COVID-19:
Mise à jour sur les traitements

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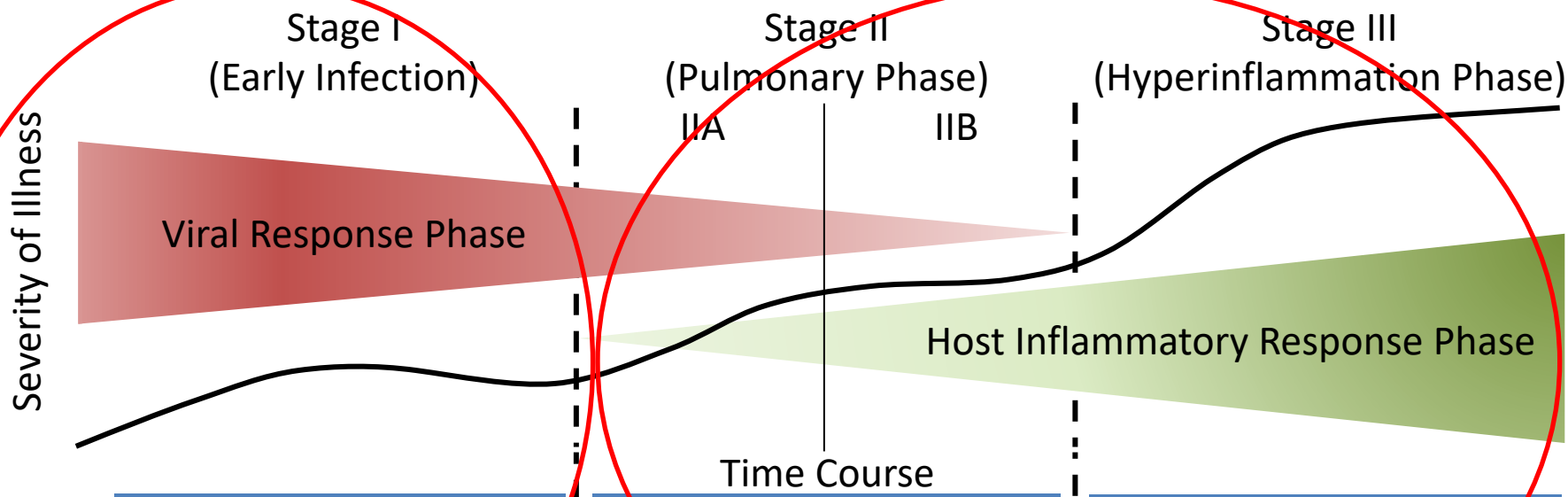
Declaration d'intérêt: 30/08/2021*

- **HIV – hépatites virales chroniques– Covid19:**
  - Réunions d'experts: ViiV Healthcare, MSD, Abbvie, Gilead, Janssen, GSK
  - Bourses de conférence: Overcome, MSD, Abbvie, Gilead, Janssen
  - Activités d'enseignement: MSD, Abbvie, Gilead, Janssen, Chiesi
  - Recherche clinique: ViiV Healthcare, MSD, Abbvie, Gilead, Janssen, Spikkim

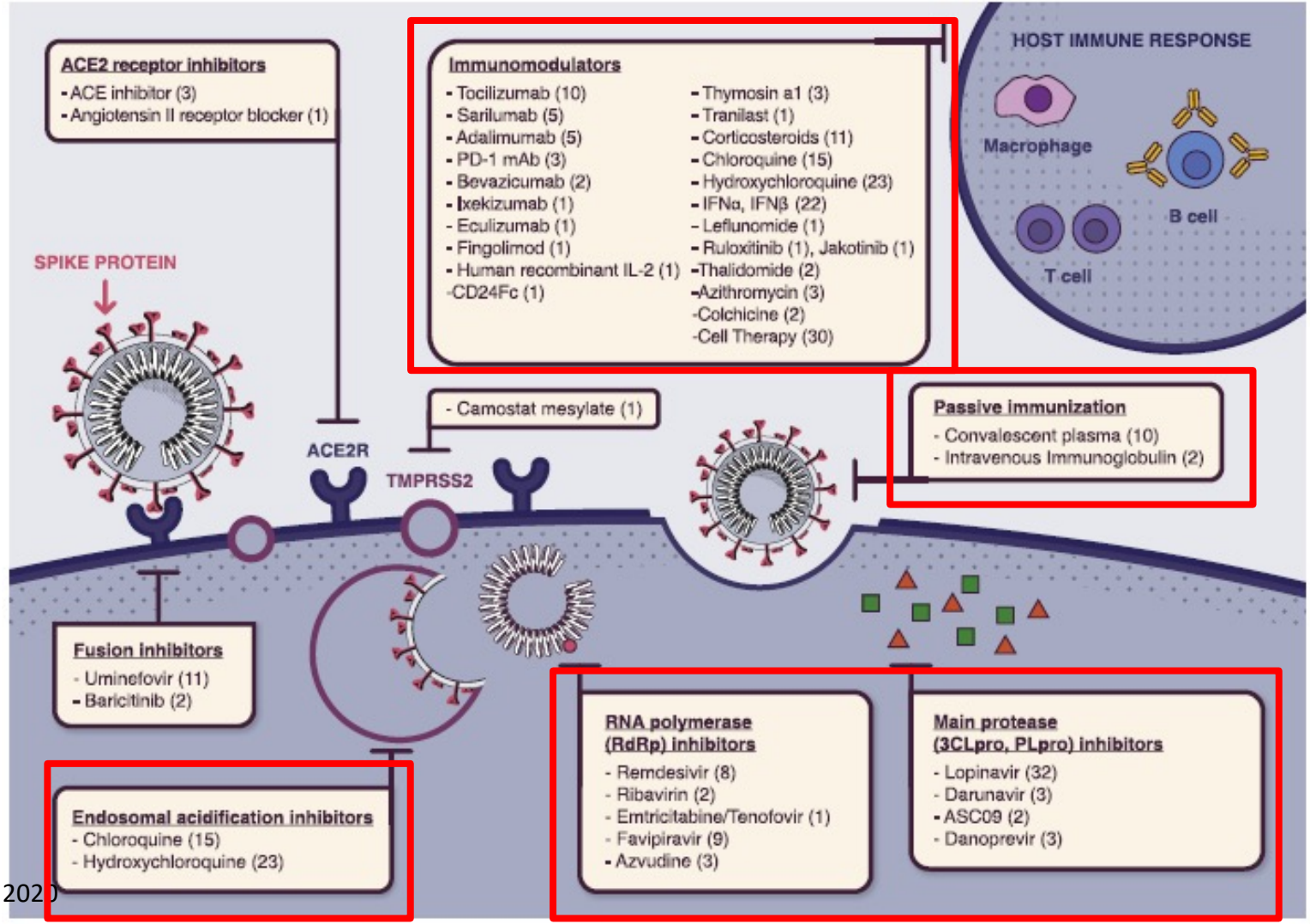
* 36 mois avant cette présentation

Histoire naturelle de la Covid-19

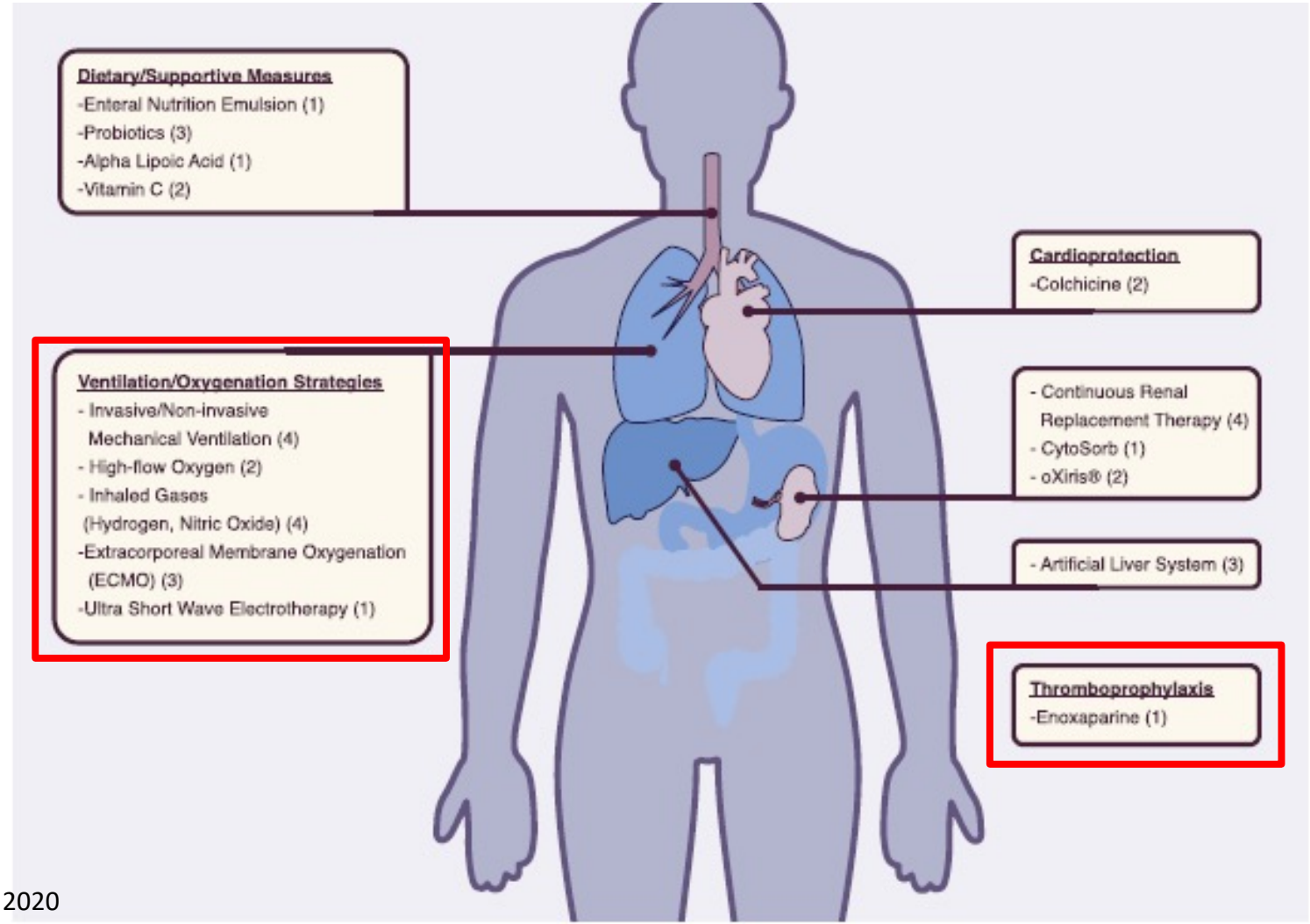


Clinical symptoms	Mild constitutional symptoms Fever > 99.6°F Dry cough	Shortness of breath without (IIA) and with hypoxia (IIB) ($PaO_2/FiO_2 \leq 300$ mm Hg)	ARDS SIRS/shock Cardiac failure
Clinical signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

Siddiqi. J Heart Lung Transplant. 2020



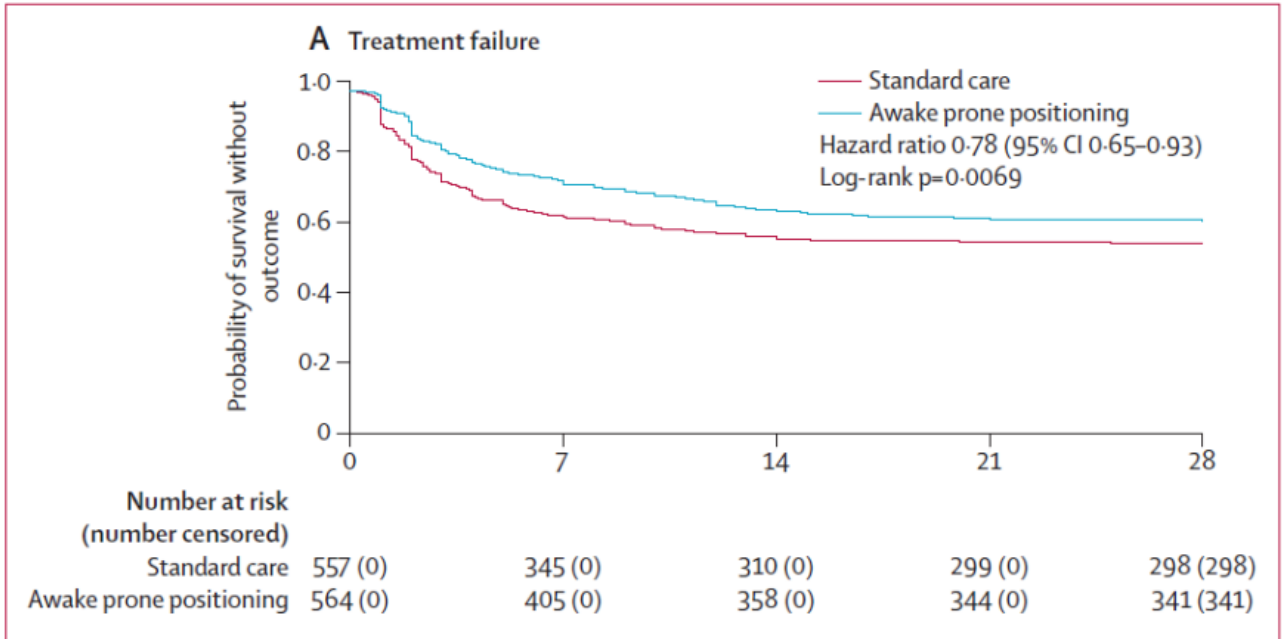
Fragkou, CMI 2020



Fragkou, CMI 2020

Efficacité du DV vigile

- Essai international / promoteur CHU de Tours
- CJP: échec du traitement = intubation ou décès
- CI: patients avec SDRA non intubé



➔ **Diminution de 22% du risque de mortalité ou intubation**

Ehrmann, Lancet Infect Dis 2021

Point sur l'antibiothérapie

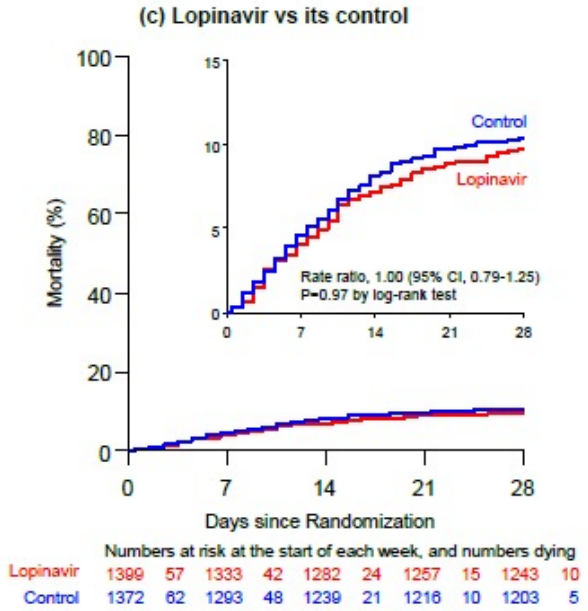
Antibiothérapie

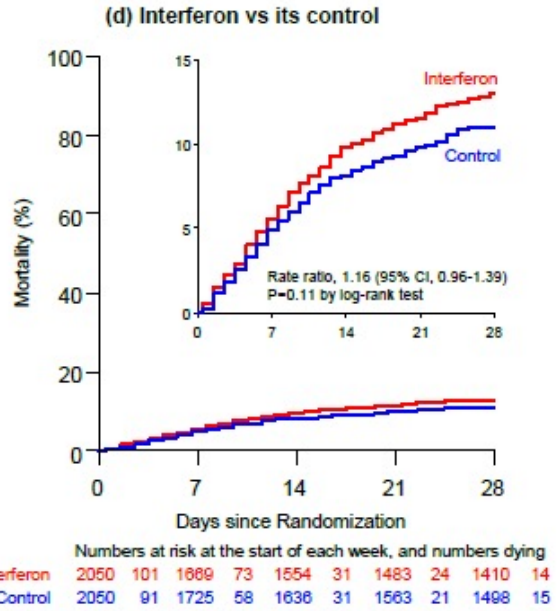
- **Constat : surconsommation majeure d'antibiotique probabiliste** au début de l'épidémie alors que les co- ou **sur-infections représentent <5% pneumonies COVID en HC**
- Recommandations : **pas d'antibiothérapie systématique en face d'une pneumonie à SARS-CoV2**
- Avant confirmation virologique, une antibiothérapie probabiliste pourra être discutée si la pneumonie présente des **critères de gravité** : besoin en oxygène > 6L/min
- Si apparition d'emblée (exceptionnel) ou secondaire (rare hors réanimation) **d'expectorations purulentes**, possibilité d'une prescription antibiotique pour une durée totale de 5 à 7 jours
  - Pneumonie non grave : **Amoxicilline + Acide clavulanique 1g x 3/j PO**
  - Pneumonie grave : **C3G + macrolides**

Rawson *et al.* Clin Infect Dis 2020, Vaughn *et al. Clin Infect Dis 2020,* Guan *et al.* N Eng J Med 2020

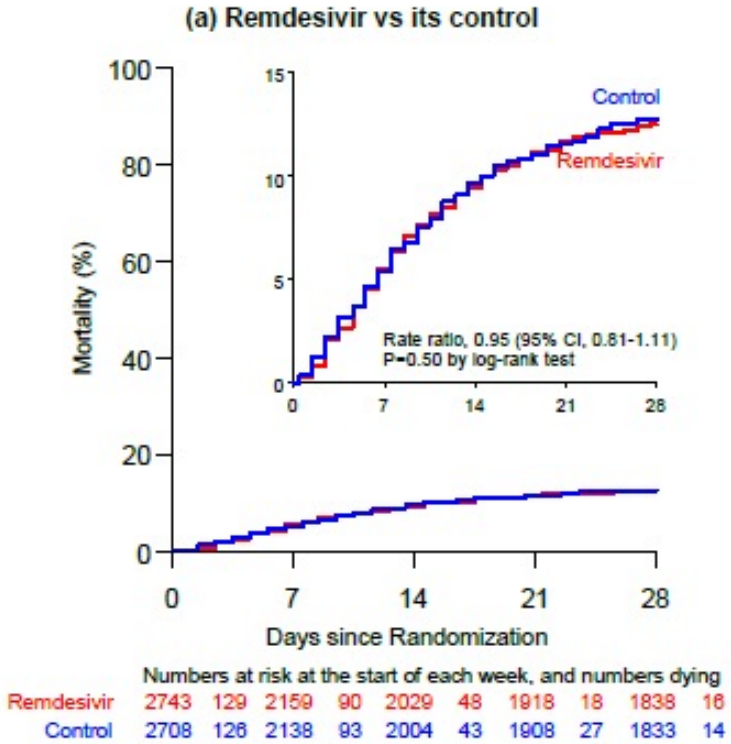
Les antiviraux

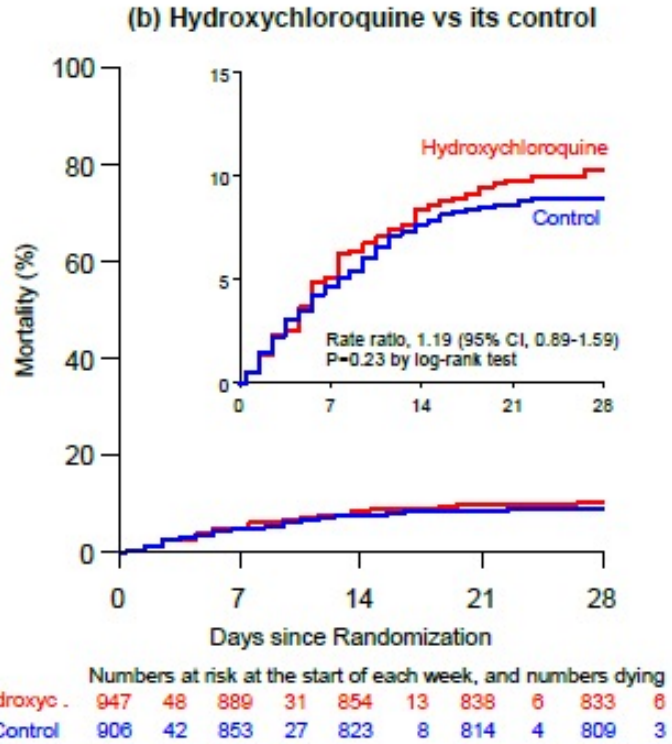
Solidarity: un méga-essai, point final sur les antiviraux en hospitalisation ?





Solidarity: un méga-essai, point final sur les antiviraux en hospitalisation ?





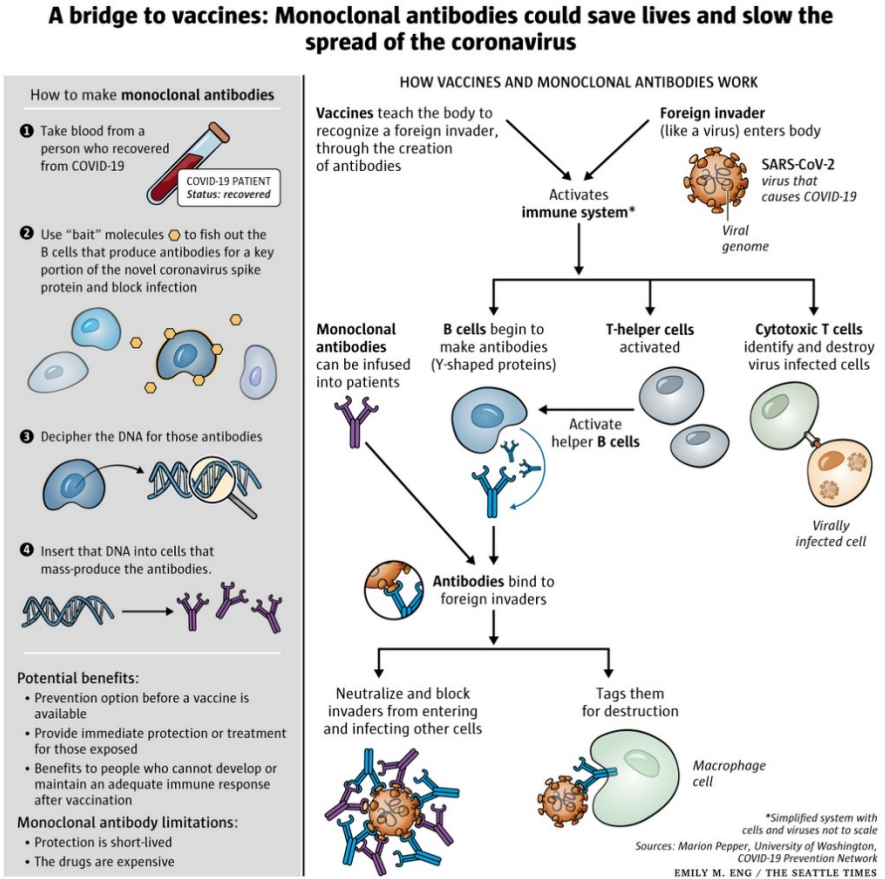
Rétractation méta-analyse Ivermectine

Dr Andrew Hill @DrAndrewHill · 16 août

Our meta-analysis of survival for ivermectin had to be retracted after one of the main studies was suspected of medical fraud. With the revised version, there is no statistically significant survival benefit for ivermectin. So the original version should not be quoted

96 1 k 2 k

Anticorps monoclonaux



➔ mAbs à la frontière entre activité antivirale et immunomodulatrice

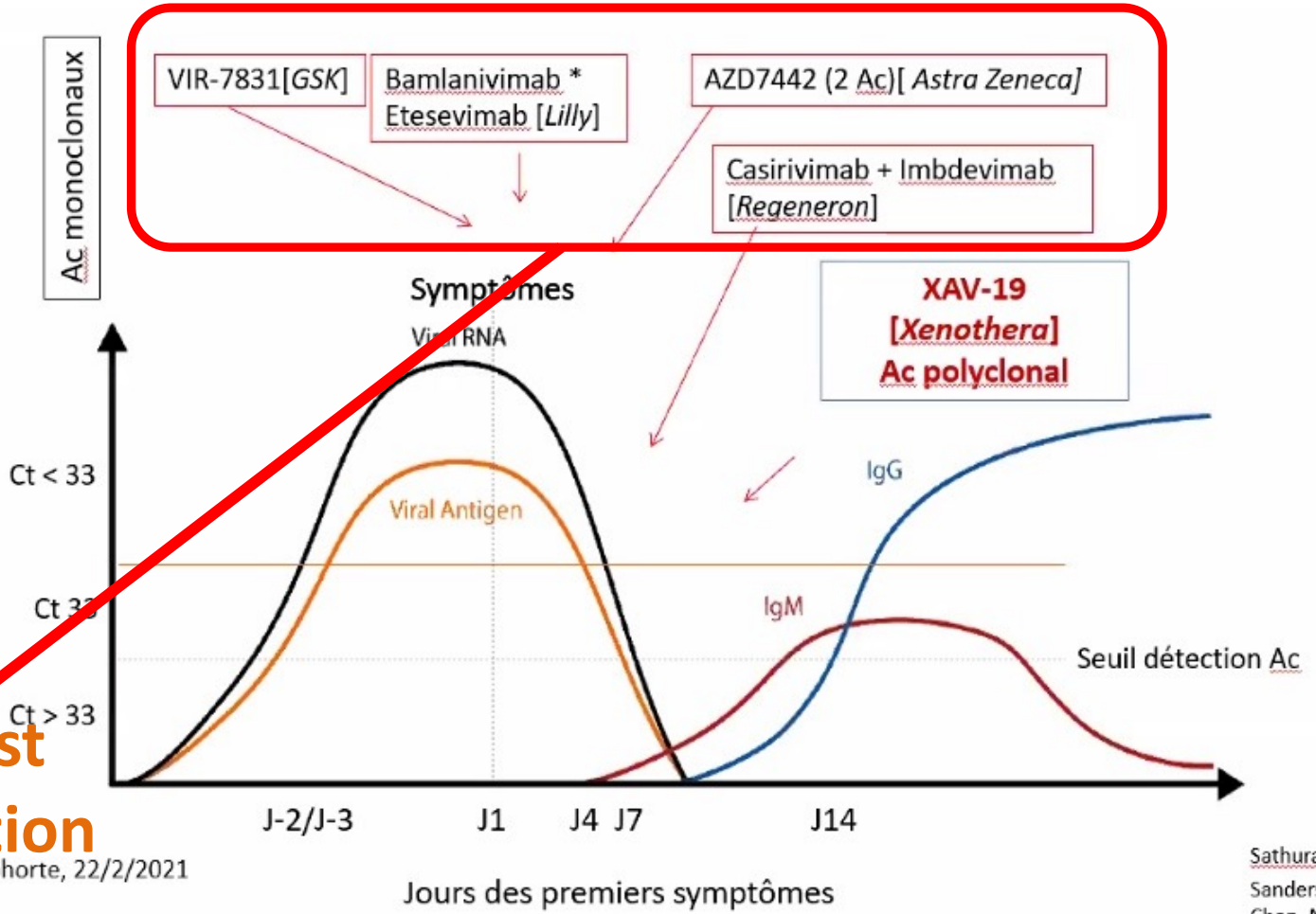
- Neutralisation des virions
- Toxicité cellulaire dépendante des Ac (médiée par les cellules NK)
- Phagocytose cellulaire dépendante des Ac (médiée par les macrophages et les cellules dendritiques)

Table 1. Monoclonal antibodies undergoing late-stage clinical studies or authorized for COVID-19*.

Primary sponsoring company	INN or code name	Molecular format	Target(s)	Most advanced phase for COVID-19	Phase 2/3 or 3 clinical study conditions
Biocon, Equillium	Itolizumab#	Humanized IgG1	CD6	EUA in India	Hospitalized Patients With COVID-19 (NCT04605926 pending)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AbCellera / Eli Lilly and Company	Bamlanivimab (LY-CoV555, LY3819253)	Human IgG1	SARS-CoV -2	EUA in US	Preventing SARS-CoV-2 Infection and COVID-19 (NCT04497987); Inpatients With COVID-19 (NCT04501978); Outpatients With COVID-19 (NCT04518410)
Regeneron Pharmaceuticals, Inc.	Casirivimab and imdevimab (REGN-COV2; REGN10933 + REGN10987)	Human IgG1 mAbs	SARS-CoV -2	EUA in US	Ambulatory Adult Patients With COVID-19 (NCT04425629); Hospitalized Adult Patients With COVID-19 (NCT04426695); Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected With SARS-CoV -2 (NCT04452318)
CytoDyn	Leronlimab	Humanized IgG4	CCR5	EUA requested in US	Severe or Critical COVID-19 (pivotal Phase 2 NCT04347239); Mild to moderate COVID-19 (pivotal Phase 2 NCT04343651)
InflaRx GmbH	Vilobelimab (IFX-1, CaCP29)	Chimeric IgG4	C5	Phase 2/3	Severe COVID-19 Pneumonia (NCT04333420)
Alexion Pharmaceuticals	Ravulizumab-cwvz#	Humanized IgG2/4	C5	Phase 3	Hospitalized adults with severe pneumonia or acute respiratory distress syndrome (NCT04369469)
Jiangsu Pacific Meinuoke Bio Pharmaceutical Co Ltd	Meplazumab	Humanized IgG2	CD147	Phase 2/3 pending	Hospitalized Adults With COVID-19 (NCT04586153)
Humanigen, Inc.	Lenzilumab	Human IgG1	GM-CSF	Phase 3	COVID-19 Pneumonia (NCT04351152)
Kiniksa Pharmaceuticals, Ltd.	Mavrilimumab	Human IgG4	GM-CSFR	Phase 2/3	COVID-19 Pneumonia and Hyper-inflammation (NCT04447469)
Swedish Orphan Biovitrum	Emapalumab#	Human IgG1	IFN gamma	Phase 2/3	Hyper-inflammation and Respiratory Distress in Patients With SARS-CoV-2 Infection (NCT04324021)
R-Pharm JSC, Cromos Pharma	Olokizumab#	Humanized IgG4	IL-6	Phase 2/3	Severe COVID-19 (NCT04380519, NCT04452474 pending)
Hoffmann-La Roche	Tocilizumab#	Humanized IgG1	IL-6 R	Phase 3	Hospitalized Patients With COVID-19 Pneumonia (NCT04372186, NCT04409262)
Sinocelltech Ltd.	SCTA01	Humanized mAb	SARS-CoV -2	Phase 2/3 pending	Hospitalized Patients With Severe COVID-19 (NCT04644185)
Vir Biotechnol./ GlaxoSmithKline	VIR-7831/GSK4182136	Human mAb	SARS-CoV -2	Phase 2/3	Early Treatment of COVID-19 in Outpatients (NCT04545060)
Celltrion	CT-P59	Human mAb	SARS-CoV -2	Phase 2/3	Mild to Moderate COVID-19 (NCT04602000)
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Human mAbs	SARS-CoV -2	Phase 3	Pre-exposure Prophylaxis (NCT04625725); Post-exposure Prophylaxis (NCT04625972)

*Data publicly available as of November 21, 2020.
#Product previously approved for a disease other than COVID-19 in at least one country.
Table notes: Table 1 includes only monoclonal antibodies evaluated in commercially sponsored, late-stage clinical studies that are listed on clinicaltrials.gov.
Abbreviations: COVID-19, coronavirus disease 2019; EUA, emergency use authorization; IFN, interferon; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Kaplon, MABS 2021



Pre/post exposition

* ATU Cohorte, 22/2/2021

Sathuraman N et al Jama 2020

Sanders JM et al. JAMA 2020

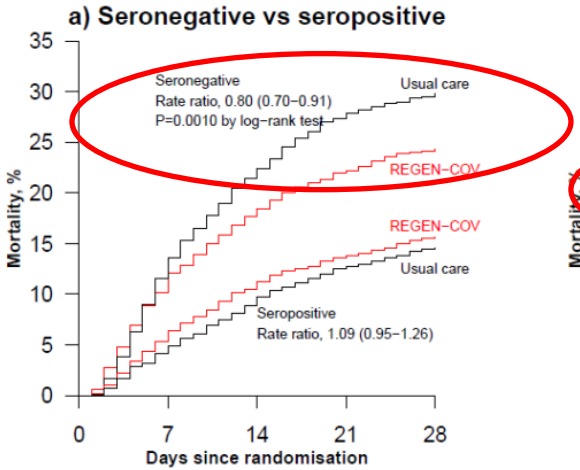
Chen, NEJM 2020

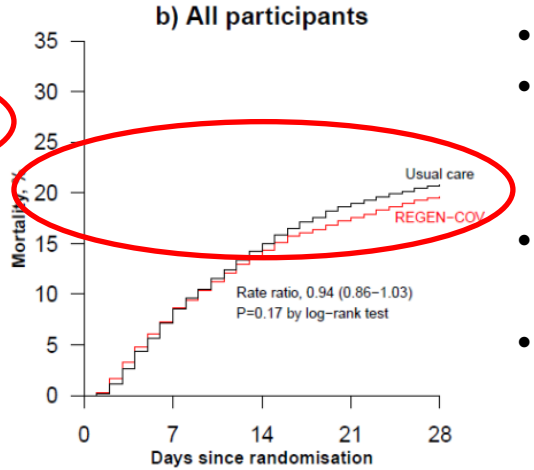
Prophylaxie pre- et post- exposition, traitement précoce ≤ 5 jours

	Curatif précoce - Sans 02 - ≥ 5 jours	PREP	PEP	Curatif 02
Bamlanivimab	X 700mg	0	0	0
Bamlanivimab + Etesevimab	X 700mg/700mg	0	0	0
Casirivimab + Imdevimab	X 1200mg/1200mg	X 600mg/600mg	X 600mg/600mg	0

Casirivimab/Imdevimab dans RECOVERY

Figure 2: Effect of allocation to REGEN-COV on 28-day mortality in: a) seronegative vs seropositive participants; and b) all participants





No. at risk, Seronegative					
REGEN-COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059

No. at risk, Seropositive					
REGEN-COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243

No. at risk					
REGEN-COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

- Inclusion de 09/20 à 05/21
- Patients sous 02, 9 jours depuis début des symptômes (7 si séroneg.)
- Mortalité globale : 20% à 28js
- Impact +++ de la présence d'Ac à baseline: -20% de mortalité
- Mortalité si pas d'Ac et usual care: 30%... 2x plus que si sérologie +!

O'Brien, NEJM 2021

Plasma convalescent en population générale

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

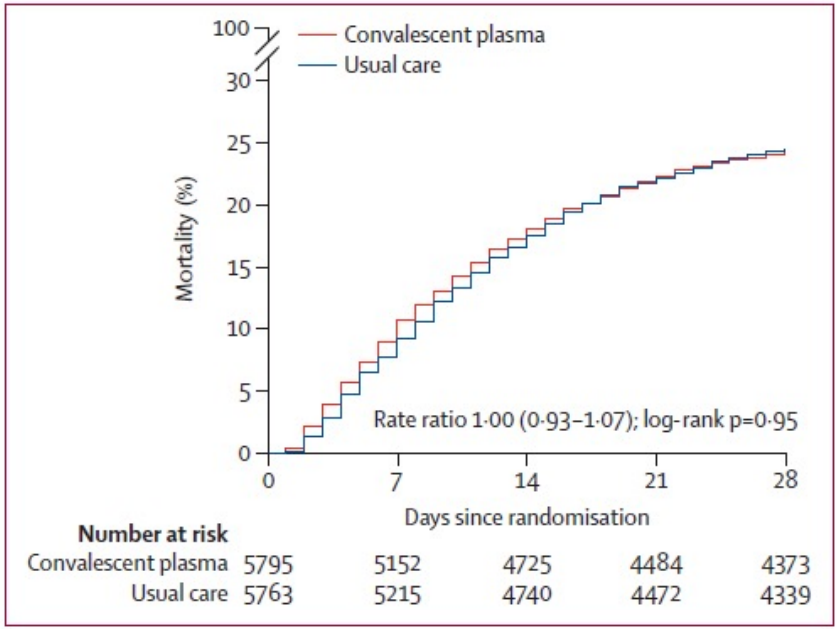


Figure 2: Effect of allocation to convalescent plasma on 28-day mortality

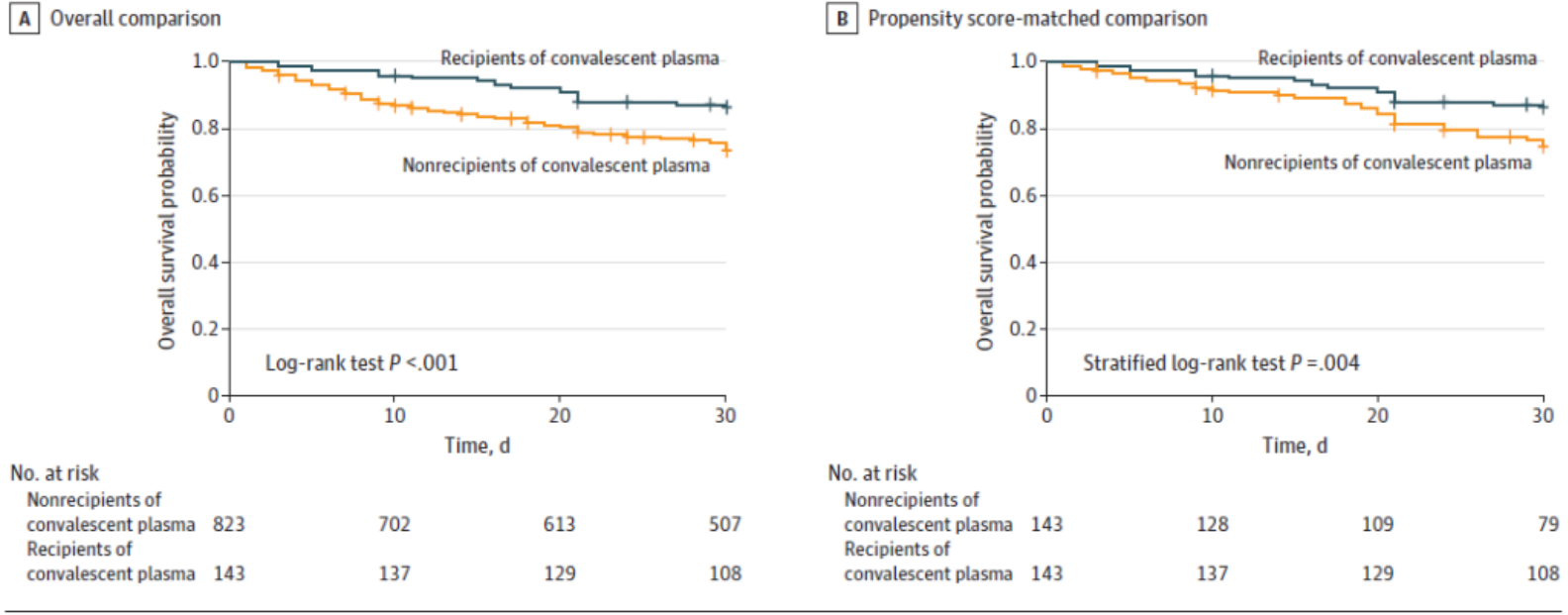
- **Essai plateforme 3 bras:**
  - SOC
  - SOC + plasma
  - SOC + mAbs (REGENERON)

- Titre Ac : 1/100
- 2 unités de plasma, 1 à J0 et 1 à J1
- Délai 1er symptômes – randomisation: 9 jours [6 – 12]
- Taux de sérologies SARS-CoV2 + = 62%

The RECOVERY Collaborative Group, Lancet, 2021

Plasma convalescent et hémopathies malignes

Figure. Overall Survival Rates Among Recipients vs Nonrecipients of Convalescent Plasma

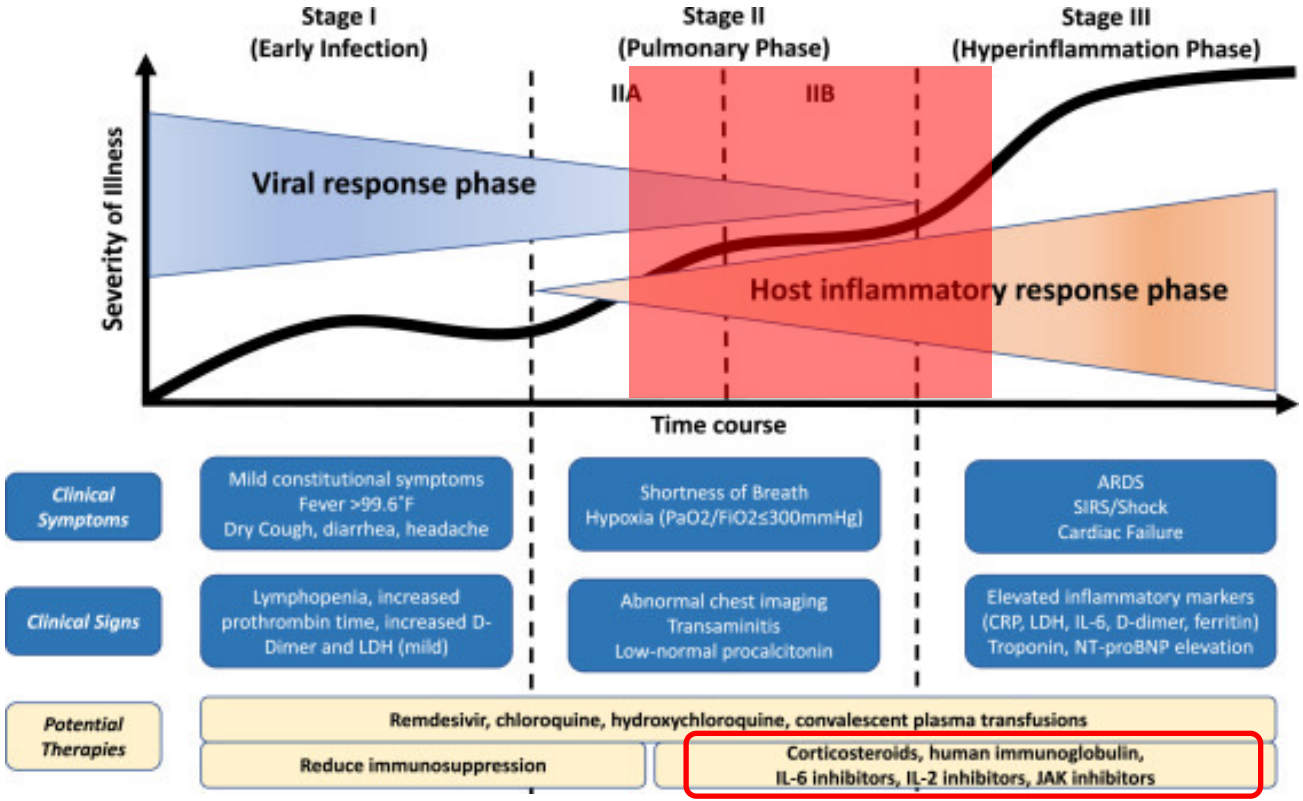


Convalescent Plasma and Improved Survival in Patients with Hematologic Malignancies and COVID-19

Thomson, JAMA Oncol 2021

Les immunomodulateurs

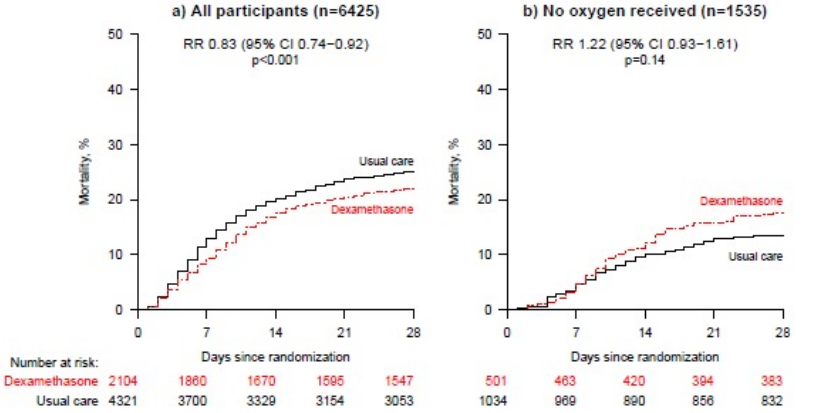
Quand utiliser les immunomodulateurs?



Adapted from: Siddiqi. J Heart Lung Transplant. 2020

Dexamethasone

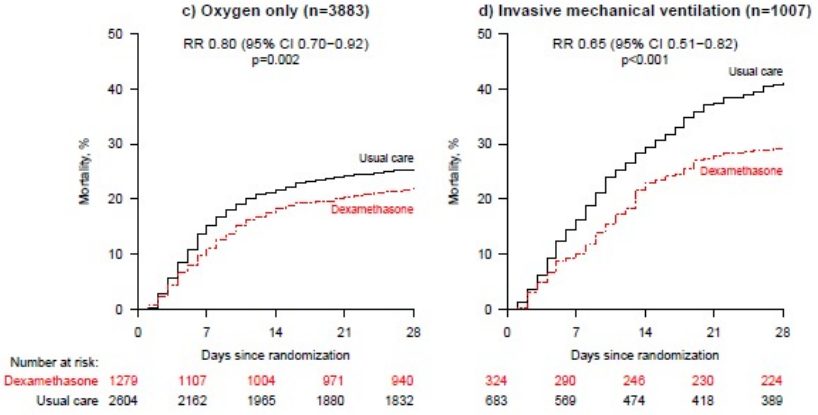
All participants
RR:0,83[0,74 – 0,92]



No O2
RR:1,22[0,93 – 1,61]

Non invasive O2
RR:0,80[0,70 – 0,92]

20% mortality



Intubation – High Flow
RR:0,65[0,51 – 0,82]

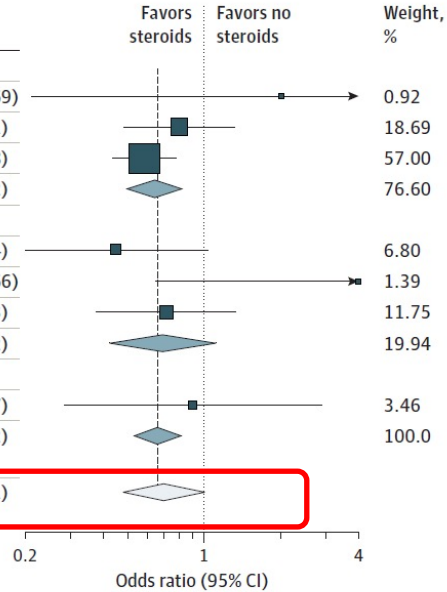
35% mortality

Hornby, New Engl J Med 2020

DXM: méta-analyse

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 steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



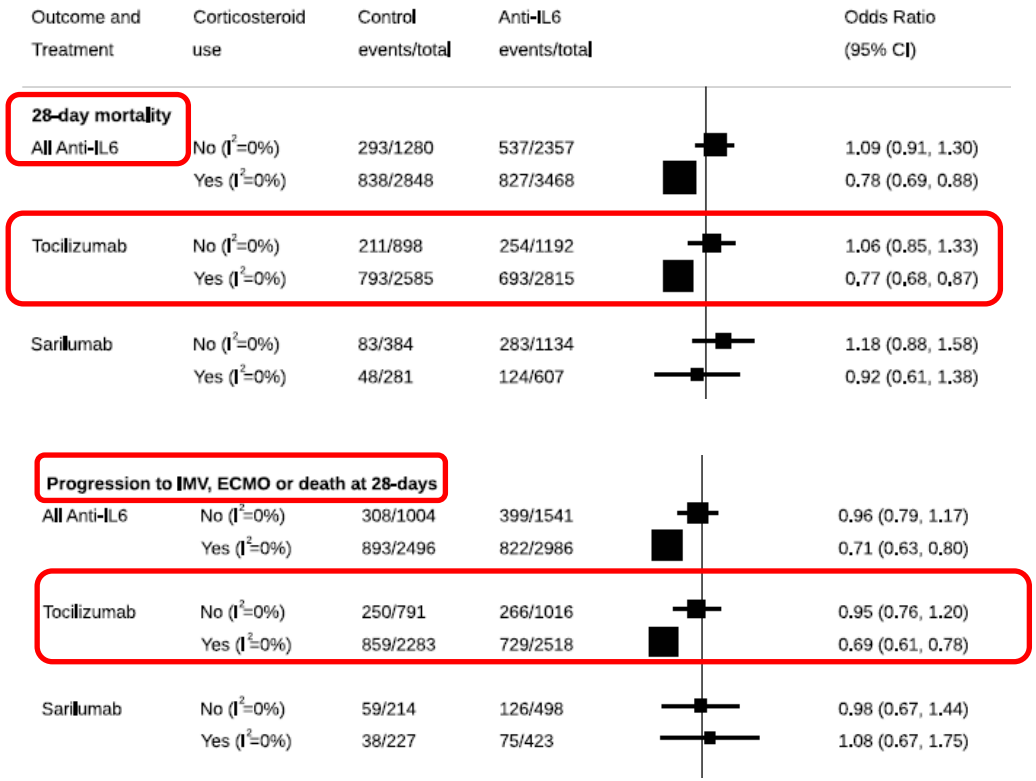
- SOC depuis juillet 2020
- Diminution de la mortalité, encore élevée dans certains groupes (mortalité différentielle)
- Risque de complications infectieuses

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT)Working Group **JAMA** Published online September 2, 2020

Anti-Il6: les nouveaux venus

- Méta-analyse commissionnées par l'OMS
- 27 essais, 10 930 patients dont 2565 sont décédés à J28
- Groupe de comparaison: SOC ou placebo

Plus grand effet de TOCI quand associé à DXM

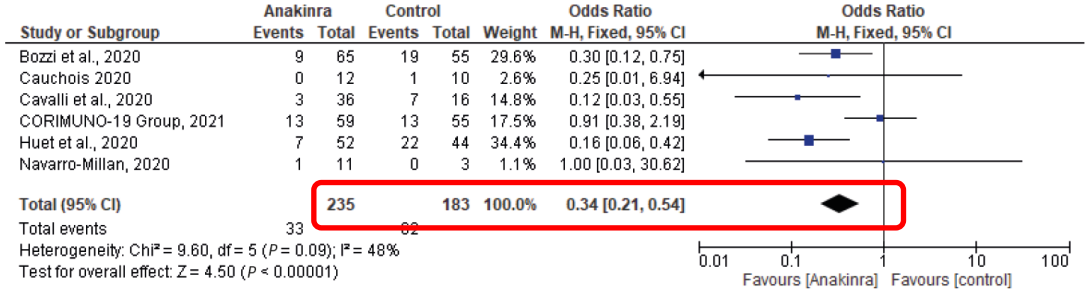


WHO REACT IL-6 antagonists PMA *In press*

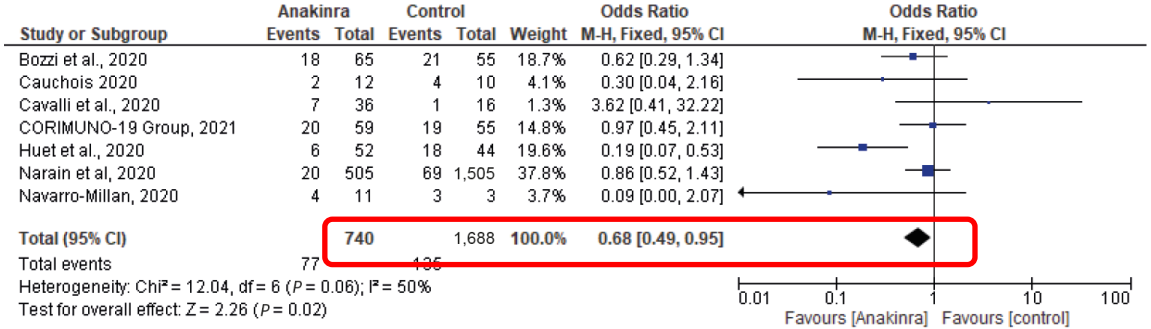
Anti-Il1: le retour ?

- Meta-analyse de 15 essais et cohortes prospectives
- 757 patients sous ANA, 1685 dans les groupes contrôles
- Signal de safety (mais non significatif) sur le risque thrombo-embolique et l'élévation des transas)

28-day mortality



Need for mechanical ventilation



Somagutta, Infect Chemother 2021

Anti-JAK: trop tôt pour savoir

Clinical Epidemiology and Global Health 11 (2021) 100755

Contents lists available at ScienceDirect

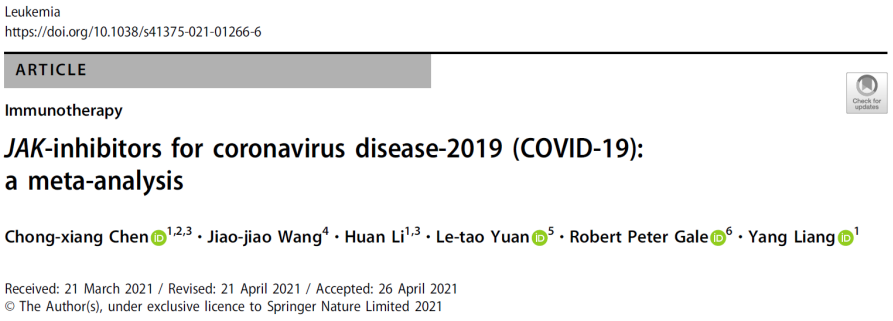
Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

Original article

The use of Janus Kinase inhibitors in hospitalized patients with COVID-19: Systematic review and meta-analysis

Indra Wijaya [a], Rizky Andhika [b], Ian Huang [c,*], Aga Purwiga [c], Kevin Yonatan Budiman [c], Muhammad Hasan Bashari [d], Lelani Reniarti [e], Rully Marsis Amirullah Roesli [b]



Leukemia
https://doi.org/10.1038/s41375-021-01266-6

ARTICLE

Immunotherapy

JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis

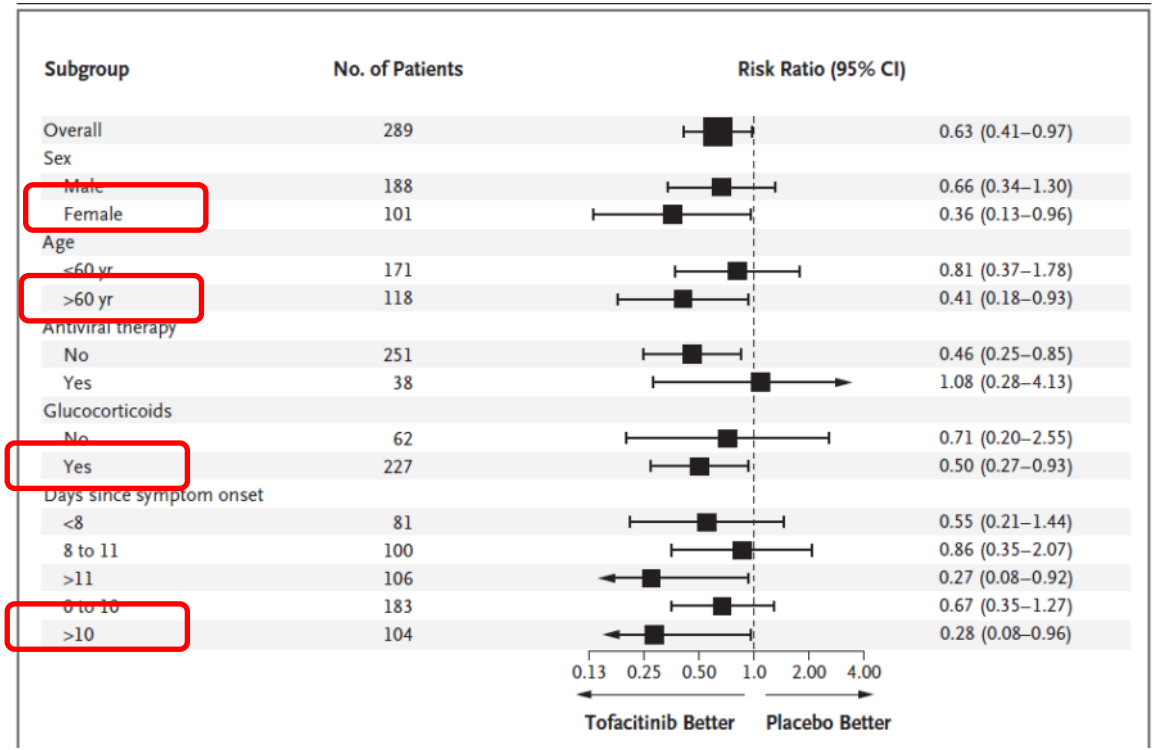
Chong-xiang Chen [1,2,3] · Jiao-jiao Wang [4] · Huan Li [1,3] · Le-tao Yuan [5] · Robert Peter Gale [6] · Yang Liang [1]

Received: 21 March 2021 / Revised: 21 April 2021 / Accepted: 26 April 2021

- Molécules évaluées: Baricitinib, ruxolitinib
- Essais avec trop peu de puissance, principalement études de cohorte prospectives
- Un essai avec assez de puissance, mais baricitinib + remdesivir
- Tendance vers un effet significatif du baricitinib (pas du ruxolitinib) sur la mortalité
- Besoin de confirmation dans de gros essais (BARI-SOLIDACT dans EU-SOLIDACT, plateforme pan-européenne d'essais adaptatifs en réponse aux pandémies)

Tofacitinib: le « new kid on the block »?

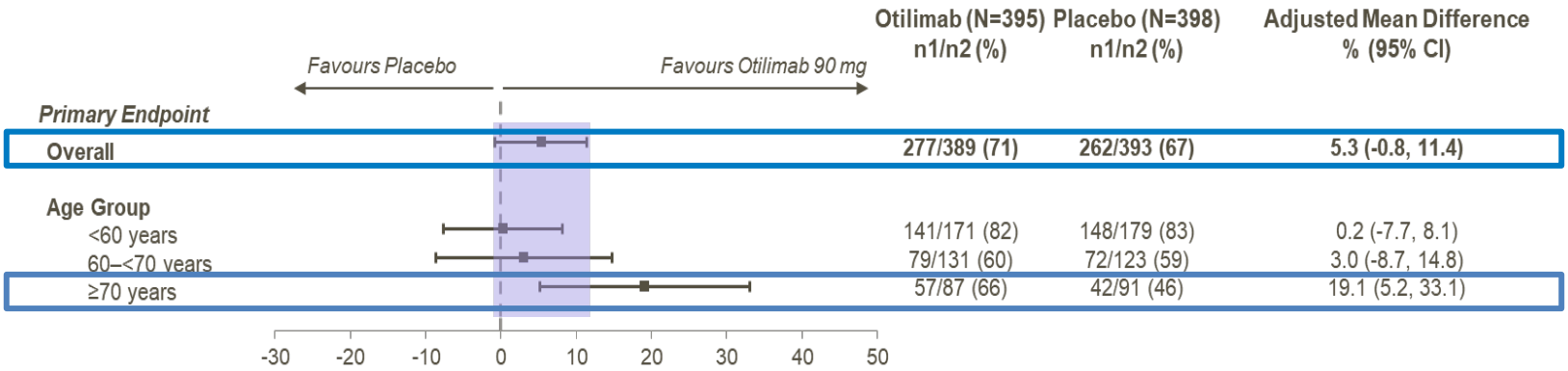
- 289 patients randomisés versus placebo + SOC au Brésil
- Décès ou détresse respiratoire aigue:
- OR = 0,63 [0,41 – 0,97]
- Pas de signal de safety



Guimaraes, NEJM 2021

Anti-GM-CSF: une voie à explorer

- Essai OSCAR: évaluation de l'otilimab dans le traitement des formes graves de Covid19



Patel, MedRxiv 2021

En conclusion

- Aucun antiviral en dehors des mAbs n'a montré d'efficacité en phase précoce
- La place des mAbs dans l'arsenal thérapeutique doit être affiné

- **« Timing matters »** pour les immunomodulateurs: pas trop tôt ni trop tard
- **Tocilizumab** : confirmation de l'effet significatif sur la mortalité, surtout si associé à la DXM ➔ ***TOCI + CTC = nouveau SOC chez les patients covid19 O2-dépendants ?***

- Nombreuses molécules encore en cours d'évaluation
- Prochain standard de traitement: un antiviral + un immunomodulateur ?

- **COVID19: avènement de la médecine personnalisée**

Merci