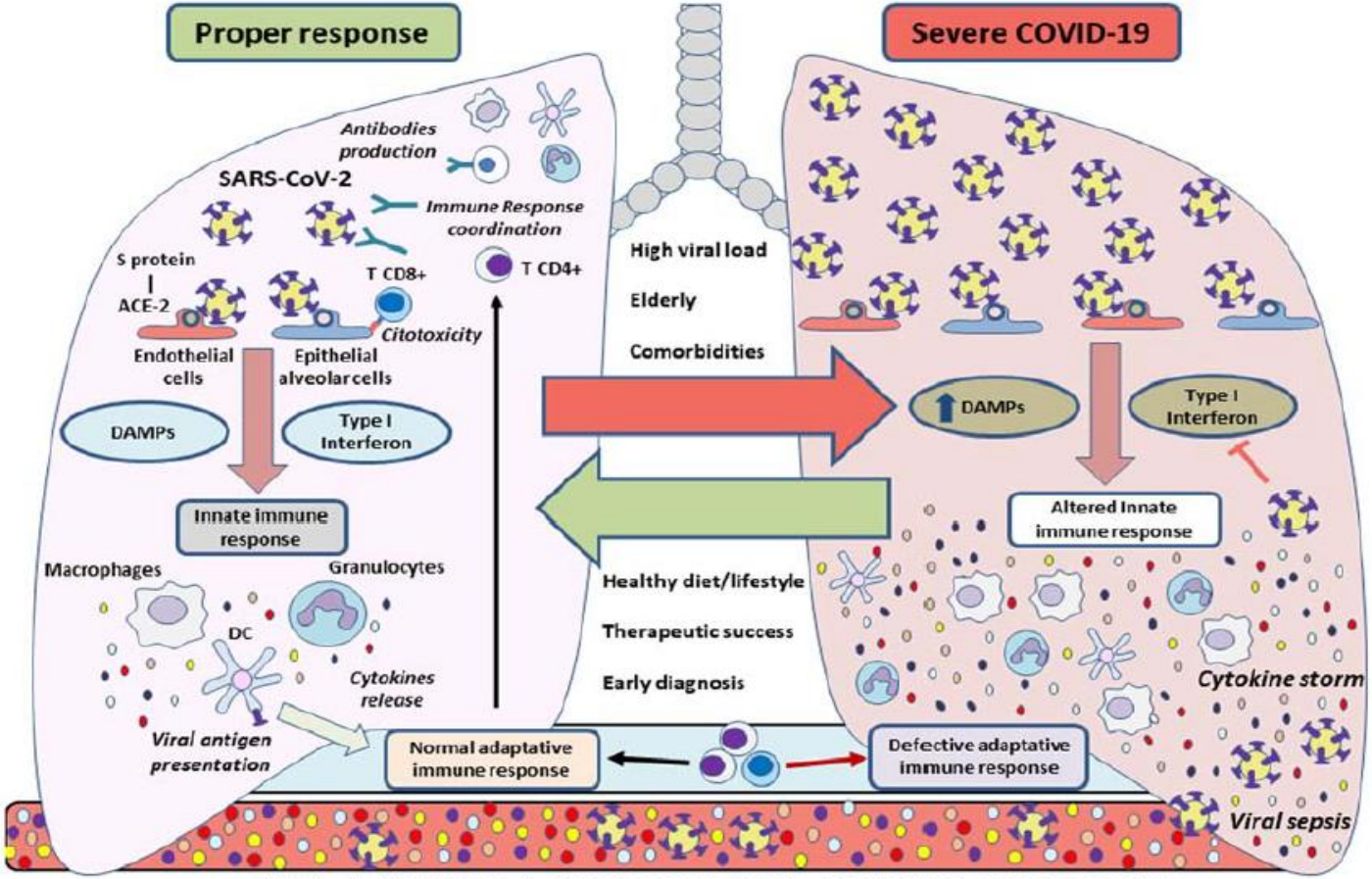
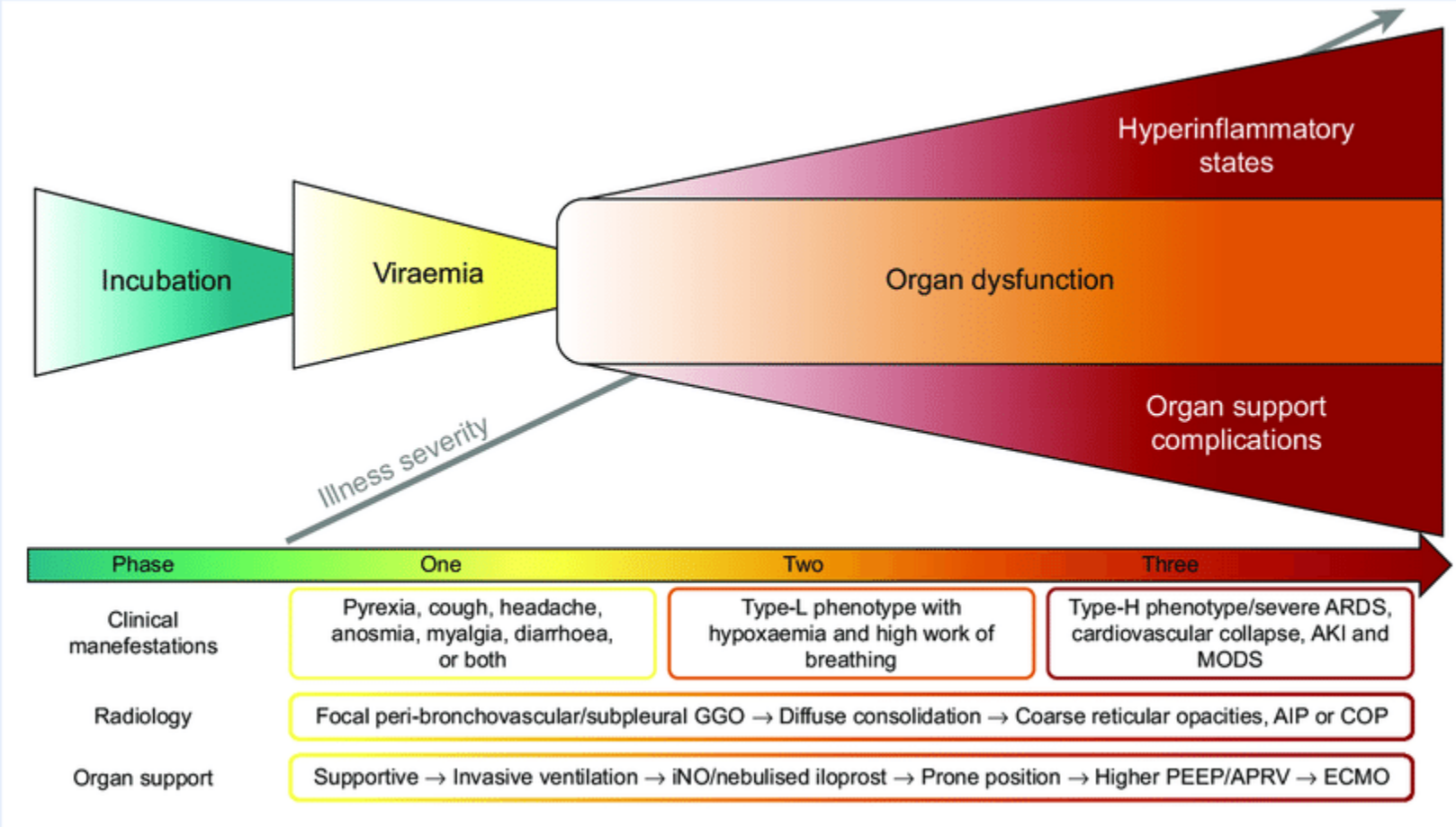
Quale ruolo oggi per i farmaci ad azione antinfiammatoria nel COVID-19

R. Parrella

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.

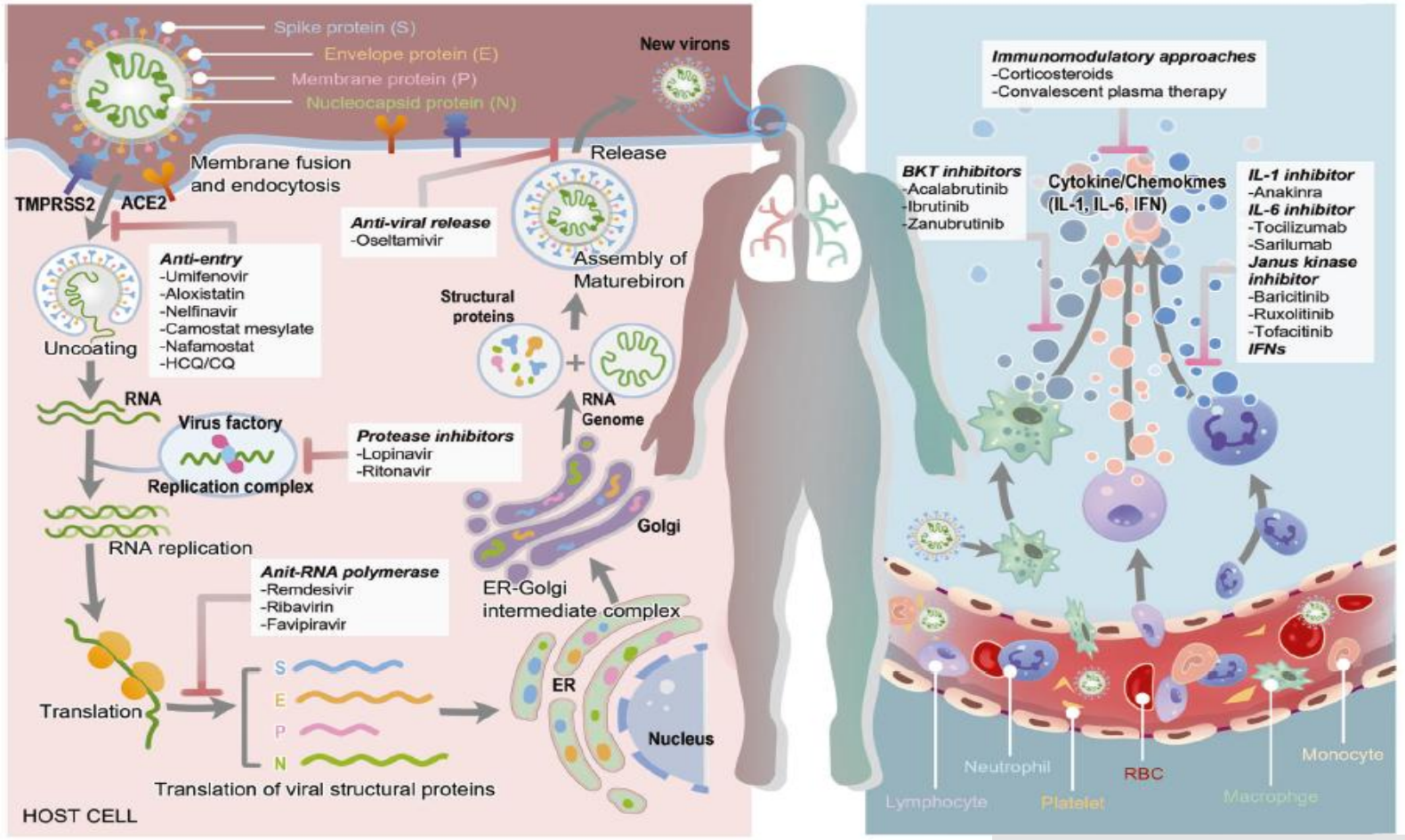
UOC Malattie infettive ad indirizzo respiratorio


Proper response
Severe COVID-19
Antibodies production
SARS-CoV-2
Immune Response coordination
S protein
ACE-2
T CD8+
T CD4+
Citotoxicity
Endothelial cells
Epithelial alveolar cells
DAMPs
Type I Interferon
Innate immune response
Macrophages
Granulocytes
DC
Cytokines release
Viral antigen presentation
High viral load
Elderly
Comorbidities
Healthy diet/lifestyle
Therapeutic success
Early diagnosis
DAMPs
Type I Interferon
Altered Innate immune response
Cytokine storm
Normal adaptative immune response
Defective adaptative immune response
Viral sepsis
High levels of IL-1β, IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-10, IFN-γ, MCP-1, MIP-1A, MIP-1B, G-CSF, TNF-α
SARS-CoV-2 dissemination


Incubation
Viraemia
Organ dysfunction
Hyperinflammatory states
Organ support complications
Illness severity
Phase
One
Two
Three
Clinical manefestations
Pyrexia, cough, headache, anosmia, myalgia, diarrhoea, or both
Type-L phenotype with hypoxaemia and high work of breathing
Type-H phenotype/severe ARDS, cardiovascular collapse, AKI and MODS
Radiology
Focal peri-bronchovascular/subpleural GGO → Diffuse consolidation → Coarse reticular opacities, AIP or COP
Organ support
Supportive → Invasive ventilation → iNO/nebulised iloprost → Prone position → Higher PEEP/APRV → ECMO

SARS-CoV2 invasion

Response of host immune system



Signal Transduction and Targeted Therapy (2021)6:317

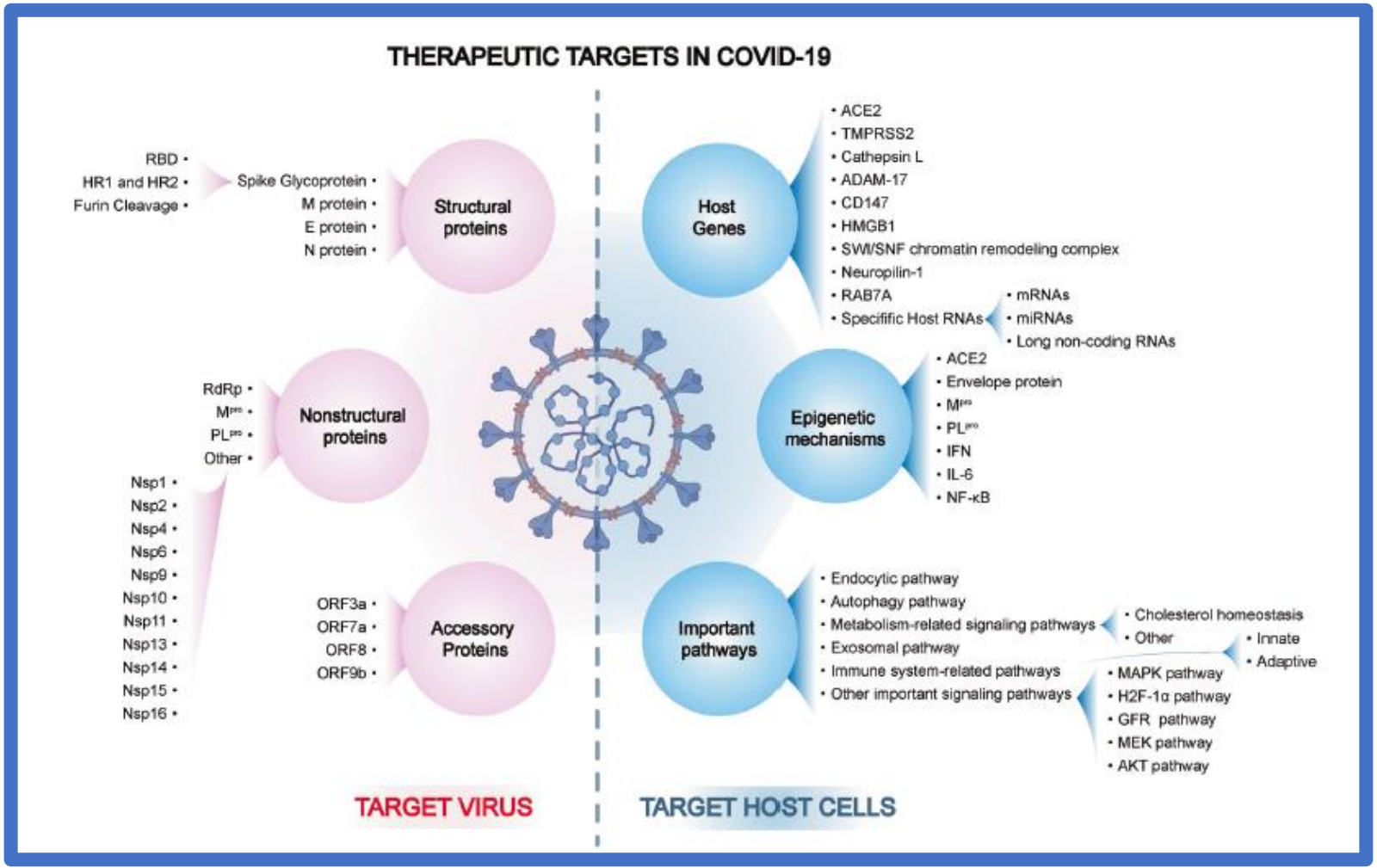

THERAPEUTIC TARGETS IN COVID-19
RBD
HR1 and HR2
Furin Cleavage
Spike Glycoprotein
M protein
E protein
N protein
Structural proteins
RdRp
Mpro
PLpro
Other
Nonstructural proteins
Nsp1
Nsp2
Nsp4
Nsp6
Nsp9
Nsp10
Nsp11
Nsp13
Nsp14
Nsp15
Nsp16
ORF3a
ORF7a
ORF8
ORF9b
Accessory Proteins
TARGET VIRUS
Host Genes
ACE2
TMPRSS2
Cathepsin L
ADAM-17
CD147
HMGB1
SWI/SNF chromatin remodeling complex
Neuropilin-1
RAB7A
Specific Host RNAs
mRNAs
miRNAs
Long non-coding RNAs
Epigenetic mechanisms
ACE2
Envelope protein
Mpro
PLpro
IFN
IL-6
NF-κB
Important pathways
Endocytic pathway
Autophagy pathway
Metabolism-related signaling pathways
Cholesterol homeostasis
Other
Exosomal pathway
Immune system-related pathways
Innate
Adaptive
Other important signaling pathways
MAPK pathway
H2F-1α pathway
GFR pathway
MEK pathway
AKT pathway
TARGET HOST CELLS

Table 2. Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection

Drug	Current use	Target	Potential target	Recommendation
Antivirus				
Antientry				
Umifenovir	Influenza	Prevents fusion of viral and membrane	Nsp7/Nsp8 complex, Nsp14, Nsp15, E-channel, or Spike	Not mentioned
Nelfinavir	HIV	Protease inhibitor	Spike (S) protein	
Aloxistatin	Nervous system disease	Cysteine protease inhibitor	Cathepsin L	
Camostat mesylate	Pancreatitis	Serine protease inhibitor	TMPRSS2	
Nafamostat	Nafamostat			
Chloroquine	Anti-malarial		ACE2, pH, PLpro	Recommend against
Hydroxychloroquine	Autoimmune diseases			
Antireplication				
Protease inhibitor				
lopinavir/ritonavir	HIV	Protease inhibitor	3CLpro	Recommend against (AI)
Darunavir/Cobicistat	HIV		Nsp3c, PLpro, E-channel, Spike proteins	
RNA polymerase inhibitors				
Remdesivir	Ebola virus	RNA-dependent RNA synthetase	Nsp3b, RdRp, E-channel, TMPRSS2	Recommends (BIIa)
Ribavirin	HCV, RSV		PLpro	Not mentioned
Favipiravir	Influenza virus		RdRp	
Anti-release				
Oseltamivir	Influenza A and B	Neuraminidase	3CLpro	Not mentioned
Immunomodulation				
Corticosteroids				
Dexamethasone	Allergic or autoimmune disease		Glucocorticoid receptor agonist	Different recommends in different situations
Anti-cytokine interventions				
Anakinra	Rheumatoid arthritis and cryopyrin-associated periodic syndromes	IL-1R		Neither recommend nor against
Tocilizumab	Rheumatoid arthritis	IL-6R		Recommend (BIIa)
Sarilumab				Not mentioned
Kinase inhibitors				
Janus kinase inhibitors				
Baricitinib	Rheumatoid arthritis	JAK1, JAK2, gp130		Recommend in combination with remdesivir if dexamethasone cannot be used (BIIa)
Ruxolitinib	Myelofibrosis	JAK1, JAK2		Recommend against
Tofacitinib	Psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis	JAK1, JAK3		
Bruton's tyrosine kinase inhibitors				
Acalabrutinib	B cell malignancies	BTK	Immune response of macrophage activation	Recommend against
Ibrutinib	B cell malignancies, chronic graft-vs.-host disease in recipients of stem cell transplantation			
Zanubrutinib	Mantle cell lymphoma			
IFNs	Cancers and hepatitis C			Recommend against
IVIG	Immunoglobulin deficiency, autoimmune diseases		SARS-CoV-2 neutralizing antibodies	Recommend against

Corticosteroids for COVID-19 ☆

Journal of Intensive Medicine 1 (2021) 14–25

Djillali Annane

Department of Intensive Care, Hôpital Raymond Poincaré (APHP), Laboratory of Infection & Inflammation – U1173, School of Medicine Simone Veil, University Versailles Saint Quentin – University Paris Saclay, INSERM, 104 boulevard Raymond Poincaré, Garches 92380, France

Mechanisms of action of corticosteroids relevant to COVID-19

Corticosteroids have pleiotropic effects resulting from complex molecular mechanisms including non-genomic and genomic effects [19]. We have recently summarized the molecular basis underlying the benefits of corticosteroids in severe infections [20]. Briefly, glucocorticoids exert anti-inflammatory by stimulating the synthesis and release of anti-inflammatory proteins and by inhibiting that of pro-inflammatory proteins. Glucocorticoids bind to the glucocorticoid receptor (GR) located in the cytoplasm of almost all cells. Upon binding with glucocorticoids, the GR dissociates from chaperone proteins heat-shock proteins 70 (Hsp70), Hsp90, and immunophilin [21]. Then, it enters into the nucleus to interact with specific DNA sequences (glucocorticoid responsive elements) of the regulatory region of target genes with subsequent chromatin remodeling [22,23]. Activated GR represses the expression of pro-inflammatory genes by inhibiting histone acetyltransferases and activating histone deacetylases. For instance, the expres-

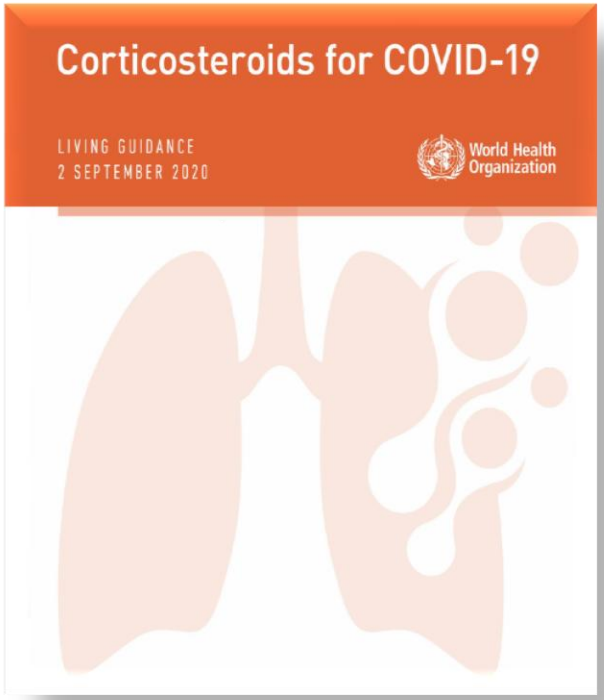
Glucocorticoids suppress the production of acute phase reactants and chemokines [30,31], thereby preventing leucocyte recruitment. They suppress the expression of endothelial-leukocyte adhesion molecule 1 (ELAM-1), intracellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1 (VCAM-1), opposing to leucocytes diapedesis [32,33]. Target cells for glucocorticoids include (1) myeloid cells: macrophages, monocytes, tissue resident, migratory and plasmacytoid dendritic cells (DC), and granulocytes; (2) lymphocytes: CD8, Th1, Th2 and Th17 as well as Treg and B cells [19,20]. Glucocorticoids repress the maturation, differentiation and proliferation of all subtypes of leucocytes. They reduce the number of monocytes/macrophages, of DC and of eosinophil and basophil granulocytes [34]. Glucocorticoids increase neutrophils released by the bone marrow and demargination, and increase DC release of the anti-inflammatory cytokines IL-10 and transforming growth factor β (TGF-β) [35]. They reduce the membrane expression of major-histocompatibility-complex (MHC) class II and Fc receptors [36,37] and suppress antigen presenting to T cells [38].

Glucocorticoids prevent B cell lymphocytes activation, proliferation and release of immunoglobulins [39]. They deplete thymic stroma cells and T cells by apoptosis [40,41].

AGENZIA ITALIANA DEL FARMACO

Corticosteroidi nella terapia dei pazienti adulti con COVID-19

Per quanto riguarda l'utilizzo per COVID-19, nelle fasi iniziali dell'epidemia, in assenza di prove affidabili da studi clinici randomizzati su larga scala, c'è stata una grande incertezza sull'efficacia dei corticosteroidi nel COVID-19 e molte linee guida sul trattamento COVID-19, tra cui quelle del WHO, dei National Institutes of Health (NIH, USA), dell'European Society of Intensive Care Medicine e Society of Critical Care Medicine (ESICM / SCCM), non ne hanno inizialmente raccomandato l'utilizzo di routine a meno che i pazienti non fossero in shock refrattario o fossero precedentemente in terapia con corticosteroidi cronici prima della diagnosi di COVID-19. Per i pazienti ventilati meccanicamente con COVID-19 e ARDS, le linee guida ESICM/SCCM suggerivano tuttavia che potessero essere usati i corticosteroidi.



Recommendation 1:

We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence).

Recommendation 2:

We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation, based on low certainty evidence).

This recommendation was achieved by consensus.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

N ENGL J MED 378;9 NEJM.ORG MARCH 1, 2018

APROCCHSS Trials

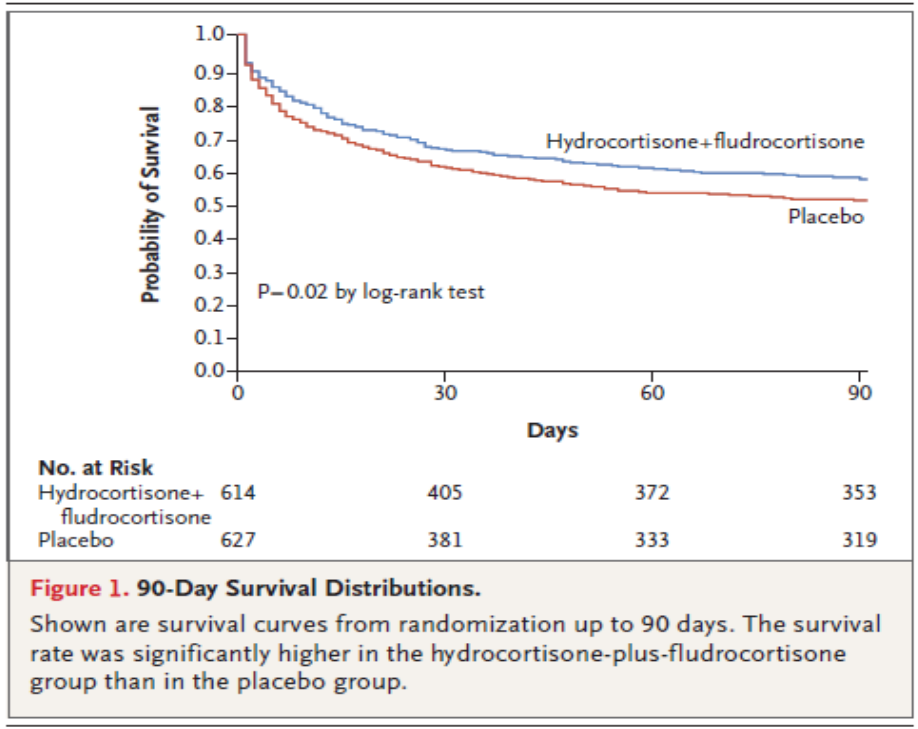


Figure 1. 90-Day Survival Distributions.

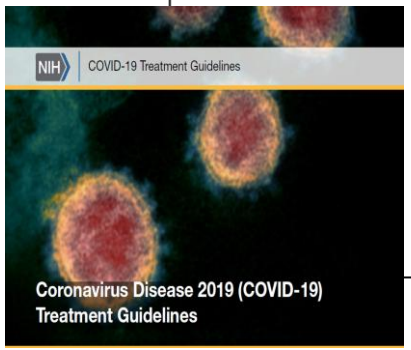
Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

CONCLUSIONS

In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom[1]		

Key Inclusion Criterion:
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion:
• Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study
Interventions:
• DEX 6 mg IV or PO once daily plus SOC for up to 10 days or until discharge (n = 2,104)
• SOC alone (n = 4,321)
Primary Endpoint:
• All-cause mortality at 28 days
	Participant Characteristics:
	• Mean age 66 years; 64% men
	• 56% had ≥1 comorbidity; 24% with diabetes
	• 89% with laboratory-confirmed SARS-CoV-2 infection
	• Median duration of DEX therapy: 7 days
	• At randomization: 16% received MV or ECMO, 60% required supplemental oxygen but not MV, 24% required no supplemental oxygen
	• Received RDV: <1% in each arm
	• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm
	Primary Outcome:
	• Mortality at 28 days
	  • All participants: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; P < 0.001).
	  • Participants who required MV or ECMO at randomization: 29% in DEX arm vs. 41% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81).
	  • Participants who required supplemental oxygen but not MV at randomization: 23% in DEX arm vs. 26% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94).
	  • Participants who did not require supplemental oxygen at randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.91–1.55).
		Key Limitations:
		• Open-label study
		• Published data did not include results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and key subgroups (e.g., patients with comorbidities)
		• Participants who required supplemental oxygen (but not MV) had variable severity. It is unclear whether all patients in this group benefited from DEX or whether benefit is restricted to those requiring higher levels of supplemental oxygen
		• Patients >80 years were preferentially assigned to supplemental oxygen therapy (and not MV)
		• High mortality of this patient population may limit generalizability of results to populations with a lower baseline mortality
		Interpretation:
		• In hospitalized patients with severe COVID-19 who required supplemental oxygen, DEX reduced mortality at 28 days, with greatest benefit in those with MV at randomization.
		• No survival benefit of DEX in patients who did not require supplemental oxygen at baseline.

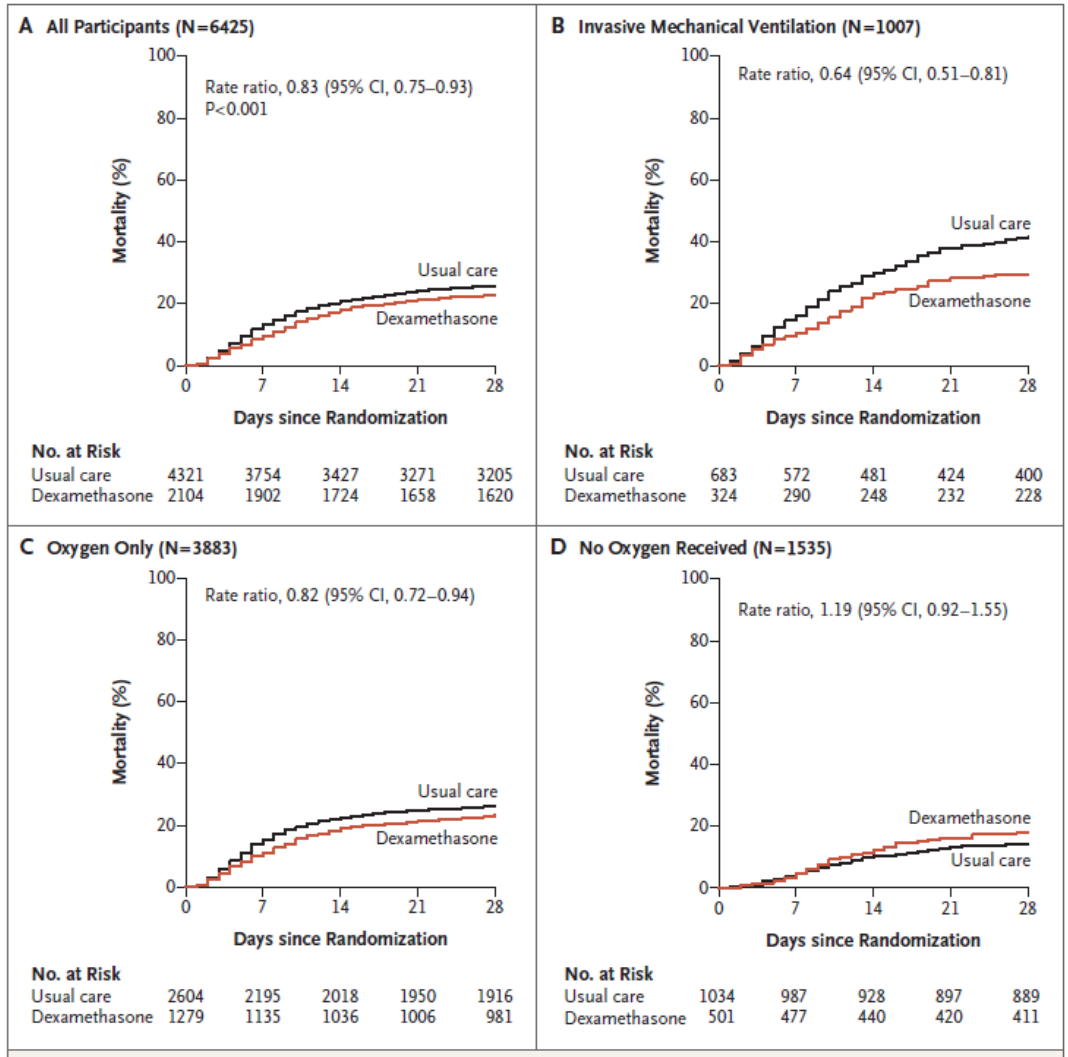


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*



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Dexamethasone in Hospitalized Patients with Covid-19

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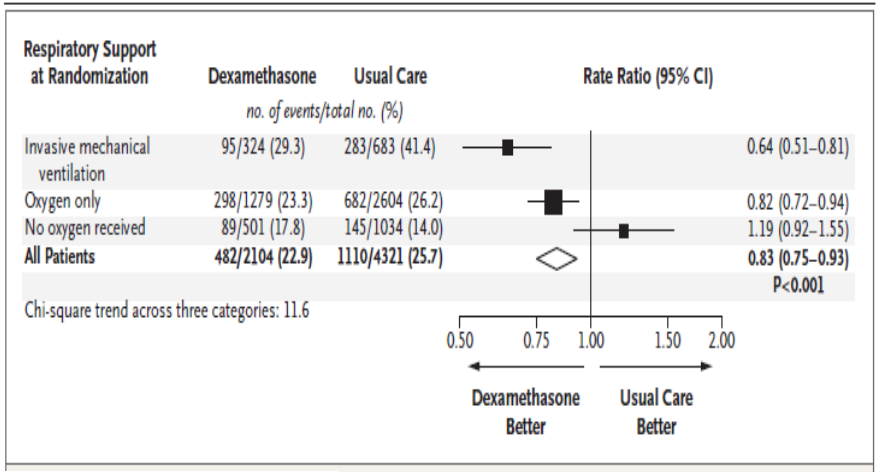


RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55).

Death

25,7 SOC % vs 22,9 % Dex

41,4 % SOC-MV vs 29.3 % Dex-MV

26,2 % SOC-O2 vs 23,3 % Dex-MV

Study Design	Methods	Results	Limitations and Interpretation
Metcovid: Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19[3]			
Double-blind, Phase 2b, RCT of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia in a single center in Brazil (n = 416)	**Key Inclusion Criteria:** • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO_2 ≤94% in room air *or* while using supplementary oxygen *or* under IMV **Key Exclusion Criteria:** • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure	**Number of Participants:** • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) **Participant Characteristics:** • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required IMV; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group	**Key Limitations:** • The median days from illness onset to randomization was longer than in other corticosteroid studies. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. **Interpretation:** • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.
METCOVID	**Interventions:** • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV **Primary Endpoint:** • Mortality by Day 28 **Secondary Endpoints:** • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups	**Primary Outcomes:** • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; $P = 0.63$). **Secondary Outcomes:** • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18). • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients ($P = 0.65$).	

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

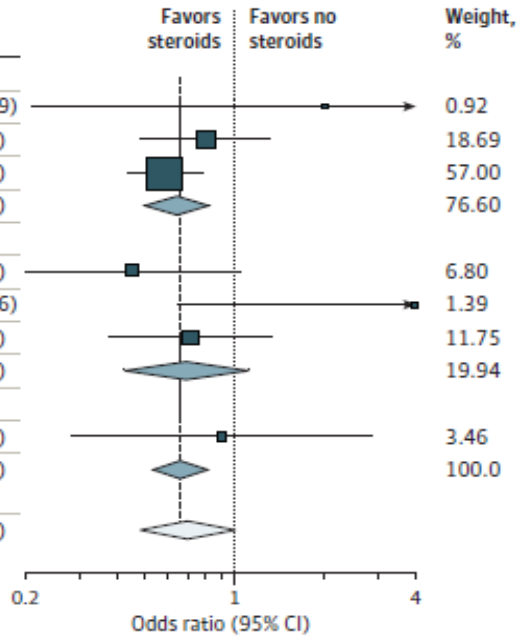
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

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

JAMA October 6, 2020 Volume 324, Number 13

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

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

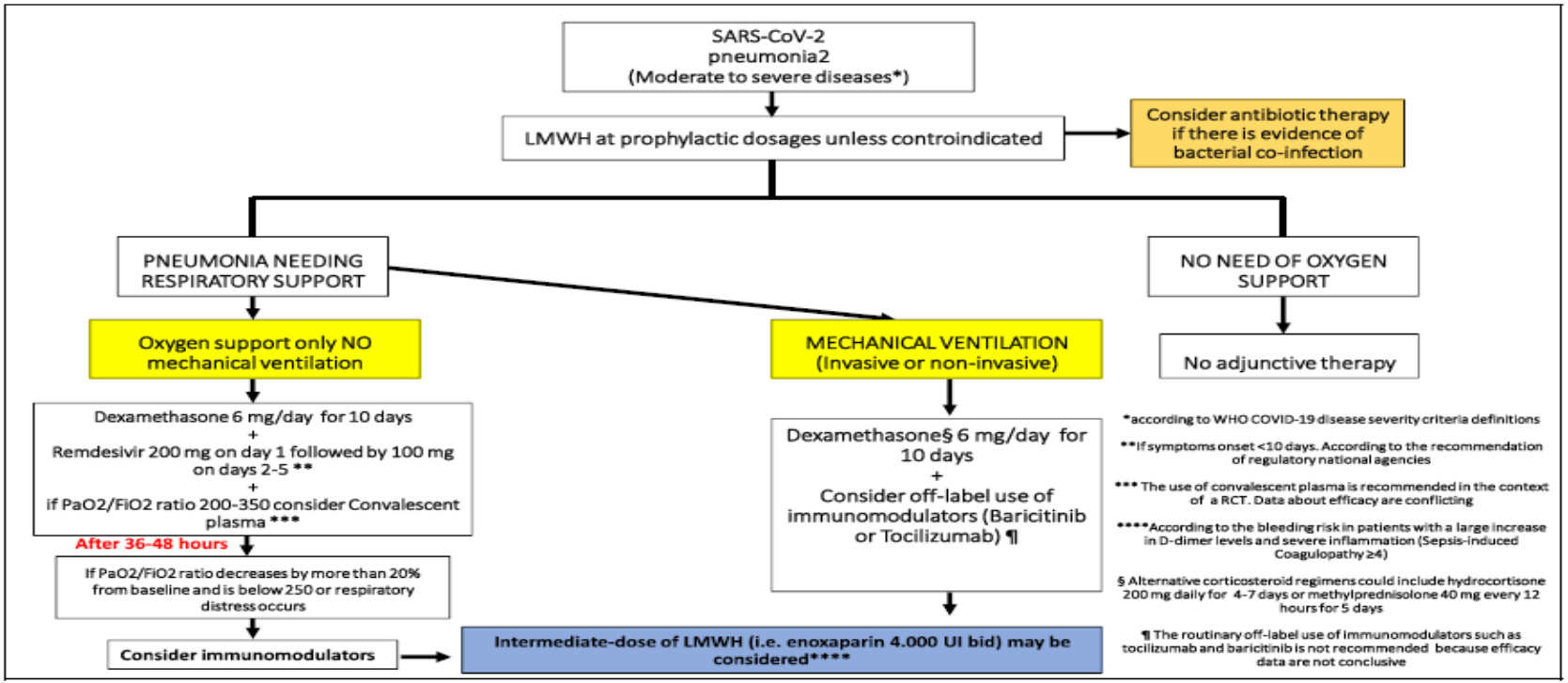


Clinical Microbiology and Infection 27 (2021) 389–395

Position paper

Therapeutic strategies for severe COVID-19: a position paper from the Italian Society of Infectious and Tropical Diseases (SIMIT)

Cristina Mussini [1, *], Marco Falcone [2], Silvia Nozza [3], Caterina Sagnelli [4], Roberto Parrella [5], Marianna Meschiari [1], Nicola Petrosillo [6], Claudio Mastroianni [7], Antonio Cascio [8], Chiara Iaria [9], Massimo Galli [10], Antonio Chirianni [11], Evangelista Sagnelli [11], Carmelo Iacobello [12], Giovanni Di Perri [13], Francesco Mazzotta [11], Giampiero Carosi [14], Marco Tinelli [15], Paolo Grossi [16], Orlando Armignacco [11], Vincenzo Portelli [11], Massimo Andreoni [17, 18], Marcello Tavio [19], for the Italian Society of Infectious and Tropical Diseases



Systemic Corticosteroids Other Than Dexamethasone

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous)[24] are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - *Long-acting corticosteroid:* Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - *Intermediate-acting corticosteroids:* Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in two divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in two to four divided doses daily.

IDSA
Infectious Diseases Society of America

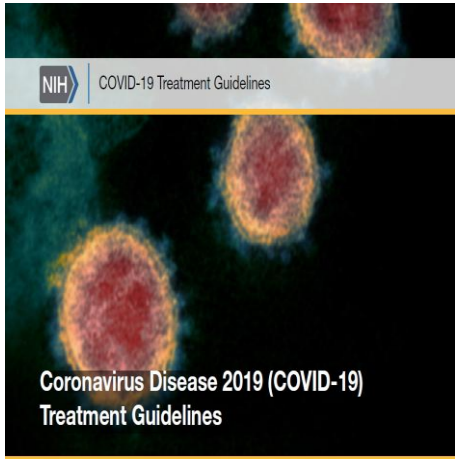
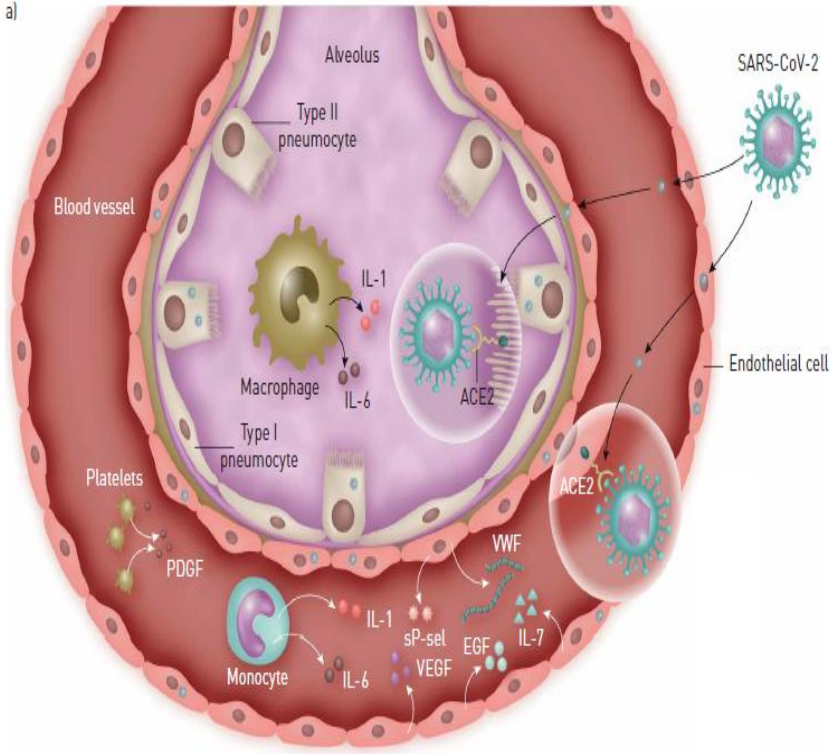


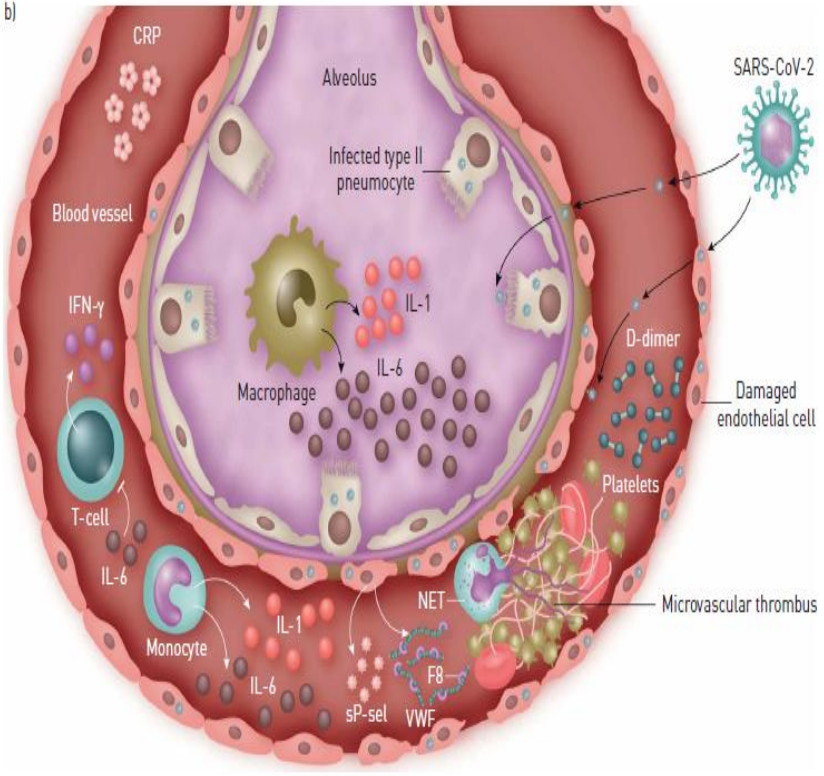
Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[f]) **(CIIa)**.	For nonpregnant patients with D-dimer For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[f] **(BIIa)** to 1 of the options above.[d,h]	contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

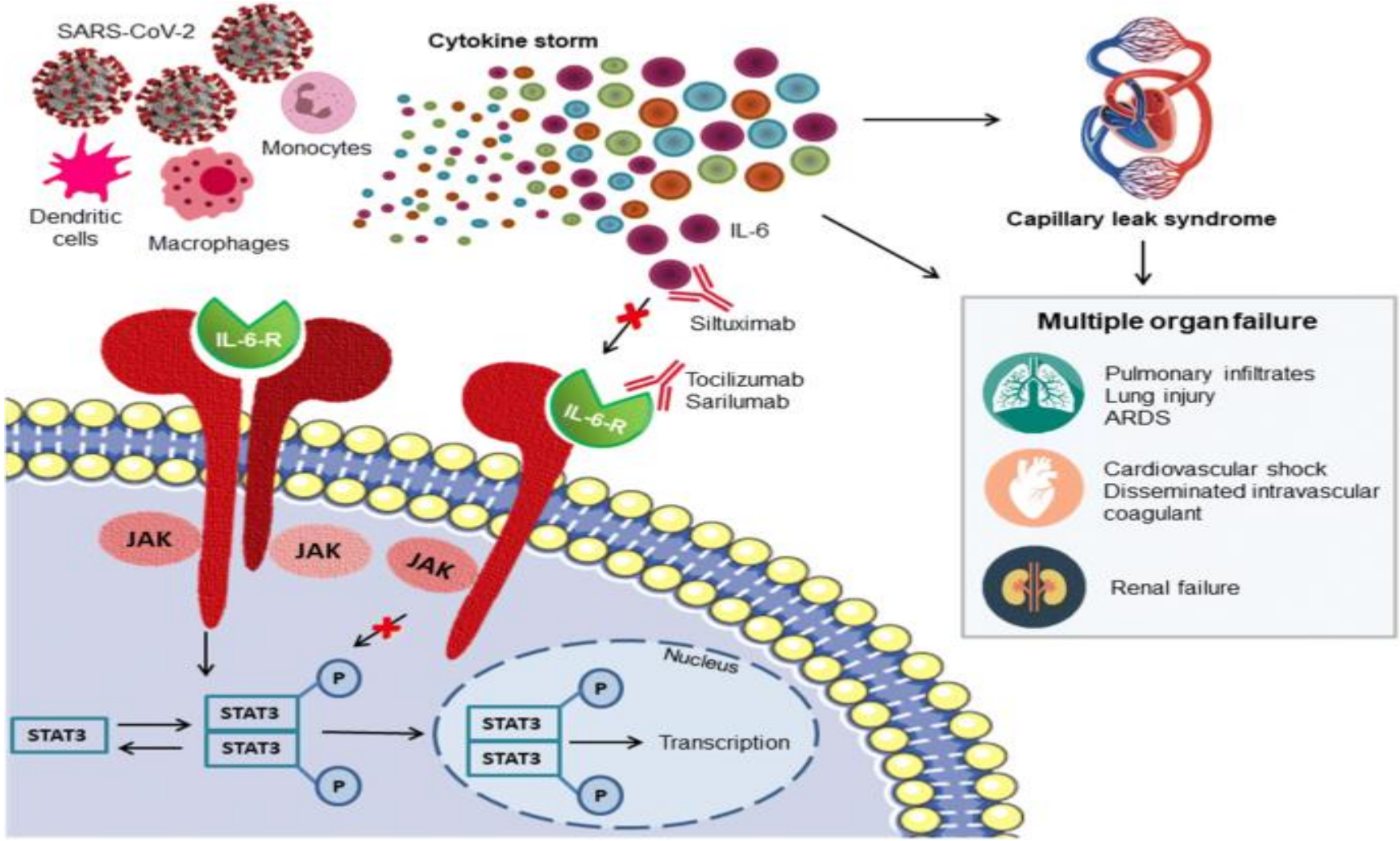
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion





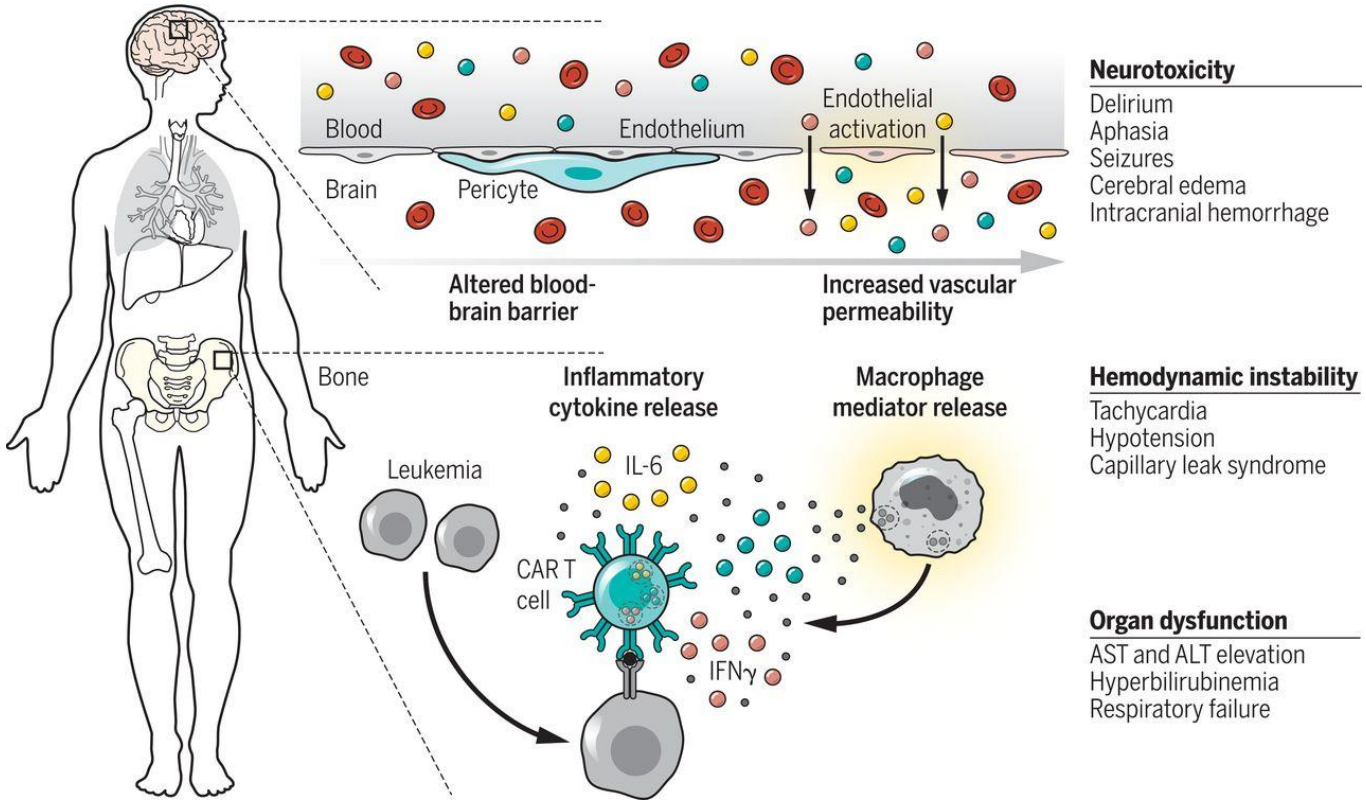
MILD DISEASE

SEVERE DISEASE


SARS-CoV-2
Monocytes
Dendritic cells
Macrophages
Cytokine storm
IL-6
Capillary leak syndrome
Siltuximab
Tocilizumab
Sarilumab
IL-6-R
IL-6-R
JAK
JAK
JAK
Nucleus
STAT3
STAT3
STAT3
STAT3
STAT3
P
P
P
P
Transcription
Multiple organ failure
Pulmonary infiltrates
Lung injury
ARDS
Cardiovascular shock
Disseminated intravascular coagulant
Renal failure

Cosa sappiamo…

Gli eventi avversi immuno-relati: CAR-T e sindrome da rilascio di citochine



Carl H. June et al. *Science* 2018;359:1361-1365

Trattamento

Non esistono trattamenti specifici per le infezioni causate dai coronavirus e non sono disponibili, al momento, vaccini per proteggersi dal virus.

Riguardo il nuovo coronavirus SARS-CoV-2, non esistono al momento terapie specifiche, vengono curati i sintomi della malattia (così detta terapia di supporto) in modo da favorire la guarigione, ad esempio fornendo supporto respiratorio.

Marzo 2020

Fu et al. J Transl Med (2020) 18:164
https://doi.org/10.1186/s12967-020-02339-3

Journal of Translational Medicine

COMMENTARY Open Access

Why tocilizumab could be an effective treatment for severe COVID-19?

Binqing Fu[1,2,3], Xiaoling Xu[3] and Haiming Wei[1,2,3*]

20/21 patients recovered from COVID-19 ARDS after a single dose of tocilizumab in 24-48 h

TOCIVID-19 Study design

Main inclusion criteria:
- Hospitalized due to clinical/instrumental diagnosis of pneumonia COVID-19
- Oxygen saturation at rest in ambient air ≤93%
- Intubated *less* than 24 hours before registration

Phase II

331 patients enrolled

Tocilizumab 8 mg/kg
(up to a maximum of 800mg per dose).

A second administration can be given after 12 hours**

FOLLOW UP

Primary endpoint:
- Lethality rate two weeks after registration in the ITT phase 2 population
- Lethality rate one month after registration in the ITT phase 2 population

Hypothesis:
P_0: two-week and 1-month lethality rates for the population defined by the selection criteria is around 20% and 35%, respectively .
P_1: the experimental drug may produce a 10% reduction of the lethality (from 20% to 10% at two weeks and from 35% to 25% at one month from registration in the study, P_1), 330 patients will provide 99% and 95% power, respectively, with a 2.5% bilateral alpha error for each test.

	Centri che hanno aderito e si sono iscritti	Centri che hanno arruolato almeno 1 paziente
NORD	**241**	**122**
Lombardia	94	52
Emilia-Romagna	40	25
Veneto	43	20
Piemonte	43	16
Liguria	8	4
Trentino Alto Adige	8	3
Friuli Venezia Giulia	4	2
Valle d'Aosta	1	0
CENTRO	**103**	**41**
Toscana	38	19
Lazio	32	12
Umbria	5	3
Marche	28	7
SUD ED ISOLE	**120**	**46**
Campania	38	15
Puglia	20	12
Sicilia	38	13
Abruzzo	8	4
Calabria	8	1
Sardegna	5	1
Molise	2	0
Basilicata	1	0
ITALIA	**464**	**209**

*** by clinical*

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Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial

Francesco Perrone[1*†], Maria Carmela Piccirillo[1†], Paolo Antonio Ascierto[2], Carlo Salvarani[3], Roberto Parrella[4], Anna Maria Marata[5], Patrizia Popoli[6], Laurenzia Ferraris[7], Massimiliano M. Marrocco-Trischitta[7], Diego Ripamonti[8], Francesca Binda[8], Paolo Bonfanti[9], Nicola Squillace[9], Francesco Castelli[10], Maria Lorenza Muiesan[10], Miriam Lichtner[11], Carlo Calzetti[12], Nicola Duccio Salerno[13], Luigi Atripaldi[4], Marco Cascella[14], Massimo Costantini[15], Giovanni Dolci[3], Nicola Cosmo Facciolongo[15], Fiorentino Fraganza[4], Marco Massari[15], Vincenzo Montesarchio[4], Cristina Mussini[16], Emanuele Alberto Negri[15], Gerardo Botti[1], Claudia Cardone[1], Piera Gargiulo[1], Adriano Gravina[1], Clorinda Schettino[1], Laura Arenare[1], Paolo Chiodini[17†] and Ciro Gallo[17†] on behalf of the TOCIVID-19 investigators, Italy

J Transl Med (2020) 18:405

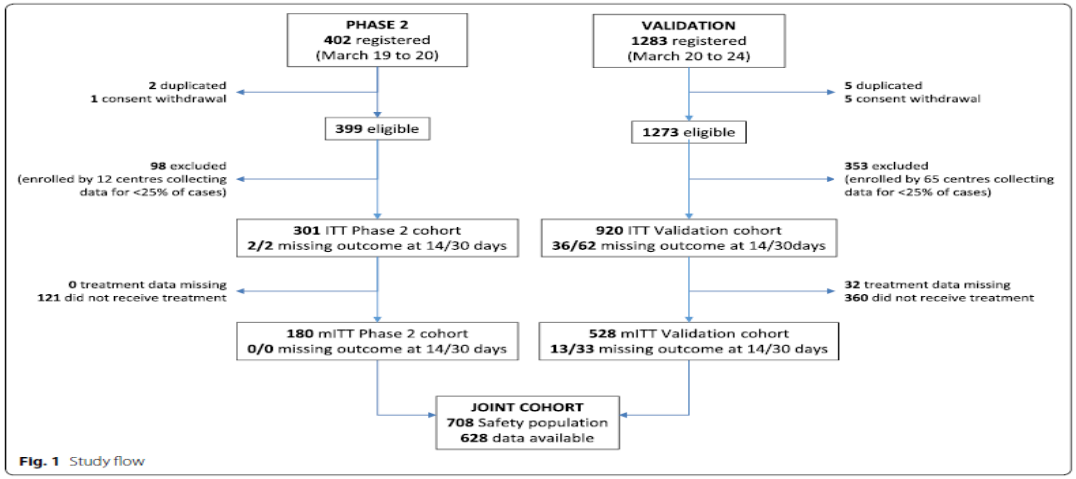


Fig. 1 Study flow

Methods: A multicenter, single-arm, hypothesis-driven trial was planned, according to a phase 2 design, to study the effect of tocilizumab on lethality rates at 14 and 30 days (co-primary endpoints, a priori expected rates being 20 and 35%, respectively). A further prospective cohort of patients, consecutively enrolled after the first cohort was accomplished, was used as a secondary validation dataset. The two cohorts were evaluated jointly in an exploratory multivariable logistic regression model to assess prognostic variables on survival.

Table 3 Efficacy analysis

	Phase 2	Validation
14 days intention-to-treat		
No. of events/no. of patients at risk	55/299	101/884
Lethality rate, % (97.5% CI)	18.4% (13.6–24.0)	11.4% (9.1–14.0)
P value (P0 = 20%)	0.52	< 0.001
14 days modified intention-to-treat		
No. of events/no. of patients at risk	28/180	56/515
Lethality rate, % (95% CI)	15.6% (10.6–21.7)	10.9% (8.3–13.9)
30 days intention-to-treat		
No. of events/No. of patients at risk	67/299	158/858
Lethality rate, % (97.5% CI)	22.4% (17.2–28.3)	18.4% (15.5–21.6)
P value (P0 = 35%)	< 0.001	< 0.001
Median time of death, days (IQR)	8 (4–14)	11 (4–18)
30 days modified intention-to-treat		
No. of events/no. of patients at risk	36/180	99/495
Lethality rate, % (95% CI)	20.0% (14.4–26.6)	20.0% (16.6–23.8)

Results: In the primary intention-to-treat (ITT) phase 2 population, 180/301 (59.8%) subjects received tocilizumab, and 67 deaths were observed overall. Lethality rates were equal to 18.4% (97.5% CI: 13.6–24.0, $P = 0.52$) and 22.4% (97.5% CI: 17.2–28.3, $P < 0.001$) at 14 and 30 days, respectively. Lethality rates were lower in the validation dataset, that included 920 patients. No signal of specific drug toxicity was reported. In the exploratory multivariable logistic regression analysis, older age and lower PaO2/FiO2 ratio negatively affected survival, while the concurrent use of steroids was associated with greater survival. A statistically significant interaction was found between tocilizumab and respiratory support, suggesting that tocilizumab might be more effective in patients not requiring mechanical respiratory support at baseline.

Perrone et al. J Transl Med (2020) 18:405
https://doi.org/10.1186/s12967-020-02573-9

Journal of
Translational Medicine

RESEARCH Open Access

Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial

Francesco Perrone[1*†], Maria Carmela Piccirillo[1†], Paolo Antonio Ascierto[2], Carlo Salvarani[3], Roberto Parrella[4], Anna Maria Marata[5], Patrizia Popoli[6], Laurenzia Ferraris[7], Massimiliano M. Marrocco-Trischitta[7], Diego Ripamonti[8], Francesca Binda[8], Paolo Bonfanti[9], Nicola Squillace[9], Francesco Castelli[10], Maria Lorenza Muiesan[10], Miriam Lichtner[11], Carlo Calzetti[12], Nicola Duccio Salerno[13], Luigi Atripaldi[4], Marco Cascella[14], Massimo Costantini[15], Giovanni Dolci[3], Nicola Cosimo Facciolongo[15], Fiorentino Fraganza[4], Marco Massari[15], Vincenzo Montesarchio[4], Cristina Mussini[16], Emanuele Alberto Negri[15], Gerardo Botti[1], Claudia Cardone[1], Piera Gargiulo[1], Adriano Gravina[1], Clorinda Schettino[1], Laura Arenare[1], Paolo Chiodini[17†] and Ciro Gallo[17†] on behalf of the TOCIVID-19 investigators, Italy

The primary analysis of the single-arm phase 2 TOCIVID-19 cohort suggests that tocilizumab may reduce lethality at 30 days, although its impact at 14 days seems less relevant. The adverse event profile is consistent with other reports and did not generate clinically relevant warnings, possibly because of the severity of clinical symptoms related to the underlying pathologic condition. [12, 13] Interestingly, the exploratory multivariable analysis showed that the possible effect of tocilizumab might be greater among patients not requiring mechanical ventilation and might be independent of the effect of corticosteroids, that were associated with lower

TOCIVID-19 also has some strengths. As mentioned above, it is the first academic trial promoted in Italy, the largest in terms of centers and patients (being available for the whole Italian territory), assessing a hard endpoint like mortality in a hypothesis-driven design, while off label use of the drug was increasing. [36] In addition, the internal validation, allowed by a companion prospective cohort, contributed to critical interpretation of the results. Further analyses will focus on secondary outcomes (e.g. respiratory outcomes, predictive and prognostic factors, epidemiology insights) and on a larger number of patients.

Conclusions

Although with limitations of a single-arm study, performed in an extremely challenging time and environment, the present study supports the use of tocilizumab, even when corticosteroids are used, while waiting for publication of phase 3 results.

Comunicato n. 598 13 maggio 2020

AGENZIA ITALIANA DEL FARMACO

STUDIO TOCIVID-19: RISULTATI INCORAGGIANTI ANCHE SE NON DEFINITIVI

Il contesto

Lo studio clinico non comparativo su tocilizumab è stato realizzato in condizioni di emergenza, in un contesto di elevate aspettative e assenza di trattamenti efficaci. Si tratta del primo studio approvato da AIFA nel corso della emergenza Covid19.

Per motivi etici si è deciso di rendere disponibile il trattamento per tutti i pazienti che a giudizio clinico ne potessero beneficiare nella prospettiva di avviare appena possibile anche studi comparativi randomizzati.

I risultati suggeriscono una moderata riduzione della mortalità. Lo studio sarà presto pubblicato su una rivista internazionale in modo da consentire una revisione approfondita da parte della comunità scientifica.

Risultati

Si tratta di risultati incoraggianti, anche se non possono essere ritenuti definitivi. Si è evidenziata una possibile moderata riduzione della mortalità nei pazienti trattati.

In particolare, a 14 giorni il tasso di letalità è risultato del 18.4% nell'analisi primaria considerando tutti i pazienti. Questi risultati non sono statisticamente significativi rispetto al 20% di letalità attesa definita a priori sulla base dei dati forniti dall'Istituto Superiore di Sanità. I risultati sono invece statisticamente significativi a 30 giorni, quando i valori di letalità sono del 22.4% in tutti i pazienti rispetto a una letalità ipotizzata a priori superiore al 30%.

Si attendono a questo punto i risultati degli studi randomizzati, attualmente in corso, a conferma e miglior definizione di questi possibili benefici.

Comunicato n. 600

17 giugno 2020

AGENZIA ITALIANA DEL FARMACO

COVID-19: STUDIO RANDOMIZZATO ITALIANO, NESSUN BENEFICIO DAL TOCILIZUMAB

Si è concluso anticipatamente, dopo l'arruolamento di 126 pazienti (un terzo della casistica prevista) lo studio randomizzato per valutare l'efficacia del tocilizumab, somministrato in fase precoce, nei confronti della terapia standard in pazienti affetti da polmonite da Covid-19 di recente insorgenza che richiedevano assistenza ospedaliera, ma non procedure di ventilazione meccanica invasiva o semi-invasiva.

Lo studio è stato promosso dall'Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia (Principal Investigators i professori Carlo Salvarani e Massimo Costantini) ed è stato condotto con la collaborazione di 24 centri.

Si tratta del primo studio randomizzato concluso a livello internazionale su tocilizumab, interamente realizzato in Italia.

Lo studio non ha mostrato alcun beneficio nei pazienti trattati né in termini di aggravamento (ingresso in terapia intensiva) né per quanto riguarda la sopravvivenza. In questa popolazione di pazienti in una fase meno avanzata di malattia lo studio può considerarsi importante e conclusivo, mentre in pazienti di maggiore gravità si attendono i risultati di altri studi tuttora in corso.

Dei 126 pazienti randomizzati, tre sono stati esclusi dalle analisi perché hanno ritirato il consenso. L'analisi dei 123 pazienti rimanenti ha evidenziato una percentuale simile di aggravamenti nelle prime due settimane nei pazienti randomizzati a ricevere tocilizumab e nei pazienti randomizzati a ricevere la terapia standard (28.3% vs. 27.0%). Nessuna differenza significativa è stata osservata nel numero totale di accessi alla Terapia Intensiva (10.0% verso il 7.9%) e nella mortalità a 30 giorni (3.3% vs. 3.2%).

Nell'ambito del trattamento dei pazienti con Covid-19, il tocilizumab si deve considerare quindi come un farmaco sperimentale, il cui uso deve essere limitato esclusivamente nell'ambito di studi clinici randomizzati.

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

A Randomized Clinical Trial

Carlo Salvarani, MD[1,2]; Giovanni Dolci, MD[3]; Marco Massari, MD[4]; et al

JAMA Intern Med. 2021;181(1):24-31. doi:10.1001/jamainternmed.2020.6615

Table 2. Clinical Outcomes in the Intention-to-Treat Population

Outcome	No. (%)		Rate ratio (95% CI)	*P* value
	Tocilizumab (n = 60)	Standard care (n = 63)		
Primary end point at 14 d				
Clinical worsening[a]	17 (28.3)	17 (27.0)	1.05 (0.59-1.86)	.87
Overall events at 14 d				
Admissions to ICU	6 (10.0)	5 (7.9)	1.26 (0.41-3.91)	
Deaths	1 (1.7)	1 (1.6)	1.05 (0.07-16.4)	
Discharges	34 (56.7)	36 (57.1)	0.99 (0.73-1.35)	
Overall events at 30 d				
Admissions to ICU	6 (10.0)	5 (7.9)	1.26 (0.41-3.91)	
Deaths	2 (3.3)	1 (1.6)	2.10 (0.20-22.6)	
Discharges	54 (90.0)	58 (92.1)	0.98 (0.87-1.09)	

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

N Engl J Med 2021;384:1503-16.
DOI: 10.1056/NEJMoa2028700

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

COVACTA ClinicalTrials.

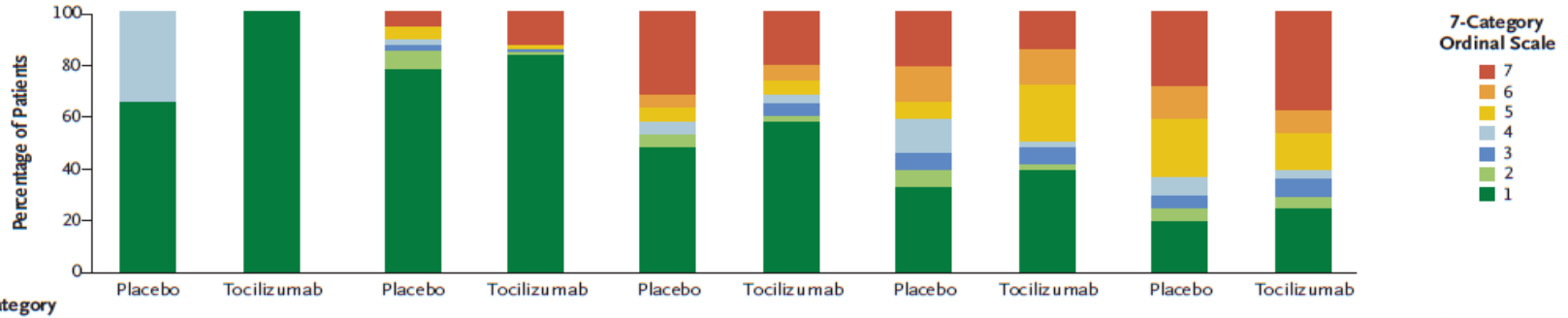
METHODS

In this phase 3 trial, we randomly assigned patients who were hospitalized with severe Covid-19 pneumonia in a 2:1 ratio receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight) or placebo. Approximately one quarter of the participants received a second dose of tocilizumab or placebo 8 to 24 hours after the first dose. The primary outcome was clinical status at day 28 on an ordinal scale ranging from 1 (discharged or ready for discharge) to 7 (death) in the modified intention-to-treat population, which included all the patients who had received at least one dose of tocilizumab or placebo.

RESULTS

Of the 452 patients who underwent randomization, 438 (294 in the tocilizumab group and 144 in the placebo group) were included in the primary and secondary analyses. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% confidence interval [CI], 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI, 1.0 to 4.0) in the placebo group (between-group difference, −1.0; 95% CI, −2.5 to 0; P=0.31 by the van Elteren test). In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points; 95% CI, −7.6 to 8.2; nominal P=0.94).

C 7-Category Ordinal Scale at Day 28



Ordinal Category at Baseline	2		3		4		5		6		All Categories	
Ordinal Category	Placebo (N=6)	Tocilizumab (N=9)	Placebo (N=44)	Tocilizumab (N=78)	Placebo (N=39)	Tocilizumab (N=94)	Placebo (N=15)	Tocilizumab (N=45)	Placebo (N=40)	Tocilizumab (N=68)	Placebo (N=144)	Tocilizumab (N=294)
						no. (%)						
7	0	0	2 (4.5)	9 (11.5)	12 (30.8)	18 (19.1)	3 (20.0)	6 (13.3)	11 (27.5)	25 (36.8)	28 (19.4)	58 (19.7)
6	0	0	0	0	2 (5.1)	6 (6.4)	2 (13.3)	6 (13.3)	5 (12.5)	6 (8.8)	9 (6.3)	18 (6.1)
5	0	0	2 (4.5)	1 (1.3)	2 (5.1)	5 (5.3)	1 (6.7)	10 (22.2)	9 (22.5)	10 (14.7)	14 (9.7)	26 (8.8)
4	2 (33.3)	0	1 (2.3)	0	2 (5.1)	3 (3.2)	2 (13.3)	1 (2.2)	3 (7.5)	2 (2.9)	10 (6.9)	6 (2.0)
3	0	0	1 (2.3)	1 (1.3)	0	5 (5.3)	1 (6.7)	3 (6.7)	2 (5.0)	5 (7.4)	4 (2.8)	14 (4.8)
2	0	0	3 (6.8)	1 (1.3)	2 (5.1)	1 (1.1)	1 (6.7)	1 (2.2)	2 (5.0)	3 (4.4)	8 (5.6)	6 (2.0)
1	4 (66.7)	9 (100)	35 (79.6)	66 (84.6)	19 (48.7)	56 (59.6)	5 (33.3)	18 (40.0)	8 (20.0)	17 (25.0)	71 (49.3)	166 (56.5)
Median (95% CI)	1.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	2.0 (1.0 to 6.0)	1.0 (1.0 to 2.0)	4.0 (1.0 to 6.0)	4.0 (1.0 to 5.0)	5.0 (4.0 to 6.0)	5.0 (4.0 to 6.0)	2.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)
Difference in Medians (95% CI)	0.0 (−3.0 to 0.0)		0.0 (0.0 to 0.0)		−1.0 (−5.0 to 0.0)		0.0 (−3.5 to 4.0)		0.0 (−1.0 to 1.5)		−1.0 (−2.5 to 0.0)	

CONCLUSIONS

In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days. (Funded by F. Hoffmann–La Roche and the Department of Health and Human Services; COVACTA ClinicalTrials.gov number, NCT04320615.)

Characteristic	Tocilizumab (N=294)	Placebo (N=144)
No. of patients with data	107	51
Mean no.	5.1±5.5	4.3±4.5
Median (range)	3.0 (0.0–28.0)	3.0 (0.0–20.0)
Symptoms at diagnosis — no. (%)		
Fever	193 (65.6)	98 (68.1)
Cough	216 (73.5)	102 (70.8)
Shortness of breath	213 (72.4)	93 (64.6)
Gastrointestinal	96 (32.7)	41 (28.5)
Headache	37 (12.6)	21 (14.6)
Fatigue	91 (31.0)	44 (30.6)
Coexisting illness — no. (%)††		
≥1 Diagnosis	231 (78.6)	124 (86.1)
Obesity	63 (21.4)	27 (18.8)
Diabetes	105 (35.7)	62 (43.1)
Cardiovascular impairment	88 (29.9)	35 (24.3)
Hypertension	178 (60.5)	94 (65.3)
Hepatic impairment	6 (2.0)	2 (1.4)
Chronic lung disease	49 (16.7)	22 (15.3)
No. of days from onset of Covid-19 symptoms		
No. of patients with data	291	143
Mean no.	12.1±6.6	11.4±6.9
Median (range)	11.0 (1.0–49.0)	10.0 (2.0–50.0)
Other treatments — no. (%)‡‡		
Glucocorticoids	57 (19.4)	41 (28.5)
Antiviral drugs	71 (24.1)	42 (29.2)
Convalescent plasma	5 (1.7)	1 (0.7)

glucocorticoids. More patients in the placebo group than in the tocilizumab group received concomitant glucocorticoids; however, this imbalance is unlikely to have obscured a significant treatment effect because mortality was similar in the two trial groups regardless of glucocorticoid use and was higher in patients who received glucocorticoids than in those who did not in each group (Table S10). In addition, it is possible that worsening clinical status among patients in the placebo group could have led to increased glucocorticoid use and more frequent administration of a second dose of placebo. Patients who received a second dose of either tocilizumab or placebo generally had worse outcomes (Fig. S7), which may reflect a selection bias, because only patients whose condition did not improve after the first dose could be considered for a second dose. The administration of

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

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

The REMAP-CAP Investigators*

REMAP-CAP

METHODS

We evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death (assigned a value of –1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with predefined criteria for superiority, efficacy, equivalence, or futility. An odds ratio greater than 1 represented improved survival, more organ support–free days, or both.

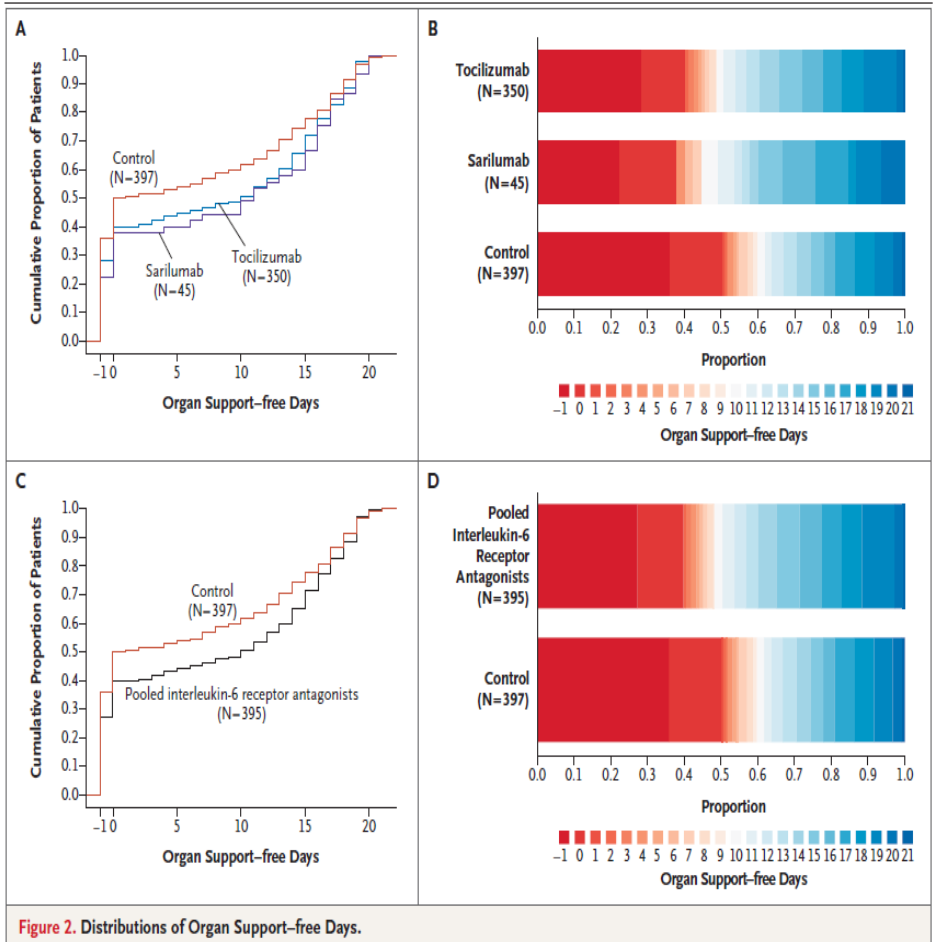


Figure 2. Distributions of Organ Support–free Days.

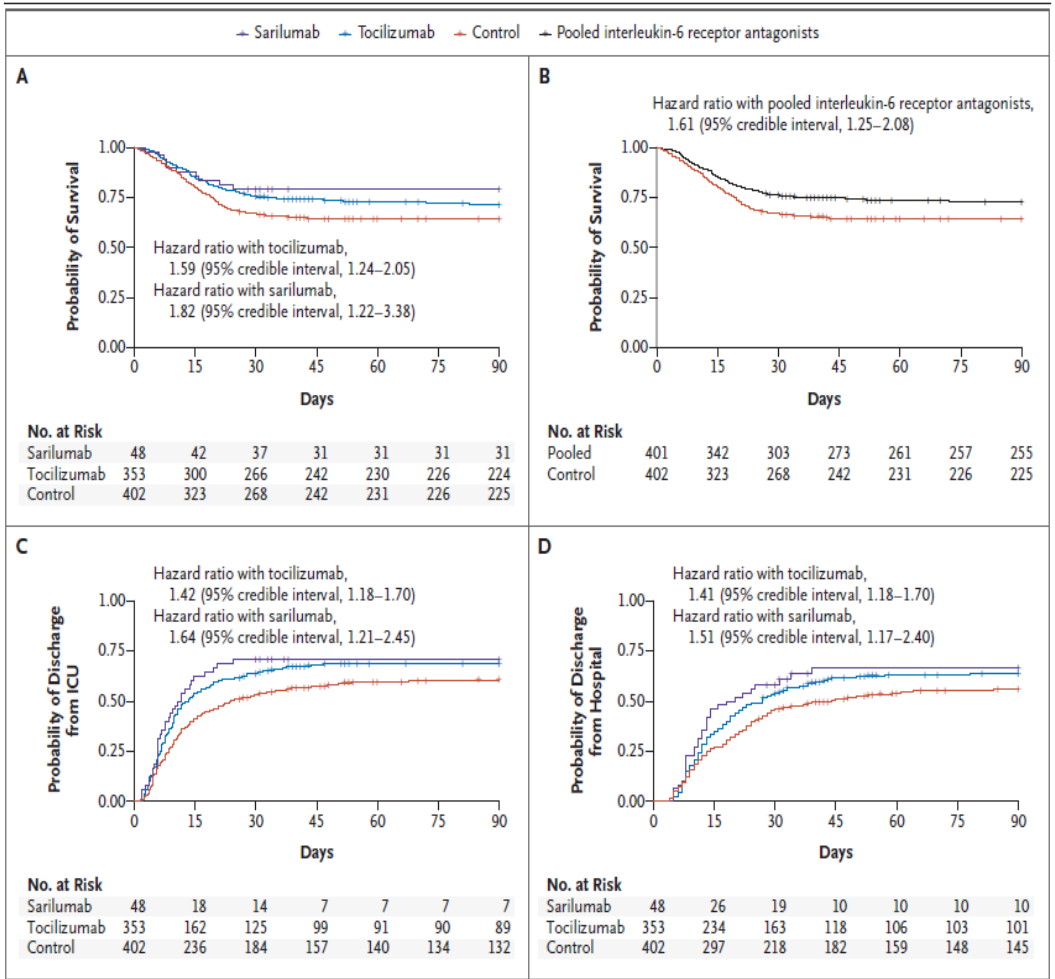


Figure 3. Time-to-Event Analyses.

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ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

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

The REMAP-CAP Investigators*

In critically ill adult patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival.

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*

Lancet Rheumatol 2020; 2: e474–84

Methods This retrospective, observational cohort study included adults (≥18 years) with severe COVID-19 pneumonia who were admitted to tertiary care centres in Bologna and Reggio Emilia, Italy, between Feb 21 and March 24, 2020, and a tertiary care centre in Modena, Italy, between Feb 21 and April 30, 2020. All patients were treated with the standard of care (ie, supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin), and a non-randomly selected subset of patients also received tocilizumab. Tocilizumab was given either intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (ie, 324 mg in total), when the intravenous formulation was unavailable. The primary endpoint was a composite of invasive mechanical ventilation or death. Treatment groups were compared using Kaplan-Meier curves and Cox regression analysis after adjusting for sex, age, recruiting centre, duration of symptoms, and baseline Sequential Organ Failure Assessment (SOFA) score.

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

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

EMPACTA ClinicalTrials.

N Engl J Med 2021;384:20-30.
DOI: 10.1056/NEJMoa2030340

METHODS

NO VM

TRIAL DESIGN AND OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the safety and efficacy of tocilizumab in hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation. Global trial sites

METHODS

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

Table 1. Characteristics of the Patients at Baseline in the Modified Intention-to-Treat Population.*

Characteristic	Tocilizumab (N=249)	Placebo (N=128)	All Patients (N=377)
Male sex — no. (%)	150 (60.2)	73 (57.0)	223 (59.2)
Age			
Mean — yr	56.0±14.3	55.6±14.9	55.9±14.4
Distribution — no. (%)			
≤60 yr	151 (60.6)	76 (59.4)	227 (60.2)
>60 yr	98 (39.4)	52 (40.6)	150 (39.8)
BMI†	32.0±7.9	33.1±7.2	32.4±7.6
Race or ethnic group — no. (%)‡			
Hispanic or Latino	143 (57.4)	68 (53.1)	211 (56.0)
American Indian or Alaska Native	33 (13.3)	15 (11.7)	48 (12.7)
Black	35 (14.1)	21 (16.4)	56 (14.9)
Non-Hispanic White	28 (11.2)	20 (15.6)	48 (12.7)
Unknown or other	10 (4.0)	4 (3.1)	14 (3.7)
Country group — no. (%)			
United States	201 (80.7)	103 (80.5)	304 (80.6)
Mexico, Kenya, South Africa, Peru, and Brazil	48 (19.3)	25 (19.5)	73 (19.4)
Category on seven-category ordinal scale for clinical status — no. (%)§			
2	24 (9.6)	11 (8.6)	35 (9.3)
3	161 (64.7)	81 (63.3)	242 (64.2)
4	64 (25.7)	36 (28.1)	100 (26.5)
Median laboratory values (range)			
C-reactive protein level — mg/liter	124.50 (2.5–2099.0)	143.40 (9.0–3776.0)	136.10 (2.5–3776.0)
D-Dimer level — μg/ml FEU	1.60 (0.2–8873.0)	1.21 (0.2–10,384.0)	1.50 (0.2–10,384.0)
Ferritin level — pmol/liter	1401.34 (29.2–38,482.1)	1353.14 (110.1–122,328.9)	1395.39 (29.2–122,328.9

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

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

TOCI + SOC
-44% MV or Death

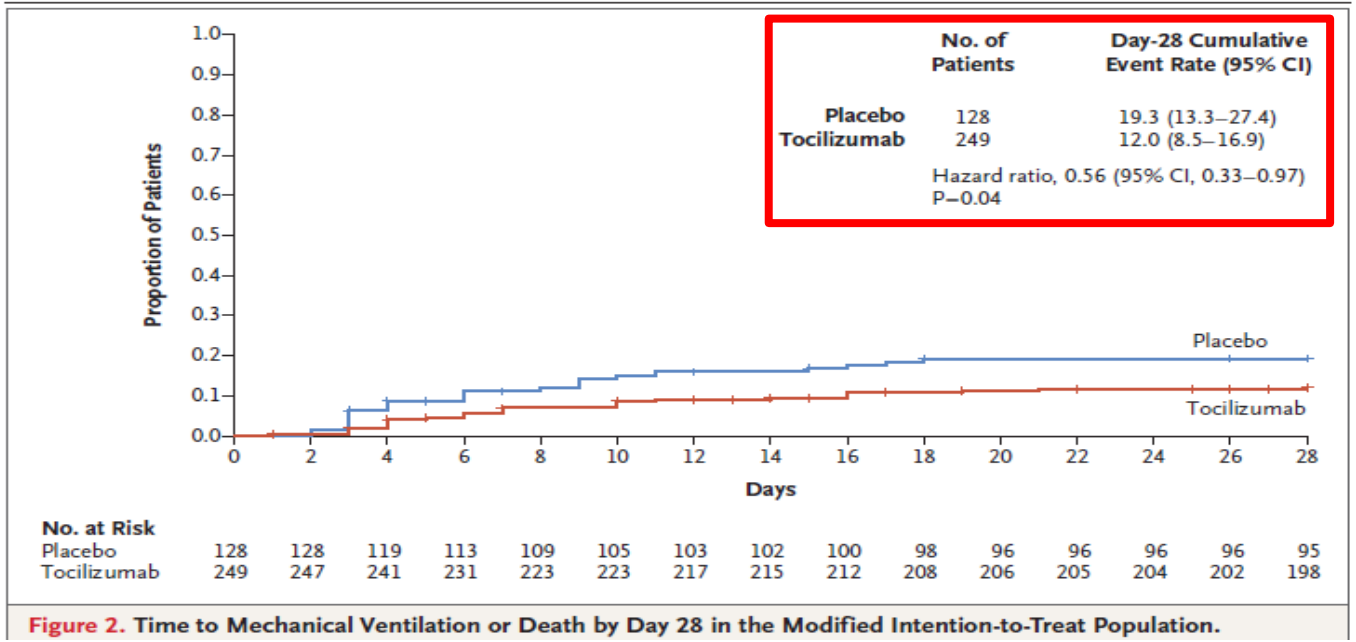


Figure 2. Time to Mechanical Ventilation or Death by Day 28 in the Modified Intention-to-Treat Population.

Our trial showed that tocilizumab plus standard care was more efficacious than placebo plus standard care in reducing the likelihood of the composite outcome of progression to mechanical ventilation or death among hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation; however, there was no difference in the incidence of death from any cause. This reduction in risk was observed in a group of patients that included underserved populations that are often underrepresented in clinical research. The results of the primary analysis according to race or ethnic group were consistent with the results in the modified intention-to-treat population.


Throw the baby out
with the bathwater

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

Lancet 2021; 397: 1637–45

RECOVERY Collaborative Group*

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg–800 mg (depending on weight) given intravenously. A second dose could be given 12–24 h later if the patient's condition had not improved. The primary outcome was 28-day mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

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

Lancet 2021; 397: 1637–45

RECOVERY Collaborative Group*

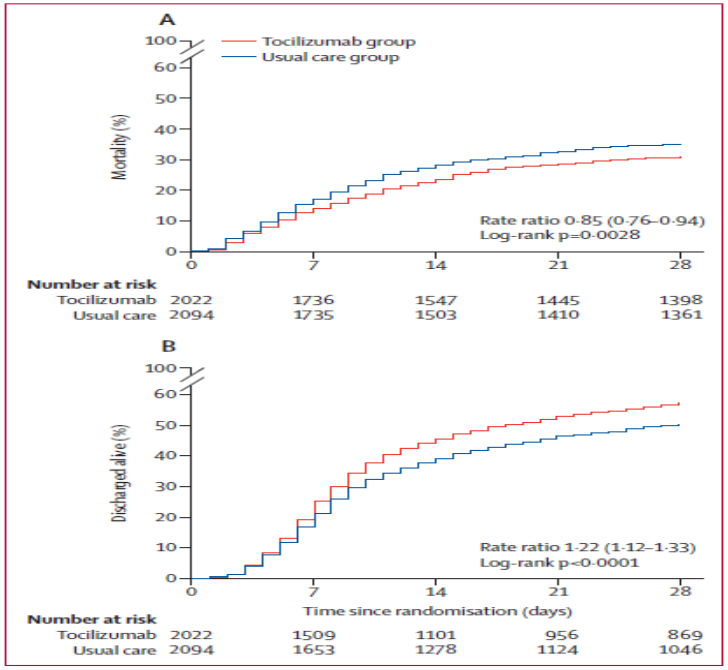


Figure 2: **Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab group (n=2022)	Usual care group (n=2094)		
Primary outcome				
28-day mortality	621 (31%)	729 (35%)	0·85 (0·76–0·94)	0·0028
Secondary outcomes				
Median time to being discharged, days	19	>28	..	..
Discharged from hospital within 28 days	1150 (57%)	1044 (50%)	1·22 (1·12–1·33)	<0·0001
Receipt of invasive mechanical ventilation or death*	619/1754 (35%)	754/1800 (42%)	0·84 (0·77–0·92)	<0·0001
Invasive mechanical ventilation	265/1754 (15%)	343/1800 (19%)	0·79 (0·69–0·92)	0·0019
Death	490/1754 (28%)	580/1800 (32%)	0·87 (0·78–0·96)	0·0055
Subsidiary clinical outcomes				
Receipt of ventilation†	290/935 (31%)	323/933 (35%)	0·90 (0·79–1·02)	0·10
Non-invasive ventilation	281/935 (30%)	309/933 (33%)	0·91 (0·79–1·04)	0·15
Invasive mechanical ventilation	67/935 (7%)	86/933 (9%)	0·78 (0·57–1·06)	0·11
Successful cessation of invasive mechanical ventilation‡	95/268 (35%)	98/294 (33%)	1·08 (0·81–1·43)	0·60
Use of haemodialysis or haemofiltration§	120/1994 (6%)	172/2065 (8%)	0·72 (0·58–0·90)	0·0046

Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

Table 2: **Effect of allocation to tocilizumab on main study outcomes**

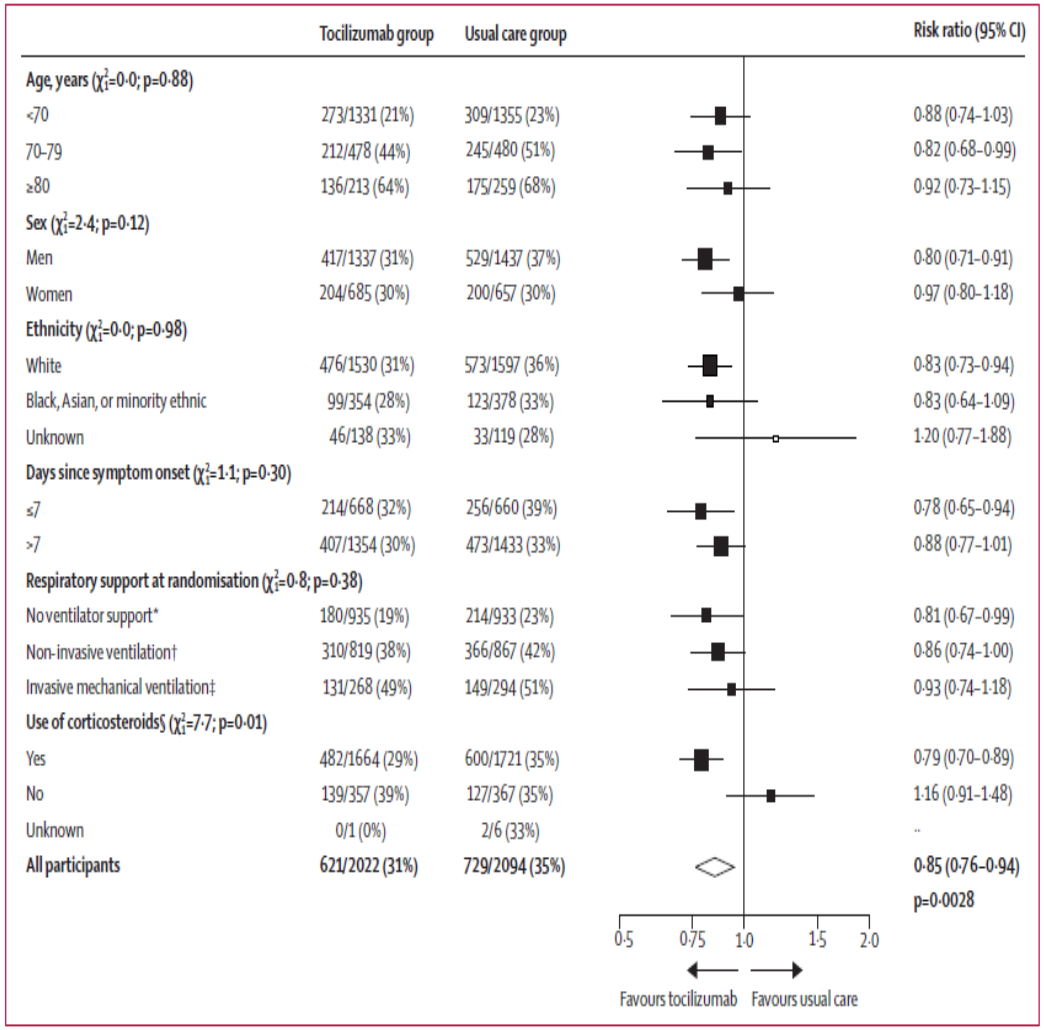


Figure 3: Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics

28-day mortality

The RECOVERY trial has shown that for patients hospitalised with severe COVID-19, treatment with tocilizumab reduces mortality, increases the chances of successful hospital discharge, and reduces the chances of requiring invasive mechanical ventilation. These benefits are additional to those previously reported for dexamethasone. These findings require an update to clinical guidelines, which has already begun, and efforts to increase the global availability and affordability of tocilizumab.[29,30]

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

Lancet 2021; 397: 1637–45

RECOVERY Collaborative Group*

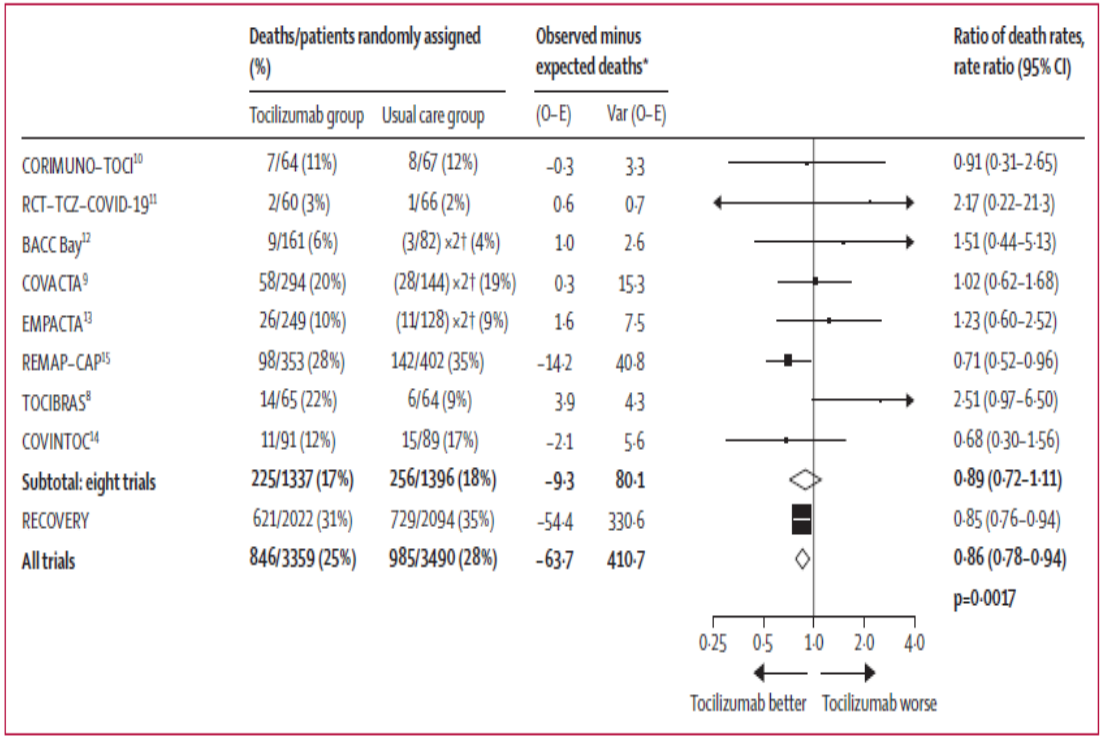


Figure 4: Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19

Previous trials have provided some evidence that tocilizumab might shorten time to discharge or reduce progression to invasive mechanical ventilation or death.[9,13] Since mid-2020, eight randomised, controlled trials of tocilizumab for the treatment of COVID-19 have reported. These include seven small trials (fewer than 100 deaths in each) and the somewhat larger REMAP-CAP trial, which recruited critically ill patients with COVID-19, over 99% of whom required non-invasive respiratory support or invasive mechanical ventilation.[8–15] Taken together, these previous trials did not show a significant mortality benefit for treatment with tocilizumab (death rate ratio 0·89, 95% CI 0·72–1·11; figure 4). The RECOVERY trial contains around four times as much information as all the previous trials combined. When all nine trials are considered together, allocation to tocilizumab is associated with a significant 14% proportional reduction in 28-day mortality. These results suggest that in COVID-19 patients who are hypoxic and have evidence of systematic inflammation, treatment with a combination of a systemic corticosteroid plus tocilizumab would be expected to reduce mortality by about one-third for patients receiving simple oxygen and nearly one-half for those receiving invasive mechanical ventilation.[6]

The RECOVERY results support the use of tocilizumab.

Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy

Vincenzo Montesarchio,[1] Roberto Parrella,[2] Chiara Iommelli,[1] Antonella Bianco,[1] Elio Manzillo,[2] Fiorentino Fraganza,[3] Cristiana Palumbo,[4] Gaetano Rea,[4] Patrizia Murino,[3] Rosanna De Rosa ,[3] Luigi Atripaldi,[4] Maurizio D'Abbraccio,[2] Marcello Curvietto,[5] Domenico Mallardo,[5] Egidio Celentano,[6] Antonio Maria Grimaldi,[5] Marco Palla,[5] Claudia Trojaniello,[5] Maria Grazia Vitale,[5] Samuel Lewis Million-Weaver ,[7] Paolo Antonio Ascierto [8]

SARILUMAB

Sarilumab dosing

Sarilumab was administered as a subcutaneous injection of 400 mg. Of the 15 patients treated, 12 received a single injection of sarilumab. Similar to the protocol used in the TOCIVID-19 study, repeat dosing could be permitted if the treating physician considered that there was no improvement after the first administration, and three patients were administered a second dose within 24 hours of the first.

Table 1 Respiratory parameters for all patients before and after sarilumab administration

Patient	Date of start of symptoms	Date of hospitalization	Initial PaO_2:FiO_2	Date(s) of sarilumab administration	PaO_2:FiO_2 after sarilumab
1	March 15, 2020	March 25, 2020	83	March 26, 2020 March 27, 2020	135 at d+1 185 at d+3 after second dose
2	March 15, 2020	March 25, 2020	120	March 27, 2020	296 at d+1
3	March 18, 2020	March 24, 2020	180	March 27, 2020	290 at d+1 305 on April 4, 2020
4	March 15, 2020	March 28, 2020	192	March 30, 2020	230 at d+1 330 on April 10, 2020
5	March 18, 2020	March 25, 2020	200	March 26, 2020	270 at d+1 370 on April 10, 2020
6	March 17, 2020	March 27, 2020	240	March 30, 2020	320 at d+1
7	March 14, 2020	March 26, 2020	90	March 27, 2020 March 28, 2020	62 at d+1
8	March 15, 2020	March 25, 2020	178	March 30, 2020 March 31, 2020	290 at d+1
9	March 18, 2020	March 26, 2020	70	March 27, 2020	260 after administration
10	March 13, 2020	March 23, 2020	137	April 3, 2020	290 at d+1 330 on April 27, 2020
11	March 12, 2020	March 26, 2020	120	27 March 2020	178 at d+1 234 at d+4 382 at d+10
12	March 18, 2020	March 26, 2020	60	March 27, 2020	290 after administration
13	March 15, 2020	March 25, 2020	122	March 26, 2020	72 at d+1
14	March 21, 2020	March 26, 2020	88	March 27, 2020	92 at d+1
15	March 23, 2020	March 30, 2020	137	March 31, 2020	290 at d+1

FiO_2, fractional inspired oxygen; PaO_2, arterial oxygen pressure.

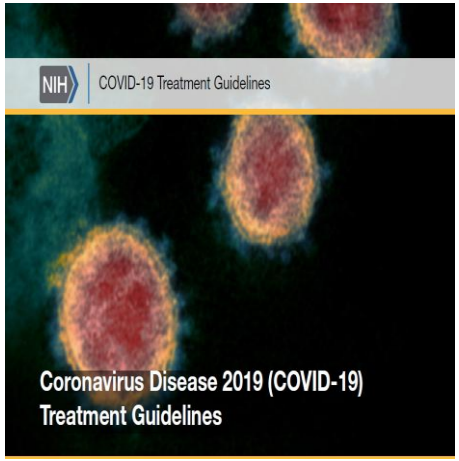


Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[f]) **(CIIa)**.	For nonpregnant patients with D-dimer For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[f] **(BIIa)** to 1 of the options above.[d,h]	contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

AGENZIA ITALIANA DEL FARMACO

Tocilizumab nella terapia dei pazienti adulti con COVID-19
CTS, 09 giugno 2021

DETERMINA 16 giugno 2021.

Inserimento del medicinale «Tocilizumab» nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento dei pazienti adulti ospedalizzati con COVID-19 grave e/o con livelli elevati degli indici di infiammazione sistemica. (Determina n. 73543/2021).

TOCILIZUMAB

Per quali pazienti è raccomandabile?	Alla luce delle attuali conoscenze l'utilizzo di tocilizumab può essere rimborsato dal SSN per il trattamento di soggetti adulti ospedalizzati con COVID-19 grave e/o con livelli elevati degli indici di infiammazione sistemica. In particolare, si considerano candidabili al trattamento con tocilizumab i pazienti ospedalizzati con condizioni cliniche rapidamente ingravescenti: • Pazienti recentemente ospedalizzati ricoverati in terapia intensiva da meno di 24/48 ore che ricevono ventilazione meccanica o ossigeno ad alti flussi; oppure pazienti recentemente ospedalizzati con fabbisogno di ossigeno in rapido aumento che richiedono ventilazione meccanica non invasiva o ossigeno ad alti flussi in presenza di elevati livelli di indici di flogosi (CRP≥75 mg/L). • Soggetti ospedalizzati in rapida progressione clinica dopo 24/48 ore di utilizzo di desametasone, o altri cortisonici. Per rapida progressione clinica si intende fabbisogno di ossigeno in rapido aumento, pur senza necessità di ventilazione non invasiva o ossigeno ad alti flussi, e con elevati livelli di indici di flogosi (CRP≥75 mg/L).

SARILUMAB

AGENZIA ITALIANA DEL FARMACO

Sarilumab nella terapia dei pazienti adulti con COVID-19

CTS, 23 settembre 2021

Per quali pazienti è raccomandabile?	Alla luce delle attuali conoscenze si ritiene che sarilumab possa essere utilizzato in alternativa a tocilizumab quando quest'ultimo non fosse disponibile, per il trattamento di soggetti adulti ospedalizzati con COVID-19 grave e/o con livelli elevati degli indici di infiammazione sistemica. In particolare, si considerano candidabili al trattamento con sarilumab i pazienti ospedalizzati con condizioni cliniche rapidamente ingravescenti: • Pazienti recentemente ospedalizzati ricoverati in terapia intensiva da meno di 24/48 ore che ricevono ventilazione meccanica o ossigeno ad alti flussi; oppure pazienti recentemente ospedalizzati con fabbisogno di ossigeno in rapido aumento che richiedono ventilazione meccanica non invasiva o ossigeno ad alti flussi in presenza di elevati livelli di indici di flogosi (CRP≥75 mg/L). • Soggetti ospedalizzati in rapida progressione clinica dopo 24/48 ore di utilizzo di desametasone, o altri cortisonici. Per rapida progressione clinica si intende fabbisogno di ossigeno in rapido aumento, pur senza necessità di ventilazione non invasiva o ossigeno ad alti flussi, e con elevati livelli di indici di flogosi (CRP≥75 mg/L). Non è consentita la co-somministrazione con altri inibitori delle interleuchine o con JAK-inibitori.

Dosaggio consigliato

Il dosaggio raccomandato di sarilumab per il trattamento del COVID nei pazienti adulti è di pari a **400 mg** da somministrare mediante **infusione endovenosa** della durata di almeno 60 minuti.

Sarilumab è disponibile come siringa preriempita. Per una dose da 400 mg due siringhe preriempite da 200 mg devono essere iniettate in una sacca per infusione da 100 ml di cloruro di sodio 0,9% (capovolgere la sacca almeno 10 volte per garantire un'accurata miscelazione).

l'indicazione ammessa alla rimborsabilità in L648/96 la prescrizione è limitata ai clinici operanti nei centri indicati dalla Regione per la gestione del COVID-19.

Treatment Effects of Interleukin-6 Receptor Antibodies for Modulating the Systemic Inflammatory Response After Out-of-Hospital Cardiac Arrest (The IMICA Trial)

A Double-Blinded, Placebo-Controlled, Single-Center, Randomized, Clinical Trial

Originally published 22 Mar 2021 |
https://doi.org/10.1161/CIRCULATIONAHA.120.053318 |
Circulation. 2021;143:1841–1851

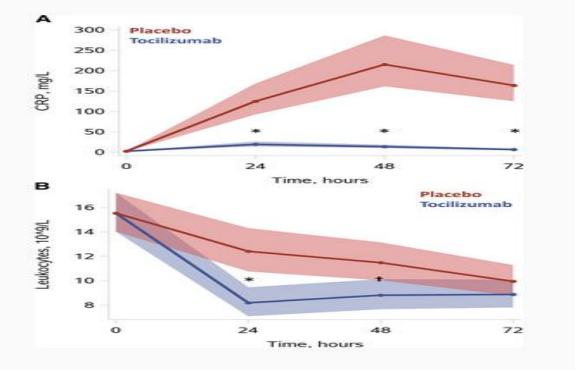
Background:

Patients experiencing out-of-hospital cardiac arrest who remain comatose after initial resuscitation are at high risk of morbidity and mortality attributable to the ensuing post–cardiac arrest syndrome. Systemic inflammation constitutes a major component of post–cardiac arrest syndrome, and IL-6 (interleukin-6) levels are associated with post–cardiac arrest syndrome severity. The IL-6 receptor antagonist tocilizumab could potentially dampen inflammation in post–cardiac arrest syndrome. The objective of the present trial was to determine the efficacy of tocilizumab to reduce systemic inflammation after out-of-hospital cardiac arrest of a presumed cardiac cause and thereby potentially mitigate organ injury.

Myocardial injury was also reduced, documented by reductions in creatine kinase myocardial band and troponin T; tocilizumab versus placebo at 12 hours: –36% [–54%; –11%] and –38% [–53%; –19%], respectively, both $P<0.01$. N-terminal pro B-type

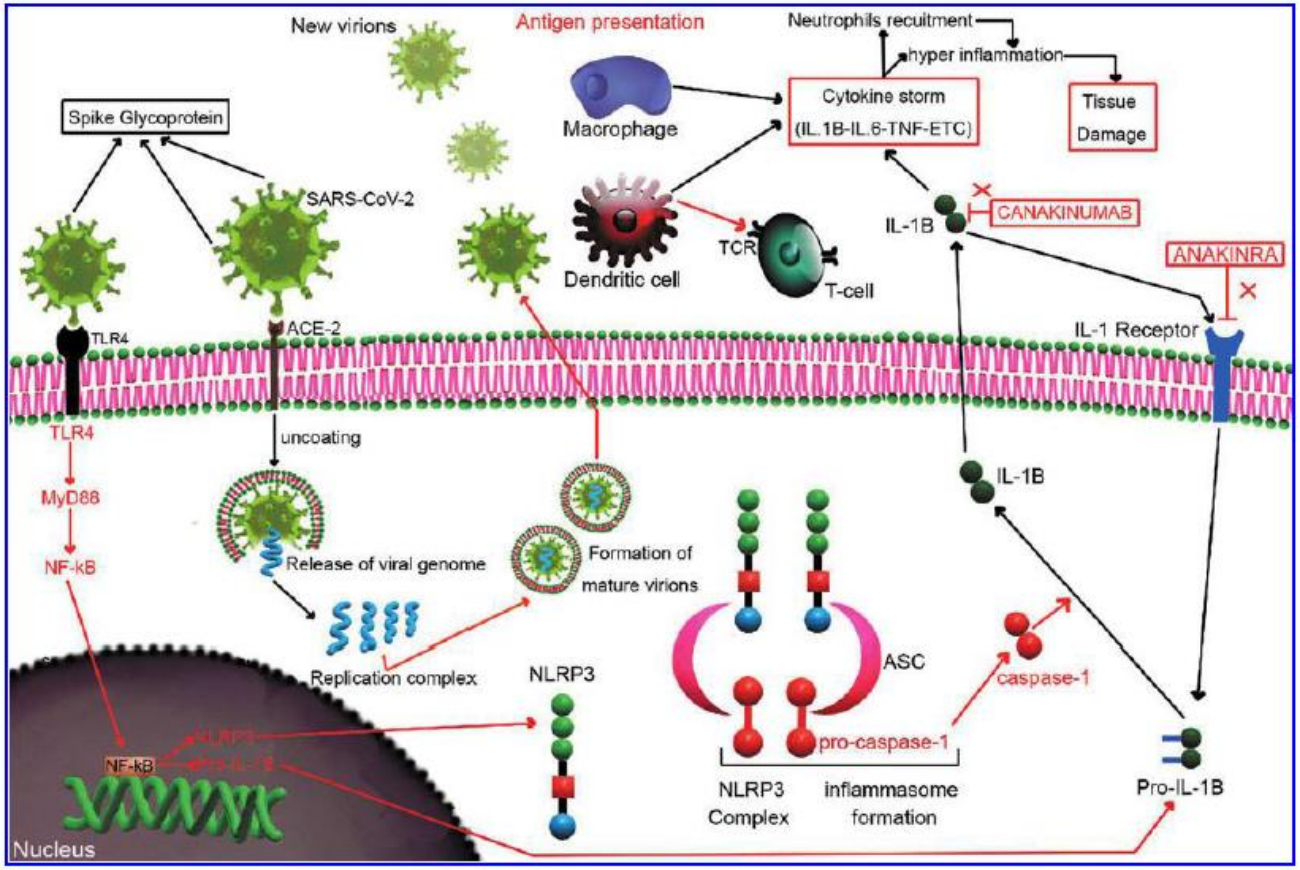
Treatment with tocilizumab resulted in a significant reduction in systemic inflammation and myocardial injury in comatose patients resuscitated from out-of-hospital cardiac arrest.

- This trial demonstrates the feasibility of reducing systemic inflammation after cardiac arrest and shows an apparent cardioprotective effect as seen by reduced levels of biomarkers of myocardial injury and stress in patients treated with tocilizumab.
- Further studies are needed to determine whether these findings translate into clinical benefits for the patients.



Interleukin-1 in COVID-19 Infection: Immunopathogenesis and Possible Therapeutic Perspective

Amirhossein Mardi,[1] Sepideh Meidaninikjeh,[2] Sepideh Nikfarjam,[3] Naime Majidi Zolbanin,[4,5] and Reza Jafari[6,i]



Interleukin (IL)-1β is the most investigated member of the IL-1 family (IL-1F) because of its functions in regulating autoinflammatory diseases. IL-1β has an effective pyrogenic effect. It stimulates immune cells and increases the upregulation of adhesion molecules on endothelial cells, thus promoting activated immune cells such as neutrophils to migrate to the infection sites (29). IL-1β can be produced from several cell types. Blood monocytes, dendritic cells, and tissue macrophages are the main sources of IL-1β in the body.

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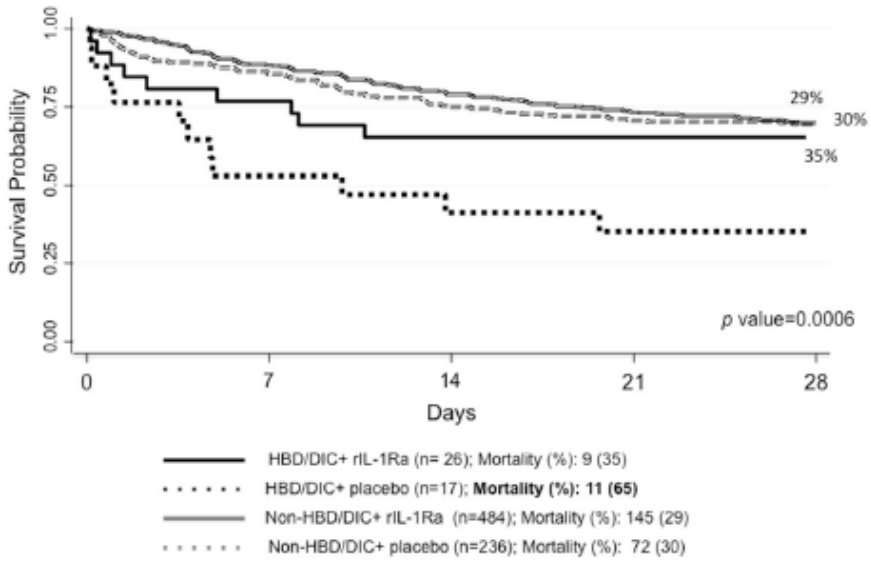
Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial

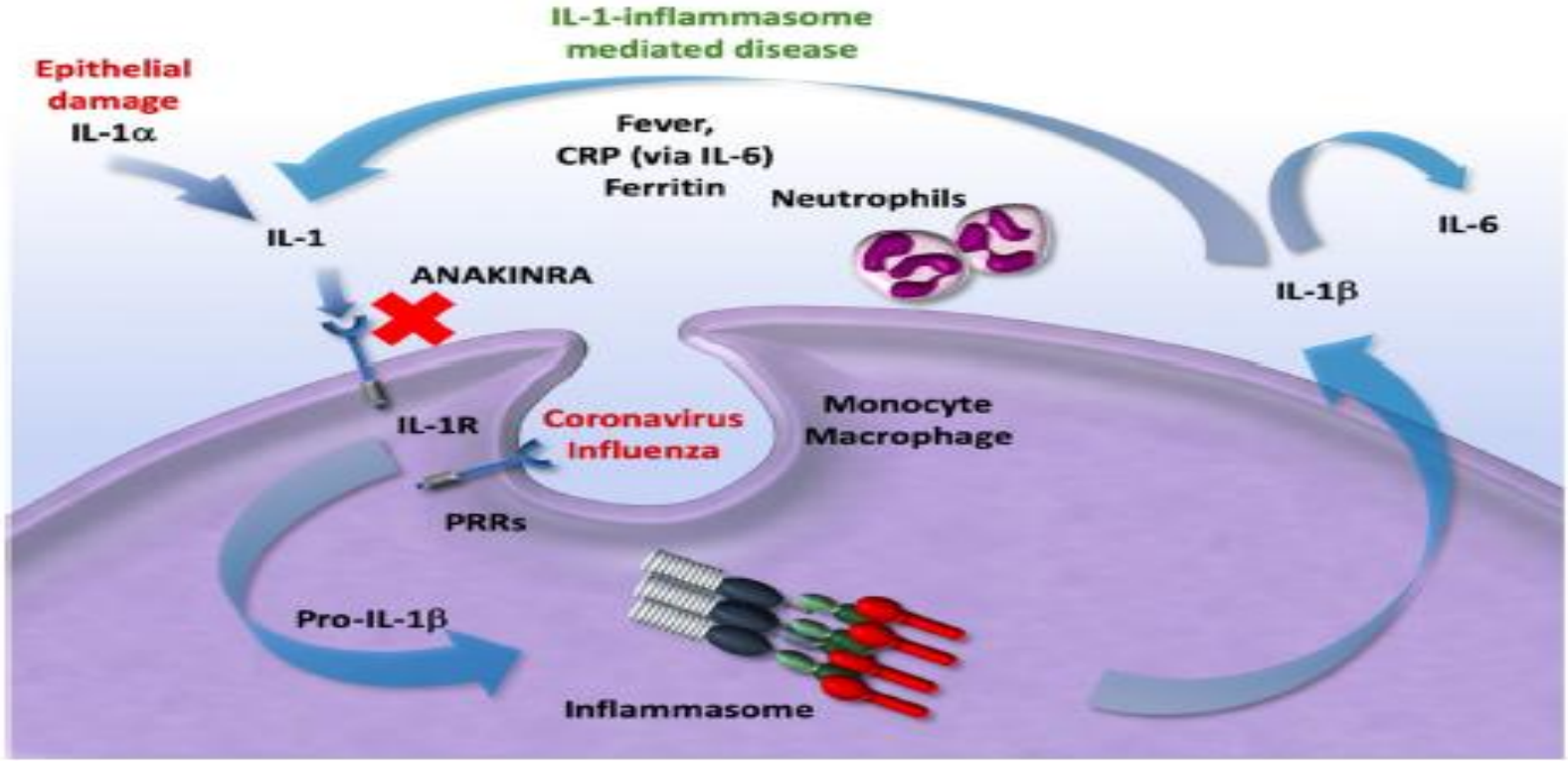


Conclusions and Relevance—In this subgroup analysis, IL-1 receptor blockade was associated with significant improvement in survival of patients with sepsis and concurrent HBD/DIC. A prospective randomized trial using features of MAS for mortality risk stratification should be undertaken to confirm the role of IL-1 blockage.

Crit Care Med. 2016 February ; 44(2): 275–281.

Blocking IL-1 to prevent respiratory failure in COVID-19

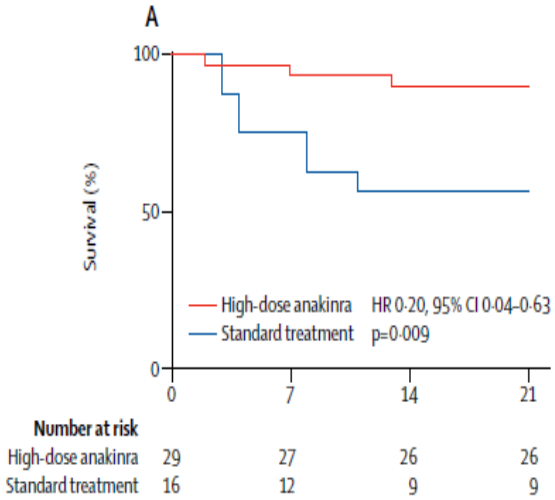
van de Veerdonk and Netea *Critical Care* (2020) 24:445
https://doi.org/10.1186/s13054-020-03166-0

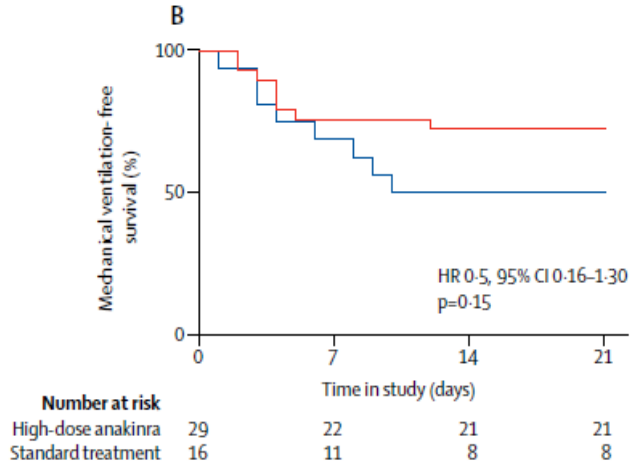


Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

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

COVID-19 outbreak. Low-dose anakinra was administered off-label subcutaneously at a dose of 100 mg twice daily. High-dose anakinra was administered off-label intravenously at a dose of 10 mg/kg per day (5 mg/kg twice daily, infused over 1 h). The duration of treatment was protracted until sustained clinical benefit, defined as a 75% reduction in serum C-reactive protein and sustained respiratory improvement (PaO_2:FiO_2>200 mm Hg) for at least 2 days, or until death, bacteraemia (appendix p 2), or side-effects arose (eg, increase in liver aminotransferase enzymes above three-fold the upper normal limit). In patients achieving sustained clinical benefit, discontinuation of high-dose anakinra was followed by daily low-dose subcutaneous administration (100 mg twice daily) for 3 days, which was deemed useful to avoid possible inflam-



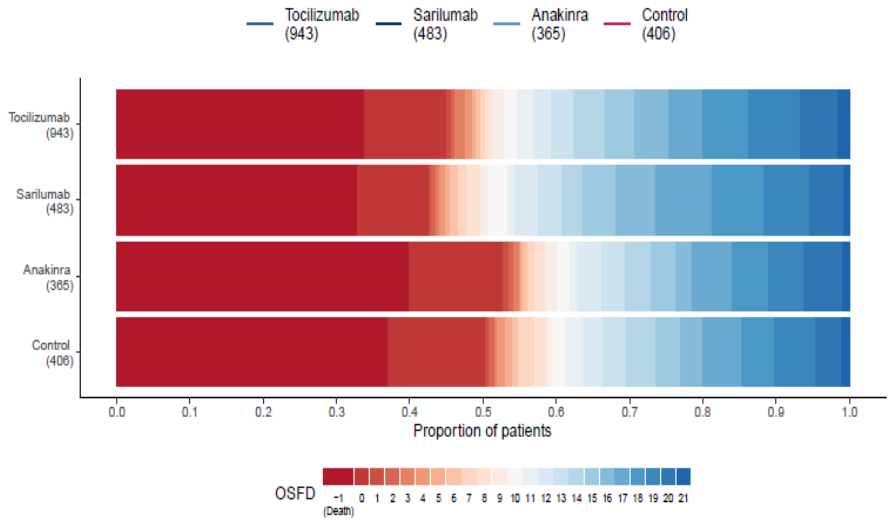


Interpretation In this retrospective cohort study of patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients. Confirmation of efficacy will require controlled trials.

Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19

The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial

The REMAP-CAP Investigators



Panel B) shows organ support–free days as horizontally stacked proportions by intervention group.

https://doi.org/10.1101/2021.06.18.21259133;

We did not observe a beneficial effect of anakinra in critically ill patients with COVID-19. Previous studies and a recent meta-analysis provided a rationale for the use of anakinra in COVID-19.[23] Anakinra treatment using soluble urokinase plasminogen activator receptor (sUPAR) to identify an at-risk group of patients for early targeting of IL-1 was effective in moderate COVID-19 in a recent study.[24] There are several possible explanations for our findings. Firstly, we could have chosen the wrong dose. However, our choice of administration regimen was informed by pharmacometric modelling data, and it is unlikely that predicted drug concentrations varied significantly. Secondly, blocking IL-1 (and IL-1 mediated IL-6 release) may benefit non-critically ill, but not critically ill patients. Such potential differential effects could not be assessed in this study as a result of the low recruitment in non-critically ill patients. Finally, we did not use a strategy of early targeting of the IL-1 pathway in selected patients as used in the SAVE-MORE trial,[24] because sUPAR is not commonly available.

CONCLUSIONS: In patients with severe COVID-19 receiving organ support, tocilizumab and sarilumab are similarly effective at improving survival and reducing duration of organ support. Anakinra is not effective in this population. (ClinicalTrials.gov number: NCT02735707)

COVID-19 and pneumonia: a role for the uPA/uPAR system

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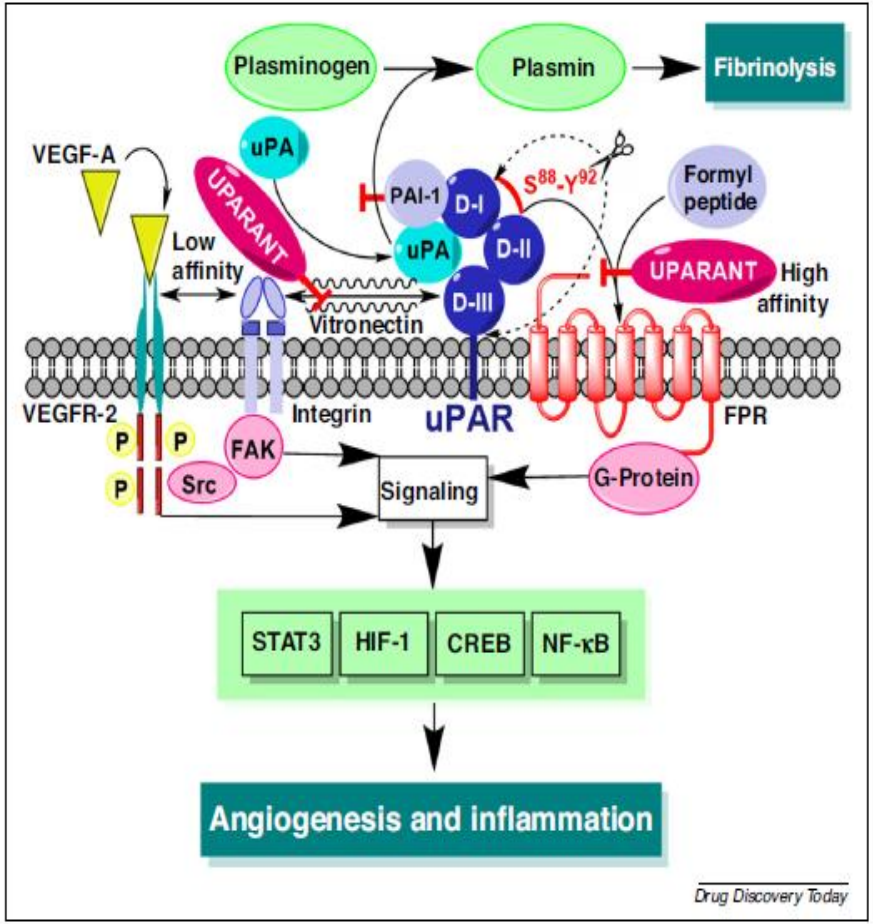
TABLE 1

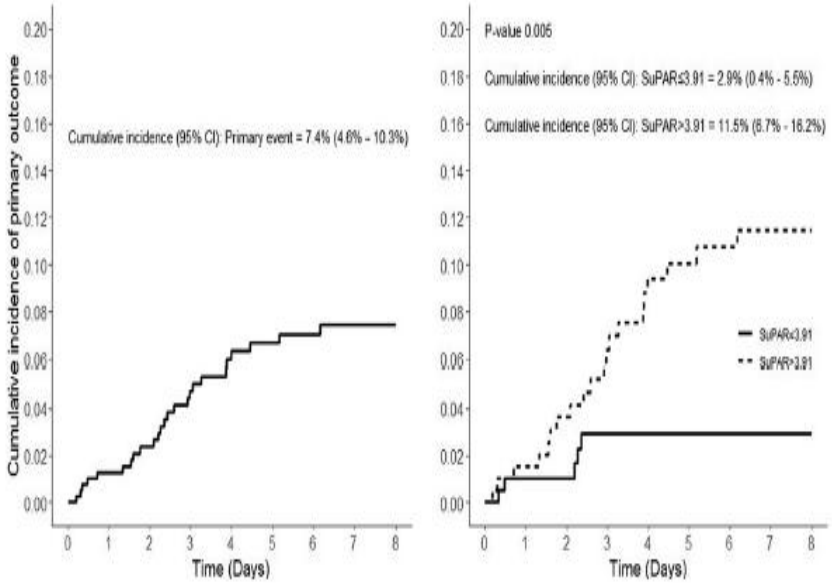
SuPAR levels (ng/mL) in serum, or otherwise specified, of healthy controls and patients[a]

Pathology	suPAR levels (ng/ml)	
	Healthy controls	Patients
Diabetic nephropathy (DN)	2.3 ± 0.5	4.4 ± 1.6
Severe acute pancreatitis (SAP)	5.2 (2.0–8.0)	16.1 (12.6–24.2)
Moderate-severe acute pancreatitis (MSAP)	5.2 (2.0–8.0)	12.2 (9.6–17.0)
Moderate acute pancreatitis (MAP)	5.2 (2.0–8.0)	9.4 (6.9–12.0)
Asthma	2.5 (1.9–3.3)	5.6 (3.6–7.7)[b]
Systemic lupus erythematosus (SLE)	3.2 (2.9–3.0)	4.5 (3.8–5.2)[c]
Cirrhosis	2.6 (1.3–7.8)	7.2 (1–27.4)[d]; 6.8 (1–29.4)[e]
Critical illness	2.1 (0.0–3.5)	5.9 (2.1–24.1)[f]; 9.7 (0.4–38.0)[g]; 8.3 (1.5–38.0)[h]; 10.8 (0.4–38.0)[i]
Cardiovascular disease (CVD)[i]	3.9 (3.3–4.7)	4.6 (3.8–5.5)[b]
Ventilator-associated pneumonia (VAP)[j]	4.7 (3.6–6.3)	6.6 (5.7–7.7)
Community-acquired pneumonia[j]	2.7 ± 1.4	4.0 ± 2.3
Acute exacerbation chronic obstructive pulmonary disease (AECOPD)	2.4 ± 0.9	4.8 ± 1.9
Diabetes type 2	2.1 (1.9–2.4)	3.0 (2.5–3.5)
Diabetes type 1[j]	2.3 (1.1–3.6)	3.0 (1.1–10.5)[j]; 3.6 (1.6–15.1)[m]; 4.9 (1.8–13.2)[n]
Cigarette smoke[k]	2.1 ± 0.1	3.3 ± 0.2
Sepsis[k]	6.0 (3.7–10.8)	18.8 (6.8–30.1)
Bacteremia in patients with systemic inflammatory response syndrome	5.6 (4.3–7.8)	8.1 (5.8–15.5)[o]; 9.6 (6.5–11.7)[p]



Admission levels of Soluble Urokinase Plasminogen Activator Receptor (suPAR) are Associated with the Development of Severe Complications in Hospitalised COVID-19 Patients: A Prospective Cohort Study

International Journal of Infectious Diseases 107 (2021) 188–194



We found plasma suPAR and neutrophil-to-monocyte ratio to be significantly associated with severe COVID-19 complications. Future studies might consider integrating plasma suPAR and other clinical and laboratory biomarkers into prognostic models to improve risk prediction accuracy, allowing them to perform treatment interventions based on the given risk for severe complications. A reliable prediction tool would allow more research into individualised treatment and better utilisation and hospital resources management.

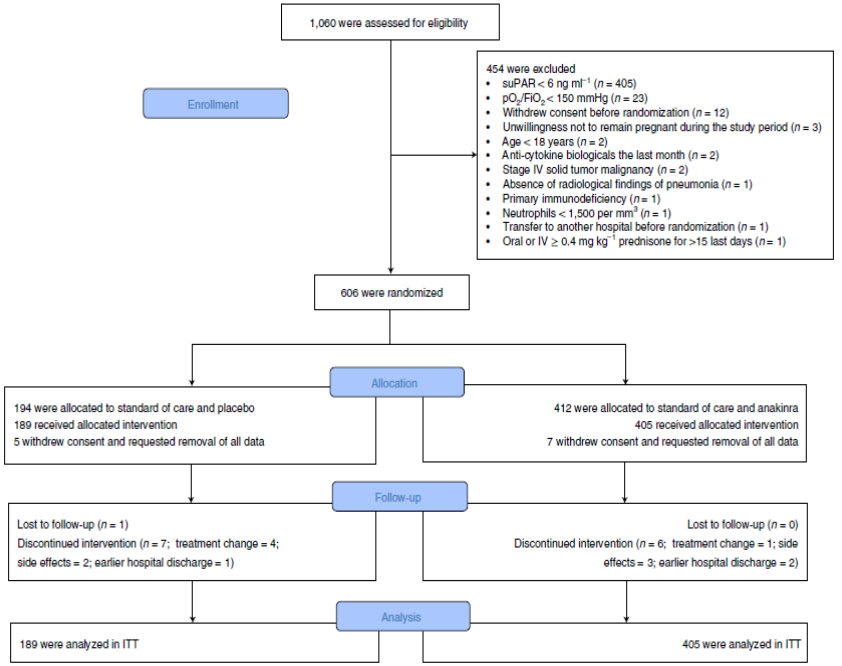
Figure 3. The cumulative incidence of the primary outcome stratified by the median soluble urokinase Plasminogen Activator Receptor (suPAR) in hospitalized COVID-19 patients.

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

Evdoxia Kyriazopoulou[1], Garyfallia Poulakou[2], Haralampos Milionis[3], Simeon Metallidis[4], Georgios Adamis[5], Konstantinos Tsiakos[6], Archontoula Fragkou[7], Aggeliki Rapti[6], Christina Damoulari[1], Massimo Fantoni[8], Ioannis Kalomenidis[9], Georgios Chrysos[10], Andrea Angheben[11], Ilias Kainis[12], Zoi Alexiou[13], Francesco Castelli[14], Francesco Saverio Serino[15], Maria Tsilika[1], Petros Bakakos[16], Emanuele Nicastri[17], Vassiliki Tzavara[18], Evangelos Kostis[19], Lorenzo Dagna[20], Panagiotis Koufargyris[1], Katerina Dimakou[21], Spyridon Savvanis[7], Glykeria Tzatzagou[22], Maria Chini[23], Giulio Cavalli[20], Matteo Bassetti[24], Konstantina Katrini[1], Vasileios Kotsis[25], George Tsoukalas[26], Carlo Selmi[27], Ioannis Bliziotis[28], Michael Samarkos[29], Michael Doumas[30], Sofia Ktena[1], Aikaterini Masgala[31], Ilias Papanikolaou[32], Maria Kosmidou[3], Dimitra-Melia Myrodia[2], Aikaterini Argyraki[33], Chiara Simona Cardellino[11], Katerina Koliakou[34], Eleni-Ioanna Katsigianni[34], Vassiliki Rapti[2], Efthymia Giannitsioti[10], Antonella Cingolani[8], Styliani Micha[34], Karolina Akinosoglou[35], Orestis Liatsis-Douvitsas[34], Styliani Symbardi[36], Nikolaos Gatselis[37], Maria Mouktaroudi[1,34], Giuseppe Ippolito[17], Eleni Florou[34], Antigone Kotsaki[1], Mihai G. Netea[38,39], Jesper Eugen-Olsen[40], Miltiades Kyprianou[34], Periklis Panagopoulos[41], George N. Dalekos[37] and Evangelos J. Giamarellos-Bourboulis[1,34]

- Early elevation of suPAR = risk of progression to SRF or death
- Two-step strategy
- First : elevated suPAR to identify patients at risk
- Second : early targeted treatment with a recomb. IL-1 recept. antag.

The SAVE-MORE study (suPAR-guided Anakinra treatment for Validation of the risk and Early Management Of seveRE respiratory failure by COVID-19) is a pivotal, confirmatory, phase 3, double-blind randomized controlled trial that evaluated the efficacy and safety of early initiation of anakinra treatment in hospitalized patients with moderate or severe COVID-19. The primary objective was to evaluate the efficacy and safety of early anakinra administration on the 11-point ordinal WHO-CPS on day 28 from the start of treatment.



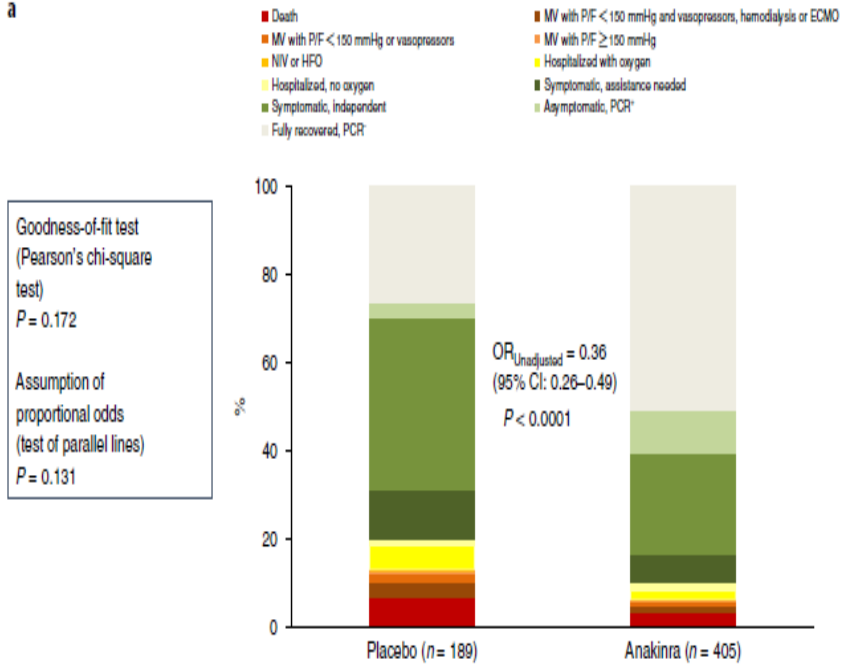
Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

Endpoints. The primary study endpoint was the overall comparison of the distribution of frequencies of the scores from the 11-point WHO-CPS between the two arms of treatment on day 28. Secondary endpoints included the changes of WHO-CPS scores at days 14 and 28 from the baseline (before start of the study drug); the change of SOFA score at day 7 from baseline; the time until hospital discharge; the time of stay in the ICU for patients eventually admitted to the ICU; and the comparison of biomarkers. The outcome by day 14 of patients excluded from enrollment because of suPAR lower than 6 ng ml^{-1} was captured post hoc.

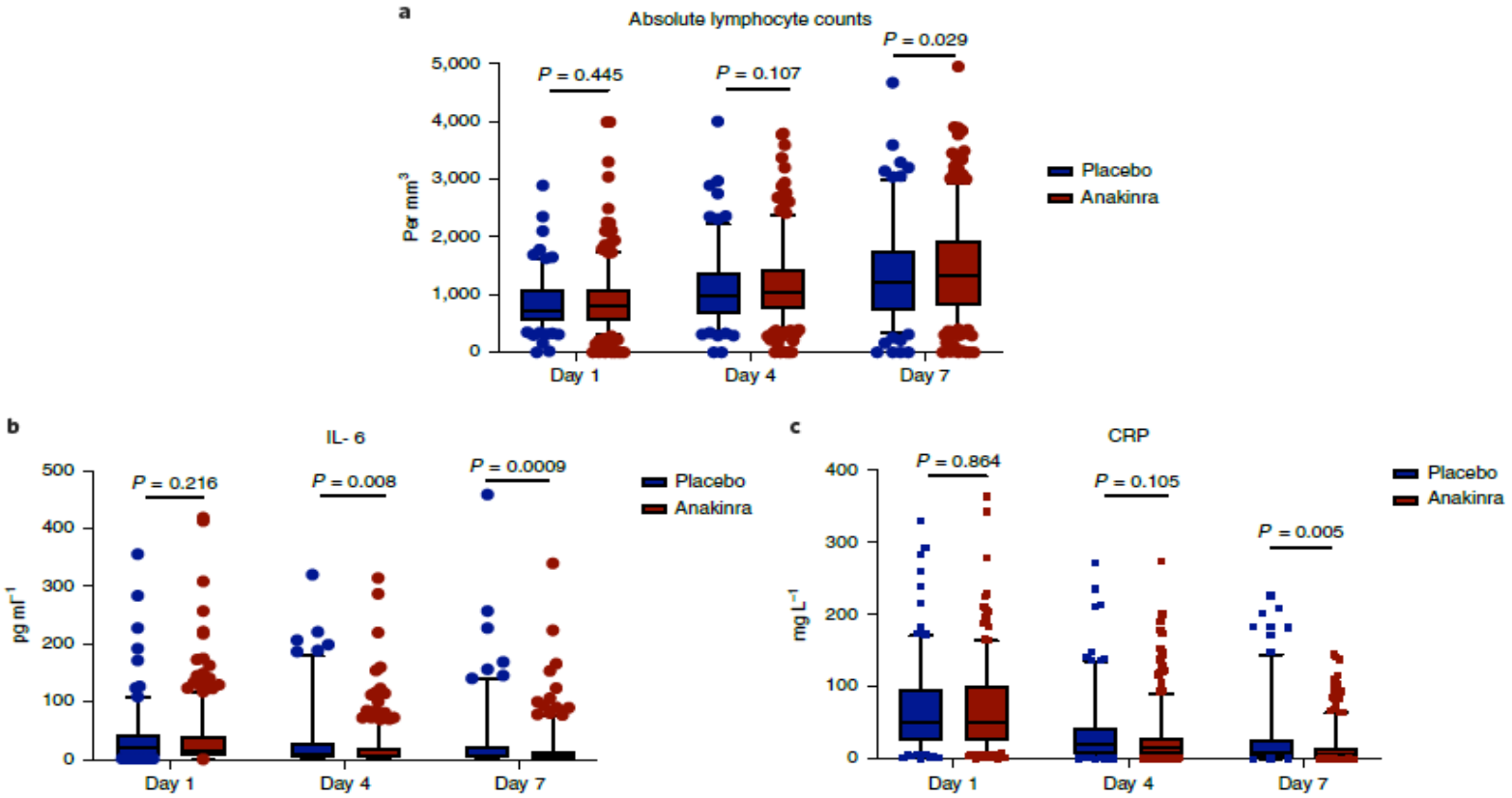
Table 2 | Primary and secondary study endpoints

	Placebo (n=189)	Anakinra (n=405)	OR (95% CI)	P value
WHO-CPS by day 28			0.36 (0.26-0.50)	<0.0001
Fully recovered PCR⁻, *n* (%)	50 (26.5)	204 (50.4)		
Asymptomatic PCR⁺, *n* (%)	6 (3.2)	40 (9.9)		
Symptomatic independent, *n* (%)	74 (39.2)	93 (23.0)		
Symptomatic assistance needed, *n* (%)	21 (11.1)	25 (6.2)		
Hospitalized with no need for oxygen, *n* (%)	3 (1.6)	9 (2.2)		
Hospitalized with nasal/mask oxygen, *n* (%)	10 (5.3)	8 (2.0)		
Need for HFO or NIV, *n* (%)	1 (0.5)	1 (0.2)		
MV with P/F>150 mmHg, *n* (%)	1 (0.5)	1 (0.2)		
MV with P/F<150 mmHg or vasopressors, *n* (%)	4 (2.1)	5 (1.2)		
MV with P/F<150 mmHg and vasopressors or hemodialysis or ECMO, *n* (%)	6 (3.2)	6 (1.5)		
Dead, *n* (%)	13 (6.9)	13 (3.2)		
Absolute decrease of WHO-CPS at day 28 from baseline day 1, median (IQR)	3 (2.5)	4 (2.0)	0.40 (0.29-0.55)	<0.0001
Absolute decrease of WHO-CPS at day 14 from baseline day 1, median (IQR)	2 (3.0)	3 (2.0)	0.63 (0.46-0.86)	0.003
Absolute decrease of SOFA score at day 7 from baseline day 1, median (IQR)	0 (1)	1 (2)	0.64 (0.47-0.88)	0.007
Median (IQR) time to hospital discharge, d	12 (8.5)	11 (7.8)	1.22 (1.02-1.47)[a]	0.033
Median (IQR) time of ICU stay, d[b]	14 (22)	10 (21)	2.33 (1.11-4.92)[a]	0.026

a



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



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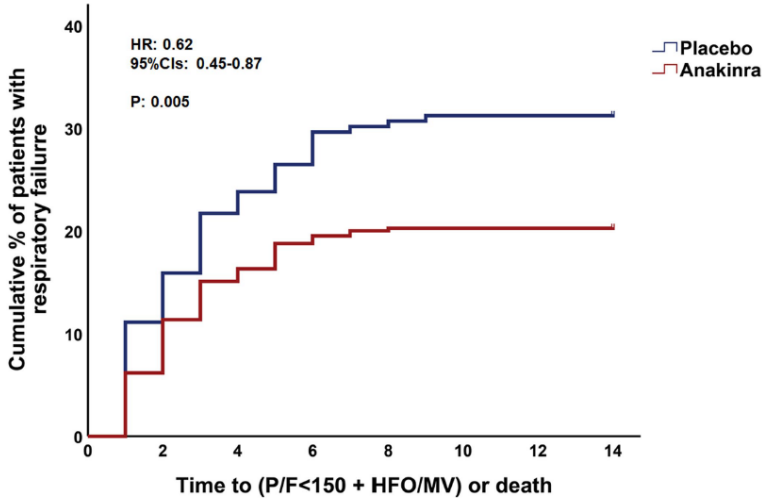
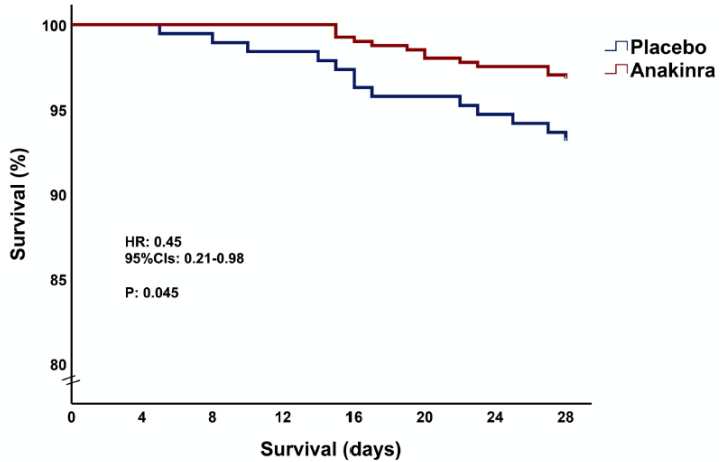


Patients at risk (n)

Placebo	189	159	144	133	131	130	130	129
Anakinra	405	359	339	326	323	323	323	321



Patients at risk (n)

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

exposure to tocilizumab[26]. Our findings suggest that suPAR should be measured upon admission of all patients with COVID-19 who do not need oxygen or who need nasal or mask oxygen, and that, if suPAR levels are 6 ng ml^{-1} or higher, anakinra treatment might be a suitable therapy. For patients with low respiratory ratio who need NIV or MV, tocilizumab might be the most appropriate drug of choice.

In conclusion, the SAVE-MORE trial showed that early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28.

Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis

Lancet Rheumatol 2021; 3: e690–97

*Evdoxia Kyriazopoulou, Thomas Huet, Giulio Cavalli, Andrea Gori, Miltiades Kyprianou, Peter Pickkers, Jesper Eugen-Olsen, Mario Clerici, Francisco Veas, Gilles Chatellier, Gilles Kaplanski, Mihai G Netea, Emanuele Pontali, Marco Gattorno, Raphael Cauchois, Emma Kooistra, Matthijs Kox, Alessandra Bandera, Hélène Beaussier, Davide Mangioni, Lorenzo Dagna, Jos W M van der Meer, Evangelos J Giamarellos-Bourboulis, Gilles Hayem, for the International Collaborative Group for Anakinra in COVID-19**

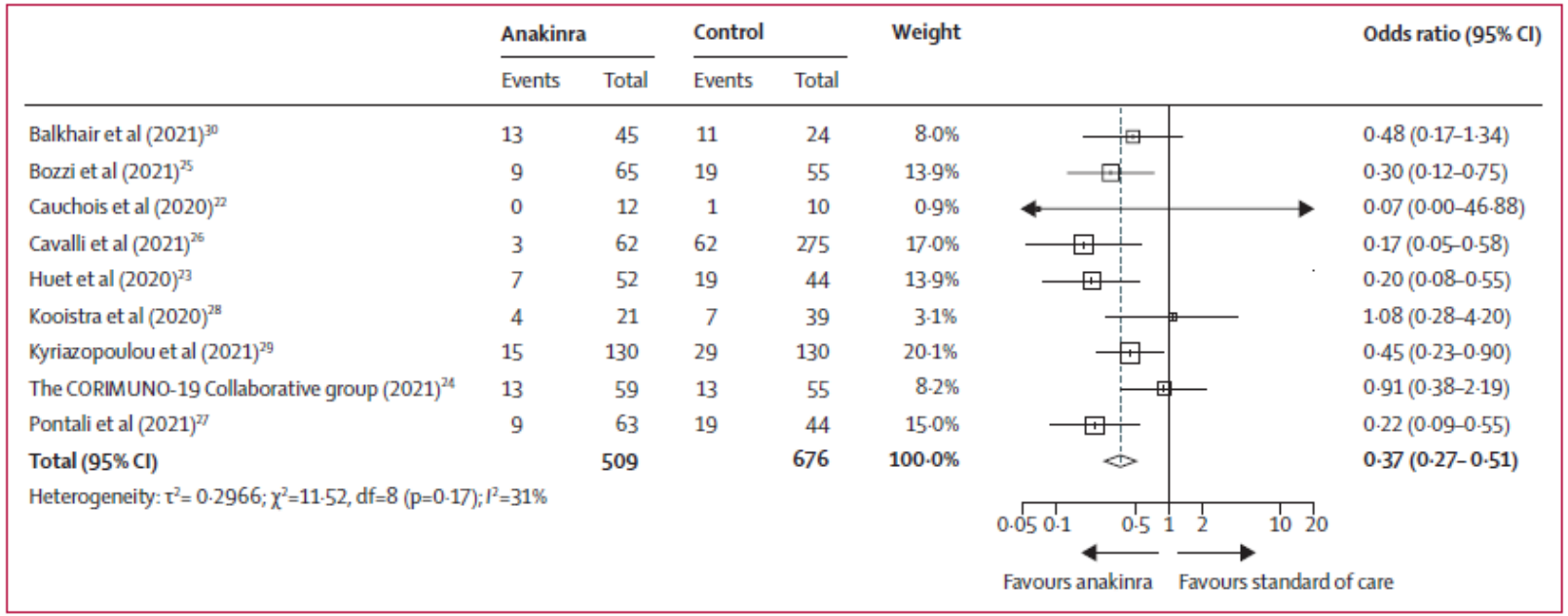


***Figure 2*: Forest plot showing mortality from aggregate data meta-analysis**

Odds ratios calculated with a fixed-effects Mantel-Haenszel test.

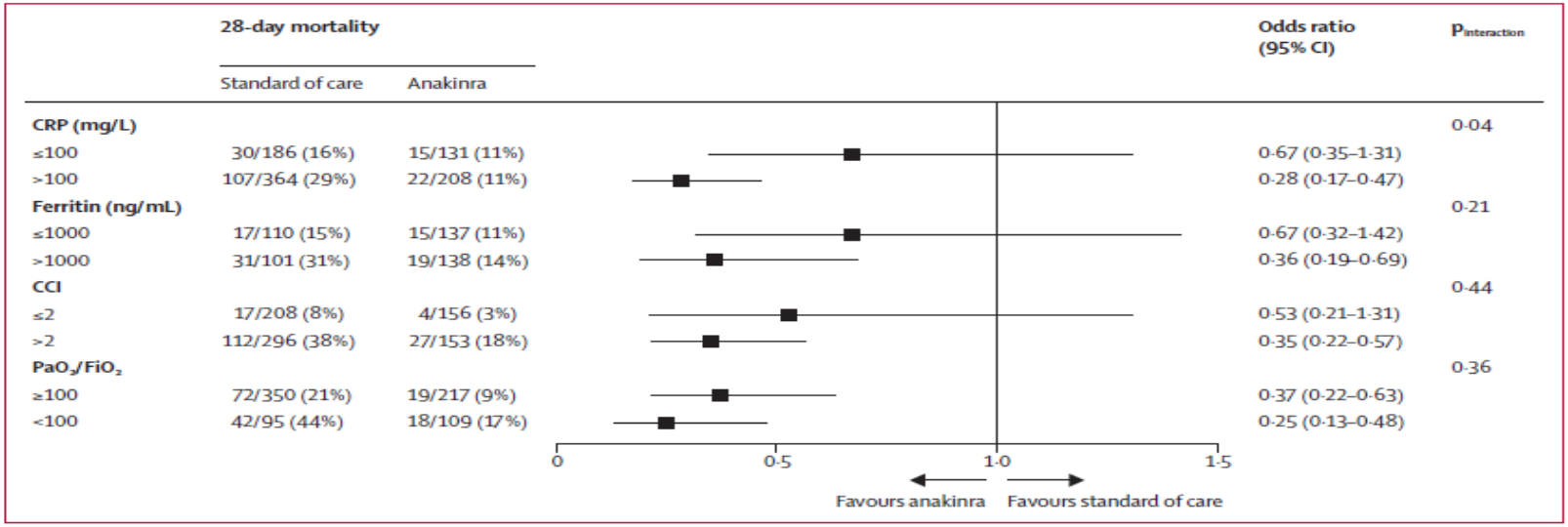


Figure 3: **Subgroup analysis of mortality in patients treated with anakinra versus those treated with standard of care**
p values of the interaction effect of the treatment on mortality, in each subgroup and among the studies are provided. CRP=C-reactive protein. CCI=Charlson comorbidity index. PaO_2/FiO_2=ratio of the arterial partial oxygen pressure divided by the fraction of inspired oxygen.

subgroup analysis, anakinra was more effective in lowering mortality in patients with CRP concentrations higher than 100 mg/L (OR 0·28 [95% CI 0·17–0·47]). Anakinra showed a significant survival benefit when given without dexamethasone (OR 0·23 [95% CI 0·12–0·43]), but not with dexamethasone co-administration (0·72 [95% CI 0·37–1·41]). Anakinra was not associated with a significantly increased risk of secondary infections when compared with standard of care (OR 1·35 [95% CI 0·59–3·10]).

Interpretation Anakinra could be a safe, anti-inflammatory treatment option to reduce the mortality risk in patients admitted to hospital with moderate to severe COVID-19 pneumonia, especially in the presence of signs of hyperinflammation such as CRP concentrations higher than 100 mg/L.

Lancet Rheumatol 2021;
3: e690–97

AGENZIA ITALIANA DEL FARMACO

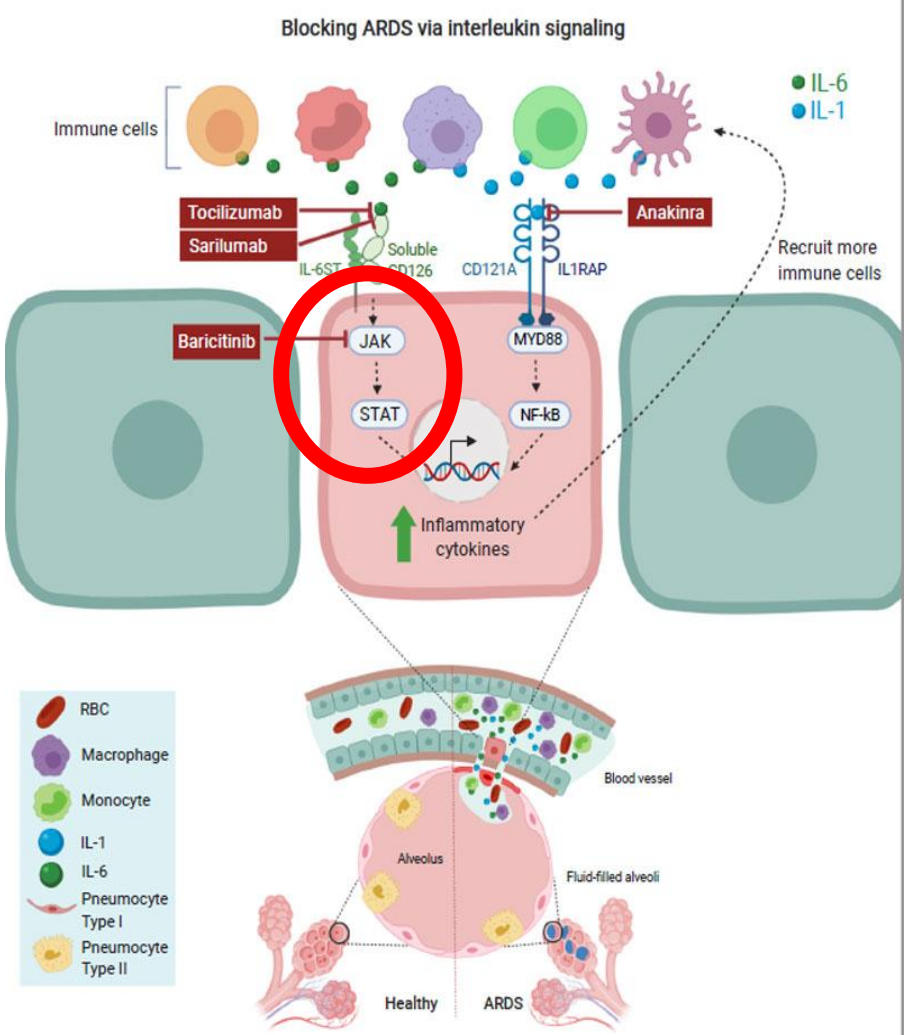
Razionale

Anakinra blocca il recettore fisiologico e antagonizza lo stato di infiammazione sistemica generato dalla produzione anomala di IL-1; il razionale di utilizzo di questo medicinale nei pazienti complessi con infezione da SARS-CoV-2 si basa proprio sull'azione inibitoria della stimolazione pro-infiammatoria da parte dell'IL-1.

Anakinra nella terapia dei pazienti adulti con COVID-19

CTS, 23 settembre 2021

Si forniscono di seguito elementi utili ad orientare la prescrizione e a definire un rapporto fra i benefici e i rischi del medicinale sul singolo paziente	
Per quali pazienti è raccomandabile?	Alla luce delle attuali conoscenze si ritiene che l'utilizzo di anakinra possa essere consentito limitatamente al trattamento di soggetti adulti ospedalizzati con polmonite da COVID-19 moderata/severa (con pO_2/FiO_2>150, e non sottoposti a C-PAP o ventilazione meccanica) e con livelli di plasma Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) ≥ 6ng/ml. Non è consentita la co-somministrazione con altri inibitori delle interleuchine o con JAK-inibitori.
A quali dosaggi è preferibilmente prescrivibile e in quali forme?	***Dosaggio consigliato*** Il dosaggio raccomandato di anakinra nei pazienti adulti è pari a 100 mg somministrati una volta al giorno per 10 giorni tramite iniezione sottocutanea.



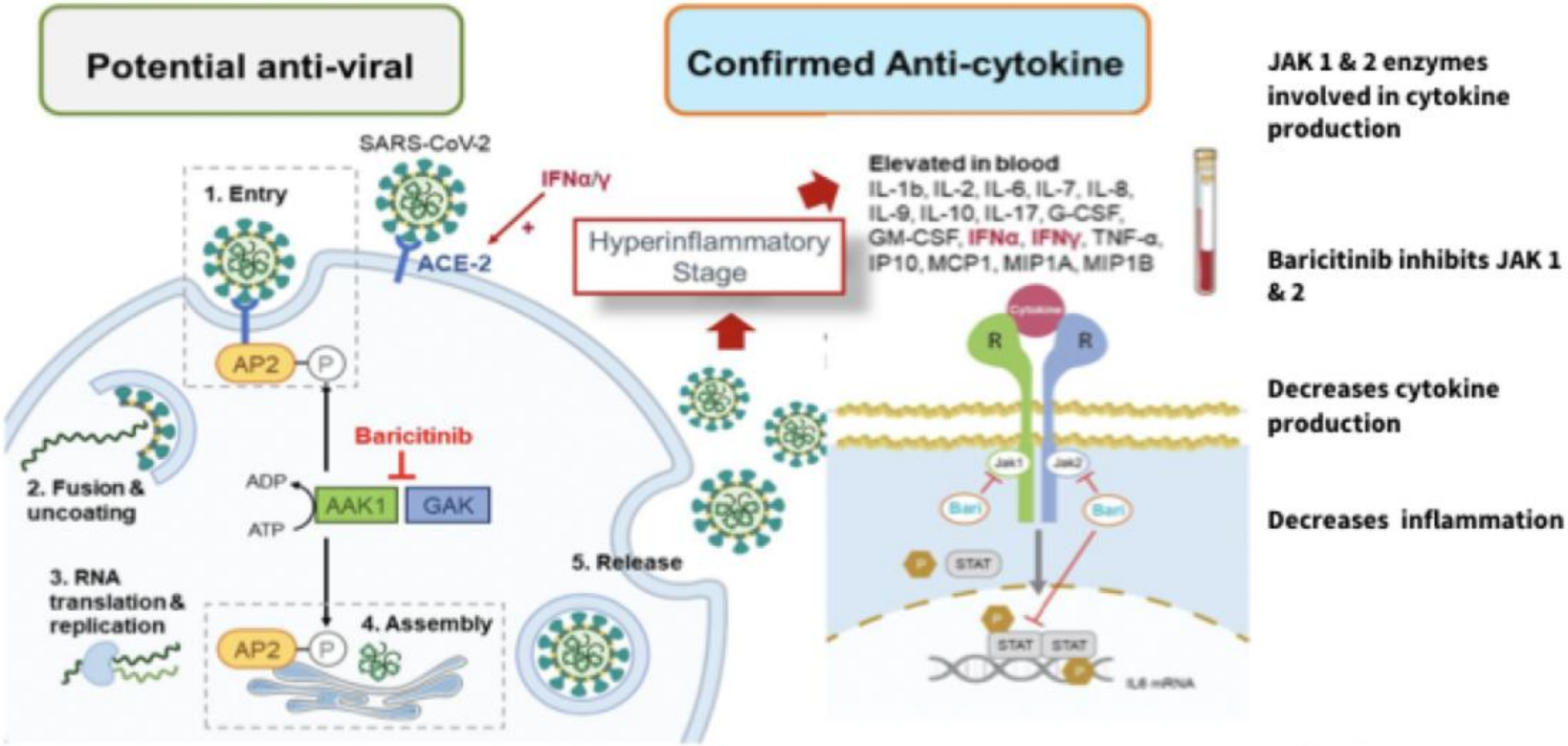
Baricitinib è un inibitore selettivo e reversibile di Janus chinasi (JAK)1 e JAK2, enzimi intracellulari coinvolti nella trasmissione del segnale di citochine e fattori di crescita, implicati nell'ematopoiesi e nella risposta immunitaria.

Baricitinib è autorizzato da EMA per le seguenti condizioni cliniche:

- trattamento dell'artrite reumatoide in fase attiva da moderata a severa nei pazienti adulti che hanno avuto una risposta inadeguata, o che sono intolleranti, ad uno o più farmaci anti-reumatici modificanti la malattia. Olumiant® può essere somministrato in monoterapia o in associazione con metotrexato;
- trattamento della dermatite atopica da moderata a severa in pazienti adulti che sono candidati ad una terapia sistemica (questa indicazione non è al momento rimborsata in Italia).

ACTT-2: Baricitinib

Baricitinib: Janus kinase (JAK) inhibitor



JAK 1 & 2 enzymes involved in cytokine production

Baricitinib inhibits JAK 1 & 2

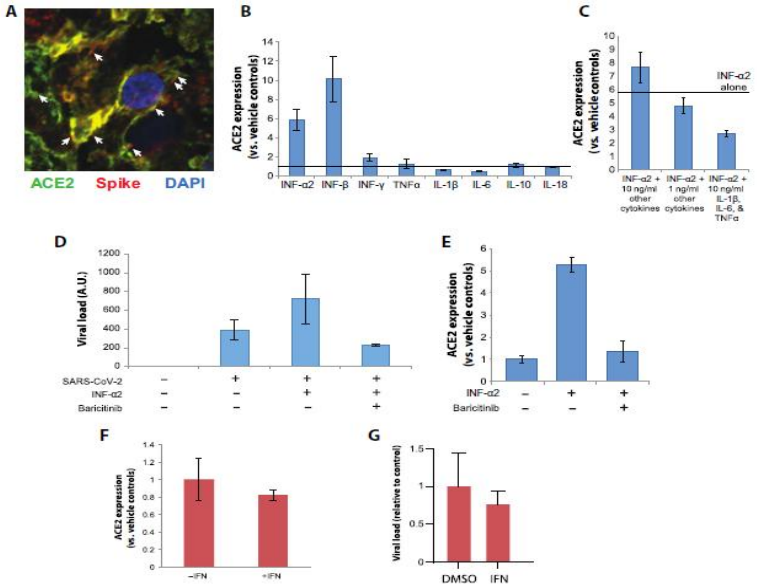
Decreases cytokine production

Decreases inflammation

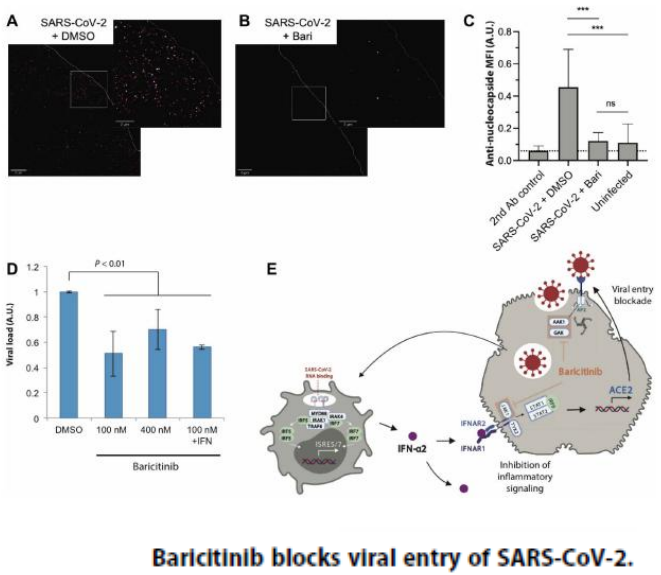
Stanford University

JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality

Justin Stebbing[1*†], Ginés Sánchez Nievas[2†], Marco Falcone[3†], Sonia Youhanna[4†], Peter Richardson[5], Silvia Ottaviani[1], Joanne X. Shen[4], Christian Sommerauer[6], Giusy Tiseo[3], Lorenzo Ghiadoni[3], Agostino Virdis[3], Fabio Monzani[3], Luis Romero Rizos[7,8], Francesco Forfori[9], Almudena Avendaño Céspedes[7,8], Salvatore De Marco[10], Laura Carrozzi[9], Fabio Lena[11], Pedro Manuel Sánchez-Jurado[7,8], Leonardo Gianluca Lacerenza[11], Nencioni Cesira[12], David Caldevilla Bernardo[13], Antonio Perrella[12], Laura Niccoli[14], Lourdes Sáez Méndez[15], Daniela Matarrese[16], Delia Goletti[17], Yee-Joo Tan[18], Vanessa Monteil[19], George Dranitsaris[20], Fabrizio Cantini[14], Alessio Farcomeni[21], Shuchismita Dutta[22], Stephen K. Burley[22], Haibo Zhang[23], Mauro Pistello[24], William Li[25], Marta Mas Romero[7], Fernando Andrés Pretel[26], Rafaela Sánchez Simón-Talero[27], Rafael García-Molina[7], Claudia Kutter[6], James H. Felce[28], Zehra F. Nizami[28], Andras G. Miklosi[28], Josef M. Penninger[29,30], Francesco Menichetti[3‡], Ali Mirazimi[18‡], Pedro Abizanda[7,8‡], Volker M. Lauschke[4*‡]



Baricitinib inhibits cytokine-mediated increased infectivity of SARS-CoV-2 in organotypic primary human liver culture.



Baricitinib blocks viral entry of SARS-CoV-2.

In summary, we have confirmed dual actions of baricitinib, demonstrating its ability to inhibit viral entry into primary human hepatocyte spheroids and the reduction in inflammatory markers in patients with COVID-19 as per our suggested model (Fig. 5C). In addition, we show that baricitinib prevents the type-1 IFN–mediated increase in expression of ACE2, the receptor for SARS-CoV-2.

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak,

N Engl J Med 2021;384:795-807.
DOI: 10.1056/NEJMoa2031994

ACTT-2 **Adaptive Covid-19 Treatment Trial – 2**

METHODS

We conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15.

RESULTS

A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; P=0.03), as were new infections (5.9% vs. 11.2%; difference, −5.3 percentage points; 95% CI, −8.7 to −1.9; P=0.003).

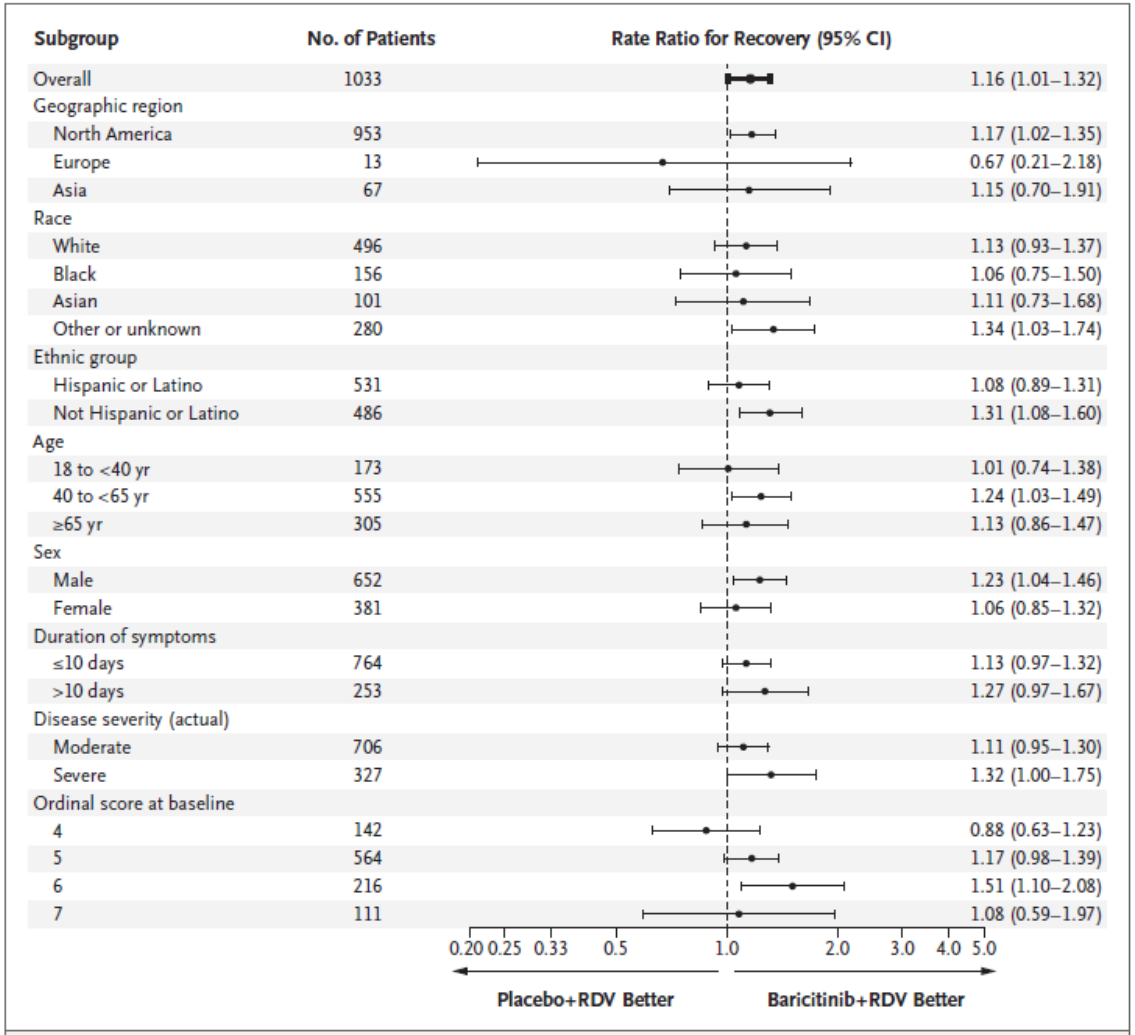


Figure 3. Time to Recovery According to Subgroup.

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status, notably among patients receiving high-flow oxygen or noninvasive mechanical ventilation. The combination was associated with fewer serious adverse events.

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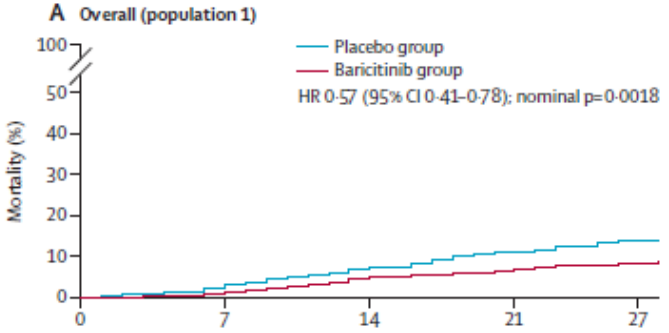
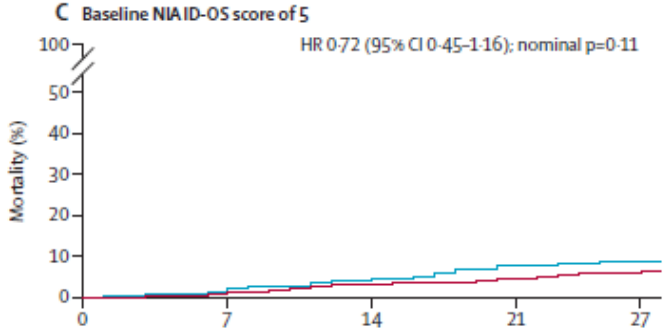
Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

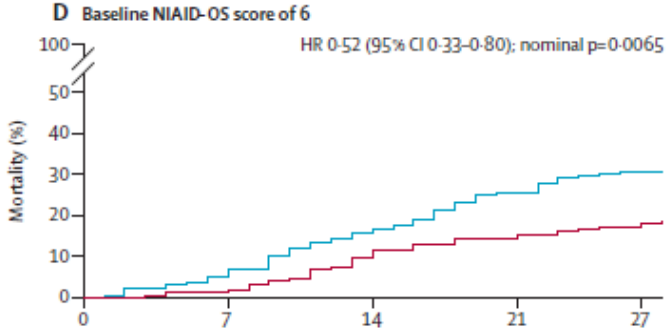
Lancet Respir Med 2021; 9: 1407–18

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

Methods In this phase 3, double-blind, randomised, placebo-controlled trial, participants were enrolled from 101 centres across 12 countries in Asia, Europe, North America, and South America. Hospitalised adults with COVID-19 receiving standard of care were randomly assigned (1:1) to receive once-daily baricitinib (4 mg) or matched placebo for up to 14 days. Standard of care included systemic corticosteroids, such as dexamethasone, and antivirals, including remdesivir. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28, assessed in the intention-to-treat population. All-cause mortality by day 28 was a key secondary endpoint, and all-cause mortality by day 60 was an exploratory endpoint; both were assessed in the intention-to-treat population. Safety analyses were done in the safety population defined as all randomly allocated participants who received at least one dose of study drug and who were not lost to follow-up before the first post-baseline visit. This study is registered with ClinicalTrials.gov, NCT04421027.







Key findings:

- Overall, there was no significant difference in meeting the primary endpoint (27.8% of baricitinib group vs. 30.5% of the placebo group progressed to death or the need for ventilatory support [OR, 0.85; 95% CI, 0.67-1.08; p=0.18).
- However, the secondary endpoint of 28-day all-cause mortality occurred in 8.1% (N=62) for baricitinib as compared to 13.1% (N=100) for placebo, corresponding to a 38.2% reduction in mortality in the baricitinib group (HR, 0·57; 95% CI, 0.41-0.78; nominal p=0.0018).
    - Number needed to treat to prevent one additional death of 20.
- The exploratory endpoint of 60-day all-cause mortality was observed in 10.3% (N=79) for baricitinib and 15.2% (N=116) for placebo (HR, 0.62; 95% CI, 0.47-0.83; p=0.0050).
- A significant reduction in mortality was observed for participants with baseline severity subgroup Ordinal Scale 6 with baricitinib compared with placebo (17.5% [32/183] vs. 29.4% [55/187]; HR, 0.52, 95% CI, 0.33-0.80; nominal p=0·0065), corresponding to a Number Needed to Treat to prevent one death of 9
- Incidence of serious adverse events was similar in the two groups (14.7% [N=110] vs. 18.0% [N=135] in the baricitinib and placebo groups, respectively).
    - Incidence of serious infections was also similar (8.5% [N=64] vs. 9.8% [N=74]) in baricitinib and placebo groups.
    - Incidence of venous thromboembolic events was also similar across groups (2.7% [n=20] in the baricitinib group vs 2.5% [n=19] in the placebo group).

Limitations:

- No control for multiple comparisons.
- Day 28 mortality was a secondary endpoint, with nominal p-value reported.
- Pronounced evolution in the standard of care over the course of the trial.
- Primary outcome based on ordinal scale reflects decisions of treating physicians, which could be based on heterogeneous and cultural factors across sites.

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

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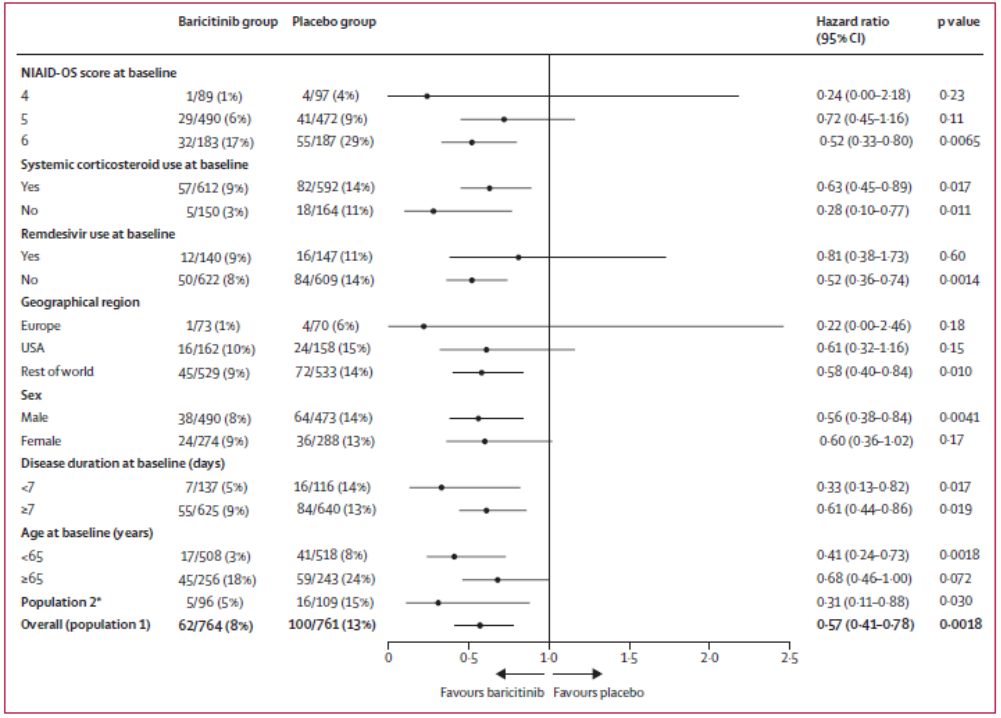

	Baricitinib group (n=750)	Placebo group (n=752)
Treatment-emergent adverse event	334 (45%)	334 (44%)
Mild	133 (18%)	115 (15%)
Moderate	90 (12%)	89 (12%)
Severe	111 (15%)	130 (17%)
Death due to adverse event*	12 (2%)	31 (4%)
Serious adverse event	110 (15%)	135 (18%)
Discontinuation from study treatment due to adverse event (including death)	56 (7%)	70 (9%)
Treatment-emergent infection	119 (16%)	123 (16%)
Serious infections	64 (9%)	74 (10%)
Herpes simplex	1 (<1%)	4 (1%)
Herpes zoster	1 (<1%)	4 (1%)
Tuberculosis	1 (<1%)	0
Opportunistic infections	6 (1%)	7 (1%)
Candida infection	1 (<1%)	0
Eye infection, fungal	0	1 (<1%)
Fungal retinitis	1 (<1%)	0
Herpes zoster	1 (<1%)	3 (<1%)
Listeriosis	0	1 (<1%)
Oropharyngeal candidiasis	0	1 (<1%)
Pulmonary tuberculosis	1 (<1%)	0
Systemic Candida	2 (<1%)	0
Varicella zoster virus infection	0	1 (<1%)
Venous thromboembolic event†	20 (3%)	19 (3%)
Deep vein thrombosis	4 (1%)	2 (<1%)
Pulmonary embolism	13 (2%)	9 (1%)
Other peripheral venous thrombosis	8 (1%)	10 (1%)
Major adverse cardiovascular event	8 (1%)	9 (1%)
Cardiovascular death	1 (<1%)	3 (<1%)
Myocardial infarction	4 (1%)	4 (1%)
Stroke	4 (1%)	4 (1%)
Gastrointestinal perforation	0	0

Data are n (%). Data were assessed from days 1–28. *Included in overall mortality together with deaths due to disease progression. †Positively adjudicated by an independent external blinded clinical event committee.

Table 3: **Adverse events in the safety population**

In summary, our results suggest that baricitinib reduces 28-day and 60-day mortality when used in addition to the current standard of care. The safety profile was similar between the baricitinib group and the placebo group. As such, baricitinib plus standard of care could be a treatment option to reduce overall deaths in the context of the global burden of mortality during the COVID-19 pandemic.

Lancet Respir Med 2021; 9: 1407–18

AGENZIA ITALIANA DEL FARMACO

Baricitinib nella terapia dei pazienti adulti con COVID-19
CTS, 23 settembre 2021

Per quali pazienti è raccomandabile?	Alla luce delle attuali conoscenze, nonché della potenziale carenza delle alternative già disponibili in L648/96 per la medesima indicazione, il baricitinib può essere usato per il trattamento di soggetti adulti ospedalizzati con COVID-19 grave, in ossigenoterapia ad alti flussi o in ventilazione meccanica non invasiva, e/o con livelli elevati degli indici di infiammazione sistemica. In particolare, si considerano candidabili al trattamento con baricitinib i pazienti ospedalizzati con condizioni cliniche rapidamente ingravescenti: • Pazienti recentemente ospedalizzati con fabbisogno di ossigeno in rapido aumento che richiedono ventilazione meccanica non invasiva o ossigeno ad alti flussi in presenza di elevati livelli di indici di flogosi (CRP≥75 mg/L). Non è consentita la co-somministrazione con inibitori delle interleuchine o con altri JAK-inibitori.

AGENZIA ITALIANA DEL FARMACO

Baricitinib nella terapia dei pazienti adulti con COVID-19
CTS, 23 settembre 2021

Principali Interazioni (da scheda tecnica):

Il trattamento concomitante di baricitinib con DMARD biologici, biologici immunomodulanti o con altri inibitori delle Janus chinasi (JAK) e con antagonisti del TNF-alfa non è raccomandato.

Dosaggio consigliato

Il dosaggio raccomandato di baricinib nei pazienti adulti è pari a 4 mg somministrati *per os* una volta al giorno per una durata massima di 14 giorni (o fino a dimissione dall'ospedale per risoluzione clinica, se antecedente).

- se eGFR 30-<60 mL/min/1.73m^2: 2 mg PO QD
- se eGFR <30 mL/min/1.73m^2: non somministrare

Quali sono i maggiori rischi in termini di reazioni avverse?	**Avvertenze** (da scheda tecnica): • Neutropenia e infezioni gravi • Eventi epatici • Diverticolite e di perforazione gastrointestinale • Tromboembolismo venoso

7605 Studies found for: **COVID-19**

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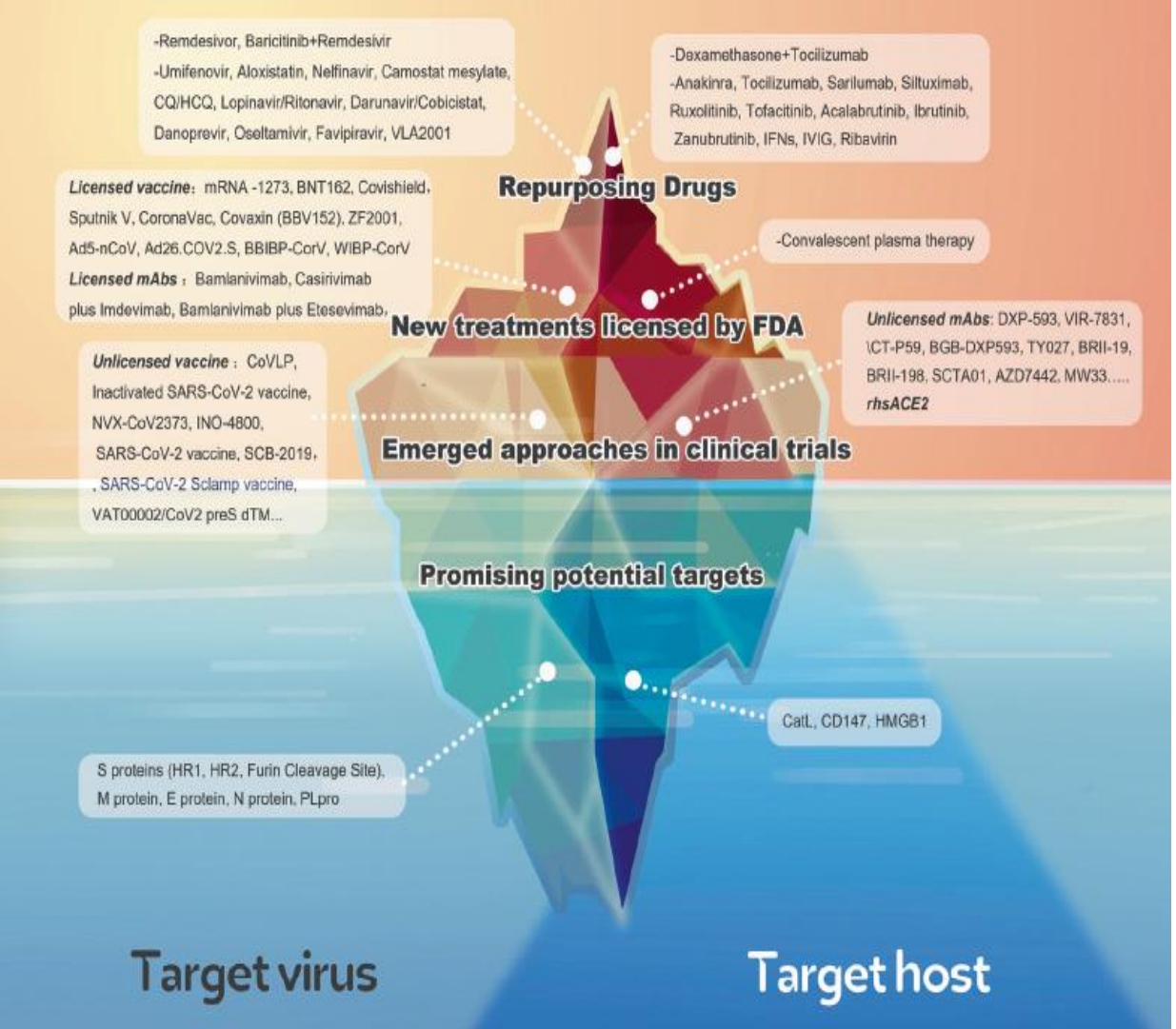
- **NIH**: COVID-19 Treatment Guidelines
- **ClinicalTrials.gov**: Views of Listed COVID-19 Studies (Beta)



- **Most targets or new drugs were a failure in the preclinical trial**
- **There is a gap between potential targets/new drug discovery and clinical translation**
- **The old drugs are really shortcuts or just distract our attention ?**
- **Several approach :**

  - concentrating on the must potential druggable targets
  - strengthening cooperation among multiple disciplines
  - long-term monitoring of virus mutations

THERE IS STILL A LONG WAY TO GO

Signal Transduction and Targeted Therapy (2021)6:317