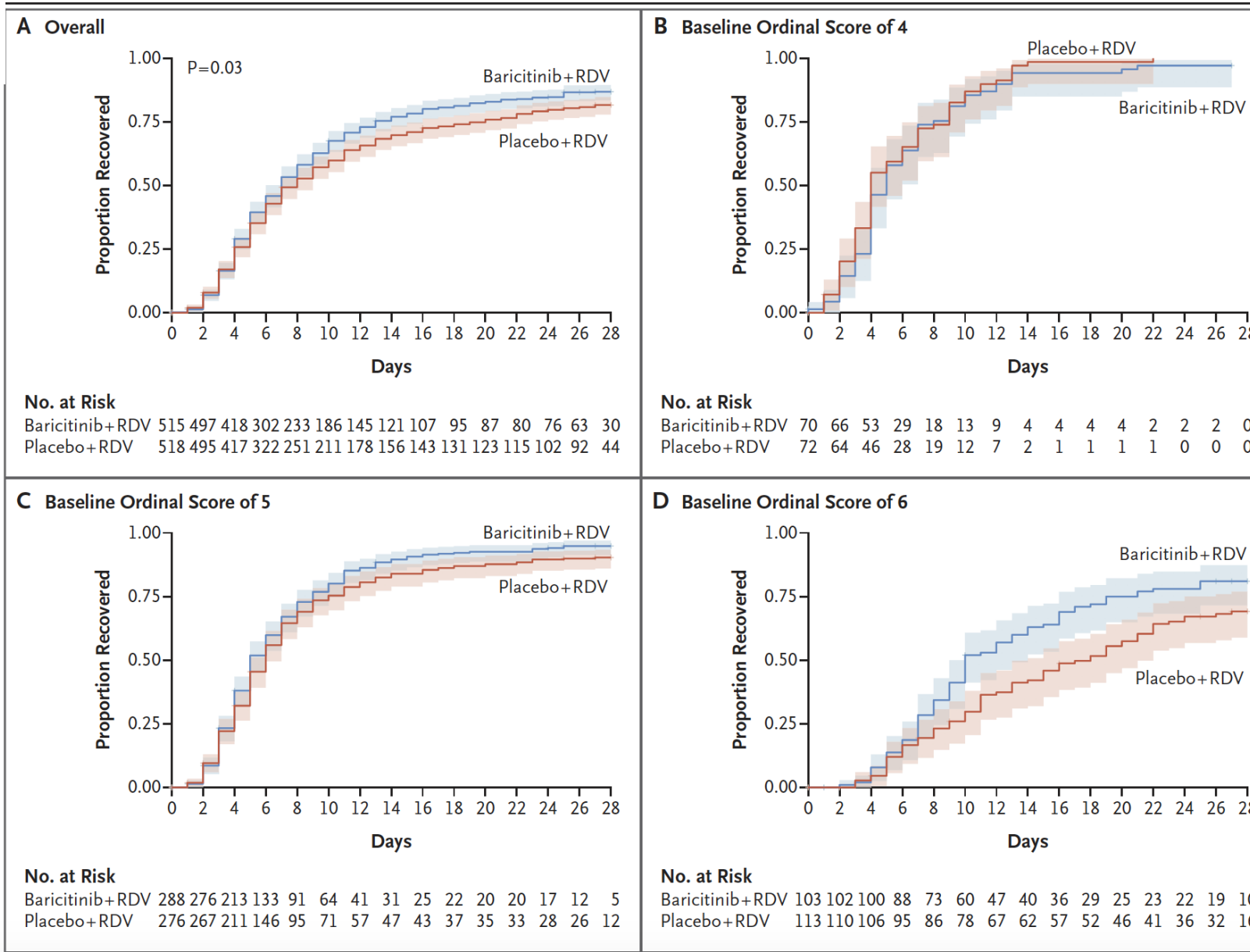
ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

This article was published on December 11, 2020, at NEJM.org.

MORTALITY

The Kaplan–Meier estimates of mortality at day 28 after randomization were 5.1% (95% CI, 3.5 to 7.6) in the combination group and 7.8% (95% CI, 5.7 to 10.6) in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). The greatest numerical differences in mortality between patients in the combination group and those in the control group were observed among those with a baseline ordinal score of 5 (1.9% vs. 4.7%; hazard ratio, 0.40; 95% CI, 0.14 to 1.14) or 6 (7.5% vs. 12.9%; hazard ratio, 0.55; 95% CI, 0.22 to 1.38). The Kaplan–Meier estimates of mortality at 14 days after randomization were 1.6% in the combination group and 3.0% in the control group (hazard ratio, 0.54; 95% CI, 0.23 to 1.28) (Table 2 and Fig. S2).



Conclusions

- Monoclonal antibodies active on the cytokine storm are probably the most promising drugs for severe COVID19 pneumonia, but for them and for glucocorticoids it is still to be determined in order to have an impact on mortality:

- The right patients
- The right dose
- The right moment in the course of the disease