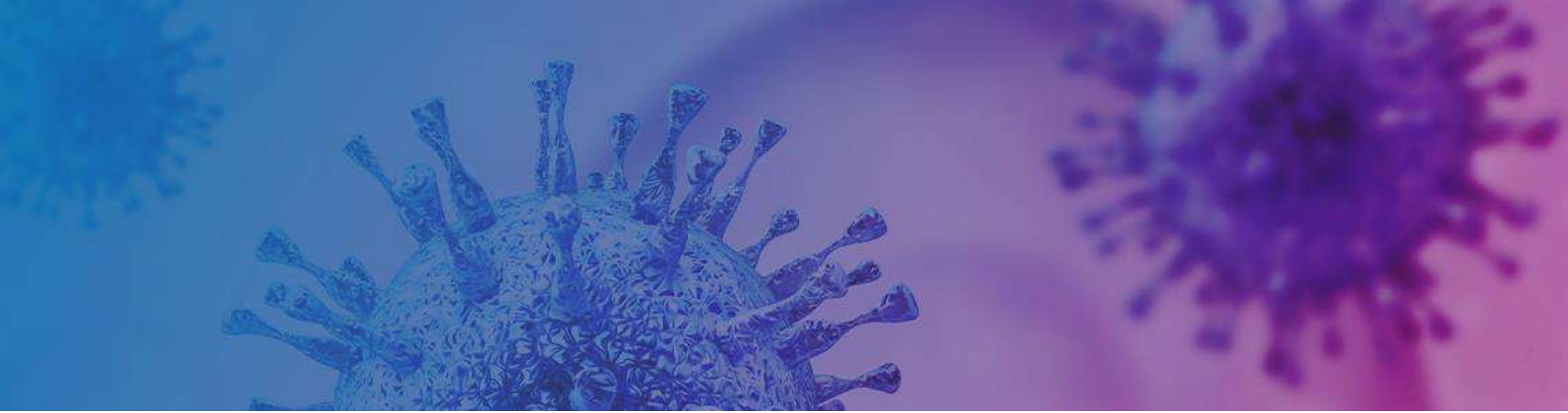


Approches thérapeutiques actuelles et à venir

Pr Bergeron, Pneumologue – Hôpital St Louis

Approches thérapeutiques (hors vaccins)

Approches thérapeutiques (hors vaccins)

- Littérature profuse, pas toujours de bonne qualité scientifique (tri)

- Objectifs pertinents face à :
  - Une pandémie
  - Une maladie qui tue et qui sature le système de soins/hôpitaux (réanimations et services conventionnels)
  - Ce qu'on connait de la maladie (virus, inflammation, thromboses)

- Impact des traitements sur:
  - Mortalité
  - Hospitalisation
  - Passage en réanimation

- Traitements:
  - Accessibles (coût, disponibilité)
  - Balance bénéfice/risque favorable

Annals of Internal Medicine®

01/11/20

Ideas and Opinions | 15 September 2020

The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic FREE

Isabelle Boutron, MD, PhD, Anna Chaimani, PhD, Joerg J. Meerpohl, MD, Asbjørn Hróbjartsson, MD, PhD, MPhil, Declan Devane, PhD, Gabriel Rada, MD, David Tovey, MBChB, Giacomo Grasselli, MD, Philippe Ravaud, MD, PhD, for the COVID-NMA consortium View fewer authors

The COVID-NMA initiative

A living mapping and living systematic review of Covid-19 trials

COVID-NMA is an international research initiative supported by the WHO and Cochrane.

We provide a living mapping of COVID-19 trials available through interactive data visualizations. We are also conducting living evidence synthesis on preventive interventions, treatments and vaccines for COVID-19 to assist decision makers.

See the description of our model here and our living review protocol here.

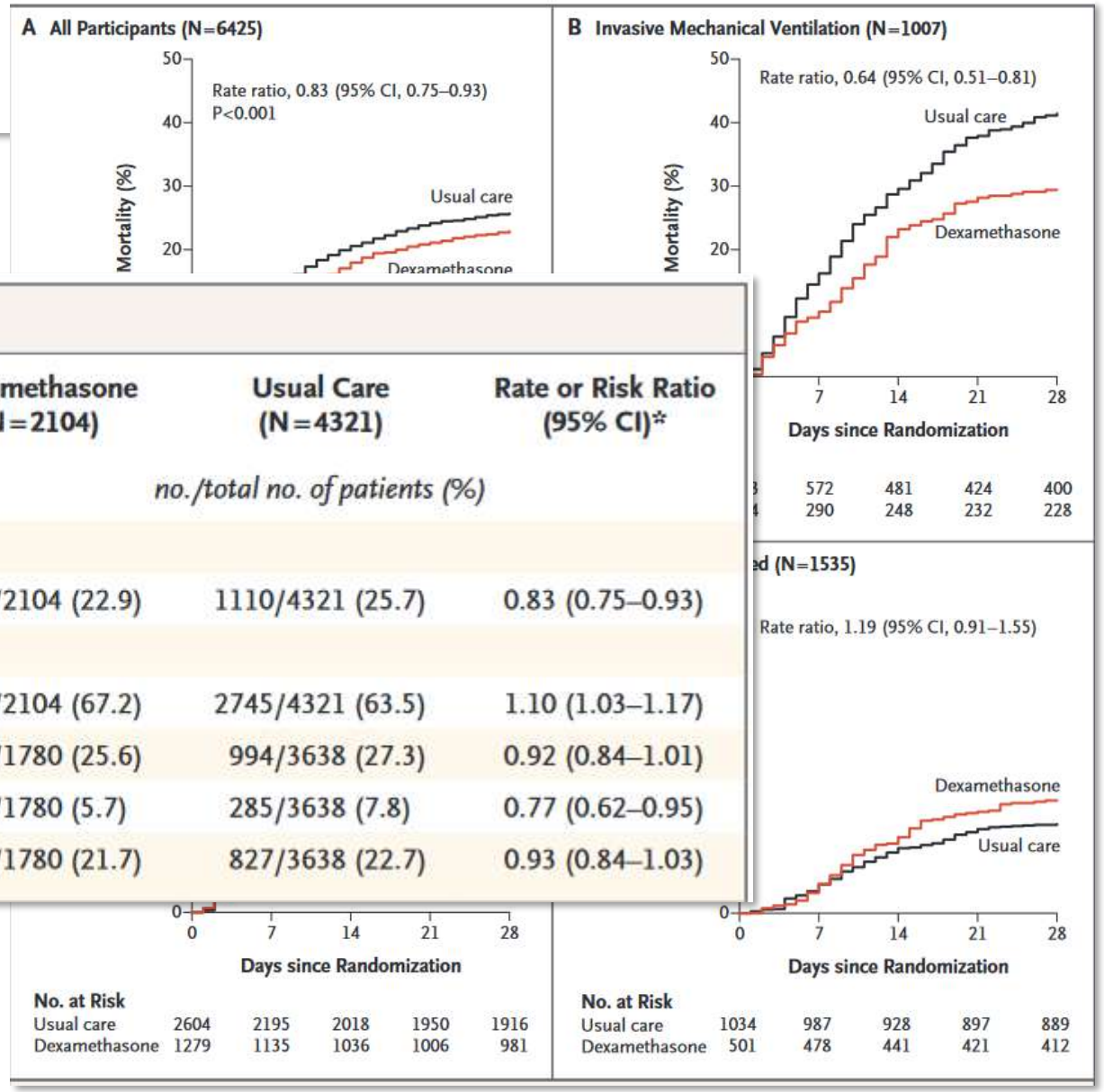
LIVING MAPPING OF TRIALS	LIVING SYNTHESIS OF PUBLISHED TRIALS
(i.e., trials registered on the WHO platform)	(include both articles and preprints)
Updated weekly	Updated daily
1940	110
Randomized Trials	RCTs with results
1107 RCTs recruiting	included in our evidence synthesis

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The NEW ENGLAND JOURNAL of MEDICINE

The RECOVERY Collaborative Group*

Randomisation: SOC vs SOC+DXM 2:1
6 mg/j po ou IV pendant 10 jours ou stop à sortie



Respiratory Support at Randomization	Dexamethasor
	no. of eve
Invasive mechanical ventilation	95/324 (29.3)
Oxygen only	298/1279 (23.3
No oxygen received	89/501 (17.8)
All Patients	**482/2104 (22.9**

Chi-square trend across three categories: 11.5

Figure 3. Effect of Dexamethasone on 2

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

Antiviraux

- Azvudine vs Standard care (1 RCTs)
- Baloxavir marboxil vs Lopinavir + Ritonavir or Darunavir/Cobicistat + Umifenovir + Interferon-a update (1 RCTs)
- Favipiravir vs Umifenovir (1 RCTs)
- Favipiravir vs Baloxavir marboxil update (1 RCTs)
- Favipiravir vs Lopinavir + Ritonavir or Darunavir/Cobicistat + Umifenovir + Interferon-a update (1 RCTs)
- Favipiravir vs Standard care update (3 RCTs)
- Favipiravir vs Favipiravir+Tocilizumab new (1 RCTs)
- Favipiravir vs Tocilizumab new (1 RCTs)
- Favipiravir Early vs Favipiravir Late (1 RCTs)
- IFN-κ plus TFF2 vs Standard care new (1 RCTs)
- Interferon α-2b + Interferon gamma+ vs Interferon α-2b (1 RCTs)
- Interferon β vs Standard care (2 RCTs)
- Leflunomide + Interferon alpha2a vs Interferon alpha2a (1 RCTs)
- Lopinavir + Ritonavir vs Standard care (3 RCTs)
- Lopinavir + Ritonavir vs Umifenovir (2 RCTs)
- Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b vs Lopinavir + Ritonavir (1 RCTs)
- Lopinavir+Ritonavir+Interferon alpha vs Ribavirin+Interferon alpha (1 RCTs)
- Novaferon vs Lopinavir + Ritonavir (1 RCTs)
- Novaferon + Lopinavir + Ritonavir vs Lopinavir + Ritonavir (1 RCTs)
- Novaferon + Lopinavir + Ritonavir vs Novaferon (1 RCTs)
- Remdesivir vs Standard Care/Placebo update (3 RCTs)
- Remdesivir 5 days vs Remdesivir 10 days (2 RCTs)
- Ribavirin+Lopinavir+Ritonavir+Interferon alpha vs Ribavirin+Interferon alpha (1 RCTs)
- Ribavirin+Lopinavir+Ritonavir+Interferon alpha vs Lopinavir+Ritonavir+Interferon alpha (1 RCTs)
- rSIFN-co vs IFN-alpha (1 RCTs)
- Sofosbuvir + Daclatasvir + Ribavirin vs Standard care (1 RCTs)
- Sofosbuvir/daclatasvir vs Standard care (1 RCTs)
- Tocilizumab vs Favipiravir+Tocilizumab new (1 RCTs)
- Triazavirin vs Placebo new (1 RCTs)
- Umifenovir vs Standard care (1 RCTs)

Antimicrobiens

- Chloroquine vs Standard Care (1 RCTs)
- Darunavir/cobicistat vs Standard Care (1 RCTs)
- Hydroxychloroquine vs Standard Care/Placebo update (11 RCTs)
- Hydroxychloroquine vs Chloroquine (1 RCTs)
- Hydroxychloroquine + Azithromycin vs Standard Care (1 RCTs)
- Hydroxychloroquine + Azithromycin vs Hydroxychloroquine (2 RCTs)
- Intravenous Immunoglobulin vs Standard care/Placebo (2 RCTs)
- Ivermectin + Doxycycline vs Hydroxychloroquine + Azithromycin (1 RCTs)
- Lincomycin vs Azithromycin (1 RCTs)

Antinflammatoires

- Colchicine vs Standard care/Placebo (3 RCTs)
- IFN-κ plus TFF2 vs Standard care new (1 RCTs)

ITK

- CIGB-325 vs Standard care (1 RCTs)
- Ruxolitinib vs Vitamin C (1 RCTs)

Immunosuppresseurs

- Leflunomide + Interferon alpha2a vs Interferon alpha2a (1 RCTs)
- Human umbilical cord mesenchymal stem cell infusion vs Standard care (1 RCTs)
- rSIFN-co vs IFN-alpha (1 RCTs)

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A
E. Hohmann, H.Y. Chu, A. Luetkeme
R.W. Finberg, K. Dierberg, V. Tapson, L
D.A. Sweeney, W.R. Short, G. Toulour
G.M. Ruiz-Palacios, T. Benfield, G. Fätke
C.B. Creech, J. Lundgren, A.G. Babiker,
T. Bonnett, M. Green, M. Makowski, A.
for the ACTT-1 Study

The NEW ENGLAND JOURN

Randomisation 1:1 SOC vs SC
Dose de charge 200-mg J1 pu
sortie de l'hôpital

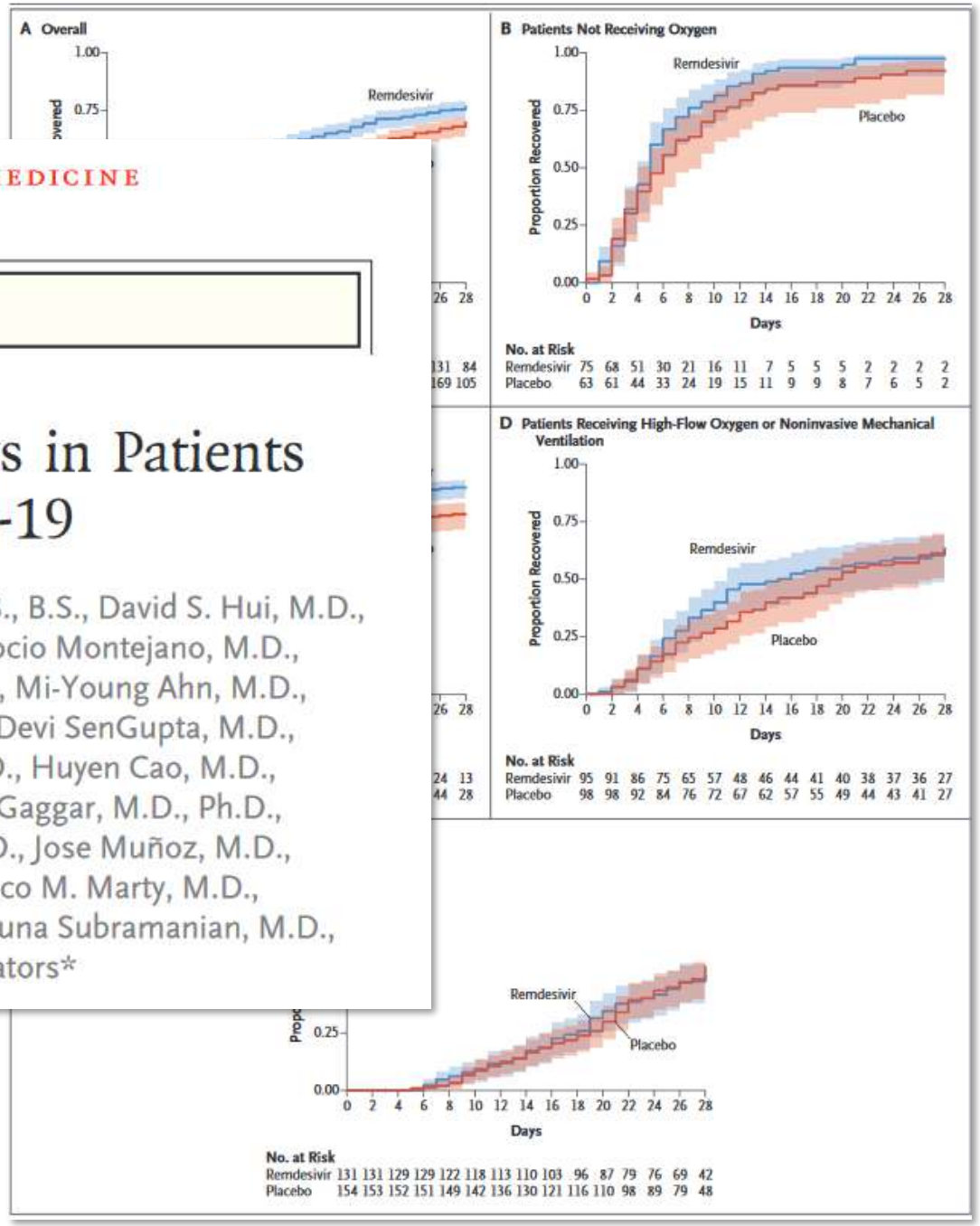
Délai de récupération (sortie
court de 5 jours avec le Remd
hospitalisés avec O2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., Robert H. Hyland, D.Phil., Anu O. Osinusi, M.D., Huyen Cao, M.D., Christiana Blair, M.S., Xuelian Wei, Ph.D., Anuj Gaggar, M.D., Ph.D., Diana M. Brainard, M.D., William J. Towner, M.D., Jose Muñoz, M.D., Kathleen M. Mullane, D.O., Pharm.D., Francisco M. Marty, M.D., Karen T. Tashima, M.D., George Diaz, M.D., and Aruna Subramanian, M.D., for the GS-US-540-5773 Investigators*



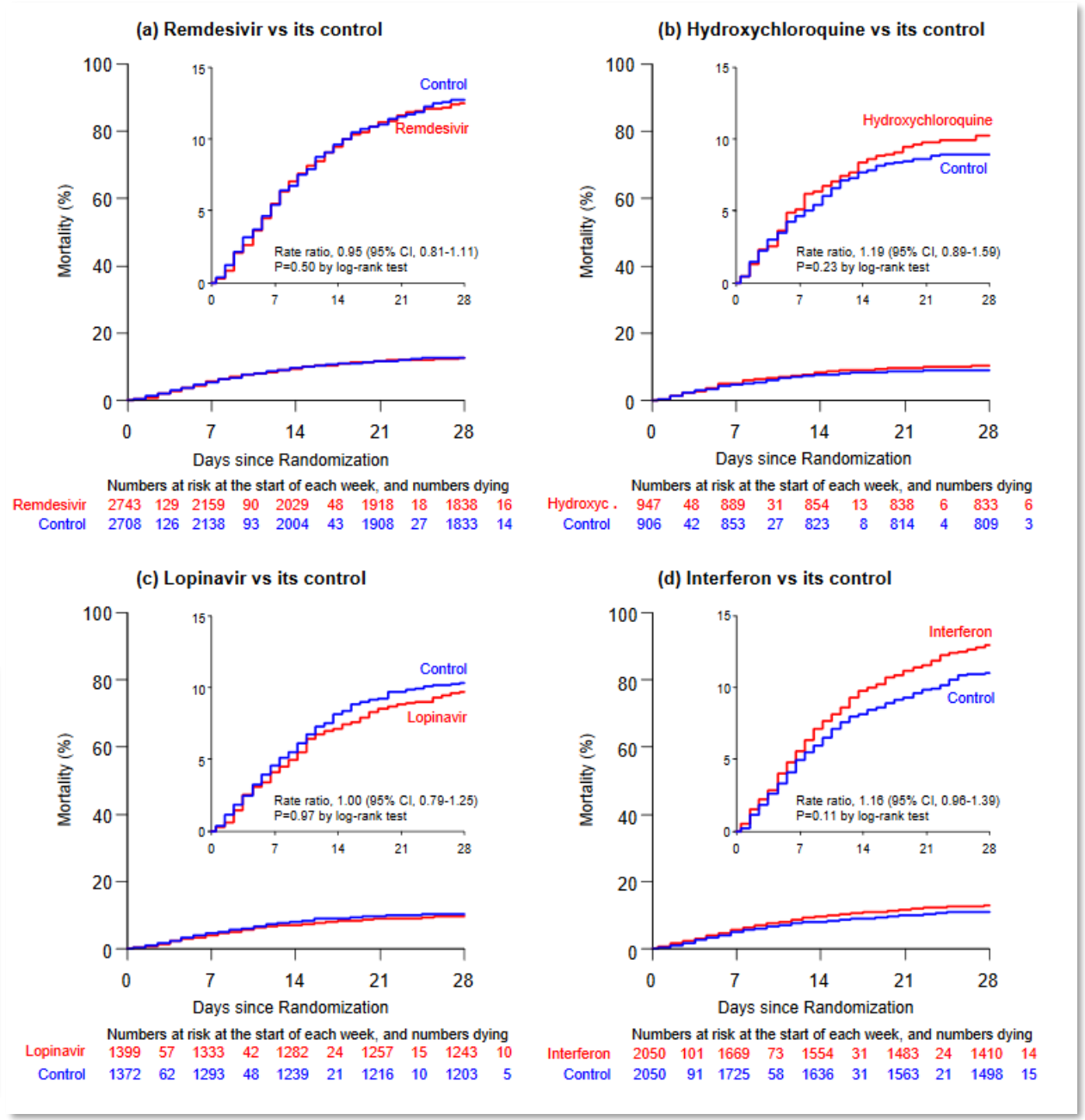
MedRxiv (October 15) version

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

Mortalité à 28 jours
Patients hospitalisés

	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%)		Active-group deaths: log-rank statistics		Ratio of death rates (RR), & 99% CI (or 95% CI, for total)
	Active	Control	O-E	Variance	Active : Control
(a) Remdesivir					
Age at entry					
<50	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 [0.67-1.73]
50-69	154/1282 (13.8)	161/1287 (14.2)	-7.6	77.5	0.91 [0.68-1.21]
70+	86/500 (20.5)	83/469 (21.6)	-2.9	41.5	0.93 [0.63-1.39]
Respiratory support at entry					
Ventilated	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 [0.80-1.80]
Not ventilated	203/2489 (9.4)	232/2475 (10.6)	-15.8	108.0	0.86 [0.67-1.11]
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**-8.3**	**148.8**	**0.95 [0.81-1.11]**
Heterogeneity around total χ^2_5: 3.9					**2p = 0.50**

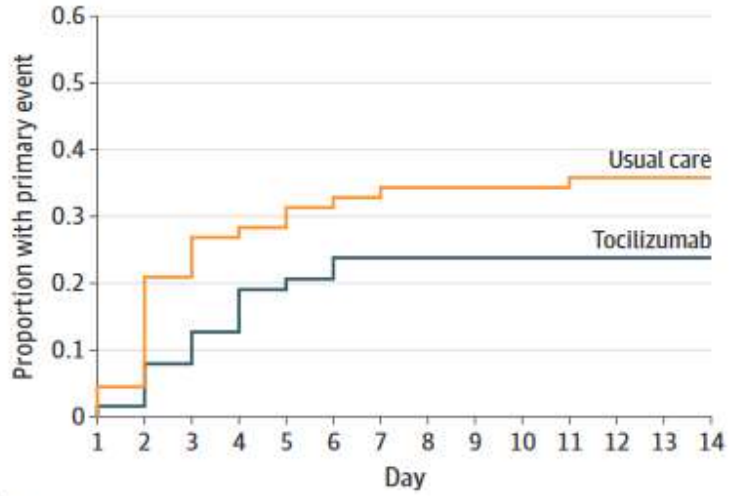


Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia
A randomized Clinical Trial

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

« RCT » Tocilizumab (n=63) vs SOC (n=67)

A Probability of primary outcome, death or MV, HFO, or NIV, at day 14

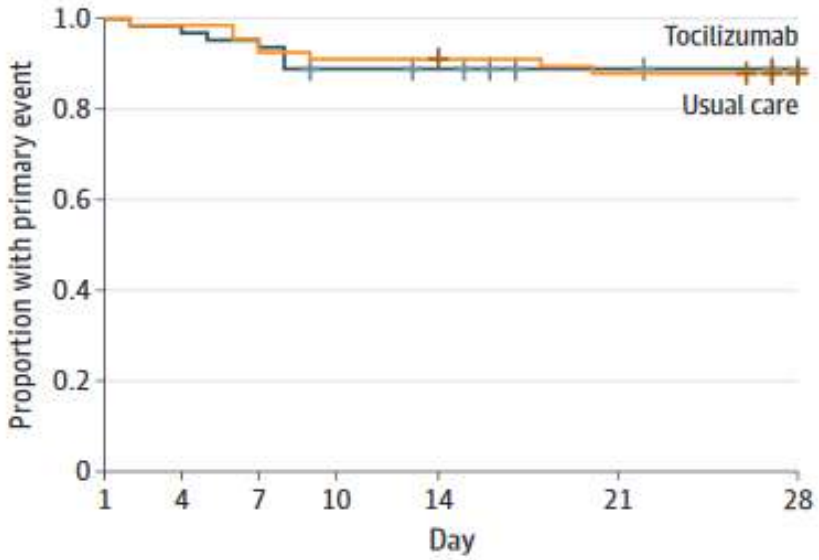


Parameter	Value
Median HR	0.58
90% CrI	0.33-1.00
95% CrI	0.30-1.11
P (HR <1)	0.95
P (HR <0.95)	0.93
P (HR <0.85)	0.87
P (HR <0.8)	0.83

No. at risk

Tocilizumab	63	62	58	55	51	50	48	48	48	48	48	48	48	48
Usual care	67	64	53	49	48	46	45	44	44	44	44	43	43	43

C Probability of overall survival at day 28



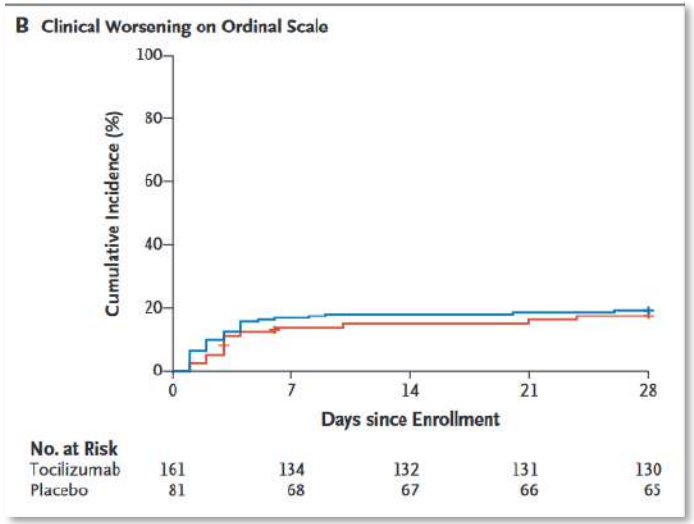
No. at risk

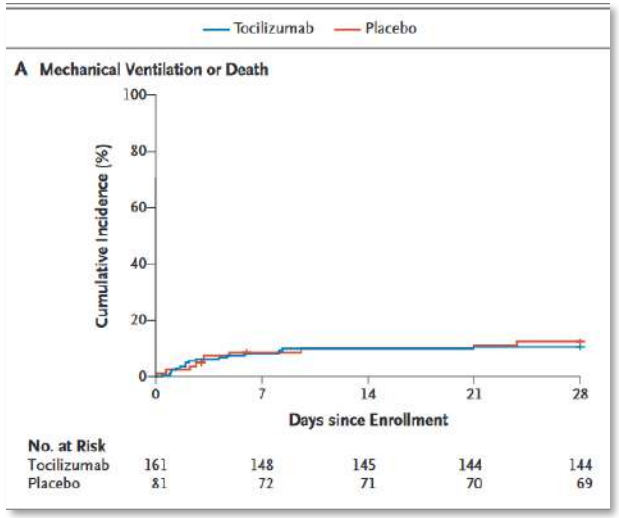
Tocilizumab	63	62	60	55	54	50	46
Usual care	67	66	64	61	61	56	50

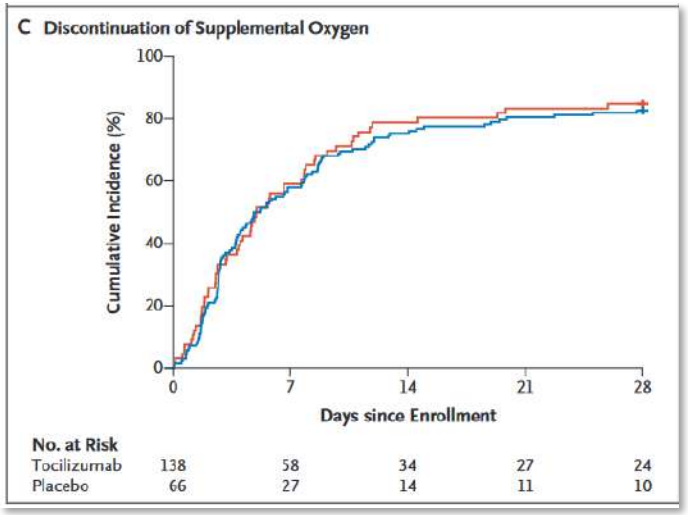
Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yinh, K.A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K.M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, and M.K. Mansour, for the BACC Bay Tocilizumab Trial Investigators*

RCT Tocilizumab (n=161) vs placebo (n=81), double aveugle







Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia

Ivan Rosas, Norbert Bräu, Michael Waters, Ronaldo C. Go, Bradley D. Hunter, Sanjay Bhagani, Daniel Skiest, Mariam S. Aziz, Nichola Cooper, Ivor S. Douglas, Sinisa Savic, Taryn Youngstein, Lorenzo Del Sorbo, Antonio Cubillo Gracian, David J. De La Zerda, Andrew Ustianowski, Min Bao, Sophie Dimonaco, Emily Graham, Balpreet Matharu, Helen Spotswood, Larry Tsai, Atul Malhotra

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

- RCT Tocilizumab (n=294) vs placebo + SOC (n=144)
- Pas de différence sur l'état clinique (haut débit d'O2, ventilation mécanique / décès) à J28
- Pas de différence en termes de mortalité toutes causes à J28
- Diminution de la durée d'hospitalisation (- 8 jours) et en réanimation (-5.8 jours)
- SAE identiques

Doi: https://doi.org/10.1101/2020.08.27.20183442

Convalescent plasma for patients with severe COVID-19; a matched cohort study

Ralph Rogers, M.D.[1], Fadi Shehadeh, M.Eng.[1], Evangelia K. Mylona, M.Eng.[1], Josiah Rich, M.D., M.Ph.[1], Marguerite Neill, M.D.[1], Francine Touzard-Romo, M.D.[1], Sara Geffert, M.D.[1], Jerome Larkin, M.D.[1], Jeffrey A. Bailey, M.D., Ph.D.[2], Shaolei Lu, M.D., Ph.D.[2], Joseph Sweeney, M.D.[2], Eleftherios Mylonakis, M.D., Ph.D.[1]

Cohort matchée
64 PC vs 177 contrôles
2.8% réactions transfusionnelles / unité transfusée

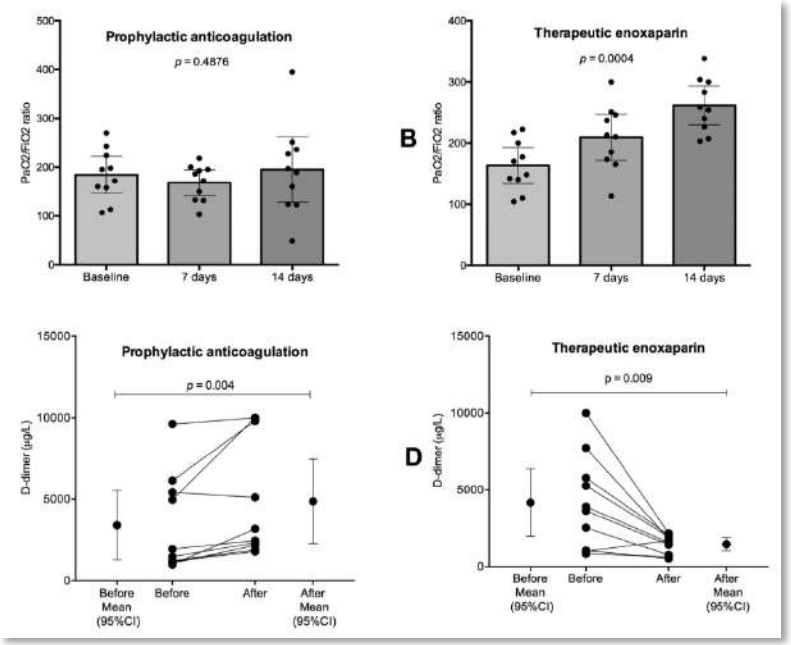
All cause in-hospital mortality	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
		Model 1[a]	Model 2[b]
Overall (n = 64)	0.73 (0.32 – 1.69)	0.91 (0.39 – 2.15)	0.93 (0.39 – 2.20)
AI ≥ 1.4[c] (n = 32)	1.08 (0.41 – 2.80)	1.09 (0.41 – 2.86)	1.17 (0.43 – 3.19)
AI ≥ 5[d] (n = 18)	0.35 (0.05 – 2.62)	0.38 (0.05 – 2.98)	0.39 (0.05 – 3.08)

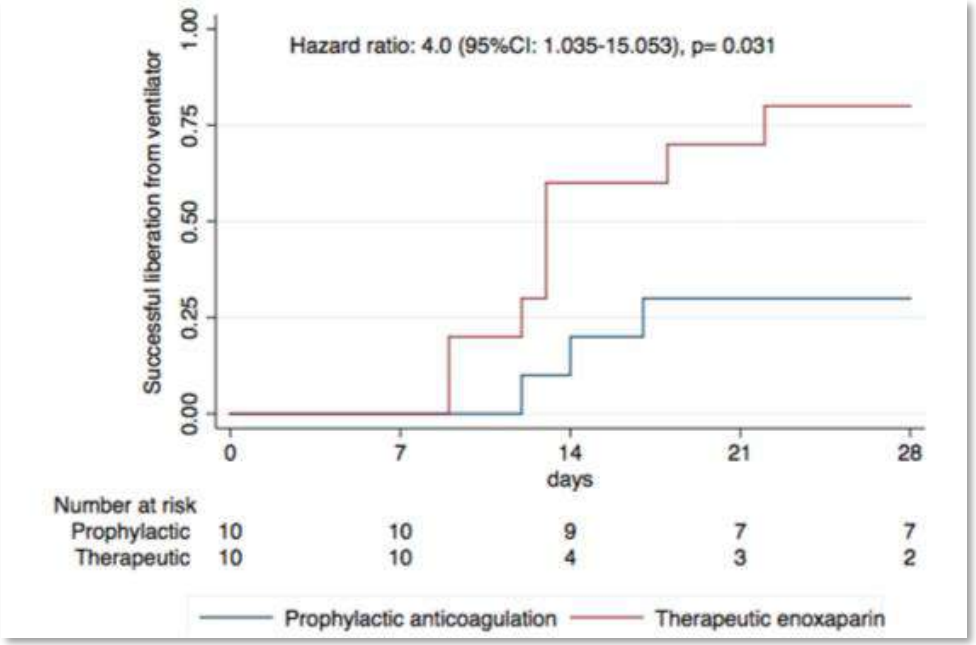
Clin Infect Dis, 2020, sous presse

Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID)

Anna Cristina Bertoldi Lemos[a], Douglas Alexandre do Espírito Santo[a], Maísa Cabetti Salvetti[b], Renato Noffs Gilio[b], Lucas Barbosa Agra[a], Antonio Pazin-Filho[a], Carlos Henrique Miranda[a,*]

- 10 patients enoxaparine curatif vs 10 patients enoxaparine prophylactique
- ARDS/ ventilation mécanique
- Ddimères > 1000

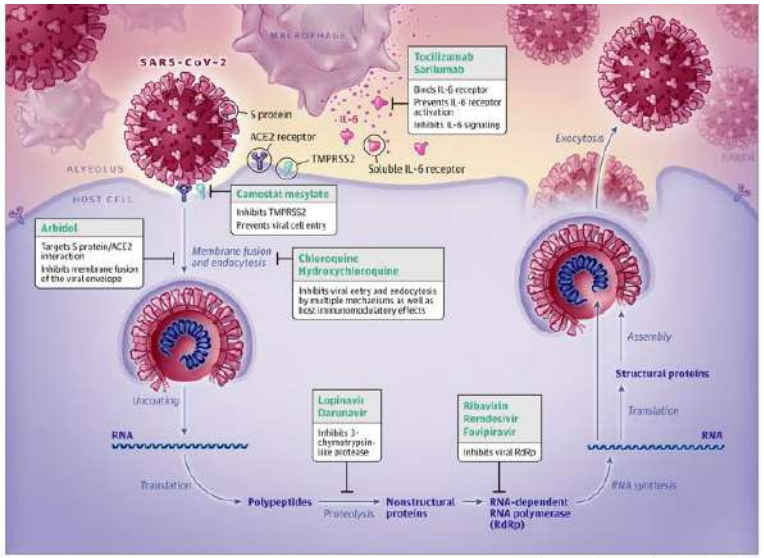




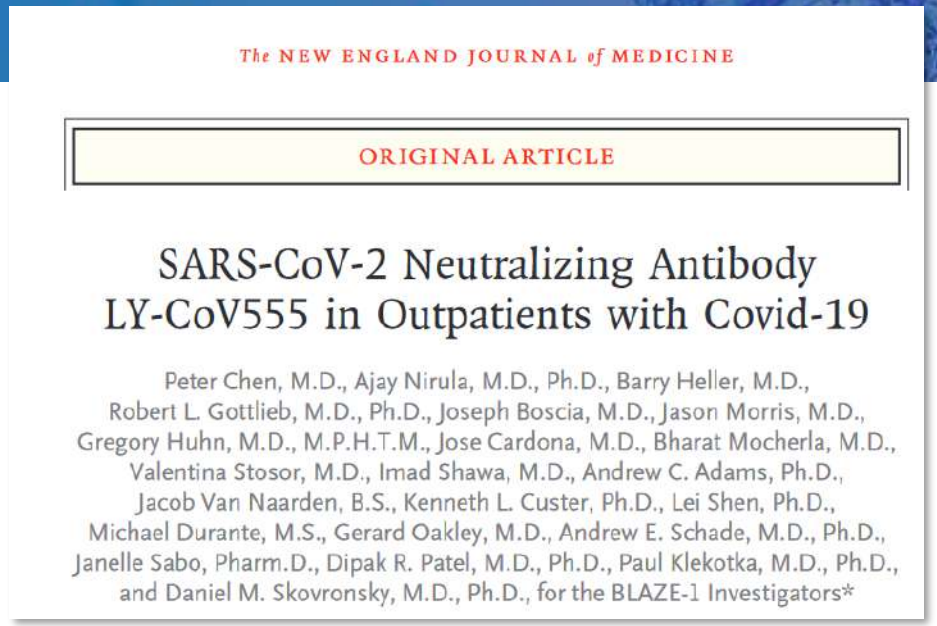
Thombosis Research 196 (2020) 359-366

Multiples molécules en cours d'évaluation

- Antiviraux
  - Molnupiravir, Atazanavir, Daclatasvir, Sofusbuvir, Galidesivir….
- Anti-inflammatoires
  - Anti-cytokines
  - Anti-JAK: baricitinib, tofacitinib…
  - Anti-BTK
  - Cellules mésenchymateuses ……
- Anti-complément



Clin Infect Dis, 2020, sous presse



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

Phase 2
Diminution de la charge virale

REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters

Alina Baum[1], Dharani Ajithdoss[1], Richard Copin[1], Anbo Zhou[1], Kathryn Lanza[1], Nicole Negron[1], Min Ni[1], Yi Wei[1], Kusha Mohammadi[1], Bret Musser[1], Gurinder S. Atwal[1], Adelekan Oyejide[1], Yenny Goez-Gazi[2], John Dutton[2], Elizabeth Clemmons[2], Hilary M. Staples[2], Carmen Bartley[2], Benjamin Klaffke[2], Kendra Alfson[2], Michal Gazi[2], Olga Gonzalez[2], Edward Dick Jr.[2], Ricardo Carrion Jr.[2], Laurent Pessaint[3], Maciel Porto[3], Anthony Cook[3], Renita Brown[3], Vaneesha Ali[3], Jack Greenhouse[3], Tammy Taylor[3], Hanne Andersen[3], Mark G. Lewis[3], Neil Stahl[1], Andrew J. Murphy[1], George D. Yancopoulos[1], Christos A. Kyratsous[1]*

- Cocktail d'anticorps monoclonaux dirigés contre la protéine Spike
- Curatif ou prophylactique
- Animaux macaques et hamster
- Phase 1-2 en cours;
  - patients hospitalisés
  - Patients ambulatoires
  - Prophylaxie chez sujets contact

Cite as : A. Baum et al., Science 10.1126/science.abe2402 (2020)