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SCIENCE MEDICINES HEALTH

La ricerca per la lotta alla pandemia globale: strategie di ricerca in Europa e nel mondo

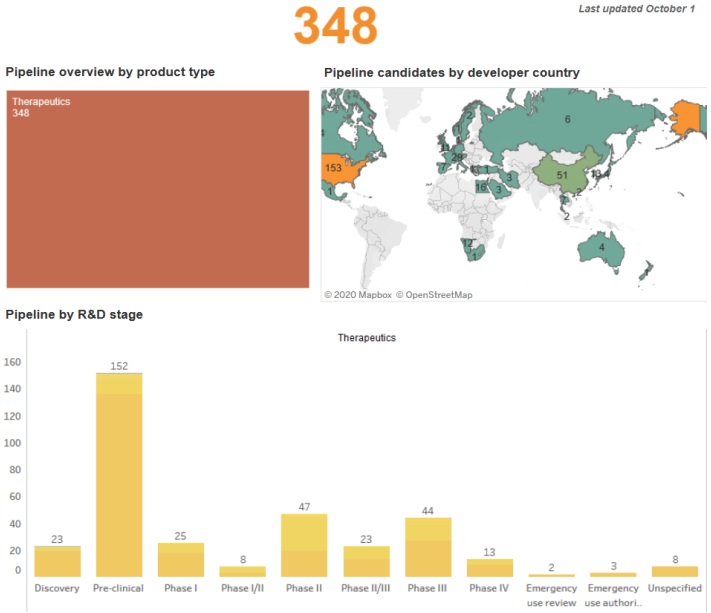
Milano Life Sciences Forum 2020

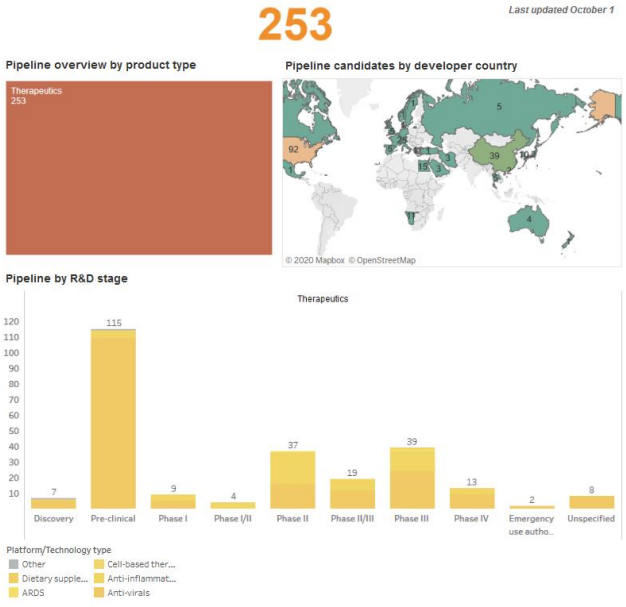
EMA 25 years

Presented by Dr. Marco Cavaleri on 11 December 2020
Head of Biological Health Threats and Vaccines Strategy

Therapeutics for COVID- pipeline (total and repurposed)

73% for repurposed drugs!





https://www.policycuresresearch.org/covid-19-r-d-tracker

1 Repurposing existing drugs – study results review

Repurposing of drugs for COVID: potential targets

Potential antivirals

- Remdesivir (EU CMA: Veklury)
- Favipiravir
- Lopinavir-ritonavir
- Hydroxychloroquine/chloroquine
- And others: cyclosporine, camostat, colchicine

Potential immune modulators

- Corticosteroids (dexamethasone)
- IFN beta
- Convalescent plasma
- IL6R inhibitors
- JAK inhibitors

In vitro testing

Infect Dis Ther (2020) 9:561–572

Table 1 Summary of in vitro EC50 values reported for hydroxychloroquine/chloroquine from selected studies

Author	Medication	Cell line	MOI	Time-point[a]	EC_{50}[b]
Liu et al. [[35]]	HCQ (chloroquine)	VeroE6	0.01	48 h	4.51 (2.71)
			0.02		4.06 (3.81)
			0.2		17.31 (7.14)
			0.8		12.96 (7.36)
Wang et al. [[36]]	Chloroquine	VeroE6	0.05	48 h	1.13
Yao et al. [[37]]	HCQ (chloroquine)	Vero[c]	0.01	24 h	6.14 (23.90)
				48 h	0.72 (5.47)
Maisonnasse et al. [25]	HCQ	VeroE6	0.01	48 h	2.19[d]
				72 h	4.39[d]

[a] Post-infection
[b] Expressed in μM
[c] Not stated in article if VeroE6 was the lineage utilized
[d] IC_{50} (not EC_{50})

https://doi.org/10.1007/s40121-020-00325-2

Tissue penetration

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Yao X, et al, 2020

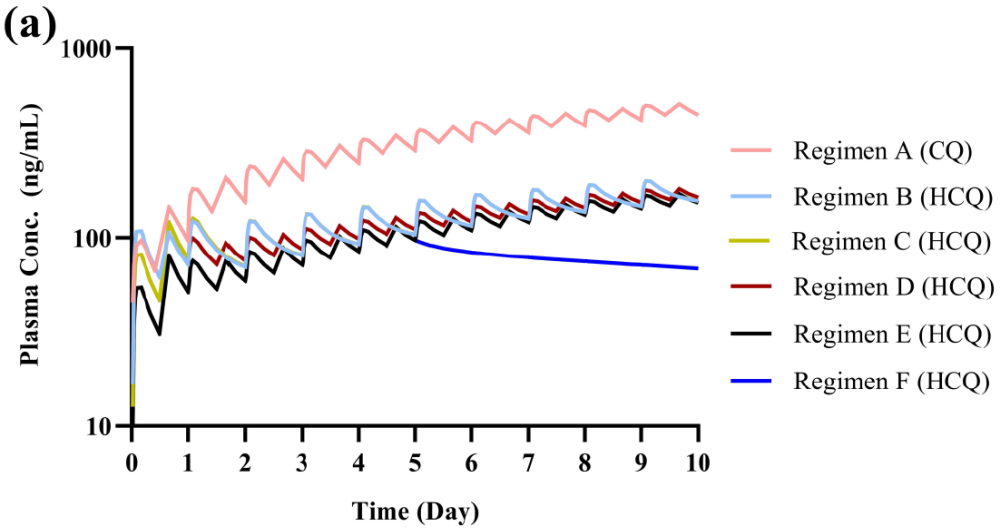
R_{LTEC}= Free lung tissue trough concentration/EC50

Free lung tissue trough concentration= lung tissue trough concentration X fup

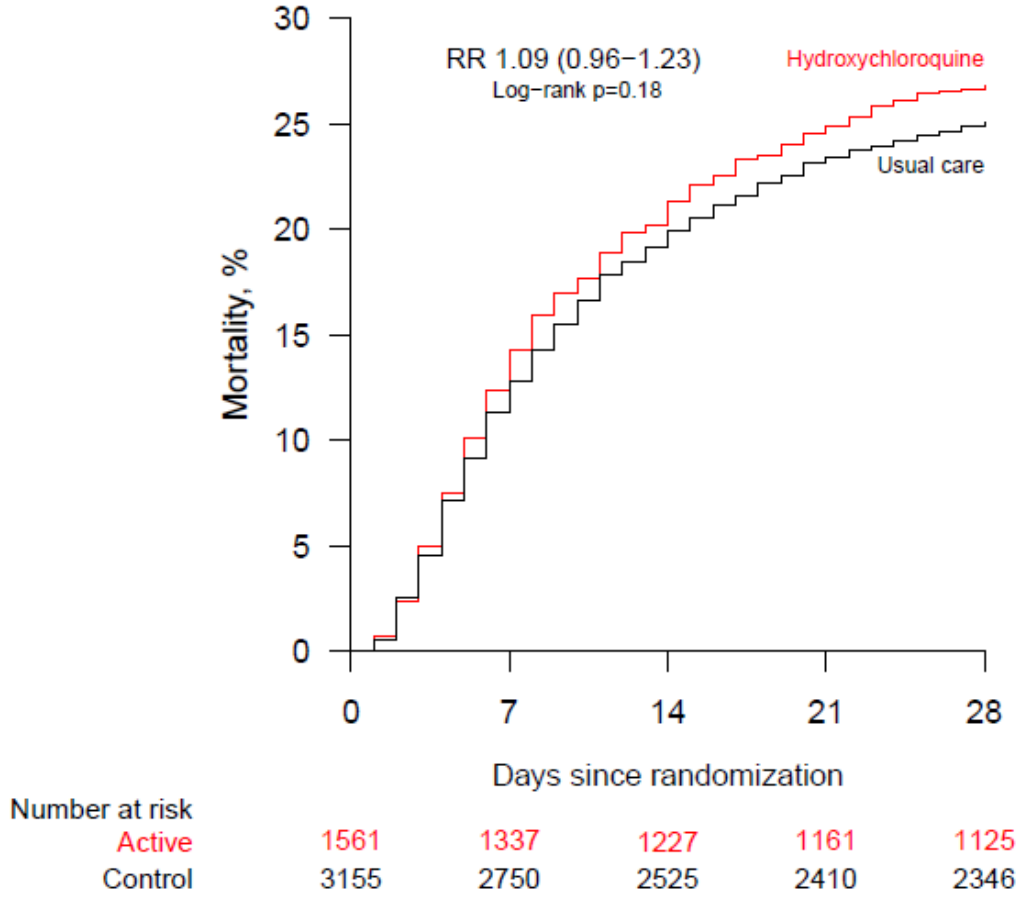
Table 1: Ratios of free lung tissue trough concentration/EC_{50} (R_{LTEC}) under different dosage regimens

Drug	NO.	Dosing Regimen	R_{LTEC}			
			Day1	Day3	Day5	Day10
Chloroquine phosphate	A.	D1-D10 500 mg BID	2.38	5.92	18.9	40.7
Hydroxychloroquine sulfate	B.	D1 800 mg+400 mg; D2-D10 400 mg QD	33.3	55.1	103	168
	C.	D1 600 mg BID; D2-D10 400 mg QD	31.7	54.7	103	169
	D.	D1 600 mg BID; D2-D10 200 mg BID	31.7	53.1	101	167
	E.	D1 400 mg BID; D2-D10 200 mg BID	21.0	38.9	85.4	154
	F.	D1 400 mg BID; D2-D5 200 mg BID	21.0	38.9	85.4	83.3

R_{LTEC}: ratio of free lung tissue trough concentration/EC_{50}.



WHO Solidarity study: CQ 2.5g on DAY 1 and 1g daily up to 10 days; HCQ 2g DAY 1 and 800mg daily up to 10 days

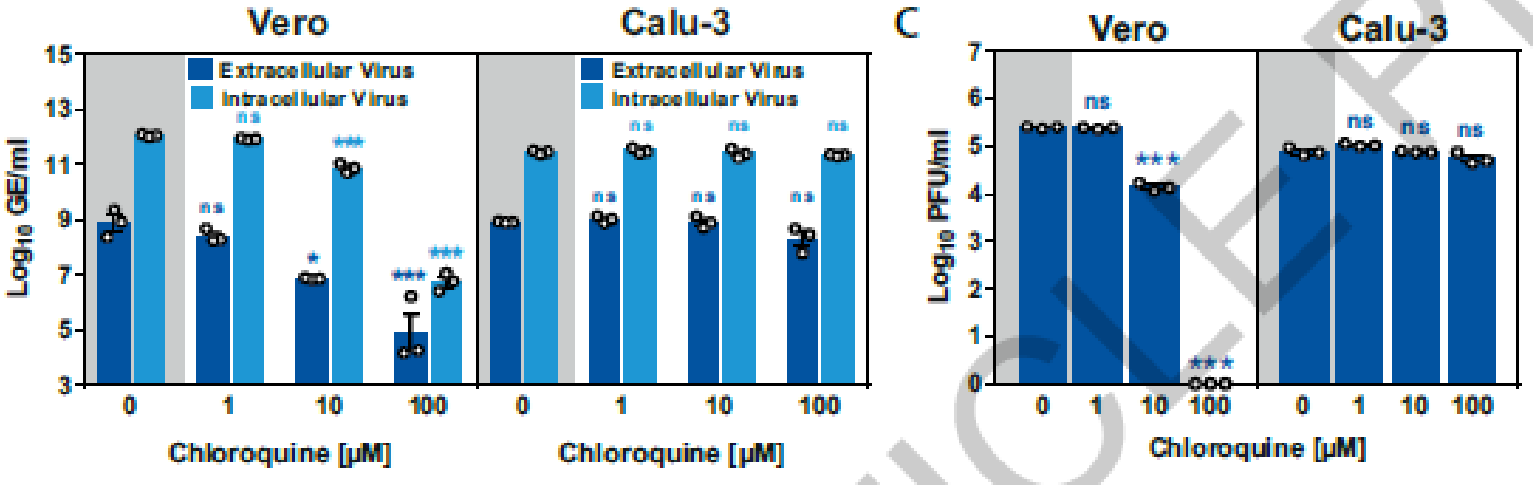


Hydroxychloquine RECOVERY study

medRxiv preprint doi: https://doi.org/10.1101/2020.07.15.20151852.this version posted July 15, 2020.

Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2

https://doi.org/10.1038/s41586-020-2575-3 Markus Hoffmann[1,2]✉, Kirstin Mösbauer[3,4], Heike Hofmann-Winkler[1], Artur Kaul[1], Hannah



Importance of protein binding

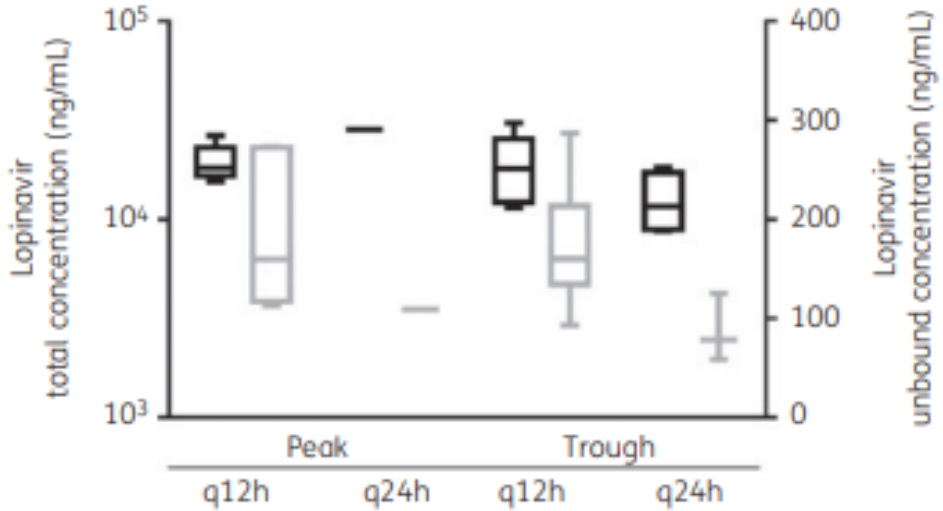


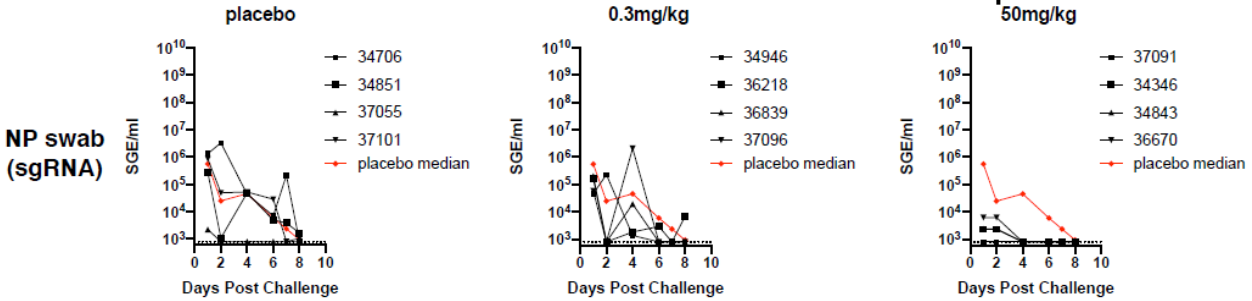
Figure 1. Lopinavir concentrations in SARS-CoV-2-infected patients after ritonavir-boosted lopinavir 400/100 mg once or twice daily. Total (black) and unbound (grey) concentrations are represented by medians, IQRs and ranges at peak (4±1 h after intake) or trough (q12h: at least 10 h after intake; and q24h: at least 18 h after intake).

Lopinavir	EC_{50} = 26.63 µM (16.75 µg/mL) (Choy et al., 2020) EC_{50} = 15.27 µM (9.60 µg/mL) (Jeon et al., 2020)

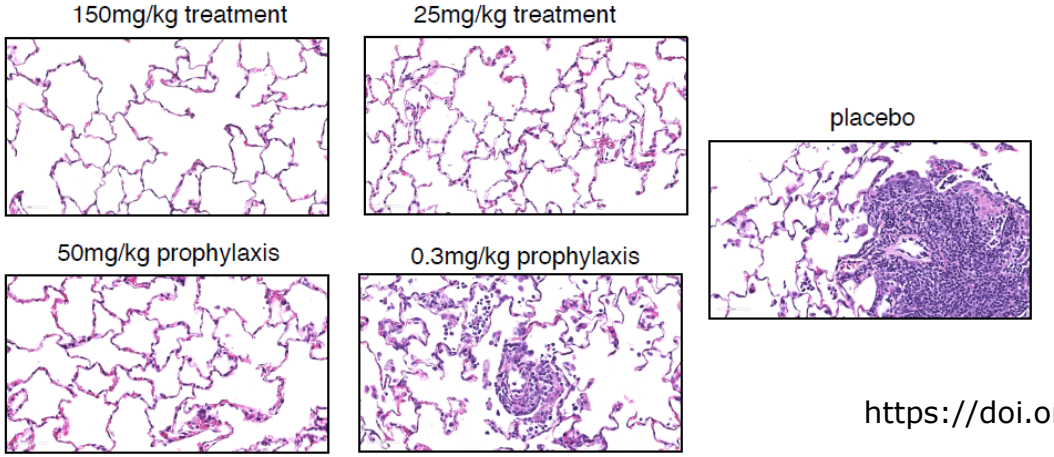
Gregoire M, Le Turnier P, Gaborit BJ, et al. Lopinavir pharmacokinetics in COVID-19 patients. *J Antimicrob Chemother*. 2020;75(9):2702-2704. doi:10.1093/jac/dkaa195

Animal models

Antiviral Monoclonal antibodies in SARS-COV2 challenge model in rhesus macaques



Prevention macaques



Treatment macaques

https://doi.org/10.1101/2020.08.02.233320.

What have we learned from the therapeutics RCTs?

A worldwide effort to conduct RCTs. BUT, coordination and size not optimal

Both researchers and regulators must reflect on the need for large collaborative RCTS

Studies registered	1178
Completed	15
Recruiting	644
Not recruiting	515
Suspended	2
Terminated	2

Sample sizes (ranging from 30 – 10000) and endpoints

https://www.covid-nma.com/dataviz/

Data from May 2020

Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?

Hans-Georg Eichler[1,2,*], Marco Cavaleri[1], Harald Enzmann[3,4], Francesca Scotti[1], Bruno Sepodes[4,5], Fergus Sweeney[1], Spiros Vamvakas[1] and Guido Rasi[1,6]

The scientific community has risen to the coronavirus disease 2019 (COVID-19) challenge, coming up with an impressive list of candidate drugs and vaccines targeting an array of pharmacological and immunological mechanisms. Yet, generating clinical evidence of efficacy and safety of these candidate treatments may be frustrated by the absence of comprehensive trial coordination mechanisms. Many small stand-alone trials and observational studies of single-agent interventions are currently running or in planning; many of these will likely not deliver robust results that could support regulatory and patient-level treatment decisions. In this paper, we discuss actions that all stakeholders in the clinical trial ecosystem need to take to ensure that the window of opportunity during this pandemic will not shut, both for patients in need of treatment and for researchers to conduct decision-relevant clinical trials.

This article has been retracted: N Engl J Med. DOI: 10.1056/NEJMc2021225.
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., and Amit N. Patel, M.D.

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation ma…ide, are b… widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although …ntrally …ic wh… used for approved indications such as autoimmune disease or malaria, the safety and bene… of th… treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroqu… …quine with… …thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp… in … ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory … for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn… included in … of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlo… …ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed … control g… . Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o… …e they w… on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc… of in… t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias … obtained o… and ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3… women) … COVID-19 were hospitalised during the study period and met the inclusion criteria. Of the … patients … were in the treatment groups (1368 received chloroquine, 3783 received chloroquine with a macrol… , 3016 … ived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and … patients … in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple … , … , … , race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fact… diabetes, … derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), … compared w… rtality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% … 1·22… 457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, …38–1·531), … loroquine with a macrolide (22·2%; 1·368, 1·273–1·468) were each independently associated … an increased … of in-hospital mortality. Compared with the control group (9·3%), hydroxychloroquine (… 2·360, 1·935–2·906), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; … , 2·…3–4·576), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associat… an increased risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretat… …e w… unabl… …firm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrol… on in… …ital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospit… …creased frequency of ventricular arrhythmias when used for treatment of COVID-19.

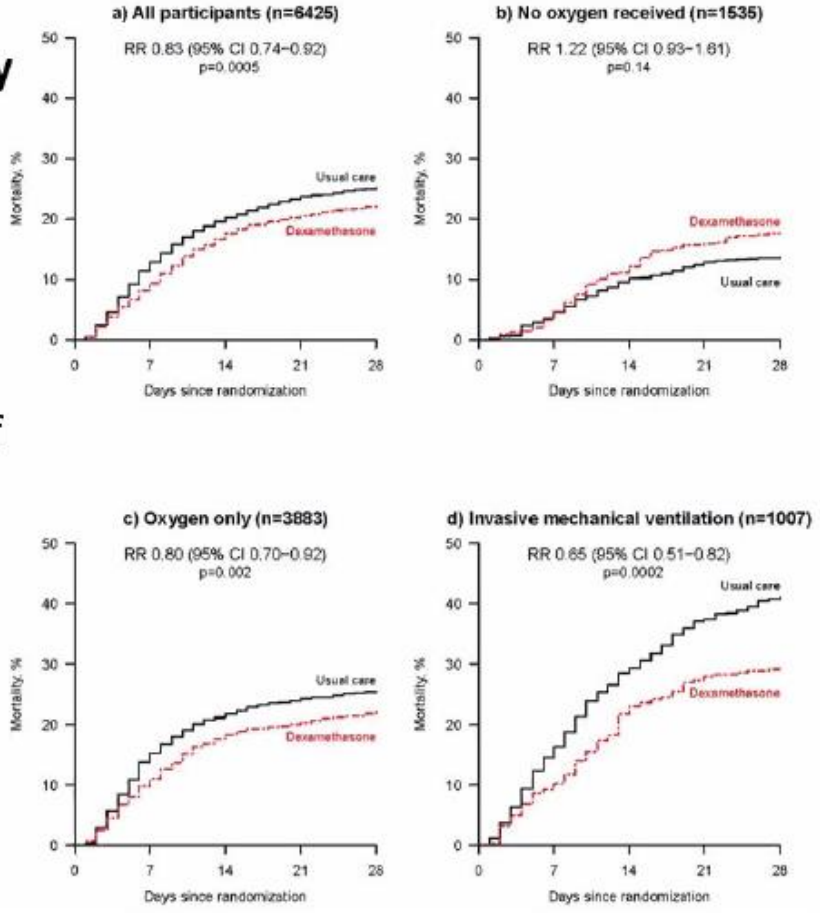
Funding Willia… …ey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

RETRACTED

RECOVERY: 6 mg/day dexamethasone vs open control

(a) All participants;

(b-d) Split by level of respiratory support



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18 September 2020
EMA/483739/2020

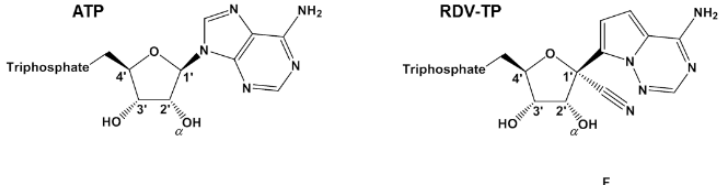
EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

EMA's human medicines committee (CHMP) has completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital, and has concluded that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).

Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days.

Remdesivir

- Nucleoside RNA polymerase inhibitor
- Broad spectrum antiviral activity, including Ebola-and coronaviruses
- Repurposed (has been tried for Ebola, MERS)



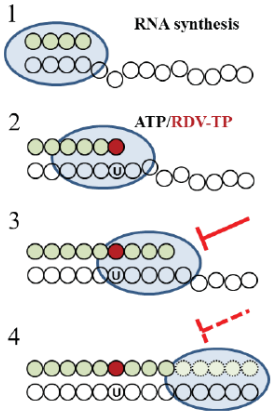
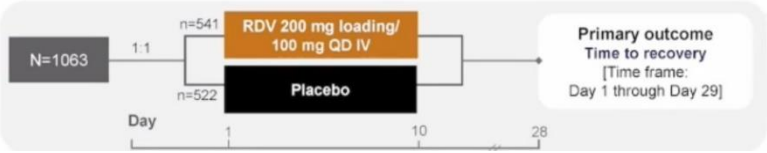


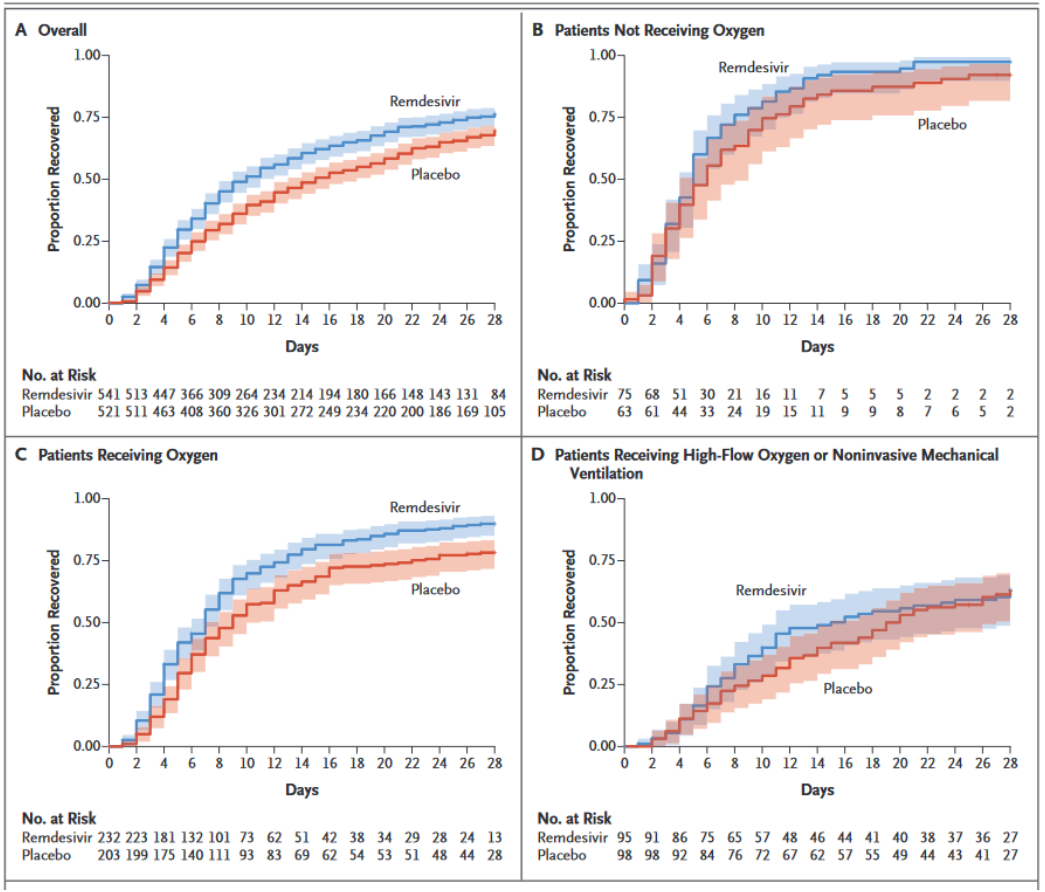
Figure 7. Mechanism of inhibition of CoV RdRp by RDV-TP. 1. The priming strand is shown with green circles, colour less circles represent residues of the template and the blue oval represents the active CoV RdRp complex. This is a schematic representation of a random elongation complex. The footprint of RdRp on its primer/template is unknown. 2. Competition of RDV-TP with its natural counterpart ATP opposite template uridine (U). The incorporated nucleotide analogue is illustrated by the red circle. 3. RNA synthesis is terminated after the addition of three more nucleotides, which is referred to as delayed chain-termination. 4. Delayed chain-termination can be overcome by high ratios of NTP/RDV-TP.

Remdesivir ACTT-1 (positive on TTCR)

- Phase 3,
- adaptive,
- randomized
- Double blind
- Placebo-controlled
- Multicentre
- Global trial

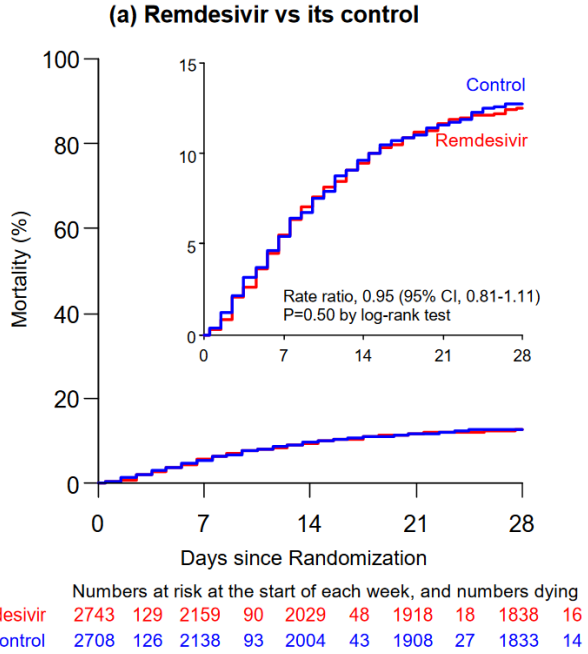
NCT04280705





Beigel, John H., et al. "Remdesivir for the Treatment of Covid-19 — Final Report." N. Engl. J. Med., 22 May. 2020, doi:10.1056/NEJMoa2007764.

RDV-Solidarity trial (negative on mortality)



Trial name, and initial respiratory support	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%) Remdesivir	Control	Remdesivir deaths: Observed-Expected (O-E)*	Var (O-E)	Ratio of death rates (RR), & 99% CI (or 95% CI, for total) Remdesivir : Control
Solidarity: no O_2	11/661 (2.0)	13/664 (2.1)	-0.6	6.0	0.90 [0.31-2.58]
Solidarity: low/hi-flow O_2	192/1828 (12.2)	219/1811 (13.8)	-16.9	101.8	0.85 [0.66-1.09]
Solidarity ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 [0.80-1.80]
ACTT: no O_2	3/75 (4.1)	3/63 (4.8)	-0.3	1.5	0.82 [0.10-6.61]
ACTT: low-flow O_2	9/232 (4.0)	25/203 (12.7)	-8.0	6.7	0.30 [0.11-0.81]
ACTT: hi-flow O_2 or non-invasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 [0.44-2.34]
ACTT: invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.7	14.3	1.13 [0.57-2.23]
Wuhan: low-flow O_2	11/129 (8.5)	(7/68) x2† (10.3)	-0.8	3.7	0.81 [0.21-3.07]
Wuhan: hi-flow O2 or ventilation	11/29 (37.9)	(3/10) x2† (30.0)	0.6	1.8	1.40 [0.20-9.52]
SIMPLE: no O_2	5/384 (1.3)	(4/200) x2† (2.0)	-0.9	2.0	0.64 [0.10-3.94]
Subtotals					
Lower risk groups (with no ventilation)	231/3309 (7.0)	282/3277 (8.6)	-27.6	121.6	0.80 [0.63-1.01]
Higher risk groups	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 [0.85-1.60]
Total	**387/3818 (10.1)**	**408/3782 (10.8)**	**-17.5**	**188.2**	**0.91 [0.79-1.05]**
					2p = 0.20

99% or 95% confidence interval (CI), K-M Kaplan-Meier.

0.0 0.5 1.0 1.5 2.0 2.5 3.0
Remdesivir better
Remdesivir worse

* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.$\log_e$HR for ACTT strata (with the weight w being the inverse of the variance of $\log_e$HR, which is got from the HR's CI). RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

COVID-19 SOLIDARITY

"Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results." medRxiv, 15 Oct. 2020, p. 2020.10.15.20209817, doi:10.1101/2020.10.15.20209817.

US convalescent plasma EAP

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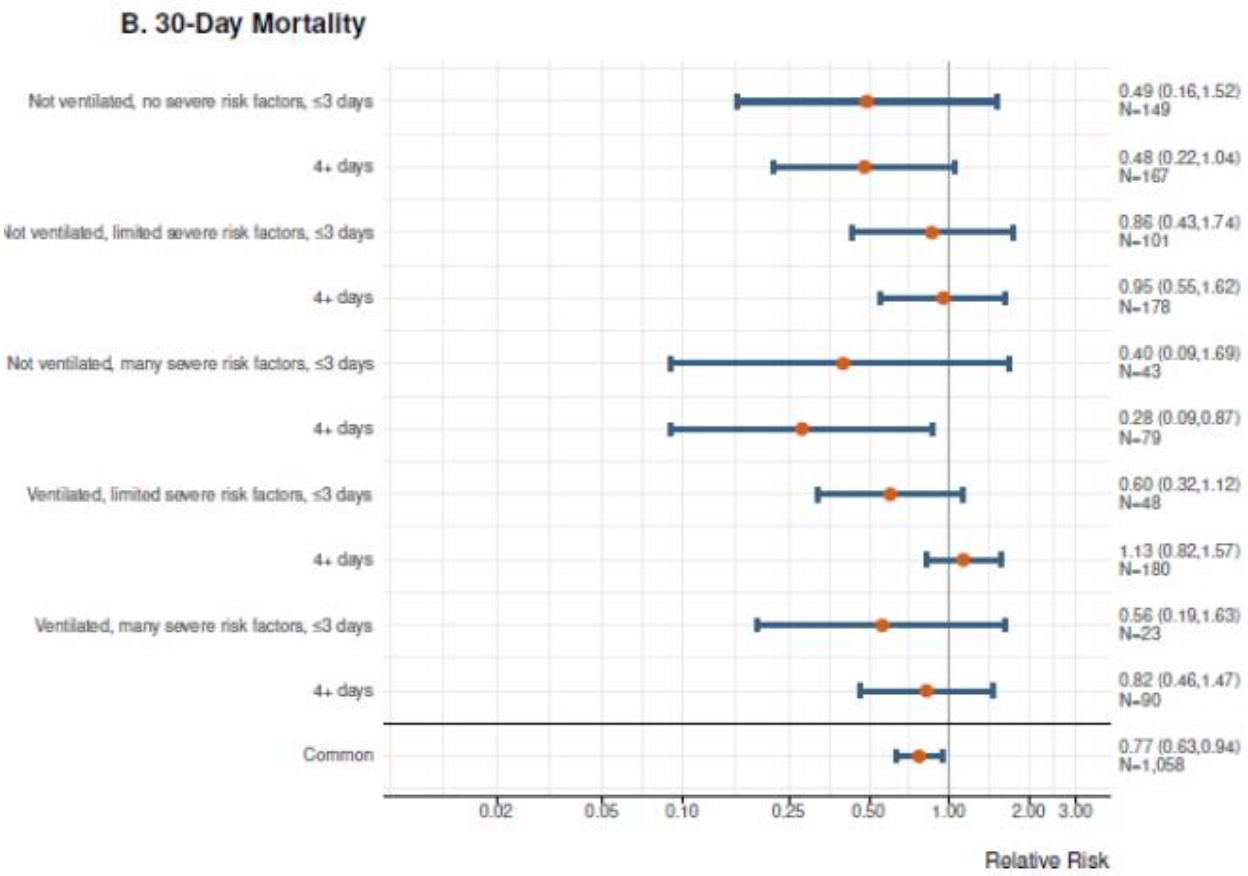

Forest plots of relative risks for 30- day (B) mortality for high versus low antibody concentration.

medRxiv preprint doi:
https://doi.org/10.1101/2020.08.12.2016935

Convalescent Plasma for COVID-19. A randomized clinical trial

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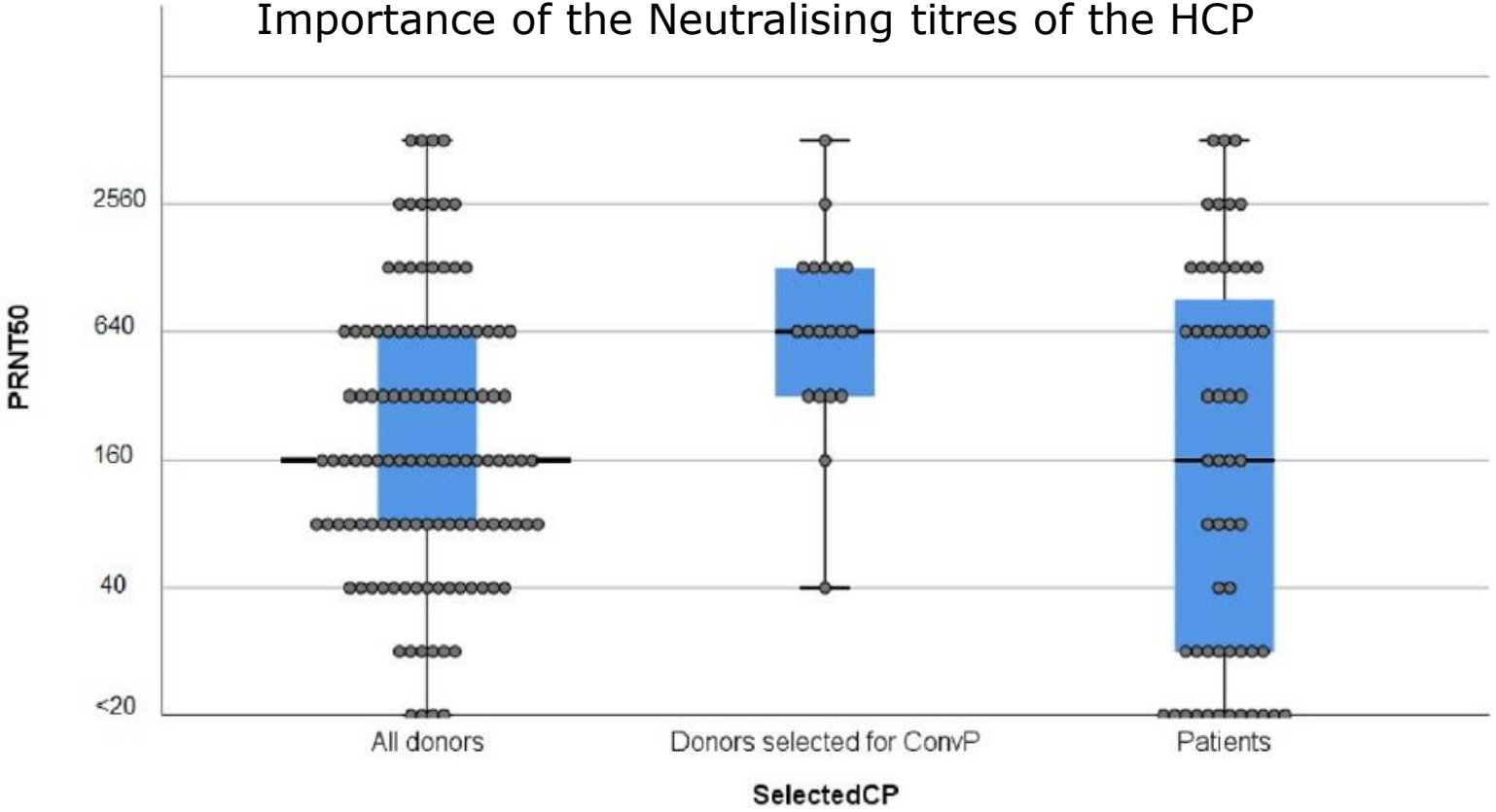
Importance of the Neutralising titres of the HCP



medRxiv preprint doi: https://doi.org/10.1101/2020.07.01.20139857

Lilly Bamlanivimab – outpatient use in mild COVID-19

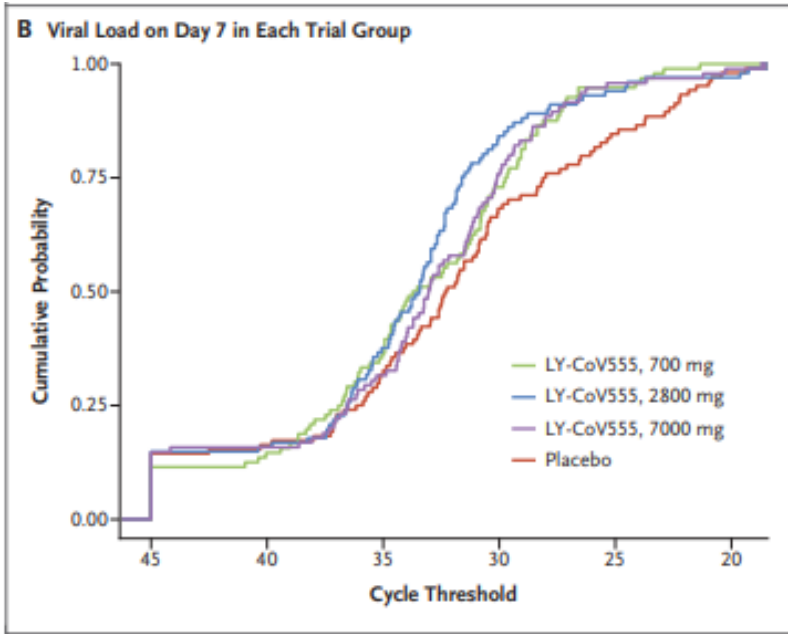


Figure 2. SARS-CoV-2 Viral Load in All Patients and According to Trial Group on Day 7.

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* Data for patients who presented to the emergency department are included in this category.

DOI: 10.1056/NEJMoa2029849

Statement—NIH-Sponsored ACTIV-3 Trial Closes LY-CoV555 Sub-Study

October 26, 2020

The ACTIV-3 clinical trial evaluating the investigational monoclonal antibody LY-CoV555 in hospitalized patients with COVID-19 will not enroll more participants into this sub-study following a recommendation from the independent Data and Safety Monitoring Board (DSMB). The trial is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

ACTIV-3 is a master protocol designed to allow for the study of multiple investigational agents compared to placebo in adults hospitalized with COVID-19. Participants in the trial are randomly assigned to receive either an experimental agent or a matched placebo. All participants also receive standard care for patients hospitalized with COVID-19, including the antiviral remdesivir. After five days, participants' clinical status is assessed based on an ordinal scale. If the investigational agent appears to be safe and effective based on an evaluation of the first 300 participants (stage 1), an additional 700 participants are randomized and followed for 90 days to assess sustained recovery, defined as being discharged, alive and home for 14 days (stage 2).

Regeneron antibodies hospitalised patients clinical study

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REGN-COV2 Independent Data Monitoring Committee Recommends Holding Enrollment in Hospitalized Patients with High Oxygen Requirements and Continuing Enrollment in Patients with Low or No Oxygen Requirements

October 30, 2020

TARRYTOWN, N.Y., Oct. 30, 2020 /PRNewswire/ --

The IDMC also recommends continuation of enrollment in the REGN-COV2 outpatient trial

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) received today a recommendation from the independent data monitoring committee (IDMC) for the REGN-COV2 antibody cocktail treatment trials for COVID-19 that the current hospitalized patient trial be modified. Specifically, based on a potential safety signal and an unfavorable risk/benefit profile at this time, the IDMC recommends further enrollment of patients requiring high-flow oxygen or mechanical ventilation be placed on hold pending collection and analysis of further data on patients already enrolled. The IDMC also recommends continuing enrollment of hospitalized patients requiring either no or low-flow oxygen as the risk/benefit remains acceptable in these cohorts. Finally, the IDMC recommends continuation of the outpatient trial without modification.

Regeneron remains blinded to the data and is implementing the IDMC recommendations. Regeneron is also informing the U.S. Food and Drug Administration, which is currently evaluating REGN-COV2 for a potential Emergency Use Authorization in mild-to-moderate outpatients at high risk for poor outcomes. Regeneron is also sharing the recommendation with the independent committee monitoring the RECOVERY trial in the UK, which is evaluating REGN-COV2 in hospitalized patients.

About the REGN-COV2 Trial in Hospitalized Patients

The trial is designed to enroll patients in four independently randomized cohorts:

- Cohort 1: patients on low-flow oxygen
- Cohort 1A: patients not requiring oxygen
- Cohort 2: patients on high-flow oxygen
- Cohort 3: patients on mechanical ventilation

GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study

Giacomo De Luca, Giulio Cavalli, Corrado Campochiaro, Emanuel Della-Torre, Piera Angelillo, Alessandro Tomelleri, Nicola Boffini, Stefano Tentori, Francesca Mette, Nicola Farina, Patrizia Rovere-Querini, Annalisa Ruggeri, Teresa D'Aliberti, Paolo Scarpellini, Giovanni Landoni, Francesco De Cobelli, John F Paolini, Alberto Zangrillo, Moreno Tresoldi, Bruce C Trapnell, Fabio Ciceri, Lorenzo Dagna

hyperinflammation, defined as elevation of serum inflammation markers C-reactive protein (CRP) to 100 mg/L or more (normal range <6 mg/L) or ferritin to 900 µg/L or more (normal range 30–400 µg/L), in the presence of any increase in lactate dehydrogenase (LDH; normal range 125–220 U/L).

Mavrilimumab for severe COVID-19

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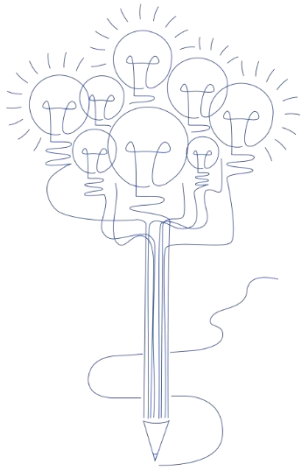
We read with interest the Article by Giacomo De Luca and colleagues[1] in *The Lancet Rheumatology*, in which the authors showed that mavrilimumab treatment was associated with improved clinical outcomes compared with standard care in non-mechanically ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. However, we would like to highlight important limitations of the study

First, the authors used arbitrary cut-off points in continuous variables (serum C-reactive protein, ferritin, and lactate dehydrogenase) for selecting patients with hyperinflammation.[2] Such cut-offs were not derived from or validated in any predictive or prognostic studies in patients with COVID-19 that we are aware of.[3]

1 De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020; **2**: e465–73.
2 Dawson NV, Weiss R. Dichotomizing continuous variables in statistical analysis: a practice to avoid. *Med Decis Making* 2012; **32**: 225–26.
3 Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. *BMJ* 2020; **369**: m1328.
4 Calfee CS, Delucchi KL, Sinha P, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; **6**: 691–98.

Summary



73% of COVID drugs in the pipeline are repurposed

Only 2 drugs currently approved: Veklury and dexamethasone

HCQ/CQ and Lopinavir did not show any benefit

Regulatory acceptance of pragmatic trials such as WHO Solidarity

Role of immunomodulators – many disappointing results so far, but many studies still ongoing

Studies in specific populations according to stage of disease and use of biomarkers for more personalised treatments

Importance of proper pharmacology investigations, dose selection and randomised controlled trials for determining benefits and risks

Any questions?

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