Immunothérapie du COVID

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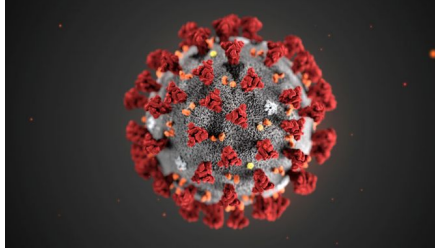
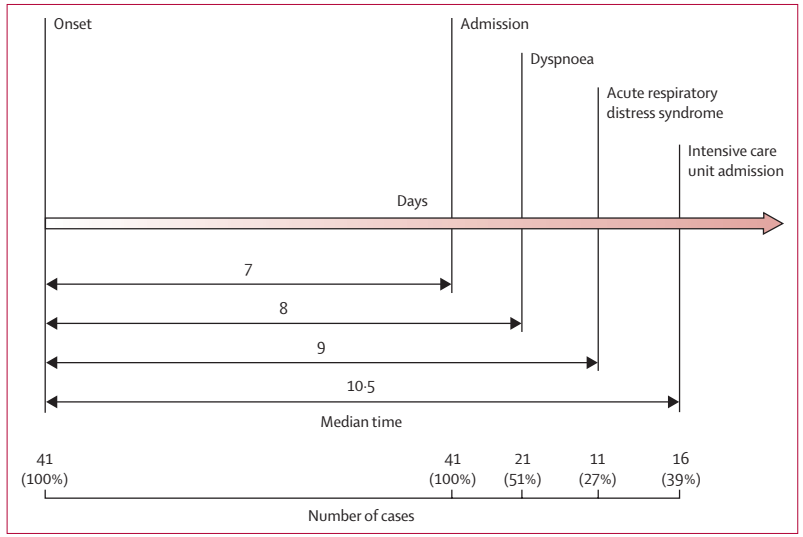
Histoire naturelle du COVID-19



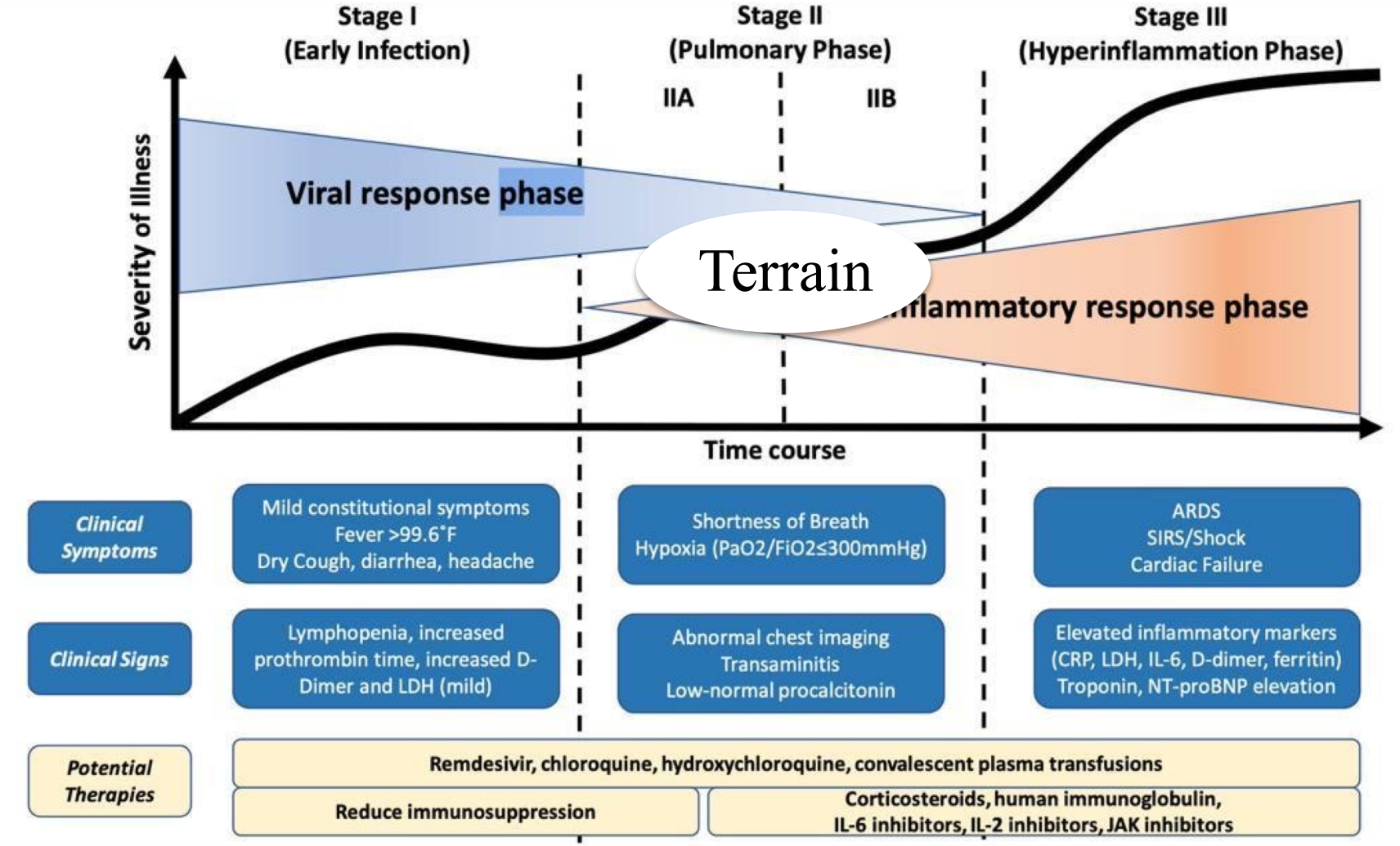
- Description des premiers cas d'infection à SARS-Cov-2 (COVID-19) a rapidement montré des tableaux cliniques différents:
  - **95%** des patients présentent des **formes faibles à modérées**
  - **<5%** évoluent vers une **forme sévère à critique**, avec syndrome de détresse respiratoire aigue
- Admission en unités de soins intensifs avec recours à la ventilation mécanique ou décès rapportée dans **6,1%** des cas initiaux en Chine
- Taux de mortalité en France **0,53%**

- Evolution classique en 2 phases avec une présentation clinique initiale modérée, suivie d'une possible aggravation après J7



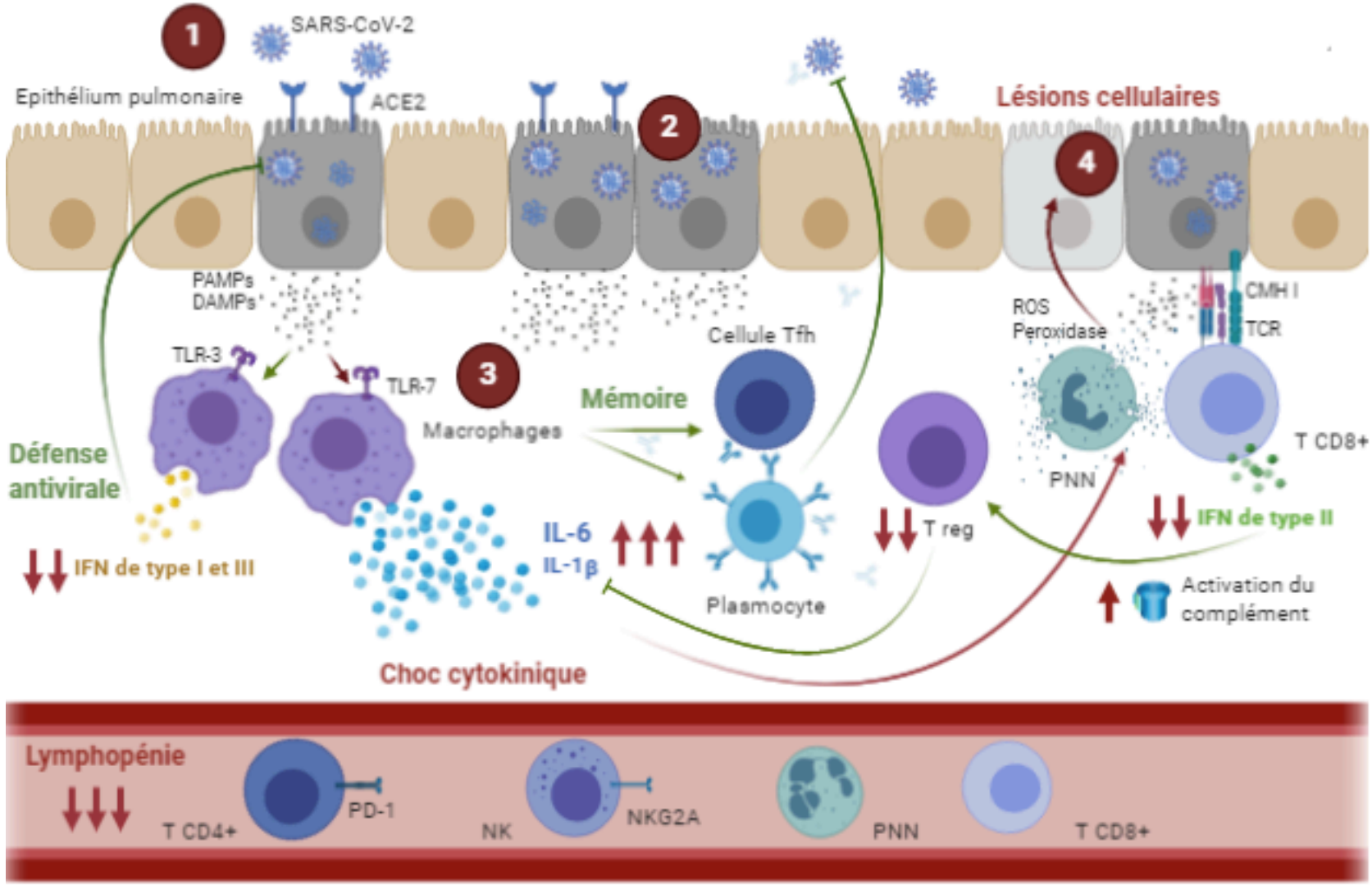
Huang, Lancet 2020

Stades de COVID-19

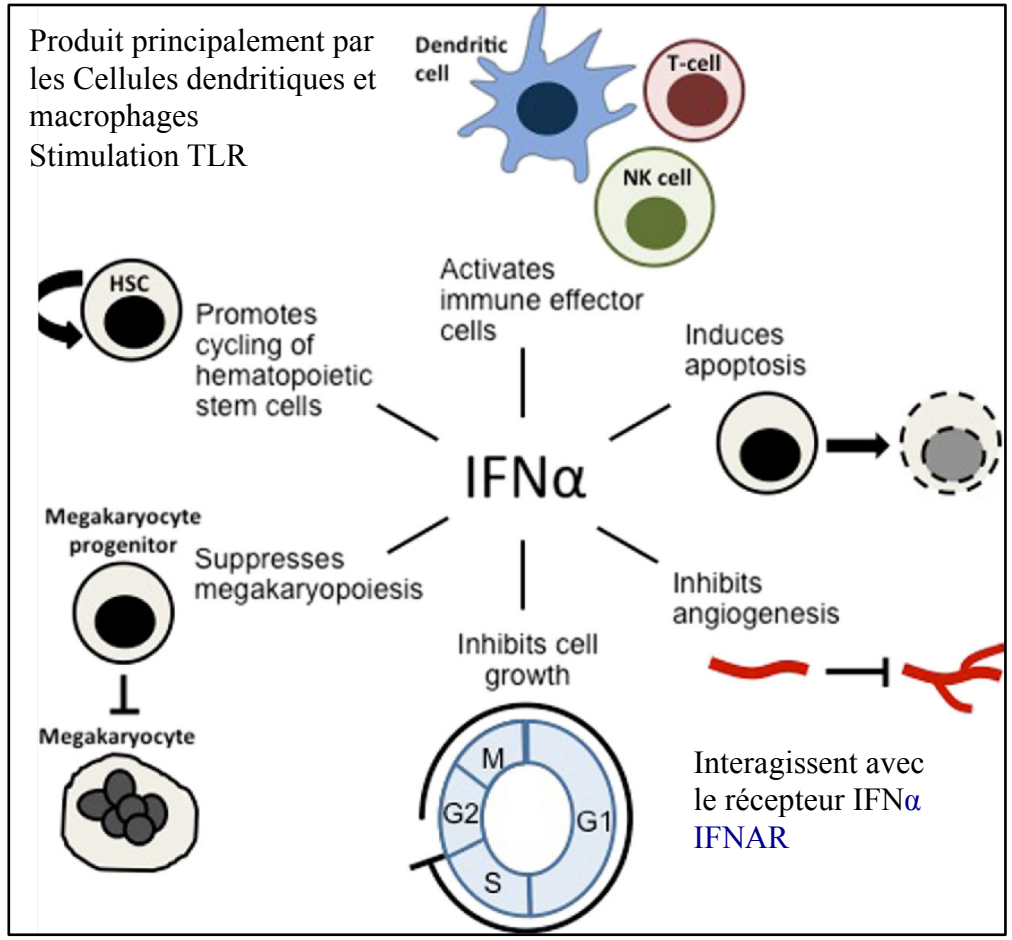


1. Physiopathologie de l’infection à SARS-Cov-2

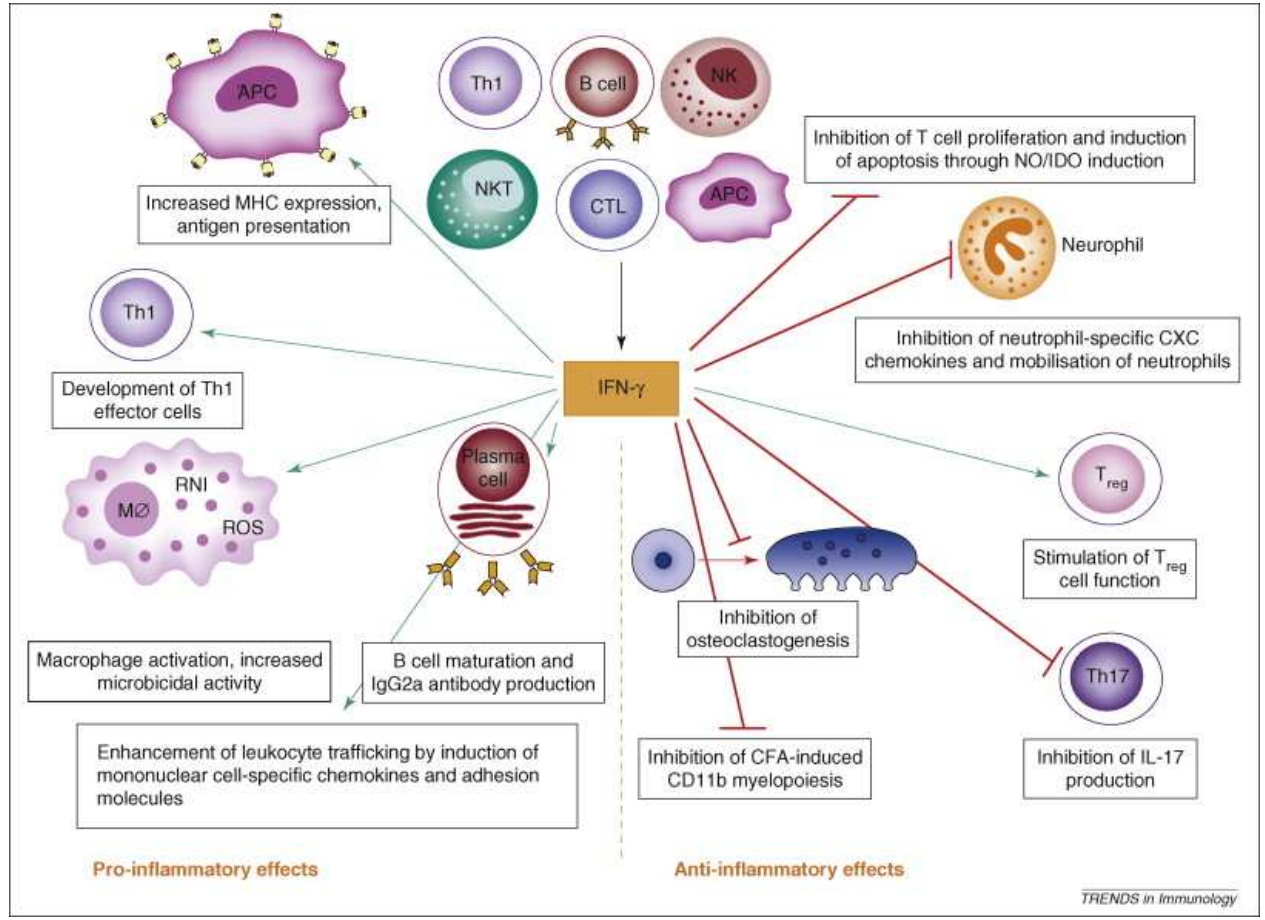
La réponse immunitaire contre le SARS-Cov-2



1.1 Déficit de la Réponse IFN



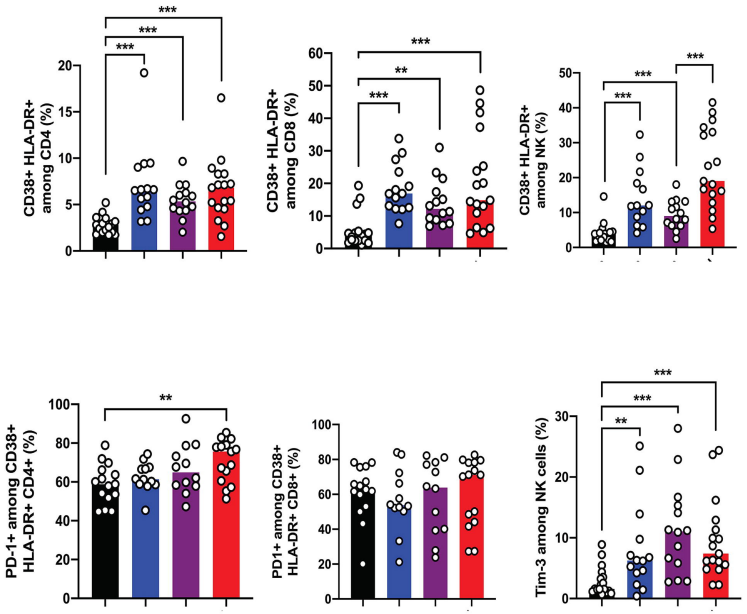
Type I

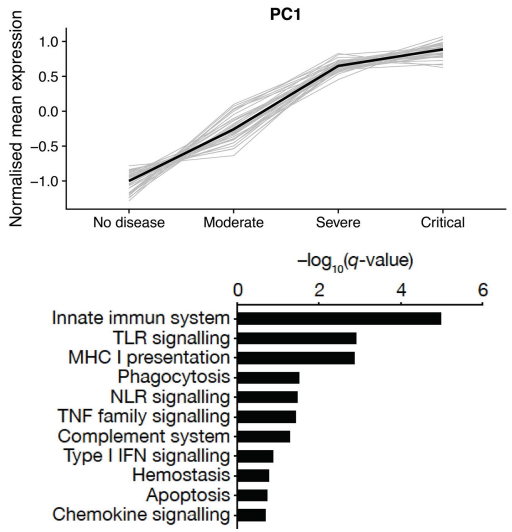


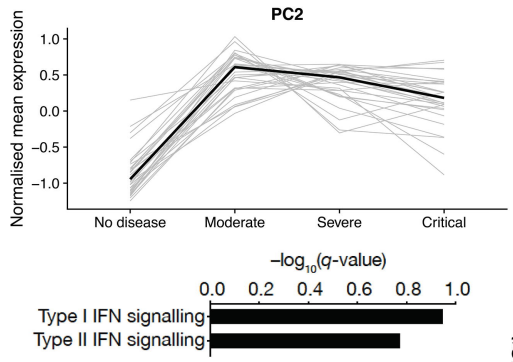
Type II

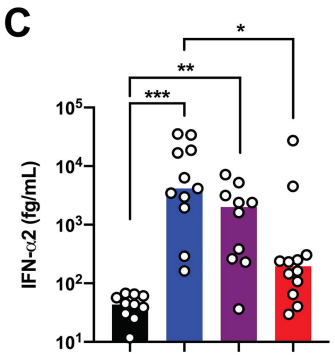
Déficit de la Réponse IFN

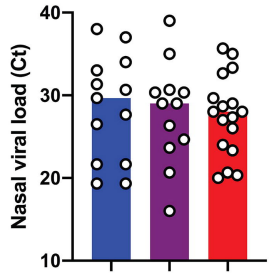
Baisse des d'activation de LT
Surexpression des marqueurs d'épuisement

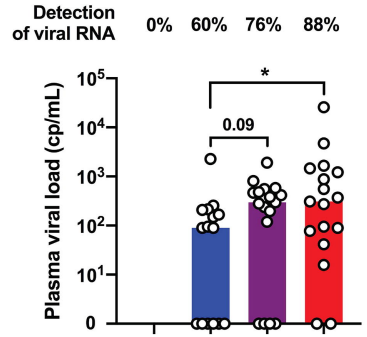










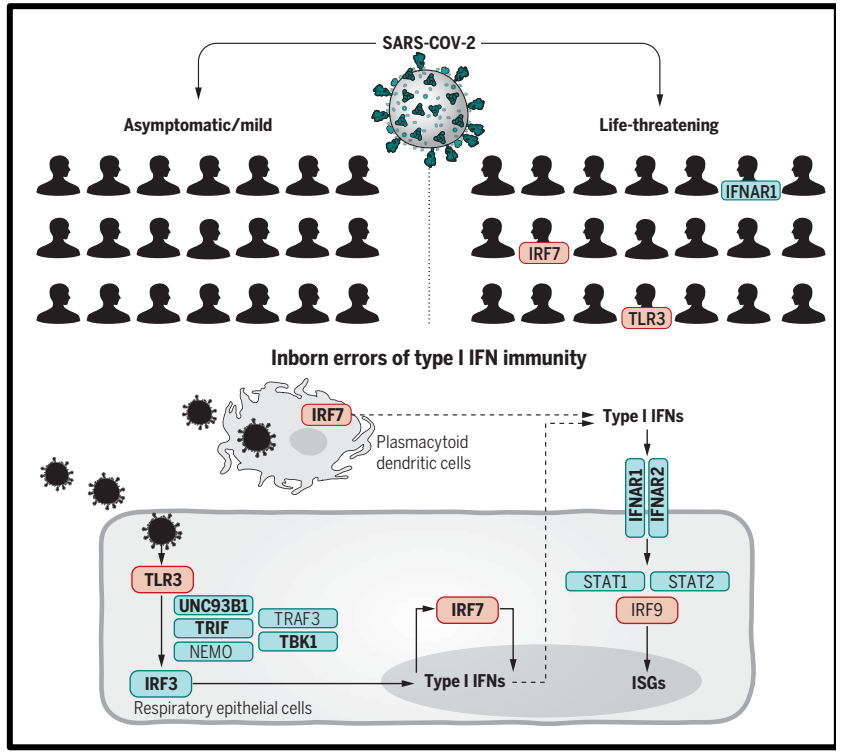


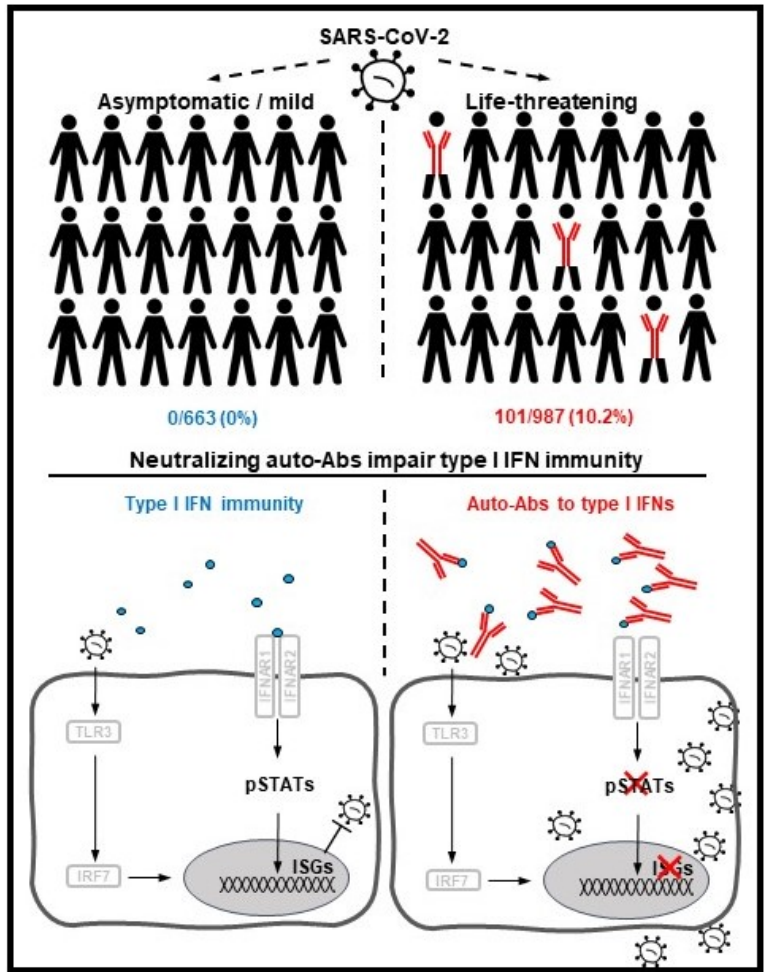
Surexpression des gènes de protéines de l'inflammation
Baisse de l'expression des gènes de l'IFN

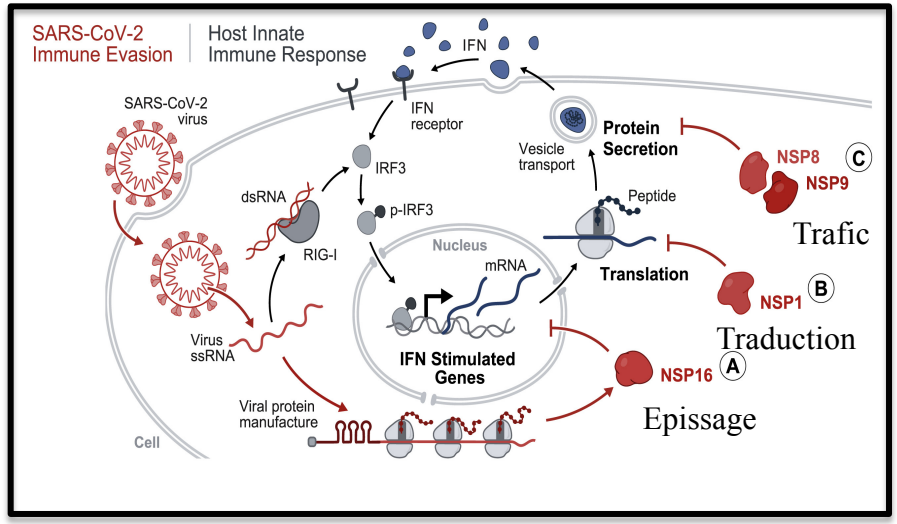
N=50

Hadjadj et al. Science 2020

Causes du déficit en IFN dans les formes graves







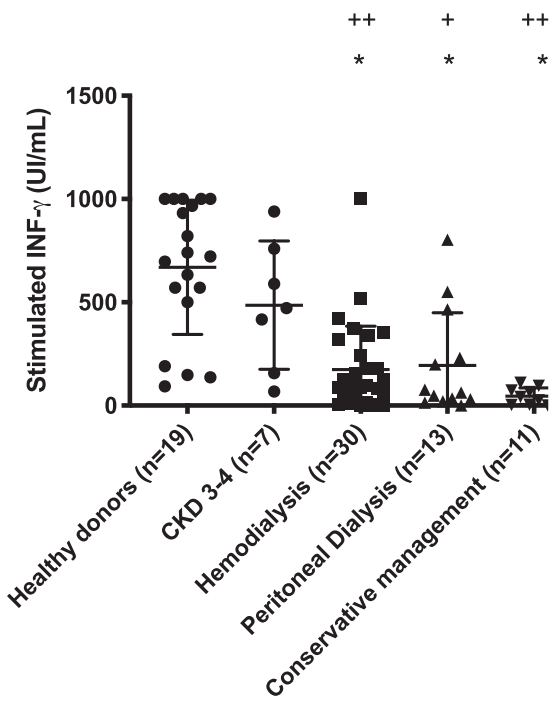
Zhang et al. Science 2020

Bastard et al. Science 2020

Banerjee, Cell 2020

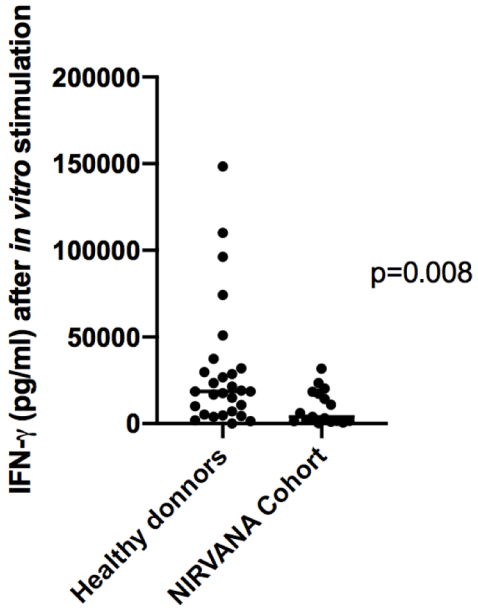
Production d'IFN chez les sujets à risque de COVID grave

Insuffisance rénale



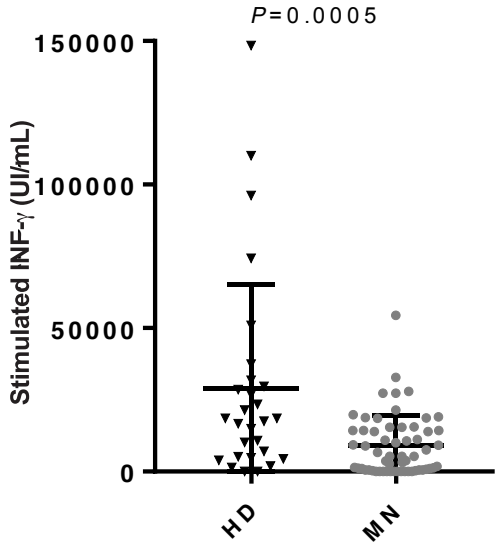
Boyer-Suavet CCA 2020

Mélanome métastatique



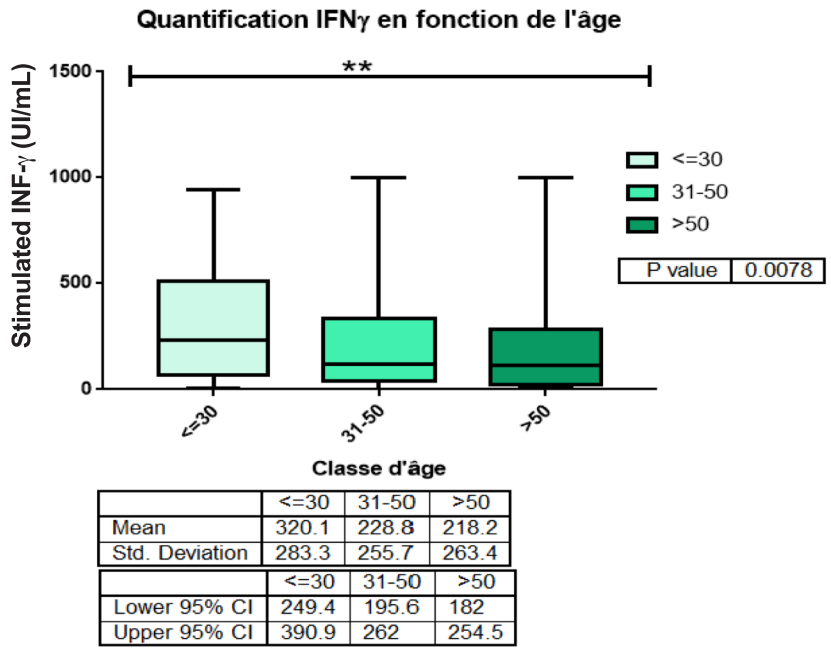
Gérard et al submitted

MAI



Crémoni et al FI 2020

Baisse associée à l'âge



	<=30	31-50	>50
Mean	320.1	228.8	218.2
Std. Deviation	283.3	255.7	263.4

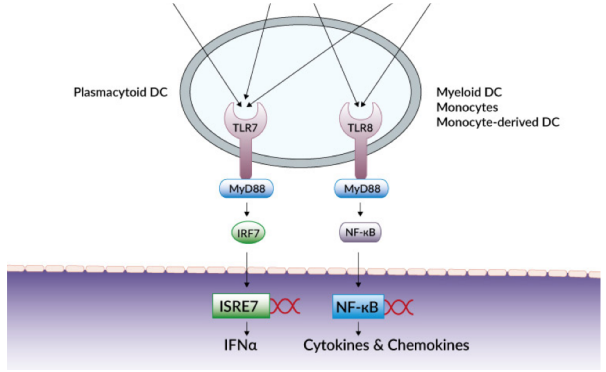
	<=30	31-50	>50
Lower 95% CI	249.4	195.6	182
Upper 95% CI	390.9	262	254.5

Données issues de la cohorte CovImmune 2 n=558 sujets sains

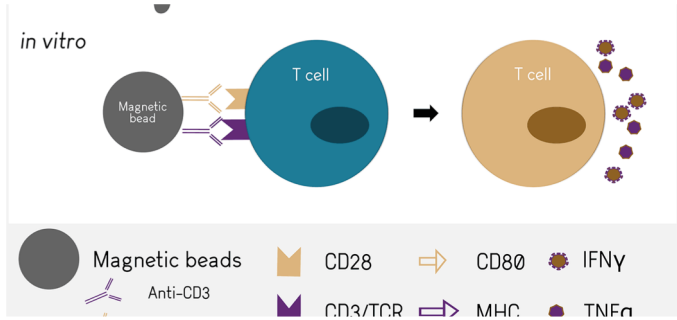
Publications de notre équipe utilisant le test QF Monitor

Test Quantiferon Monitor

Stimule l'Immunité Innée



Stimule l'Immunité Adaptative



Dosage ELISA du taux d'IFNγ

1 ml de sang total sur tube
Héparinate de Lithium

Ajoute billes stimulants
(Anti-TLR7/8, Anti-CD3)

Incubation 16h à 37°

Test produit par Qiagen
5000 tests disponibles

Cellules stables 8h à température ambiante ou 48h à 4°

Test faisable en routine dans tout laboratoire de ville, aucune contrainte structurelle

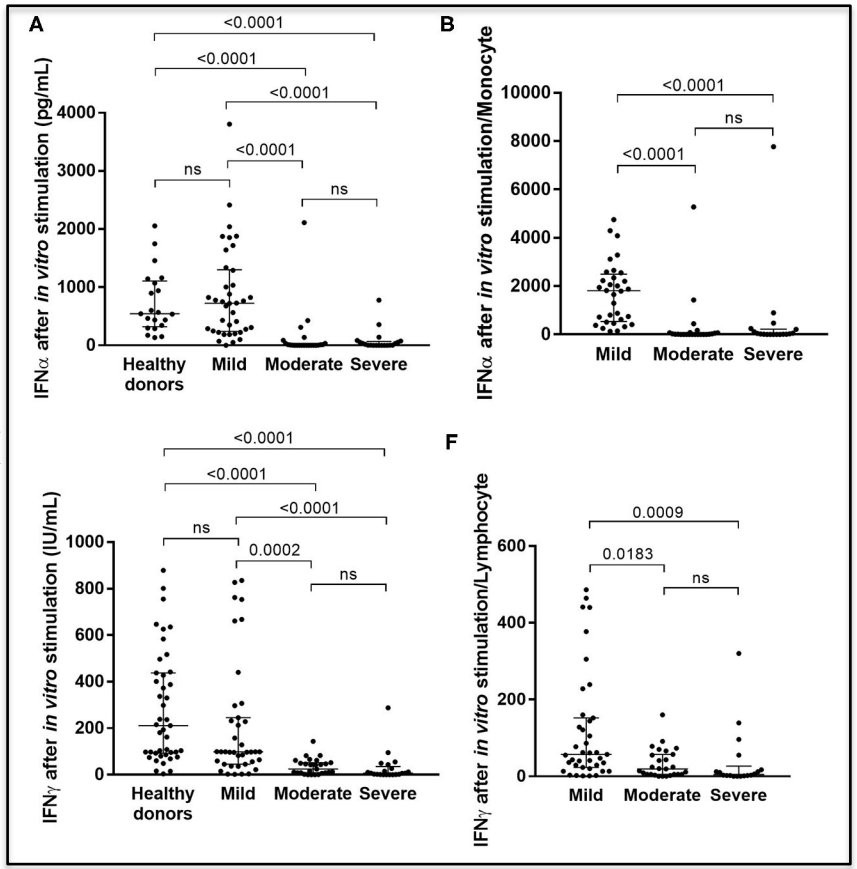
Etude fonctionnelle de la réponse IFN dans des formes graves de COVID

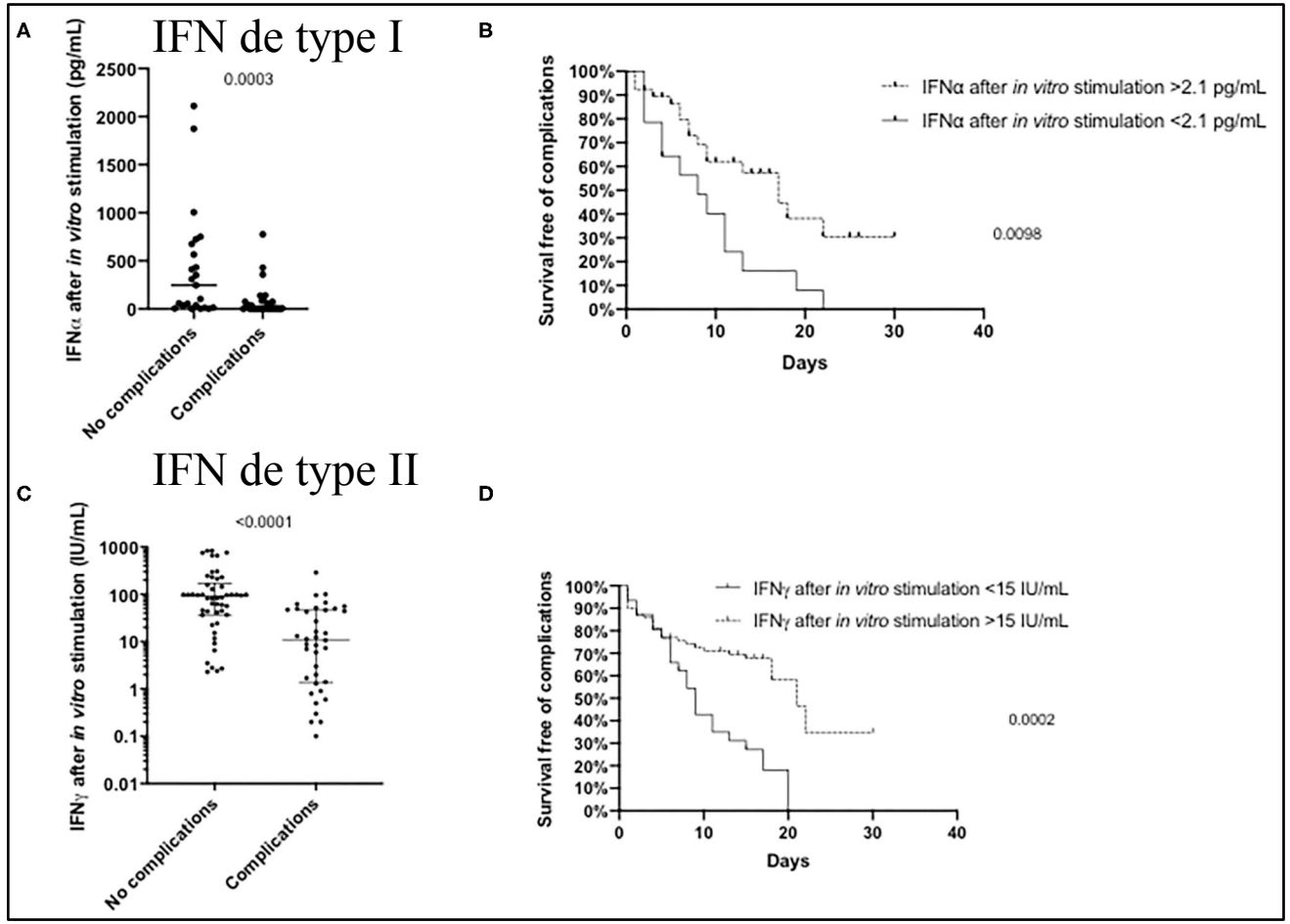
Au moment de l'hospitalisation

IFN de type I

IFN de type II

Healthy donors	Mild cases	Moderate cases	Severe cases
n = 50	*n* = 41	*n* = 30	*n* = 30

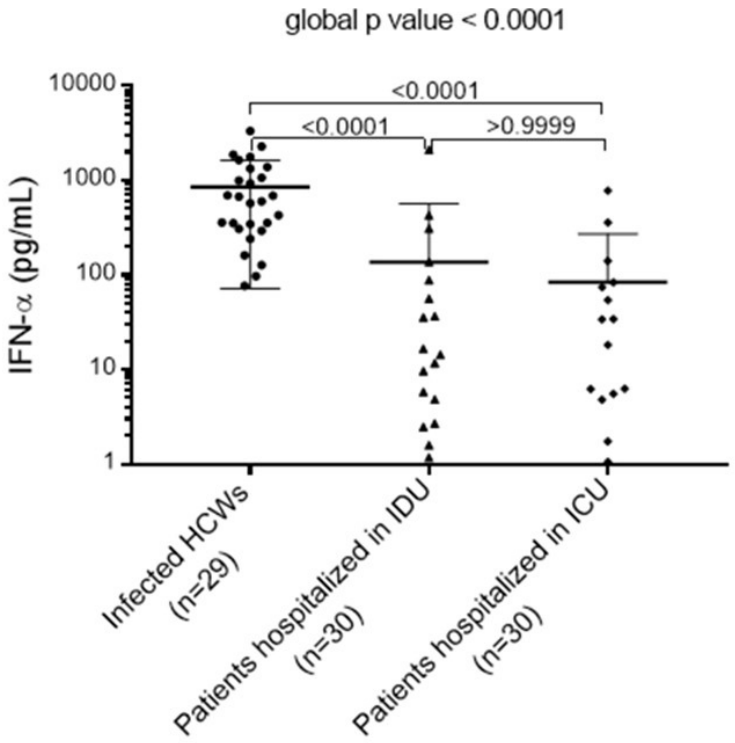


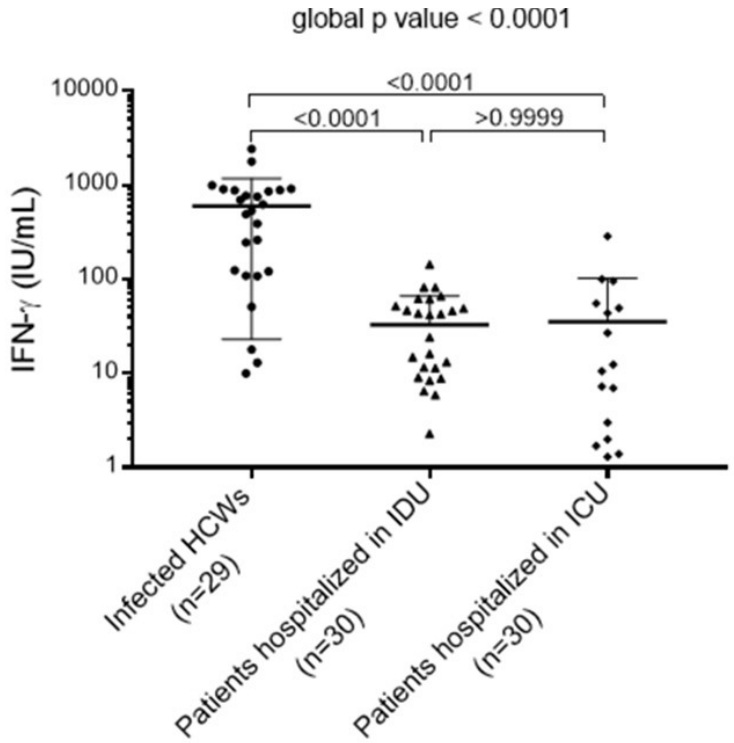


	Odds ratio (95% CI)	*P*-value
Age (years)	1.041 (0.977–1.110)	0.2157
Gender (M/F)	4.119 (0.466–36.402)	0.2029
BMI	1.218 (0.966–1.536)	0.0954
Plasma IL6 (pg/mL)	1.072 (1.015–1.133)	0.0128
Stimulated IFNγ (pg/mL)	0.980 (0.962–0.999)	0.0349

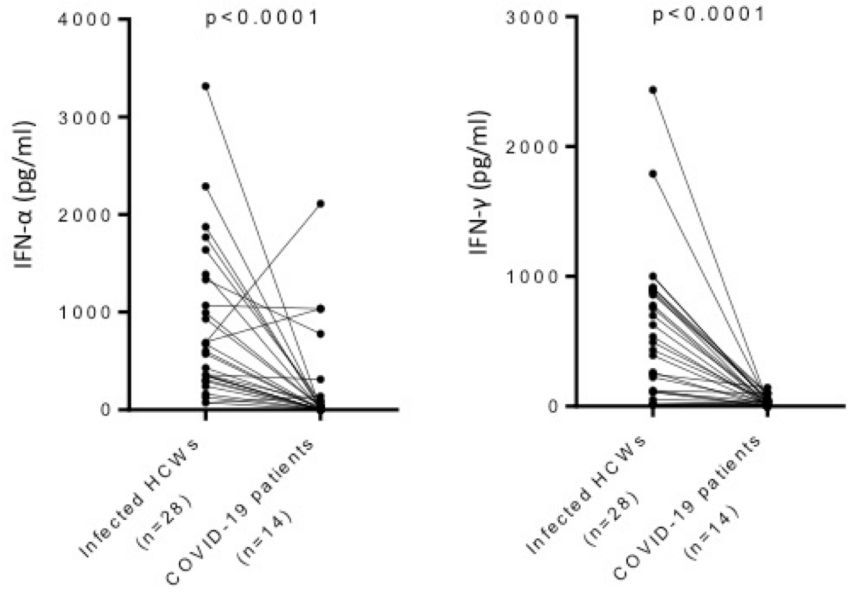
Ruestch, Brglez* et al. Front Med 2020*

Etude fonctionnelle de la réponse IFN dans des formes pauci-symptomatiques de COVID





Après appariement
Âge et sexe



Objectif du traitement → Renforcer la réponse IFN

Cremoni et al. Front in Med 2020

Etude fonctionnelle de la réponse IFN dans les atteintes cutanées de COVID-19

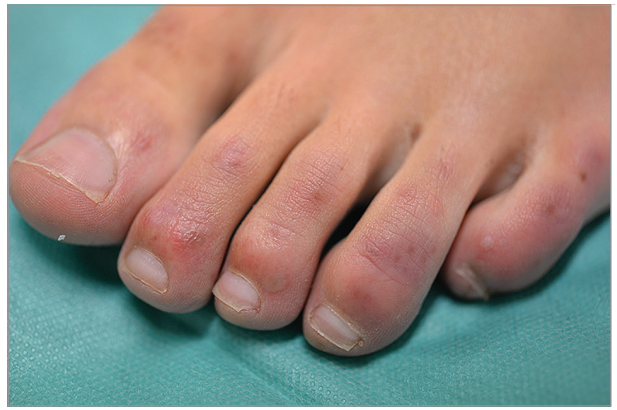
40 patients consécutifs en 30j

Characteristic	No. (%)
Epidemiologic data	
Age, median (range), y	22 (12-67)
Female sex, No./total No. (%)	21/40 (52.5)
Contact with patients presenting criteria for possible COVID-19 infection[a]	24 (60.0)
Patients with criteria for previous possible COVID-19 infection[a]	11 (27.5)
Clinical data	
Delays between, median (range), d	
Previous symptoms and onset of chilblain	21 (2-77)
Onset of chilblain and clinical assessment	14 (3-47)
Onset of chilblain and last follow-up	27 (18-68)
Other manifestations at clinical assessment	
Livedo reticularis	3 (7.5)
Facial erythema	3 (7.5)
Cold toes/acrocyanosis (cyanotic extremities)	19 (47.5)
Laboratory test results	
COVID-19 tests	
Positive rt-PCR (nasopharyngeal and/or stool swabs)	0
Serologic positive results	12 (30.0)
Abnormal d-dimers	24 (61.5)
Positive antinuclear antibodies	9 (22.5)
Positive antiphospholipid antibodies	5 (12.5)
Abnormal CH50	10 (25)
Cryoglobulinemia, No. positive/tested (%)	0/25
Parvovirus B19 serology, No. positive/tested (%)	0/33

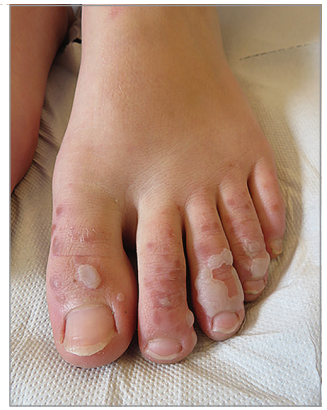
Aspect d'Interferonopathie mimant atteintes lupiques

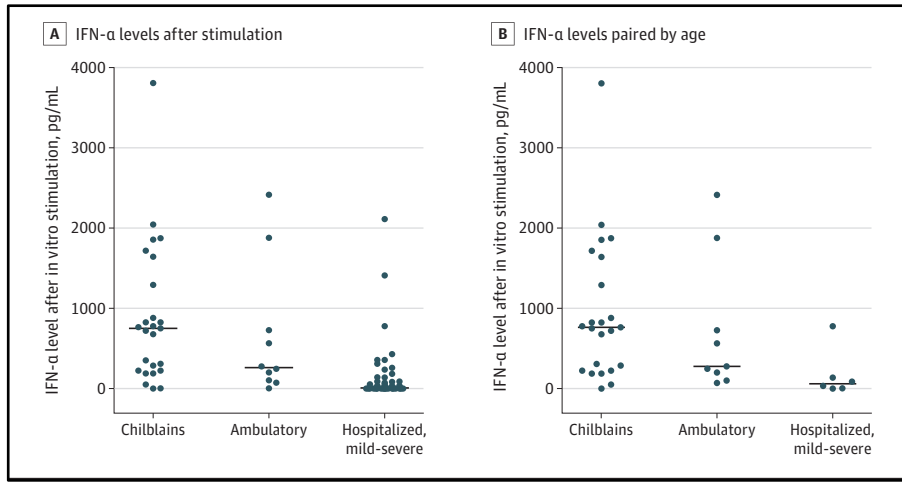
Figure 1. Clinical and Histologic Presentation of Chilblain-like Lesions

A Purpuric lesions on the toes



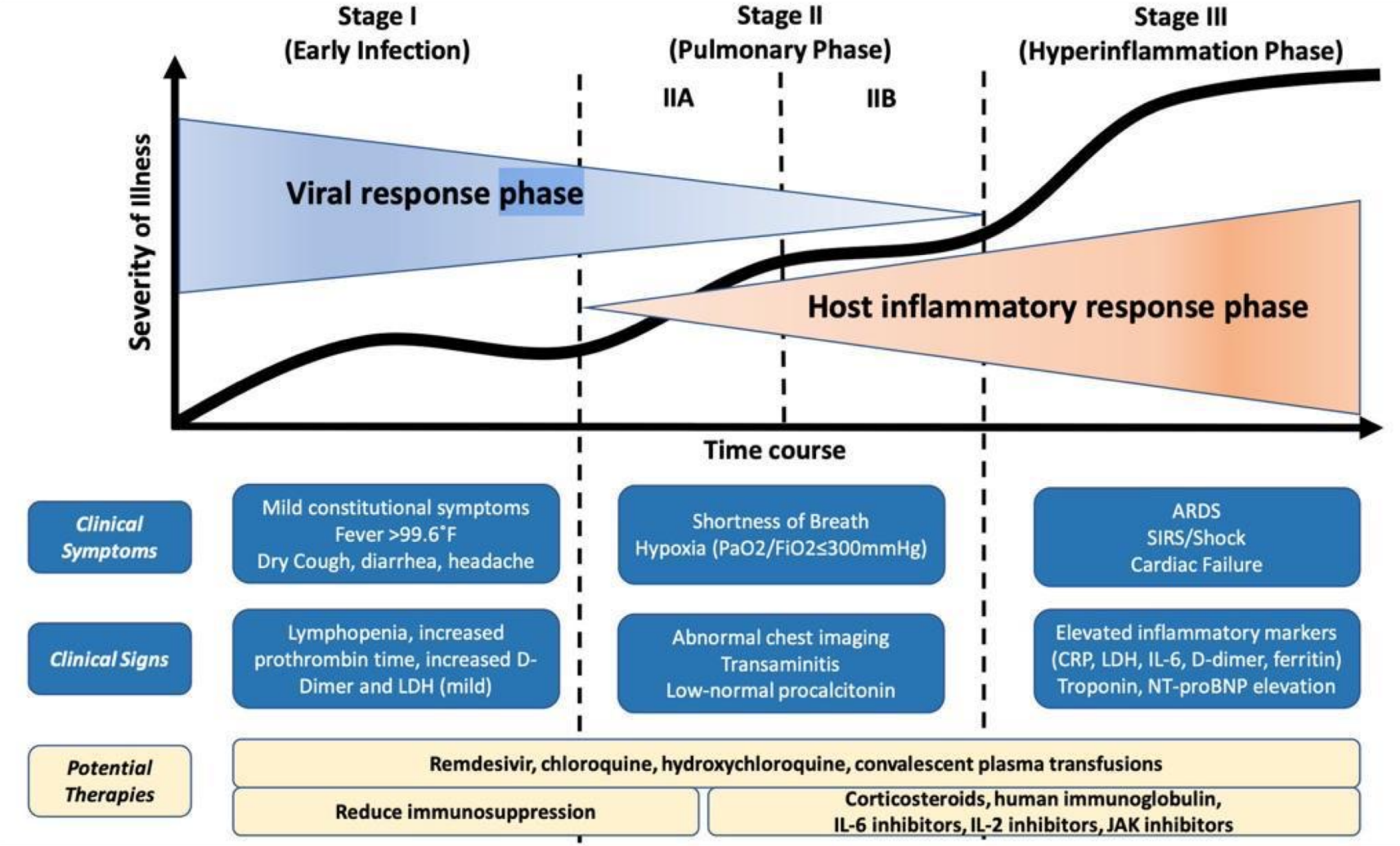
B Papules with bullous evolution



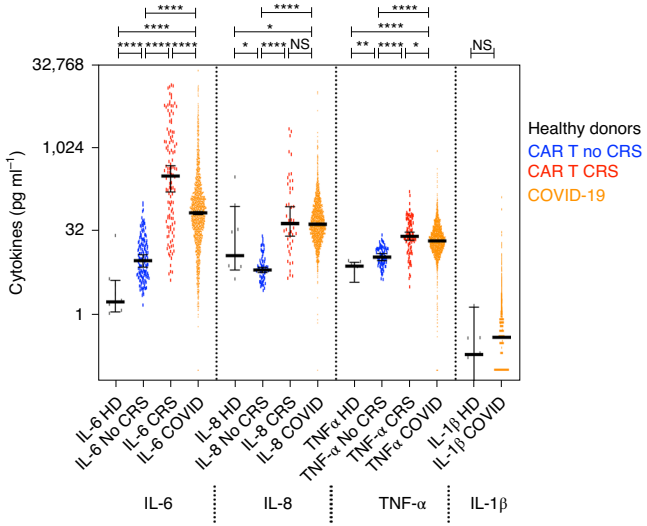


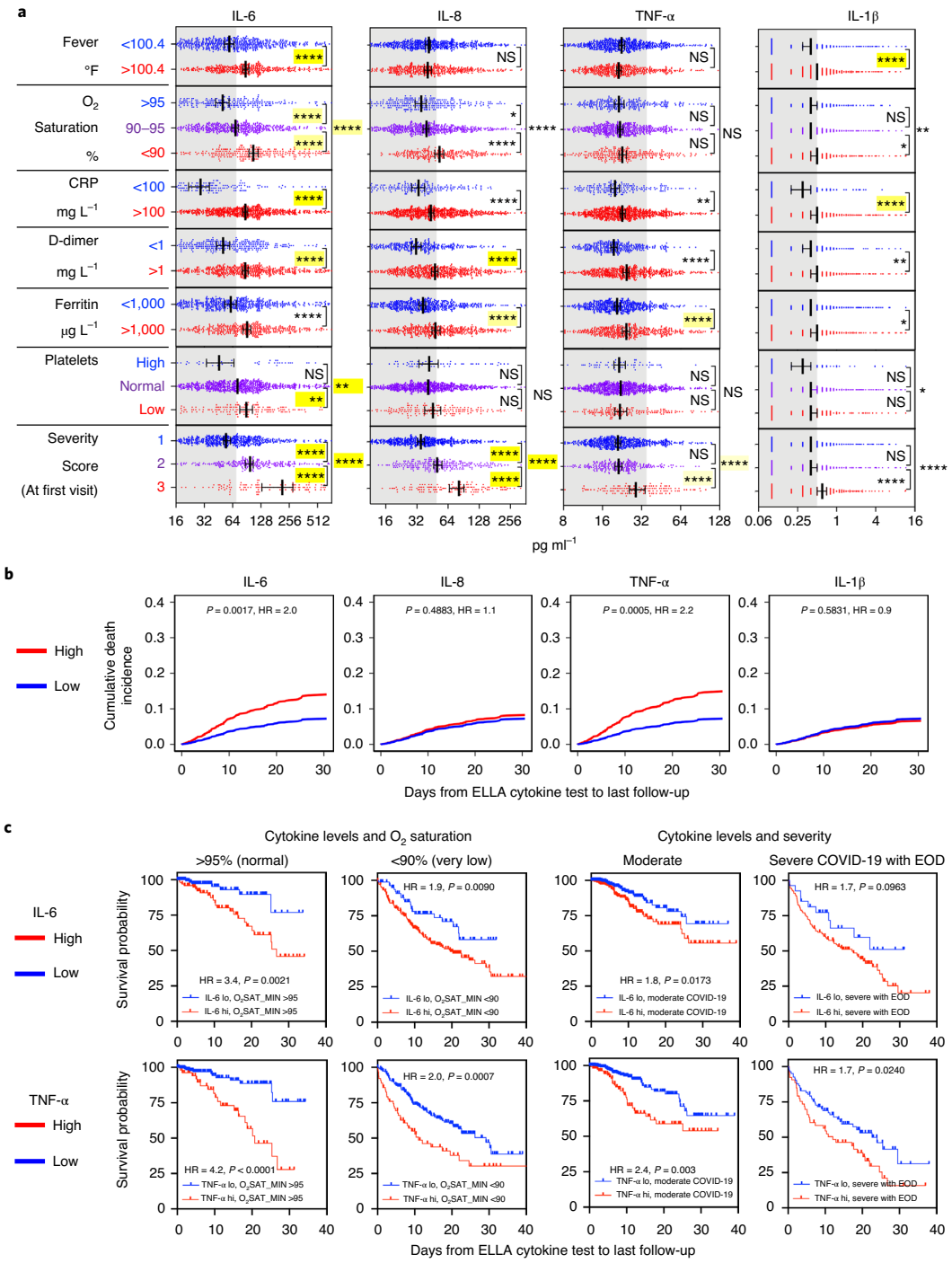
Hubiche et al. JAMA Derm 2020

Stades de COVID-19



1.2 Cytokine Storm





Objectif du traitement → Limiter l'inflammation

Marie Del Valle et al. Nature 2020

Sepsis Bactérien vs COVID

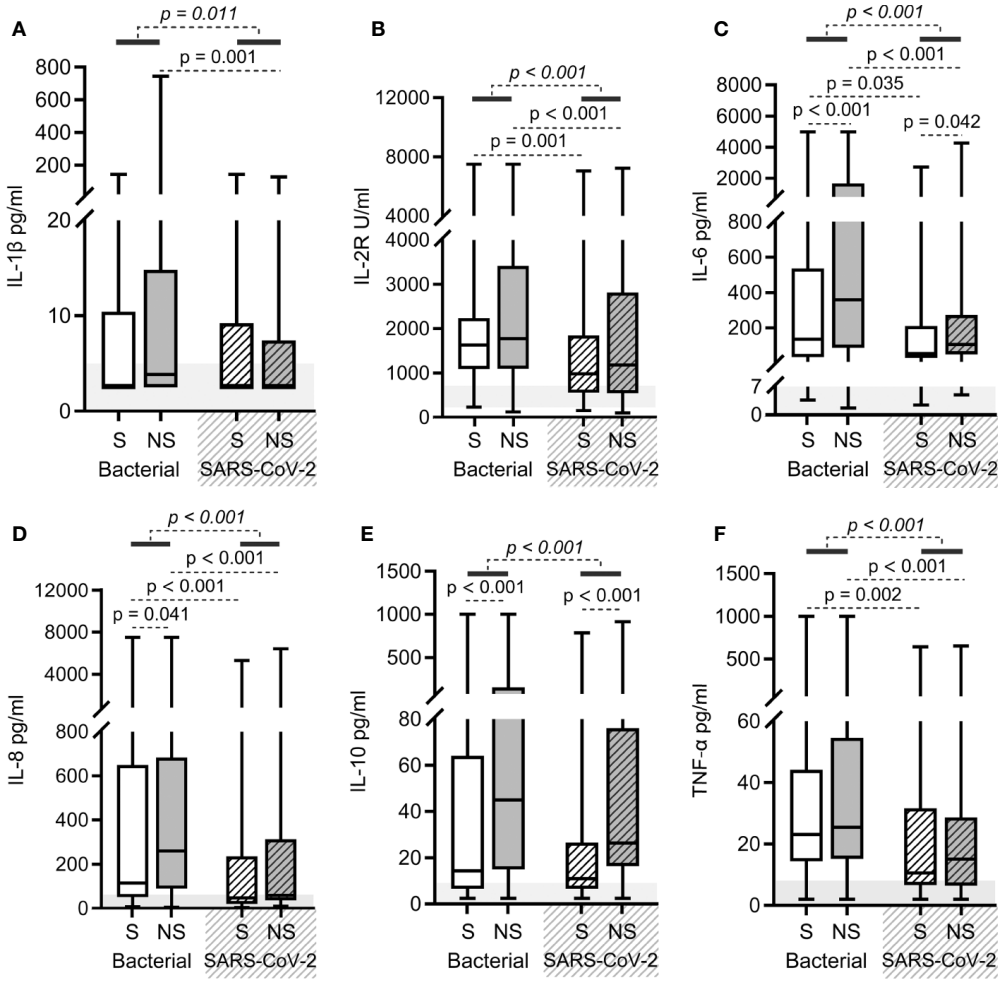
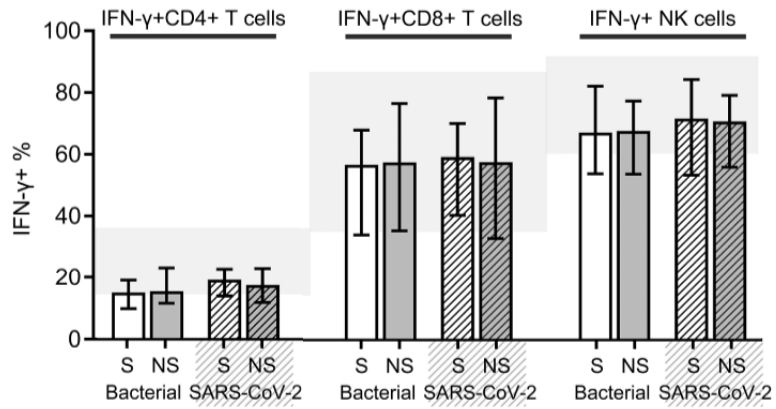


TABLE 1 | Baseline characteristics of patients with bacterial sepsis and SARS-CoV-2 sepsis.

	Bacterial sepsis			SARS-CoV-2 sepsis		
	Total	Survivors	Nonsurvivors	Total	Survivors	Nonsurvivors
	(n = 64)	(n = 41)	(n = 23)	(n = 43)	(n = 29)	(n = 14)
Age[a,b], years	58.0 (51.0, 63.0)	54.0 (50.0, 62.0)	61.0 (57.0, 66.0)	57.0 (50.0, 68.0)	53 (48.5, 63.0)	63.5 (59.0, 71.0)
Age range[a,b], years						
20–39	3 (4.7)	3 (7.3)	0	2 (4.7)	2 (6.9)	0
40–59	32 (50.0)	24 (58.5)	8 (34.8)	21 (48.8)	18 (62.1)	3 (21.4)
≥ 60	29 (45.3)	14 (34.1)	15 (65.2)	20 (46.5)	9 (31.0)	11 (78.6)
Female	23 (35.9)	15 (36.6)	8 (34.8)	14 (32.6)	10 (34.5)	4 (28.6)
SOFA score[a,b]	5.5 (4.5, 7.0)	4.0 (3.0, 6.0)	6.5 (5.0, 8.0)	5.0 (4.0, 7.0)	4.5 (3.0, 5.0)	6.0 (4.5, 8.0)
APACHE II score[a,b]	16.0 (12.0, 20.0)	14.5 (11.0, 18.5)	20.0 (16.0, 22.5)	17.0 (14.0, 18.5)	16.0 (13.5, 17.0)	19.0 (16.0, 20.0)
Chronic medical illness						
Hypertension	13 (20.3)	7 (17.1)	6 (26.1)	10 (23.3)	6 (20.7)	4 (28.6)
Chronic obstructive pulmonary disease	9 (12.5)	5 (12.2)	4 (17.4)	3 (7.0)	2 (6.9)	1 (7.1)
Diabetes mellitus	7 (10.9)	5 (12.2)	2 (8.7)	5 (11.6)	3 (10.3)	2 (14.3)
Coronary artery disease	2 (3.1)	1 (2.4)	1 (4.3)	1 (2.3)	0	1 (7.1)
Cerebrovascular disease	1 (1.6)	1 (2.4)	0	0	0	0



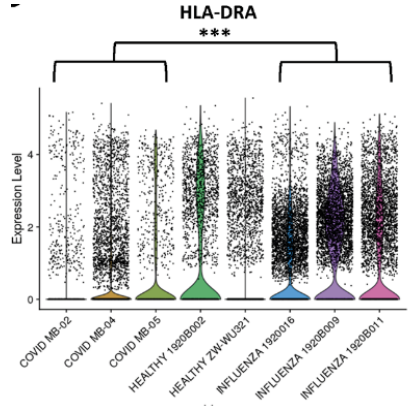
Déficit IFN dans une réponse virale

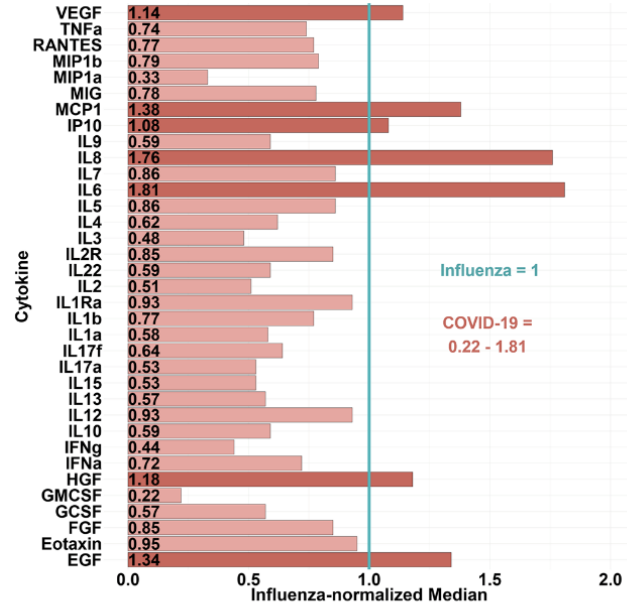
Dong et al. FI 2020

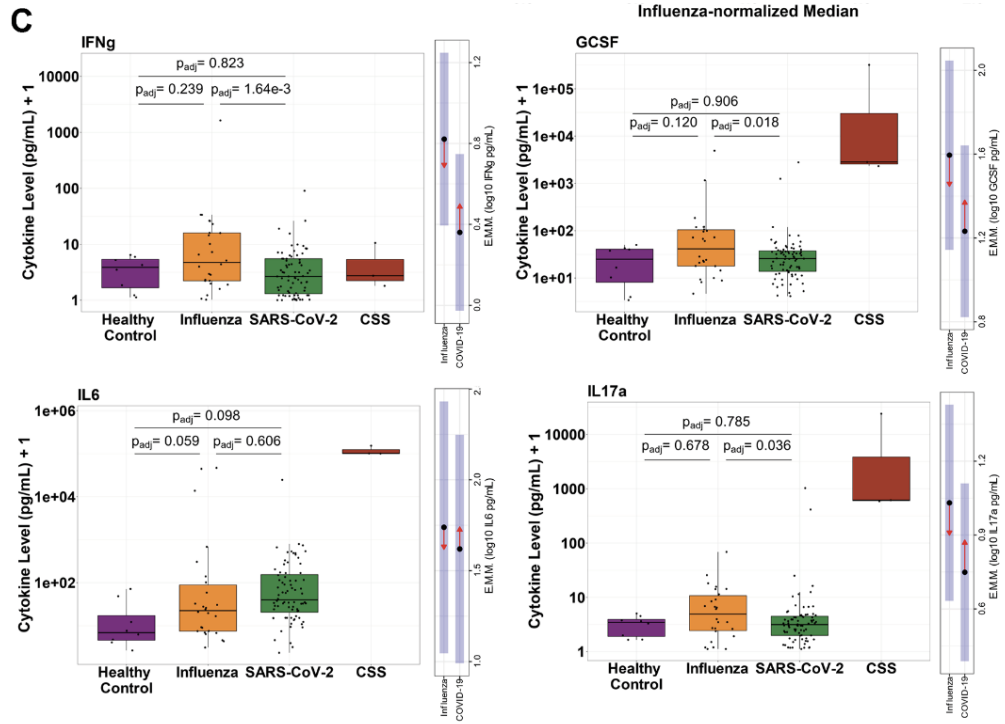
Influenza vs COVID

	SARS-CoV-2 (n = 79)	Healthy Control (n = 16)	Influenza (n = 26)	COVID19-Healthy comparison	COVID19-Influenza comparison
Demographics					
Mean ± SD (range) age, in years	61 ± 15 (25-89)	32 ± 7 (22-49)	42 ± 17 (18-89)	p < 0.001, OR = 0.85	p = 0.007, OR = 0.93
Female	44% (35/44)	50% (8/8)	58% (15/26)	p = 1, *N.S.*	p = 1, *N.S.*
Ethnicity					
African American	80% (63/79)	44% (7/16)	65% (17/26)	-	-
White	18% (14/79)	56% (9/16)	27% (7/26)	p < 0.05, OR = 9.59	p = 0.718, *N.S.*
Other	<3% (2/79)	0% (0/16)	8% (2/26)	-	p = 1, *N.S.*
Clinical characteristics					
Mean (IQR) symptom duration at study enrollment, in days	6.4 (3-9)		4.1 (2-7)		p = 0.229, *N.S.*
Hospital admission	90% (71/79)		58% (15/26)		p = 0.229, *N.S.*
ICU admission	56% (44/79)		35% (9/26)		p = 0.285, *N.S.*
Intubation and mechanical ventilation	44% (35/79)		27% (7/26)		p = 0.285, *N.S.*
In-hospital death	30% (24/79)		8% (2/26)		p = 0.234, *N.S.*
Comorbidities					
Immunocompromised	6% (5/79)		0% (0/26)		p = 0.33, *N.S.*
Chronic lung disease	34% (27/79)		42% (11/26)		p = 0.682, *N.S.*
Chronic heart failure	13% (10/79)		23% (6/26)		p = 0.101, *N.S.*
End stage renal failure	5% (4/79)		8% (2/26)		p = 0.582, *N.S.*
Diabetes mellitus	43% (34/79)		27% (7/26)		p = 0.628, *N.S.*
Active cancer	6% (5/79)		8% (2/26)		p = 0.234, *N.S.*

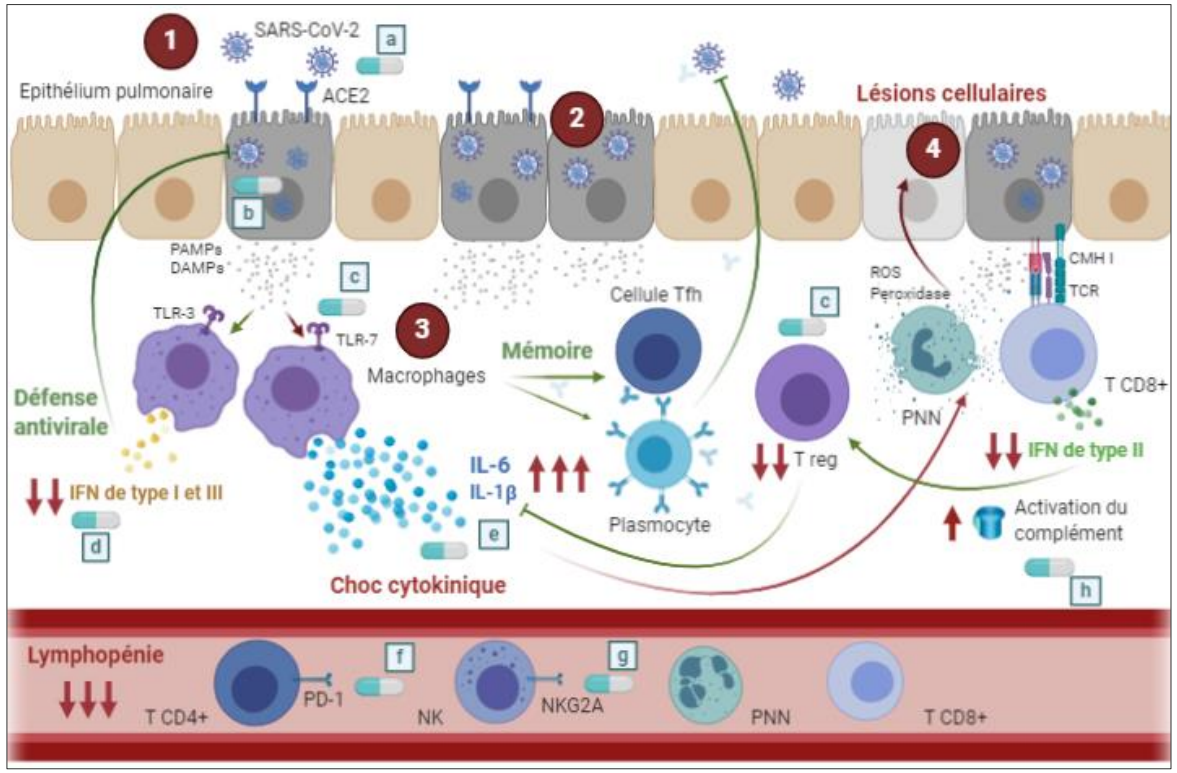
Mudd et al. Science Advances 2020







2. Immunothérapie du COVID-19



Inhibition — Stimulation — Réaction immunitaire inadaptée — Réaction immunitaire adaptée

Etapes :

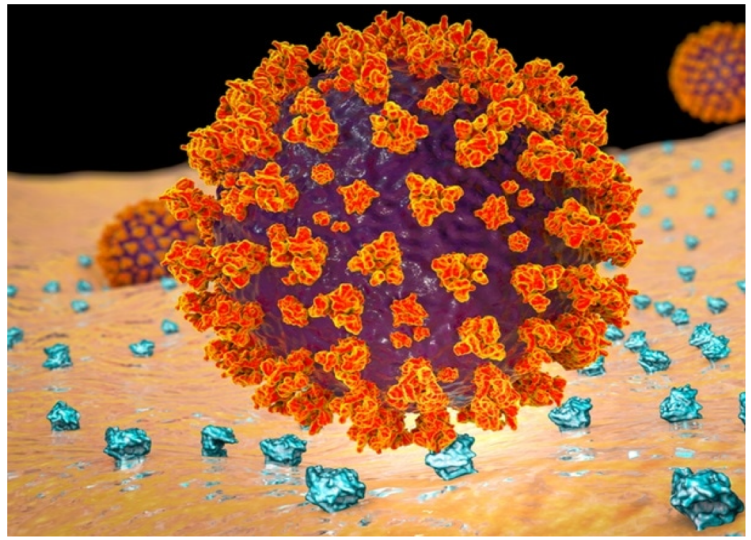
1	J0	Entrée du virus
2	J1-2	Réplication virale
3	J3-7	Réponse immunitaire inadaptée
4	J7-14	Syndrome de détresse respiratoire aiguë (SDRA)

Thérapeutiques proposées :

a	Anticorps monoclonal ciblant la protéine Spike
b	Antiviraux (ex : Remdesivir)
c	Hydroxychloroquine
d	Interféron-α
e	Anti-IL-6 (ex : Tocilizumab)
f	Anti-PD-1 (ex : Nivolumab)
g	Inhibiteur NKG2A
h	Anti-C5 (ex : Eculizumab), anti-C3

2.1 Limiter l'entrée du virus dans la cellule cible

Objectif: Neutraliser l'interaction Spike / ACE2
→ bloquer l'entrée du virus dans la cellule cible



2.1.1 Hydroxychloroquine

- CQ et HCQ augmentent le Ph intracellulaire limiter fusion membranaire
- Modifie glycosylation ACE et Spike limitant entrée du virus

Non traité 34.3% des virions sont transportés endosome-lysosome (LAMP1)
CQ 2.4% et 0.03% HCQ $p<0.001$

EEA1: Early endosome
LAMP1: late endosome

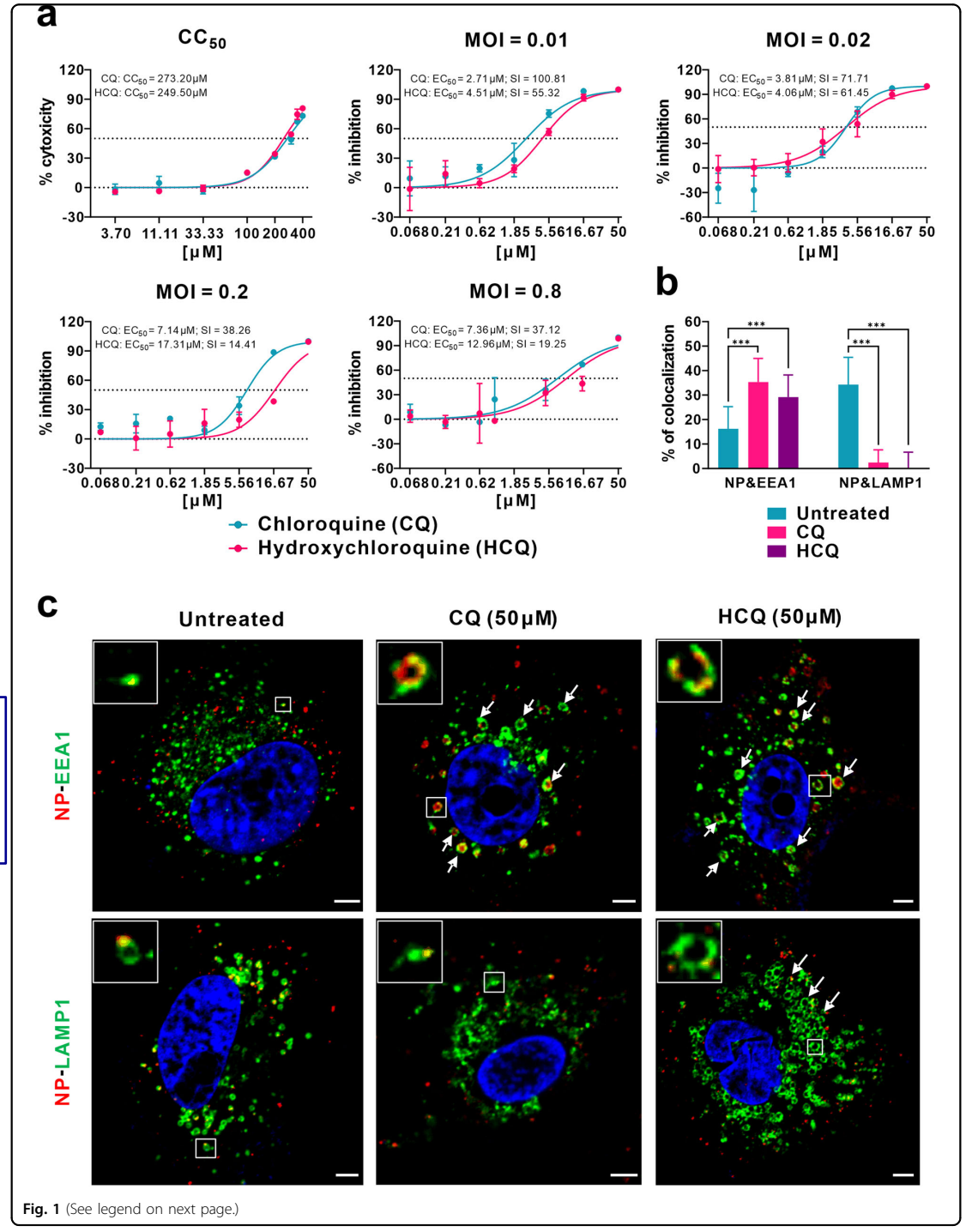


Fig. 1 (See legend on next page.)

Liu et al., Cell Discovery 2020

2.1.2 Anticorps polyclonaux thérapeutiques

1891-1894

Les premiers anticorps sur le marché…

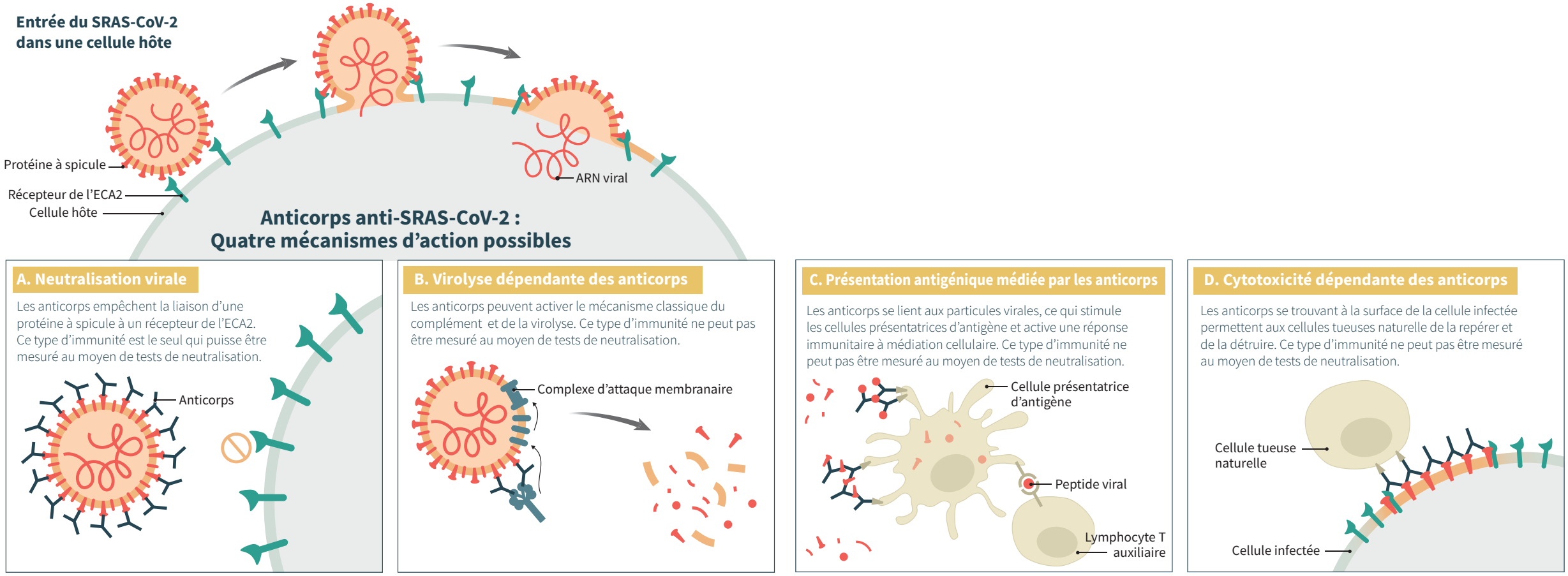
Sérum de chevaux immunisés

- Purification de la fraction Ig
- Recours plasmas humains

Améliorer la Tolérance

Sérothérapie anti-tétanique, anti-diphtérique, anti-pesteuse ou anti-méningococcique

Mécanismes d'action des Ig polyvalentes issus de patients convalescents



Devasenapathy et al. CMAJ 2020

Applications au COVID19

10 patients présentant des formes sévères →traités 200 ml de Plasma de patients convalescents (Ac anti-SARS Cov2 1:640)

Clinical factors	Before CP transfusion	After CP transfusion
CRP (mg/L, normal range 0 to 6)	55.98 (15.57 to 66.67)	18.13 (10.92 to 71.44)
Lymphocyte (10^9 per L, normal range 1.1 to 3.2)	0.65 (0.53 to 0.90)	0.76 (0.52 to 1.43)
Alanine aminotransferase (U/L, normal range 9 to 50)	42.00 (28.25 to 61.85)	34.30 (25.75 to 53.90)
Aspartate aminotransferase (U/L, normal range 15 to 40)	38.10 (28.50 to 44.00)	30.30 (17.30 to 38.10)
Total bilirubin (μmol/L, normal range 0 to 26)	12.40 (11.71 to 22.05)	13.98 (12.20 to 20.80)
SaO_2 (%, normal range ≥ 95)	93.00 (89.00 to 96.50)	96.00 (95.00 to 96.50)

SaO_2, oxyhemoglobin saturation.

		Before CP transfusion			After CP transfusion		
Patient no.	CP transfusion date	Date	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)	Date	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)
1	February 9	February 8	1:160	37.25	February 10	1:640	Negative
2	February 9	February 8	Unavailable	35.08	February 11	Unavailable	Negative
3	February 13	February 12	1:320	38.07	February 14	1:640	Negative
4	February 13	February 12	1:160	37.68	February 14	1:640	Negative
5	February 12	February 11	1:640	Negative	February 14	1:640	Negative
6	February 12	February 11	1:640	Negative	February 14	1:640	Negative
7	February 12	February 11	1:320	34.64	February 14	1:640	Negative
8	February 12	February 11	1:640	35.45	February 14	1:640	Negative
9	February 12	February 11	1:160	Negative	February 14	1:640	Negative
10	February 9	February 8	1:640	38.19	February 14	1:640	Negative

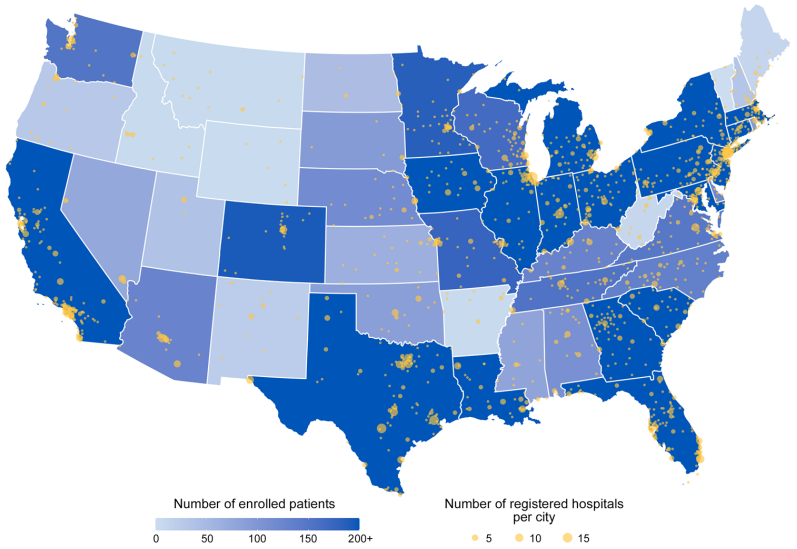
Duan et al., PNAS 2020

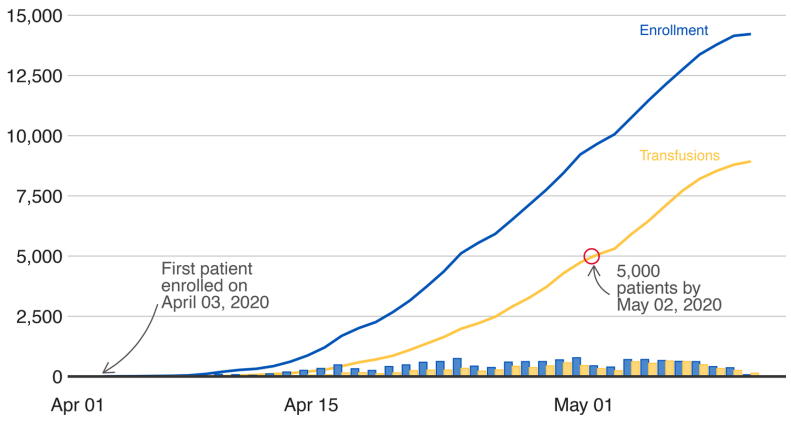
→ Etude Coviplasm en France

200 patients convalescents prélevés – 60 patients COVID inclus

- Bras: plasma de patients convalescents pour le COVID 19
- Bras: plasma de sujets contrôles

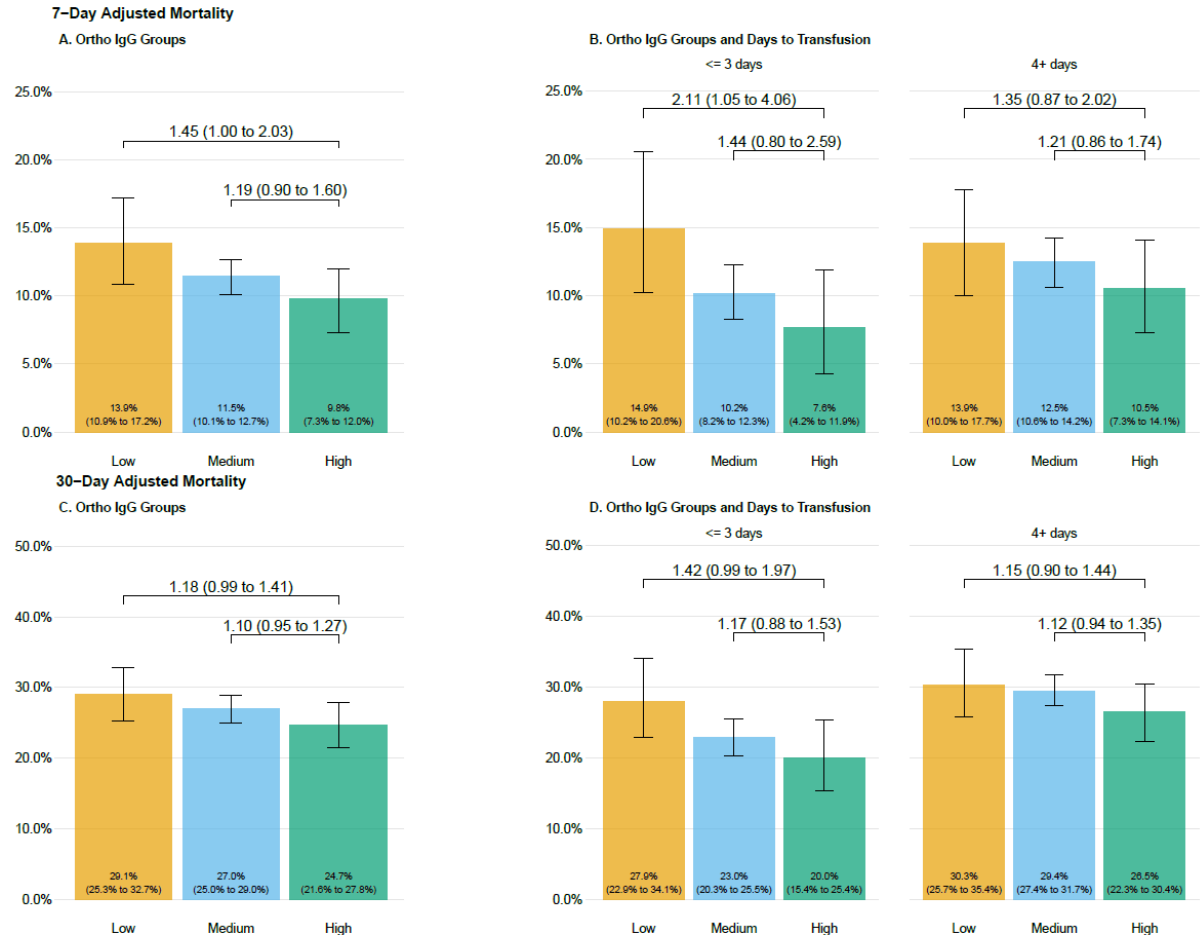
Mortalité des patients COVID-19 traités par plasmas issus de patients convalescents





Joyner et al. Medrxiv 2020

N=35 000



→ *Impact sur la mortalité si injection dans les 3 jours à fortes doses d'IgG*

→ *Risque de sélection de souches*

2.1.3 Ac monoclonal

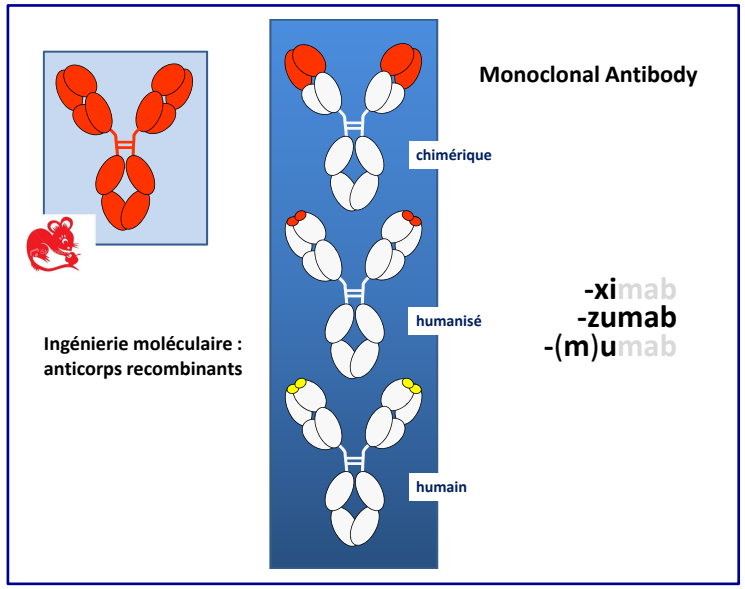
Technique de l'hybridome (1970):

Immortaliser et faire proliférer des clones de cellules B de souris produisant un seul type d'Ac par la fusion de clones B avec cellules myélomateuses immortelles.

Polyclonaux → Monoclonaux : dirigés contre un seul épitope.

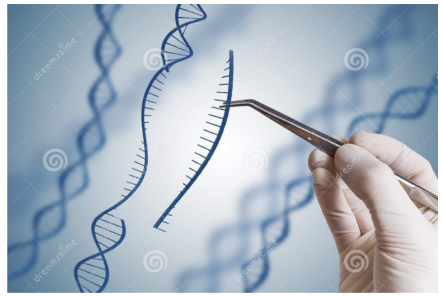
Souris à l'humain.

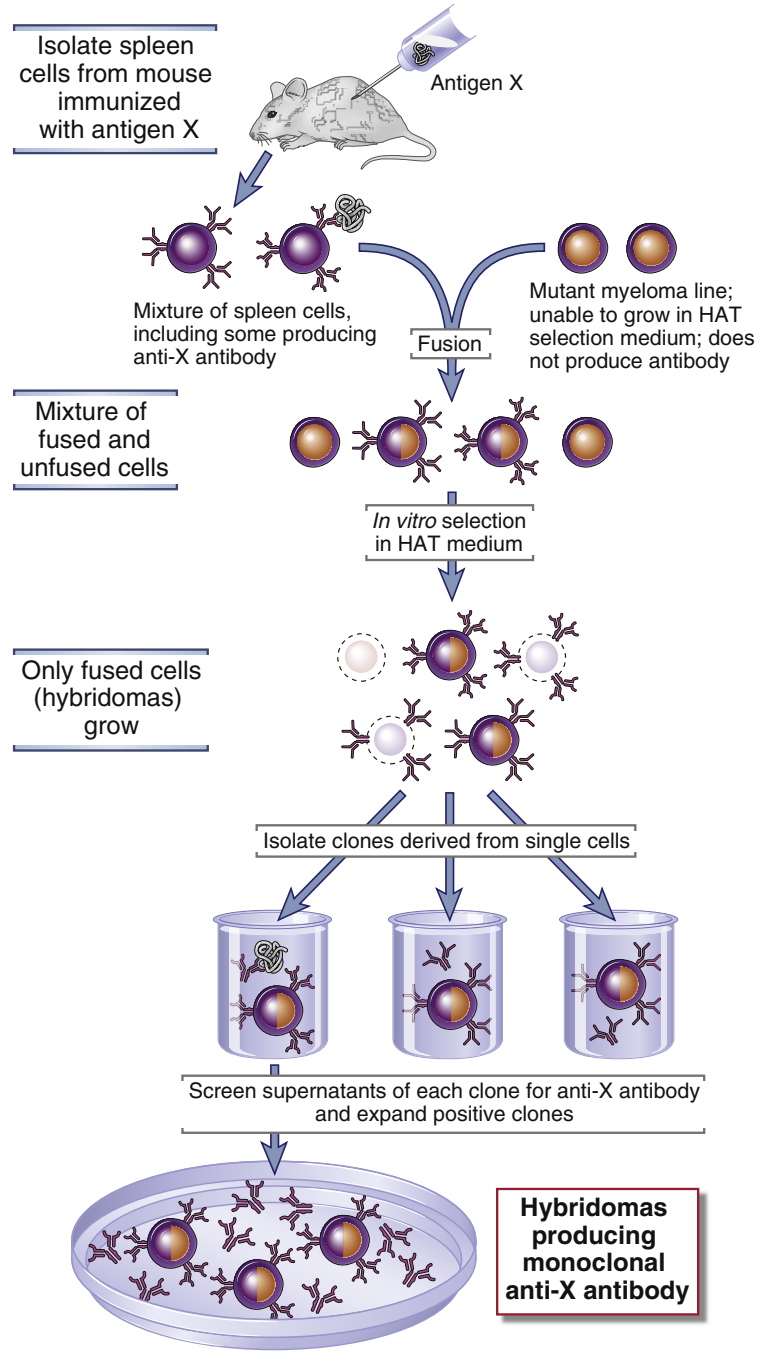
Faible efficacité des monoclonaux thérapeutiques murins lié à leur immunogénicité et leur faible demi-vie (x: OKT3)



Par génie génétique

- Remplacement progressif des domaines constants
- Remplacement des régions charpentes des domaines variables des Ig murines par leurs homologues humains





Anticorps neutralisant : COVID19

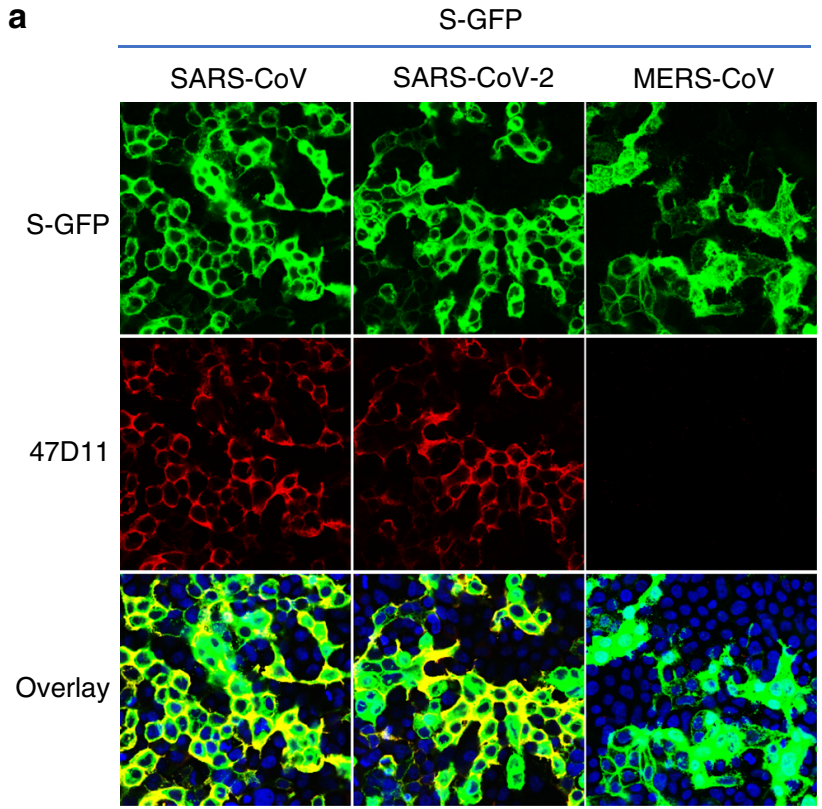
Prot S1

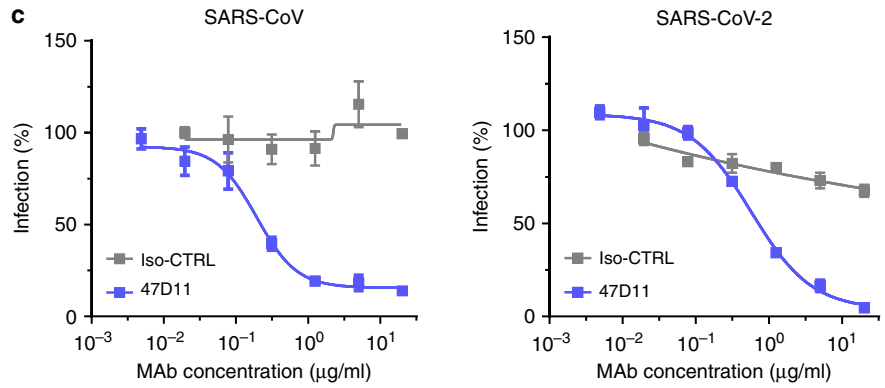
Sélection de l'hybridome

Souris tg codant pour Ig chimérique
Chaine lourde humaine
Chaine légère rat
→ Humanisé

Wang et al. Nature Com 2020

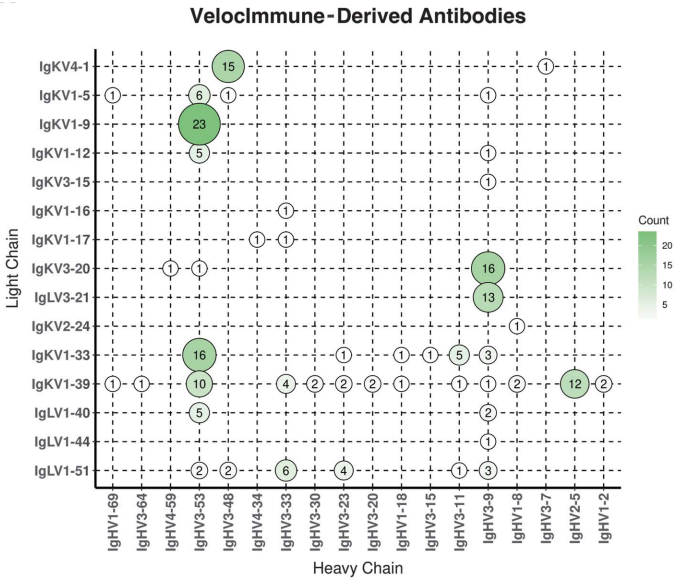
Hybridoma	SARS-S_{ecto}	SARS-S1	SARS-$S1_A$	SARS2-S1
44B3	2,5	2,7	3,3	0,1
45E10	3,0	0,8	1,7	0,0
46F11	2,4	2,7	3,3	0,0
39F9	2,9	3,3	3,5	0,0
41A7	2,6	1,0	1,9	0,0
28 E3	2,4	2,3	3,2	0,0
34C10	1,3	1,0	1,9	0,0
16C10	2,4	0,6	1,7	0,1
14B1	2,6	2,9	3,3	0,1
30B1	0,6	0,5	1,1	0,0
28G10	1,0	1,3	2,6	0,0
28F6	2,4	2,9	3,0	0,0
40H10	1,2	0,7	1,9	0,0
39A4	1,7	1,5	2,8	0,0
37G1	1,3	0,9	1,7	0,0
44E11	2,8	3,3	3,5	0,1
19C1	1,9	0,4	1,2	0,1
58D2	2,6	2,8	3,4	0,1
14C1	2,8	1,2	2,6	0,0
45H1	2,3	3,1	3,6	0,0
24F5	3,3	3,4	3,6	0,0
52D9	1,5	1,6	2,3	1,3
45E6	2,4	2,6	3,3	0,0
47D11	3,4	3,0	0,0	1,5
47G10	2,6	2,8	0,1	0,0
48G1	3,3	3,4	0,1	0,0
49F1	1,8	2,0	0,0	1,3
43C6	3,1	3,4	0,1	0,1
22E10	3,2	3,4	0,1	0,0
28D11	2,7	3,1	0,1	0,0
28H3	2,8	1,8	0,0	0,0
25E7	3,1	3,3	0,1	0,1
22E8	1,2	1,2	0,1	0,0
35F4	3,2	3,6	0,1	0,0
43G5	3,2	3,3	0,1	0,1
47F8	1,4	1,4	0,0	0,0
43B4	3,2	3,3	0,1	0,0
49B10	1,1	0,6	0,0	0,2
51C11	1,9	1,9	0,0	0,0
36F6	1,7	2,7	0,1	0,3
65H8	3,2	3,3	0,1	0,1
65H9	1,6	1,7	0,1	2,5
48D5	3,3	3,5	0,1	0,0
35E2	2,5	3,3	0,2	0,0
44G3	2,4	2,8	0,1	0,0
9H9	1,8	0,1	0,0	0,1
25C3	3,0	0,1	0,1	0,1
29E6	1,1	0,1	0,1	0,0
43F11	2,8	0,1	0,1	0,0
47C4	1,5	0,0	0,1	0,0
13F11	3,0	0,0	0,0	0,0

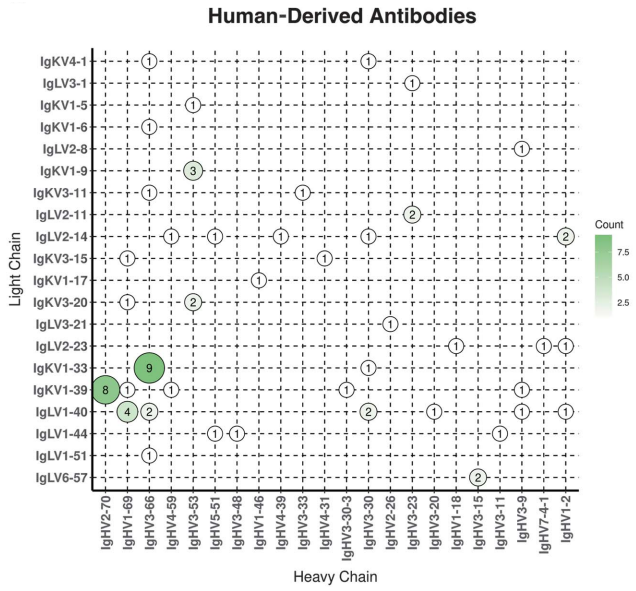


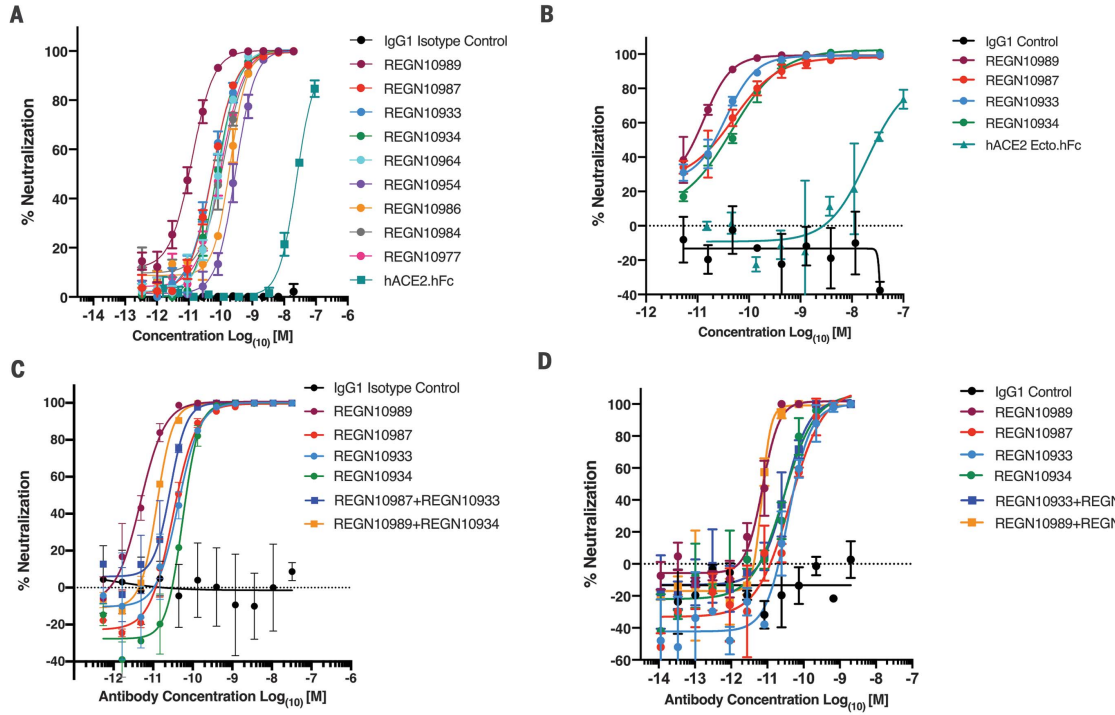


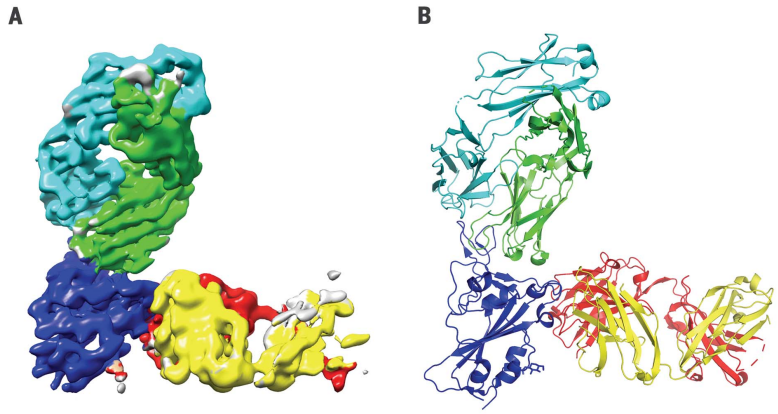
Regeneron (Casirivimab – Imdevimab)

Cocktail de 2 Ac monoclonaux l'un issu de souris Tg l'autre issu de sérum de sujets convalescents









Hansen et al. Science 2020

Autorisation FDA sans aucune publication des essais de phase 1/2/3.
Visée préventive sujets à risque de formes graves éviter la surcharge des hôpitaux.
30/10 Arrêt de l'essai de phase 3 chez les patients hospitalisés

Etude de Phase 2 LY-COV555
(Bamlavinimab)

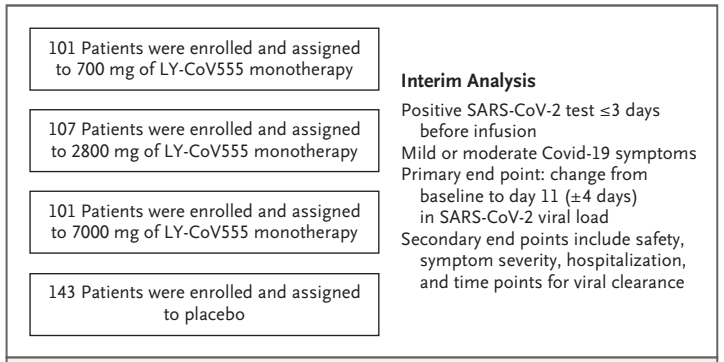


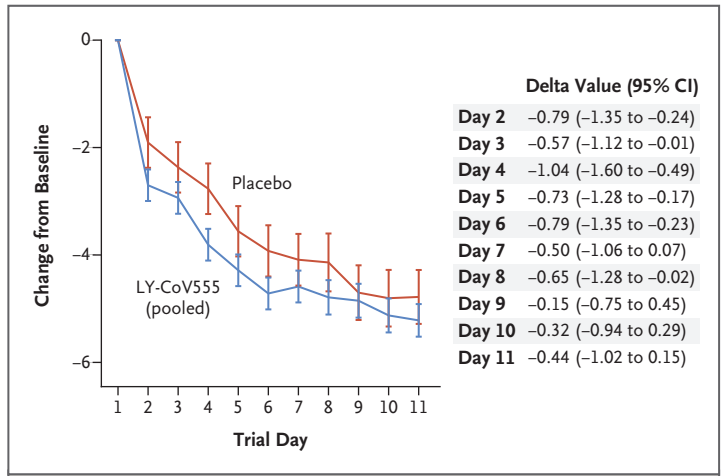
Figure 1. Enrollment and Trial Design.

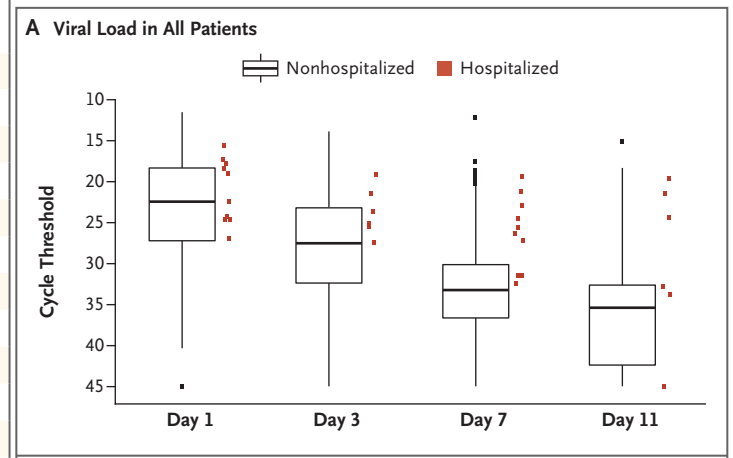
Table 1. Characteristics of the Patients at Baseline.*

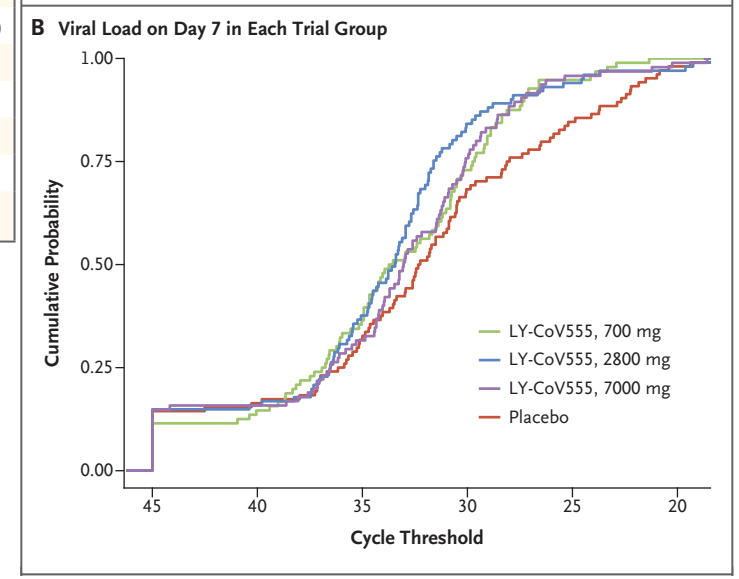
Characteristic	LY-CoV555 (N=309)	Placebo (N=143)
Age		
Median (range) — yr	45 (18–86)	46 (18–77)
65 Yr or older — no. (%)	33 (10.7)	20 (14.0)
Female sex — no. (%)	171 (55.3)	78 (54.5)
Race or ethnic group — no./total no. (%)†		
White	269/305 (88.2)	120/138 (87.0)
Hispanic or Latino	135/309 (43.7)	63/143 (44.1)
Black	22/305 (7.2)	7/138 (5.1)
Body-mass index‡		
Median	29.4	29.1
≥30 to <40 — no./total no. (%)	112/304 (36.8)	56/139 (40.3)
≥40 — no./total no. (%)	24/304 (7.9)	9/139 (6.5)
Risk factors for severe Covid-19 — no. (%)§	215 (69.6)	95 (66.4)
Disease status — no. (%)		
Mild	232 (75.1)	113 (79.0)
Moderate	77 (24.9)	30 (21.0)
Median no. of days since onset of symptoms	4.0	4.0
Mean viral load — Ct value¶	23.9	23.8

Table 2. Change from Baseline in Viral Load.

Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		−0.85	
	700 mg, −1.27		−0.42 (−0.89 to 0.06)
	2800 mg, −1.50		−0.64 (−1.11 to −0.17)
	7000 mg, −1.27		−0.42 (−0.90 to 0.06)
	Pooled doses, −1.35		−0.49 (−0.87 to −0.11)
Mean change from baseline in viral load at day 7		−2.56	
	700 mg, −2.82		−0.25 (−0.73 to 0.23)
	2800 mg, −3.01		−0.45 (−0.92 to 0.03)
	7000 mg, −2.85		−0.28 (−0.77 to 0.20)
	Pooled doses, −2.90		−0.33 (−0.72 to 0.06)







Chen, NEJM 2020

Etude de Phase 3
LY-CoV555

Table 1. Characteristics of the Patients at Randomization.*

Characteristic	LY-CoV555 (N=163)	Placebo (N=151)	Total (N=314)
Median age (IQR) — yr	63 (50–72)	59 (48–71)	61 (49–71)
Female sex — no. (%)	66 (40)	71 (47)	137 (44)
Current pregnancy — no. (%)	1 (1)	2 (1)	3 (1)
Race or ethnic group — no. (%)†			
White	76 (47)	71 (47)	147 (47)
Hispanic	41 (25)	33 (22)	74 (24)
Black	33 (20)	34 (23)	67 (21)
Other	13 (8)	13 (9)	26 (8)
Body-mass index — no. (%)‡			
≥30	81 (50)	83 (55)	164 (52)
≥40	20 (12)	22 (15)	42 (13)
Coexisting illness — no. (%)			
Any	117 (72)	98 (65)	215 (68)
Hypertension requiring medication	82 (50)	72 (48)	154 (49)
Diabetes requiring medication	54 (33)	36 (24)	90 (29)
Renal impairment	24 (15)	9 (6)	33 (11)
Asthma	14 (9)	14 (9)	28 (9)
Heart failure	12 (7)	1 (1)	13 (4)
Median no. of days since symptom onset (IQR)	7 (5–9)	8 (5–9)	7 (5–9)
Medication — no. (%)			
Remdesivir	60 (37)	66 (44)	126 (40)
Antibacterial agent	54 (33)	36 (24)	90 (29)
Glucocorticoid	80 (49)	74 (49)	154 (49)
Antiplatelet or anticoagulant agent§	106 (65)	95 (63)	201 (64)
ACE inhibitor or ARB	41 (25)	31 (21)	72 (23)
NSAID	17 (10)	16 (11)	33 (11)
Oxygen requirement — no. (%)			
Supplementary oxygen			
None	44 (27)	42 (28)	86 (27)
<4 liters/min	60 (37)	57 (38)	117 (37)
≥4 liters/min	29 (18)	34 (23)	63 (20)
Noninvasive ventilation or high-flow device	30 (18)	18 (12)	48 (15)
Invasive ventilation or ECMO	0	0	0
Laboratory measures			
Median C-reactive protein (IQR) — mg/liter	94 (47–156)	90 (45–139)	92 (47–151)
Median B-lymphocyte count (IQR) — cells/mm^3	784 (560–1056)	810 (550–1310)	799 (552–1116)

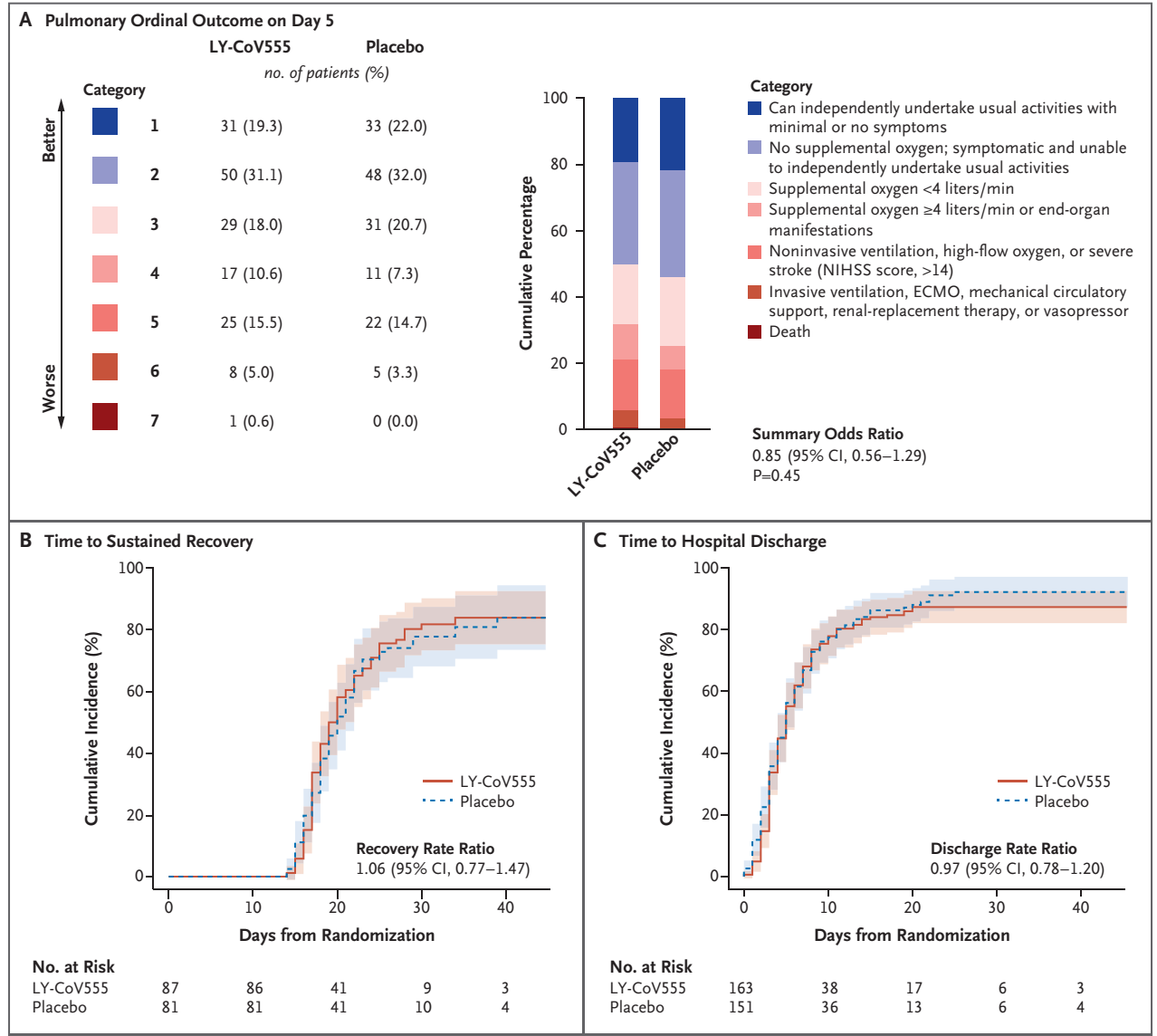


Figure 1. Pulmonary Ordinal Outcome at Day 5 and Time until Sustained Recovery and Hospital Discharge.

Panel A shows the pulmonary ordinal outcome at day 5 in the LY-CoV555 group and the placebo group. The summary odds ratio was estimated with the use of a proportional-odds model after adjustment for the baseline pulmonary category and trial pharmacy. In Panels B and C, the cumulative time until a sustained recovery and hospital discharge, respectively, are Aalen–Johansen estimates; rate ratios were calculated with the use of Fine–Gray models, stratified according to trial pharmacy. The rate ratios estimate the subdistribution hazard ratios after accounting for the competing risk of death. ECMO denotes extracorporeal membrane oxygenation, and NIHSS National Institutes of Health Stroke Scale.

Lundgren et al. NEJM 2020

Place des Monoclonaux ATU

Table 1. Eligible Patients Considered High Risk[1]

Patients with ≥1 of the following:

- BMI ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment
- ≥65 years old

Patients ≥55 years old and ≥1 of the following:

- Cardiovascular disease
- Hypertension
- COPD or other chronic respiratory disease

Patients 12-17 years old and ≥1 of the following:

- BMI ≥85th percentile for their age and gender[2]
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- A medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])
- Asthma, reactive airway or other chronic respiratory disease that requires daily treatment

BMI = body mass index; COPD = chronic obstructive pulmonary disease

1. Patients ≥12 years old who weigh ≥40 kg with ≥1 of the criteria listed are considered at high risk for progressing to severe COVID-19 and/or hospitalization. FDA fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab. Available at: https://www.fda.gov/media/143603/download. Accessed November 19, 2020.
2. Based on CDC growth charts (https://www.cdc.gov/growthcharts/clinical_charts.htm).

1. Les patients ayant un déficit de l'immunité lié à une pathologie ou à des traitements :

- Chimiothérapie en cours
- Transplantation d'organe solide
- Allogreffe de cellules souches hématopoïétiques
- Maladie rénale avec DFG <30 mL/min ou dialyse
- Lupus systémique ou vascularite avec traitement immunodépresseur
- Traitement par corticoïde >15 mg/semaine
- Traitement immunodépresseur incluant rituximab

2. Les patients à risque de complications :

○ *Les patients parmi la liste suivante quel que soit l'âge :*

- Fibrose pulmonaire idiopathique
- Sclérose latérale amyotrophique
- Pathologies rares du foie y compris hépatites auto-immunes
- Myopathies avec capacité vitale forcée <70%
- Autres pathologies rares définies par les filières de santé maladies rares (FSMR)
- Trisomie 21

○ *Les patients entre 70 et 80 ans avec au moins une des pathologies suivantes :*

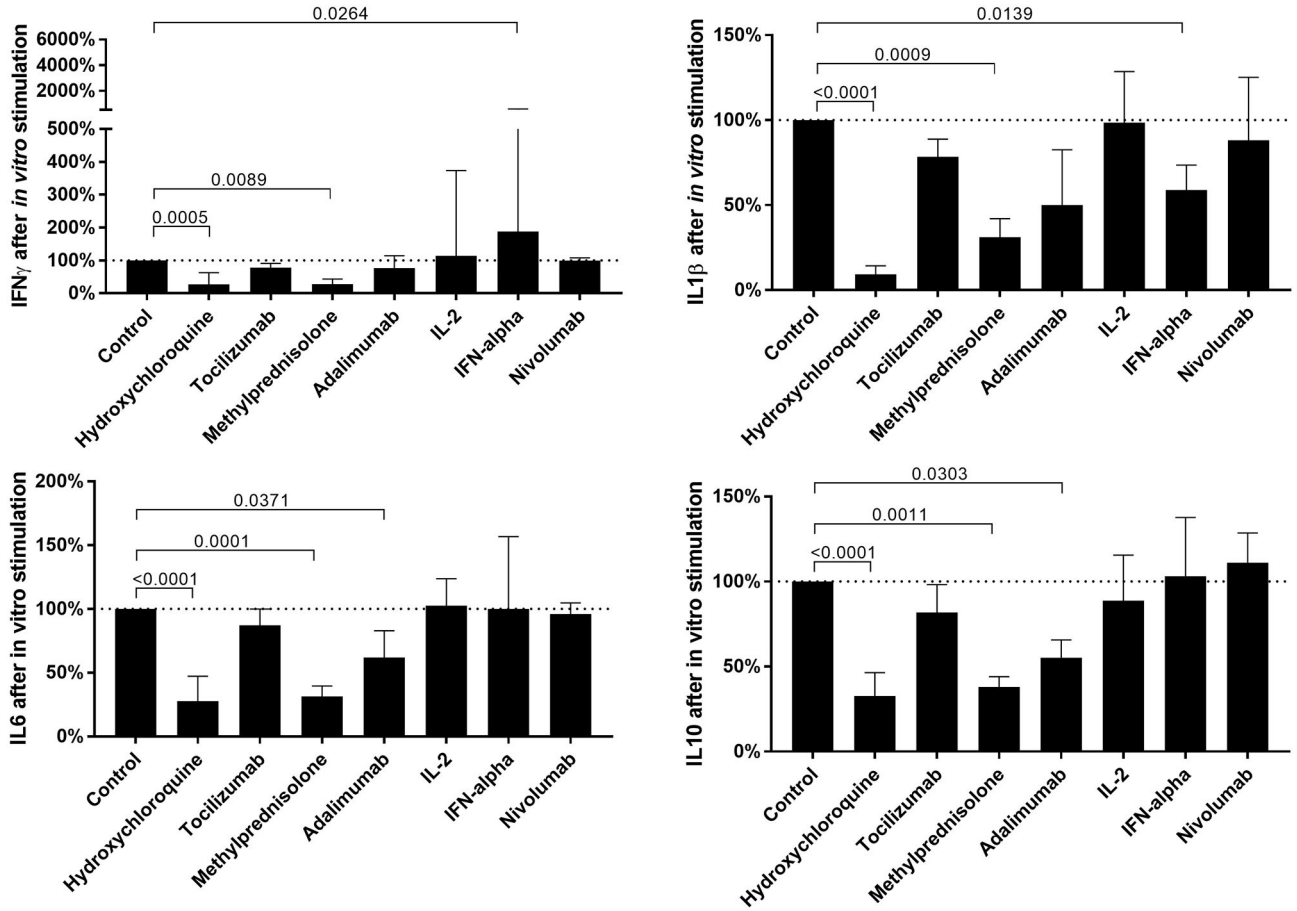
- Obésité (IMC>30)
- BPCO et insuffisance respiratoire chronique
- Hypertension artérielle compliquée
- Insuffisance cardiaque
- Diabète (de type 1 et de type 2)
- Insuffisance rénale chronique

Risque de sélection de souches

Risque de sélection de souches

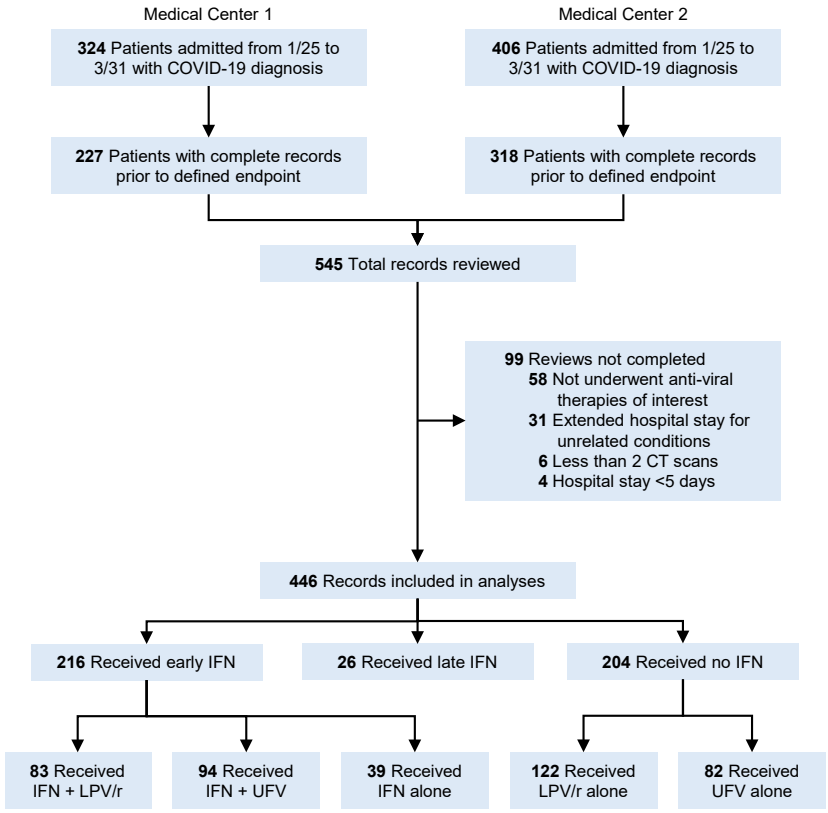
3. Les patients de plus de 80 ans

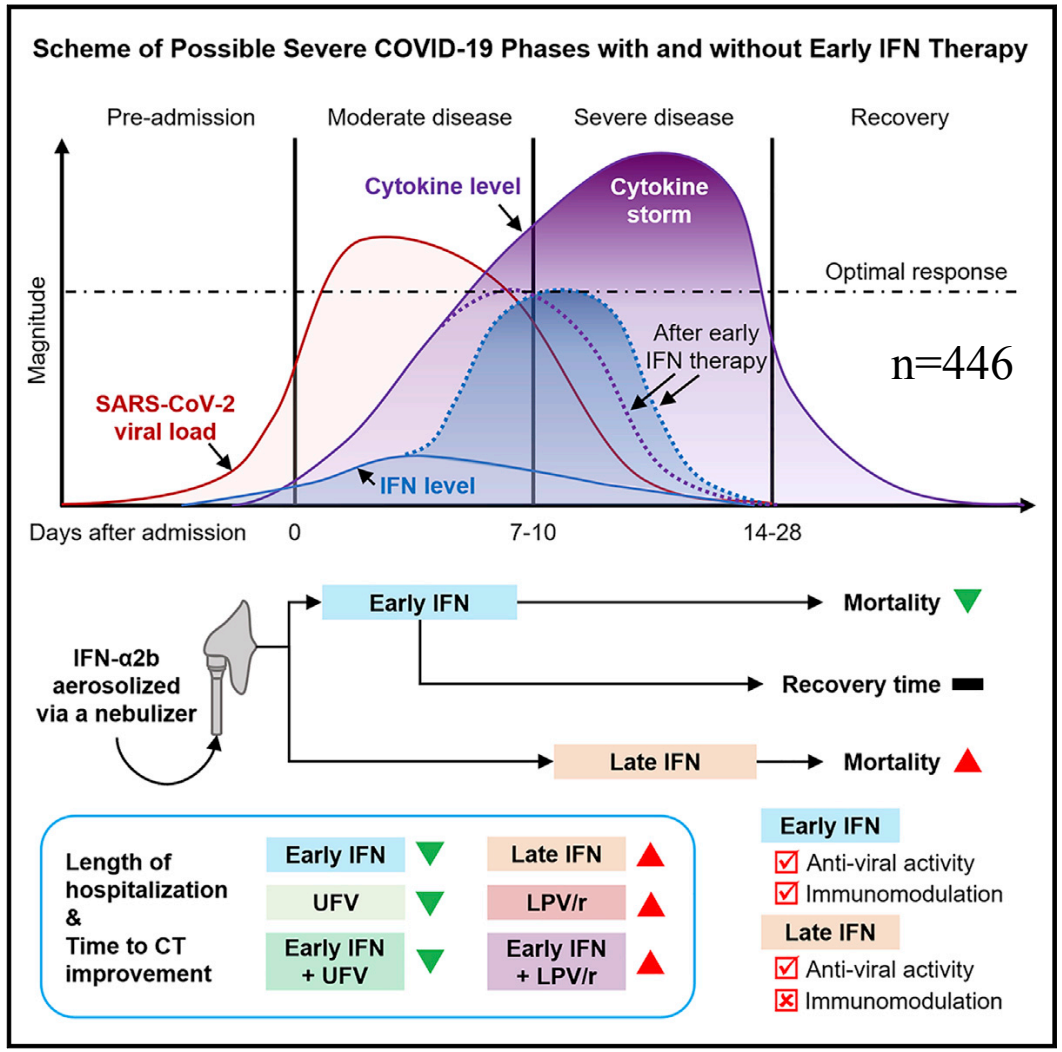
2.2 Renforcer la Réponse IFN



Ruestch, Brglez* et al. Front Med 2020*

Etudes rétrospectives sur l'IFN dans le COVID-19

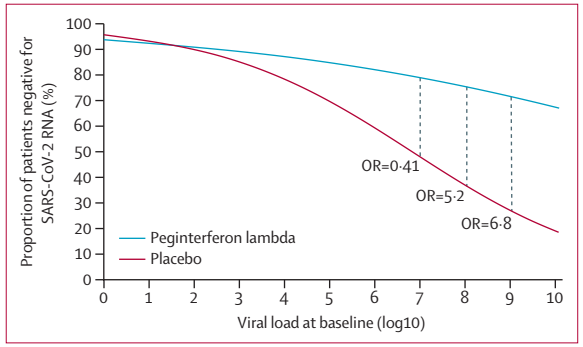




Wang et al. Cell Host & Microbe 2020

IFNλ en systémique chez des patients COVID en ambulatoire

	Peginterferon lambda (n=30)	Placebo (n=30)
Sex		
Female	18 (60%)	17 (57%)
Male	12 (40%)	13 (43%)
Age, years	48 (30–53)	39 (33–55)
Race or ethnicity		
White	15 (50%)	16 (53%)
Black	1 (3%)	5 (17%)
Asian	8 (27%)	7 (23%)
Other	6 (20%)	2 (7%)
Comorbidity*	5 (17%)	4 (13%)
Body-mass index, kg/m²	27·3 (5·2)	26·1 (4·2)
Body-mass index category		
<25 kg/m²	9 (30%)	11 (37%)
25–30 kg/m²	15 (50%)	13 (43%)
>30 kg/m²	6 (20%)	6 (20%)
Interferon lambda 4 genotype		
TT	18 (60%)	16 (57%)
Non-TT	12 (40%)	12 (43%)
Asymptomatic	5 (17%)	6 (20%)
Time from symptom onset to injection, days	4·3 (1·7)	4·7 (1·7)
Time from positive SARS-CoV-2 test to injection, days	3·2% (1·1)	3·3 (1·2)
Baseline laboratory results		
Haemoglobin, g/L	14·7 (1·4)	14·9 (1·6)
White blood cells, ×10⁹/L	4·9 (2·1)	5·1 (1·7)
Lymphocytes, ×10⁹/L	1·5 (0·4)	1·5 (0·5)
Neutrophils, ×10⁹/L	2·9 (1·8)	3·1 (1·6)
Platelets, ×10⁹/L	221 (62)	213 (64)
Creatinine, µmol/L	80 (14)	81 (18)
Alanine aminotransferase, U/L	32 (16)	39 (52)
Aspartate aminotransferase, U/L	28 (11)	32 (24)
Total bilirubin, µmol/L	10 (5)	12 (10)
Baseline SARS-CoV-2 viral load, log copies per mL	6·16 (3·14)	4·87 (3·68)
SARS-CoV-2 RNA undetectable at baseline	5 (17%)	10 (33%)
SARS-CoV-2 RNA ≥10⁶ copies per mL at baseline	19 (63%)	16 (53%)
Anti-SARS-CoV-2 S protein IgG antibody at baseline†	0/27	5/24 (21%)



	Odds ratio (95% CI)*	p value
Overall	5·88 (1·37–25·00)	0·017
Fever or systemic	6·06 (1·48–25·00)	0·012
Respiratory	4·93 (0·94–25·64)	0·060
Gastrointestinal	11·9 (2·24–62·50)	0·038
Musculoskeletal	5·81 (1·31–25·64)	0·020
Skin	0·37 (0·05–2·99)	0·36
Mood	8·00 (0·98–66·67)	0·052
Neurological and vascular	52·63 (1·93–infinity)	0·019

*Association with high viral load (yes *vs* no).

Table 3: **Association between symptoms and a viral load of 10^6 copies per mL or higher**

	Peginterferon lambda (n=30)	Placebo (n=30)
Severe symptoms		
Reports (number of participants*)	20 (7)	30 (7)
AEs	2	1
SAEs	1	1
Treatment-related AEs	0	0
Treatment-related SAEs	0	0
Emergency room visits	1	4
Hospital admissions	1	1
Laboratory abnormalities (grade 3 or 4)		
Haemoglobin	0	0
White blood cells	0	0
Lymphocytes	0	0
Neutrophils	0	1
Platelets	0	0
Creatinine	0	0
Alanine aminotransferase	1	3
Aspartate aminotransferase	1	1
Total bilirubin	0	0

AE=adverse event. SAE=serious adverse event. *Some participants reported multiple severe symptoms.

Table 4: **Summary of AEs and SAEs by treatment group.**

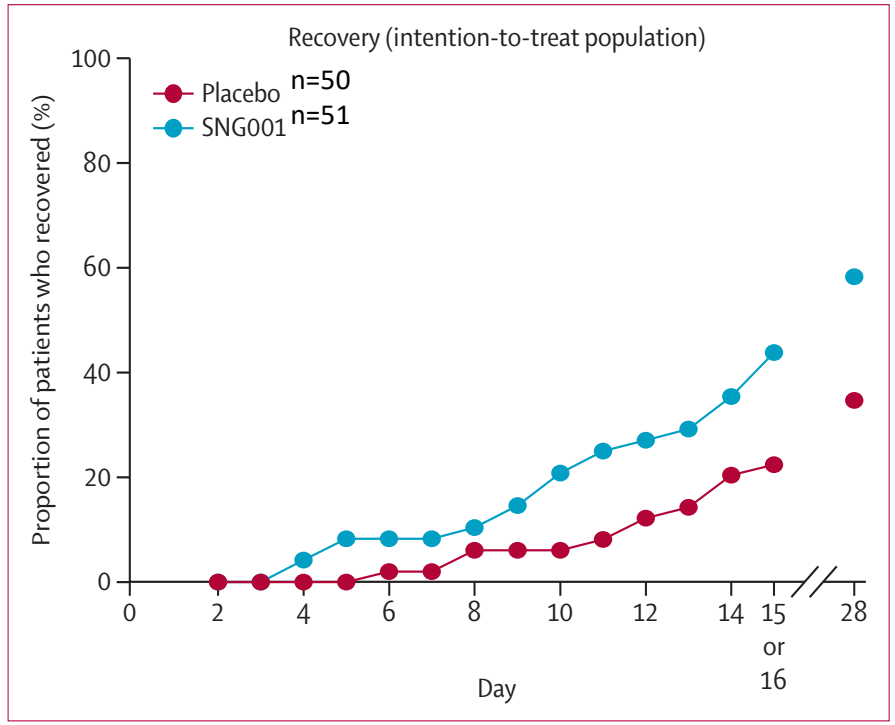
Feld et al. Lancer 2021

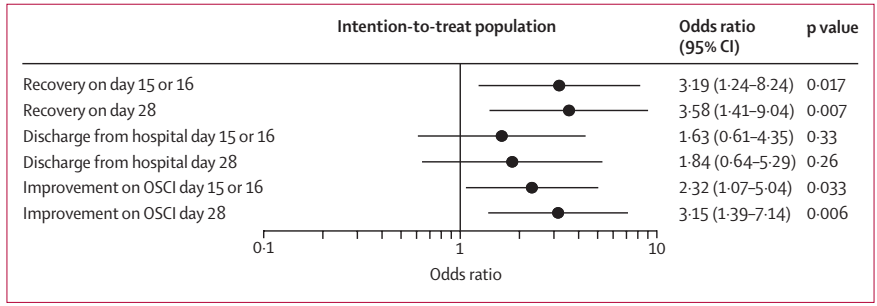
IFNβ inhalé pour les patients COVID hospitalisés

	Placebo (n=50)	SNG001 (n=48)
Age at inclusion, years	56·5 (11·9)	57·8 (14·6)
Sex		
Male	31 (62%)	27 (56%)
Female	19 (38%)	21 (44%)
Ethnicity		
White	39 (78%)	39 (81%)
Non-White	11 (22%)	9 (19%)
Comorbidities		
All	27	26
Hypertension	11/27 (41%)	18/26 (69%)
Chronic lung condition	12/27 (44%)	11/26 (42%)
Cardiovascular disease	8/27 (30%)	5/26 (19%)
Diabetes	9/27 (33%)	3/26 (12%)
Cancer	1/27 (4%)	0
Severity of disease at baseline*		
No limitation of activities	1 (2%)	0
Limitation of activities	1 (2%)	0
Hospitalised (no oxygen therapy)	19 (38%)	11 (23%)
Oxygen by mask or nasal prongs	28 (56%)	36 (75%)
Non-invasive ventilation or high-flow oxygen	1 (2%)	1 (2%)
Duration of symptoms, days†	9·5 (7·0–12·0)	10·0 (8·0–11·0)
Current smoking status		
Currently uses tobacco	1 (2%)	1 (2%)
Former smoker	16 (32%)	11 (23%)
Never smoked	33 (66%)	36 (75%)

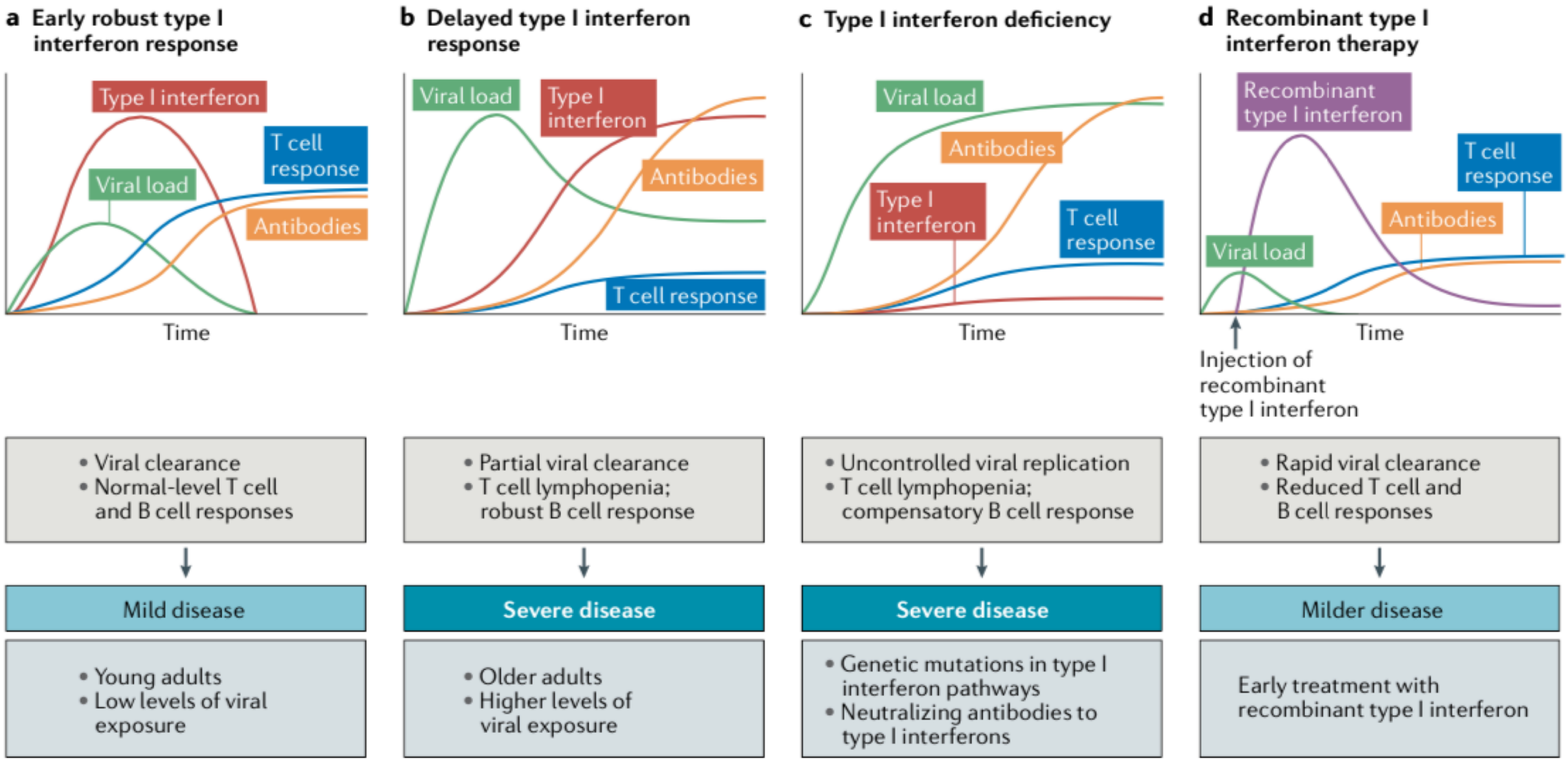
Data are n (%) or mean (SD), unless otherwise indicated, and are presented for the intention-to-treat population. *Severity of disease at baseline followed the WHO Ordinal Scale for Clinical Improvement. †Duration of symptoms is presented as median (IQR).

***Table 2*: Demographic and baseline characteristics of participants**

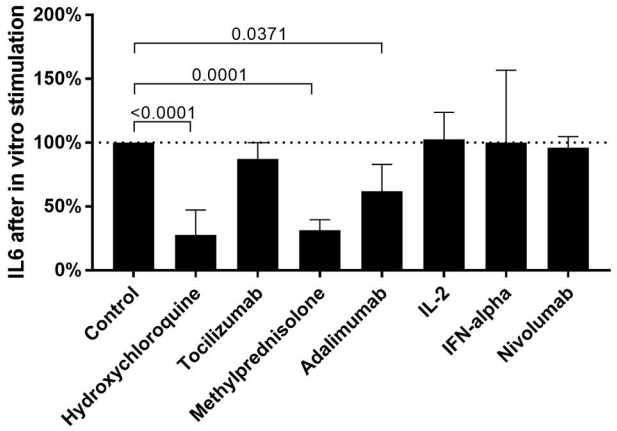


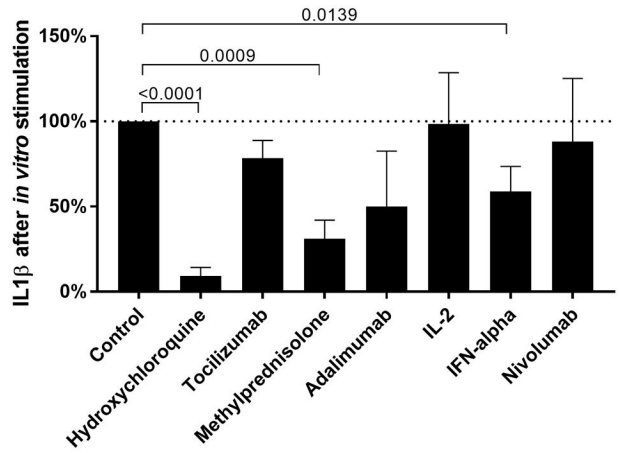


Monk et al. Lancet 2020

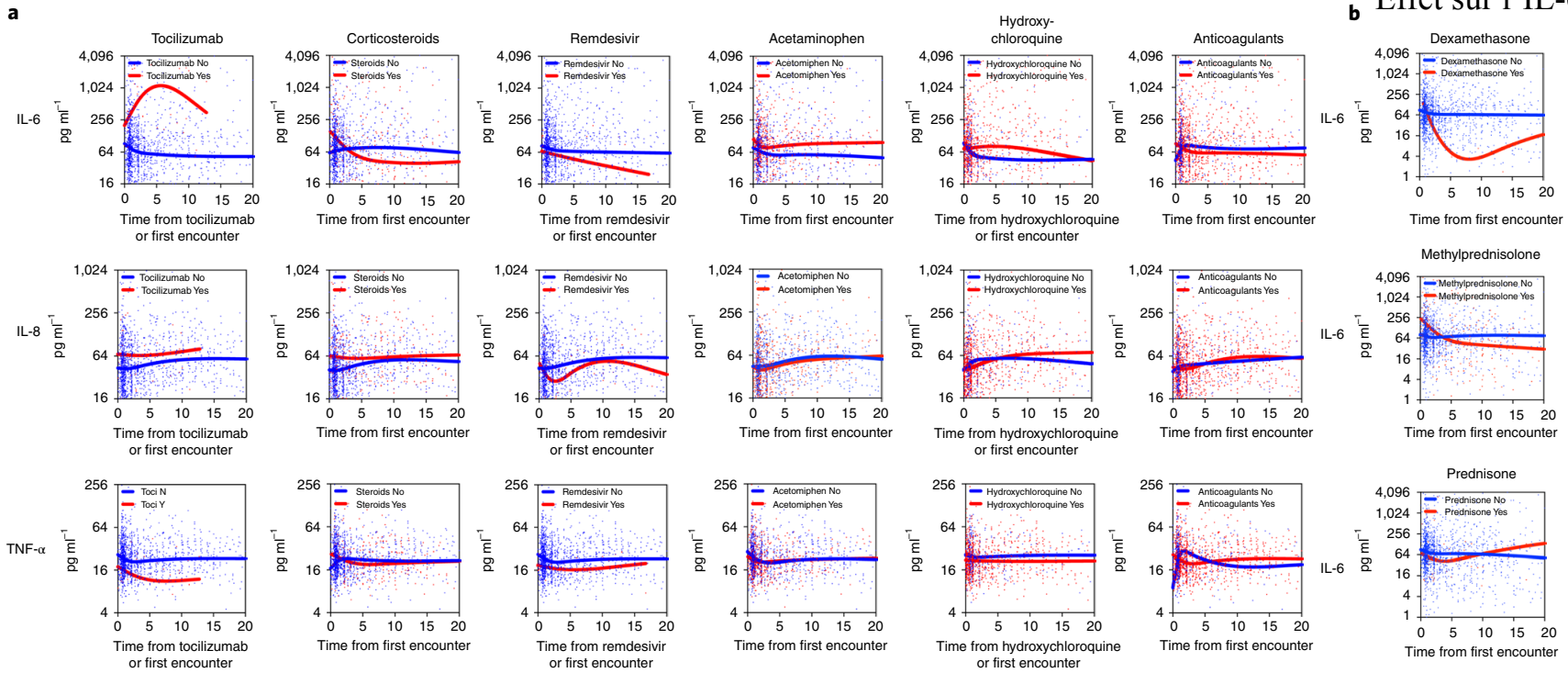

a Early robust type I interferon response
Type I interferon
T cell response
Viral load
Antibodies
Time
b Delayed type I interferon response
Viral load
Type I interferon
Antibodies
T cell response
Time
c Type I interferon deficiency
Viral load
Antibodies
Type I interferon
T cell response
Time
d Recombinant type I interferon therapy
Recombinant type I interferon
T cell response
Antibodies
Viral load
Time
Injection of recombinant type I interferon
• Viral clearance
• Normal-level T cell and B cell responses
Mild disease
• Young adults
• Low levels of viral exposure
• Partial viral clearance
• T cell lymphopenia; robust B cell response
Severe disease
• Older adults
• Higher levels of viral exposure
• Uncontrolled viral replication
• T cell lymphopenia; compensatory B cell response
Severe disease
• Genetic mutations in type I interferon pathways
• Neutralizing antibodies to type I interferons
• Rapid viral clearance
• Reduced T cell and B cell responses
Milder disease
Early treatment with recombinant type I interferon

2.3 Contrôler l'Inflammation





Ruestch, Brglez* et al. Front Med 2020*



Marie Del Valle et al. Nature 2020

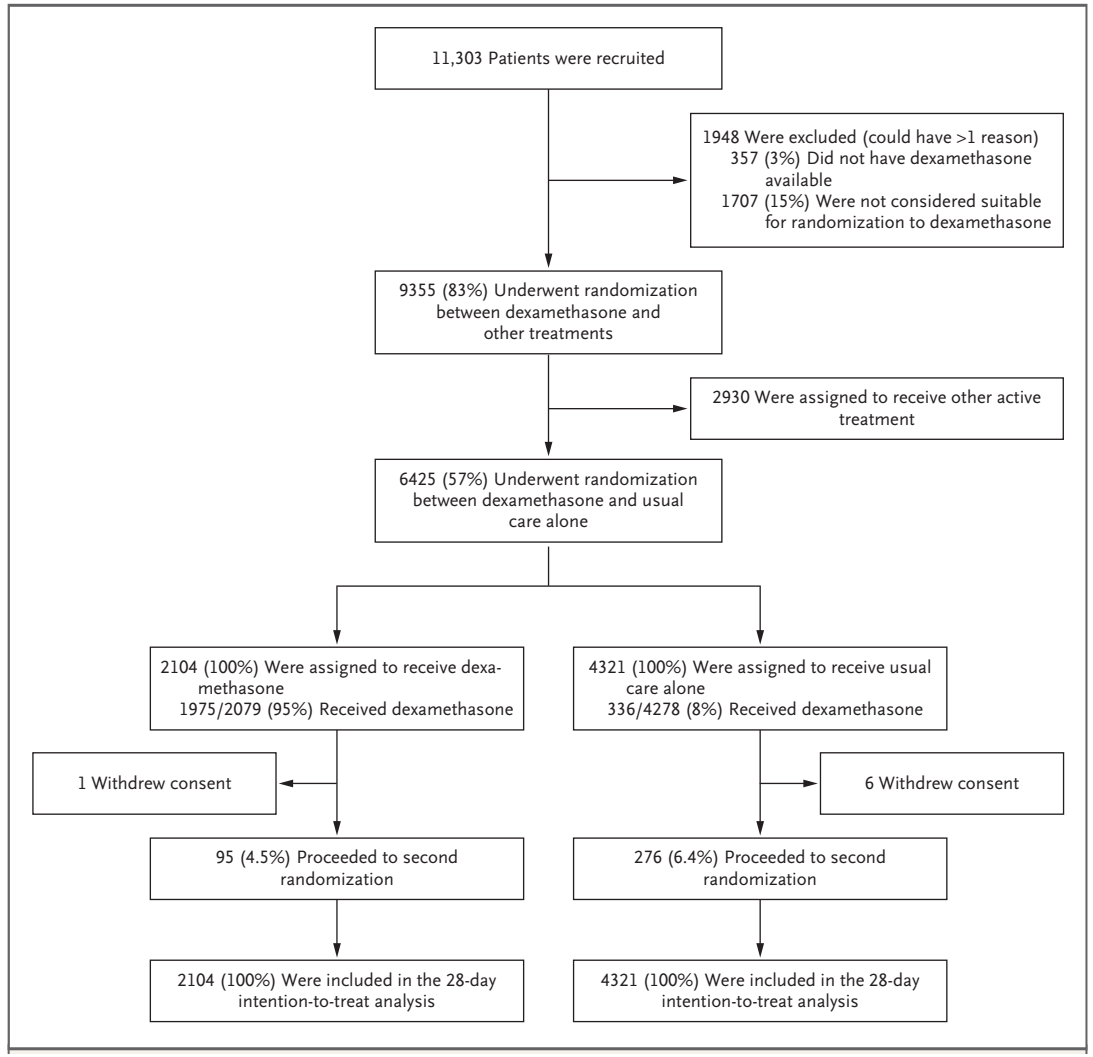
2.3.1 Corticothérapie

Effets pharmacologiques	Mécanisme d'action	Conséquences biologiques
Effets anti-inflammatoires	Inhibition de la production de cytokines pro-inflammatoires (IL-1, IL-6, IL-8, TNFalpha	Diminution de l'afflux de macrophages et de granulocytes sur le site inflammatoire
	Inhibition de l'expression de molécules d'adhésion (ICAM)	Diminution de la migration transendothéliale des cellules phagocytaires
	Inhibition de la phospholipase A_2 et de la cyclooxygénase de type 2	Inhibition de la synthèse d'eicosanoïdes pro-inflammatoires (Prostaglandines, thromboxane, leucotriènes)
	Inhibition de la NO synthase inductible	Diminution de la production d'espèces radicalaires
Effets immunosuppresseurs	Diminution de l'expression des molécules du CMH II	Diminution de l'antigénicité des protéines
	Inhibition de la production d'IL-2	Diminution de la prolifération lymphocytaire
Effets pro-apoptotiques	Induction de gènes de mort cellulaire ou répression de facteurs ou de gènes indispensables à la vie cellulaire	Mort cellulaire

Résultats

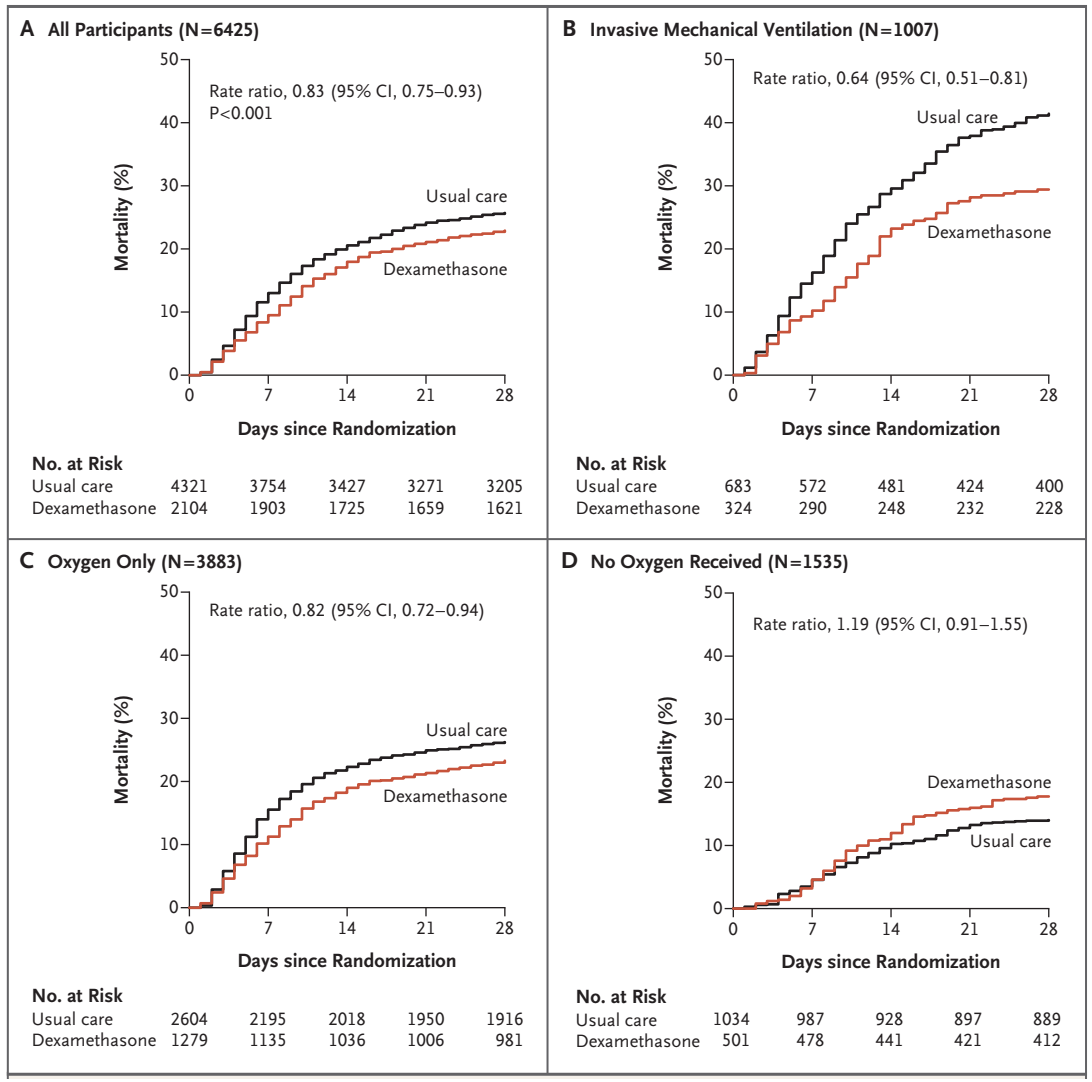
Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)



Horby et al. NEJM 2020

Résultats



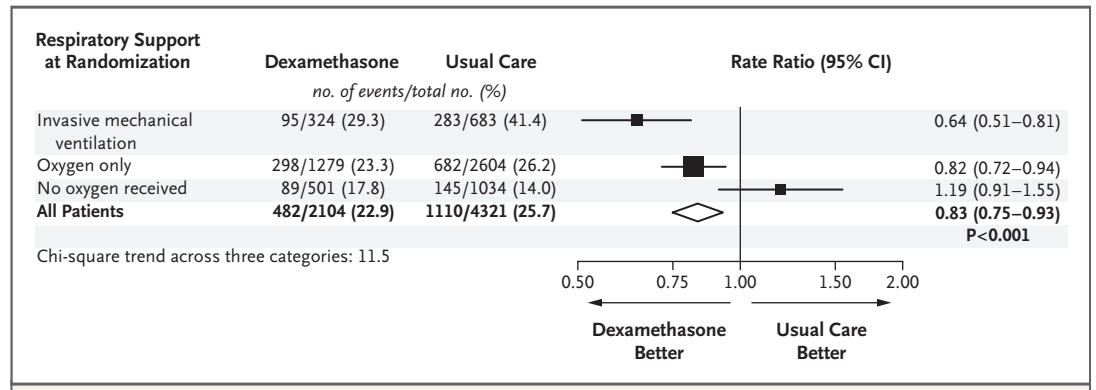


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.
Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

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)

Horby et al. NEJM 2020

Corticoïdes en USI

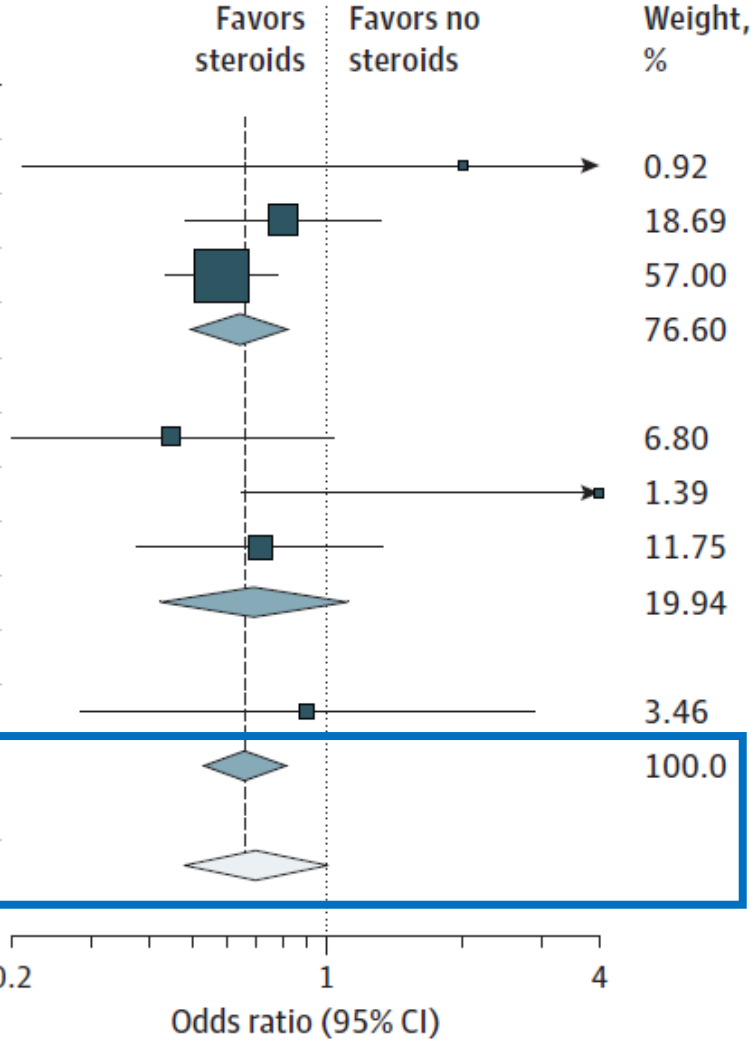
Table 1. Characteristics of Included Trials

	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with FIO_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with PaO_2:FIO_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	6 mg/d orally or intravenously	Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)	50 mg intravenously every 6 h × 7 d[d]	40 mg intravenously every 12 h × 5 d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days to 21 d	Lower lung injury score at 7 d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	• Secondary infections of pneumonia, sepsis, or other similar • Pulmonary embolism	• Mortality • Infections • Insulin use	• Cause-specific mortality • Ventilation • Dialysis • Cardiac arrhythmia (in a subset) • Other that were believed to be related to study treatment	• Any • Excluded some listed in protocol • Excluded expected adverse events related to the patient's disease or comorbidity	• New episodes of septic shock (Sepsis-3 criteria) • Invasive fungal infection • Clinically important gastrointestinal bleeding • Anaphylaxis	• Per ICH good clinical practice guidelines (events not already captured as a trial end point; eg, mortality) • When the event may reasonably have occurred because of study participation	• Secondary bacterial infections • Barotrauma • Severe hyperglycemia • Gastrointestinal bleeding requiring transfusion • Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

Corticoïdes en USI

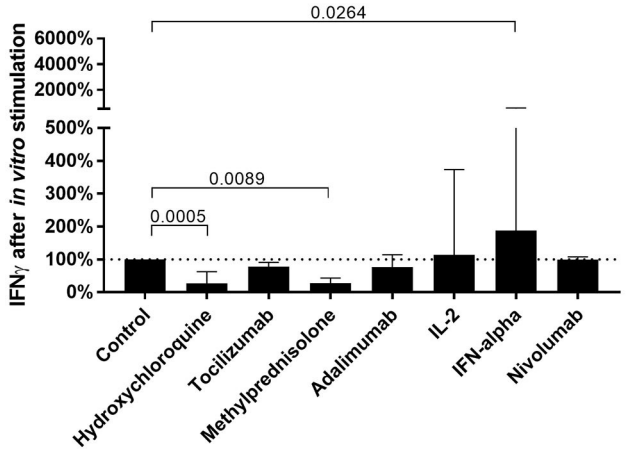
Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

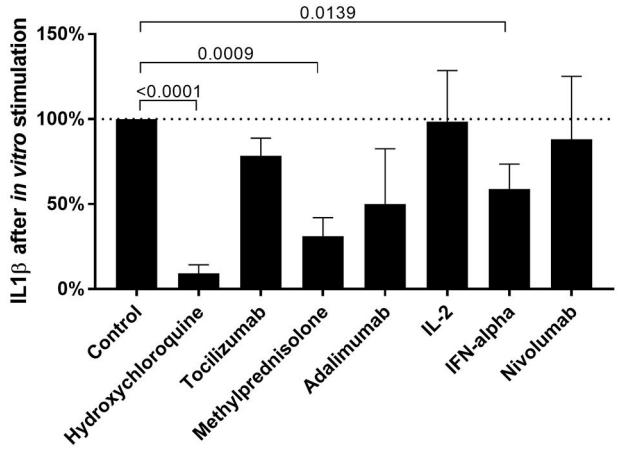
Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients		Odds ratio (95% CI)	Weight, %
			Steroids	No steroids		
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 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) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

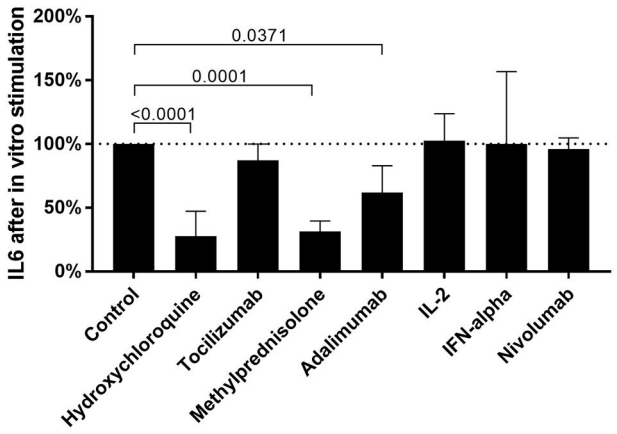


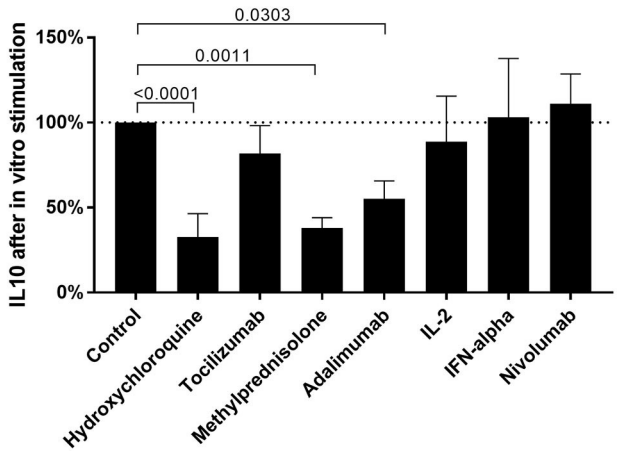
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT)Working Group **JAMA** Published online September 2, 2020

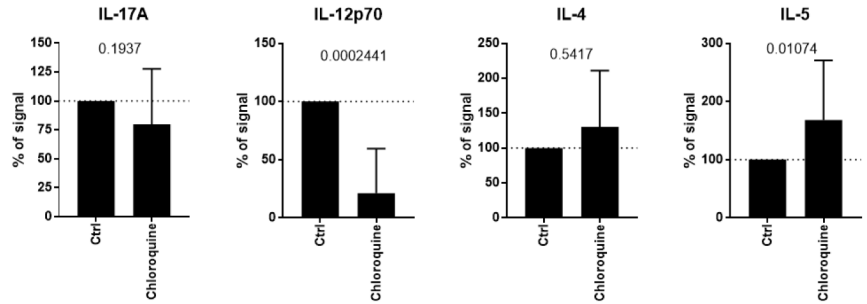
2.3.2 L'hydroxychloroquine comme Immunomodulateur







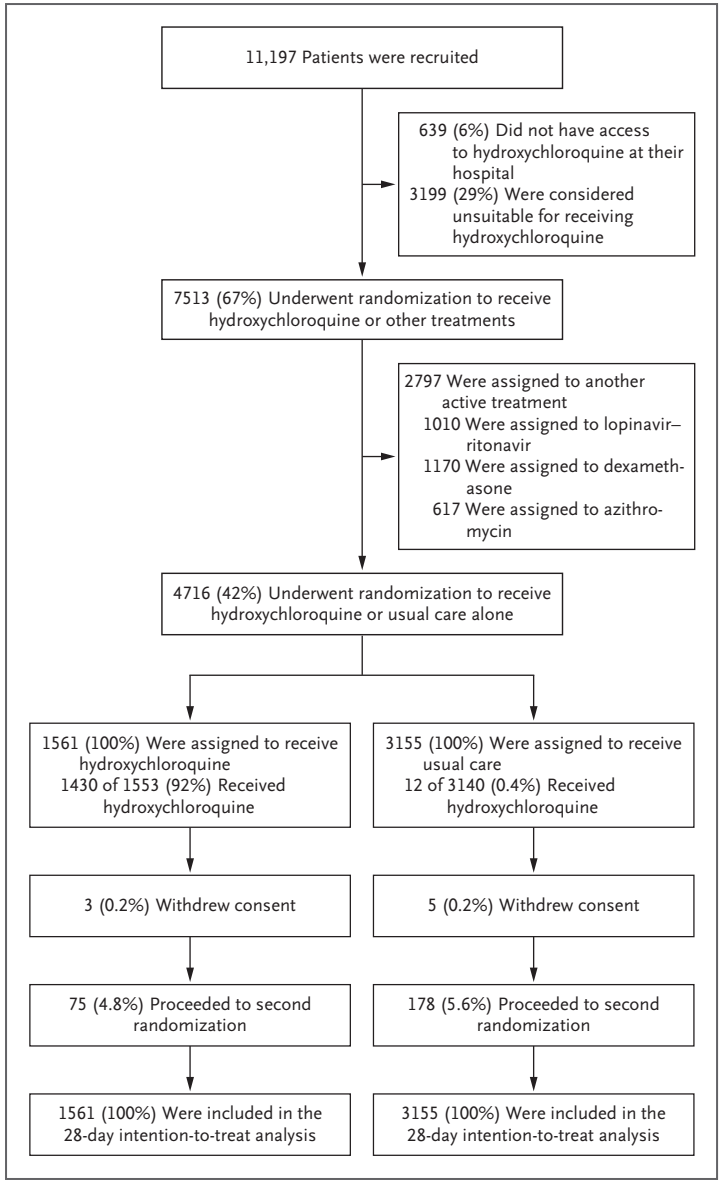




- Effet anti-inflammatoire
- Effet anti-Th1
- Effet pro-Th2

Ruestch, Brglez* et al. Front Med 2020*

Efficacité de l'HCQ dans le traitement du COVID-19



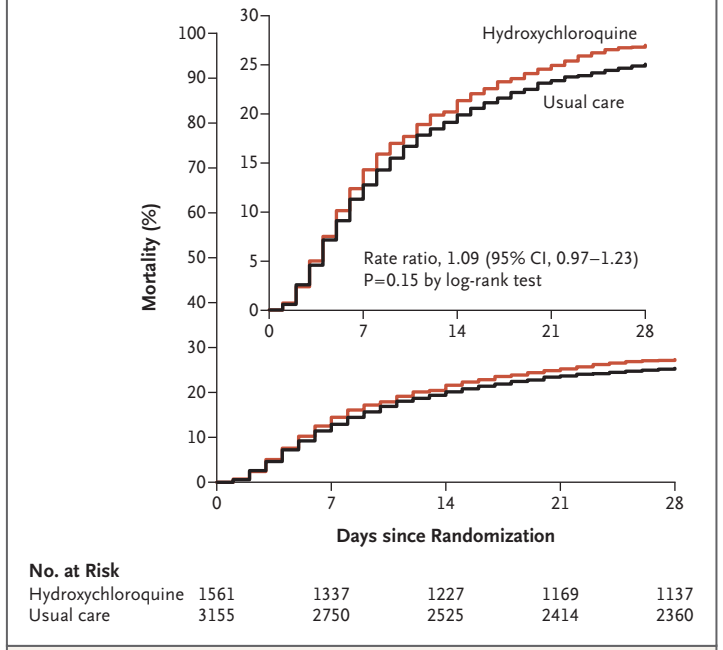


Figure 2. Mortality at 28 Days.

Death at 28 days (the primary outcome) occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group. The inset shows the same data on an expanded y axis.

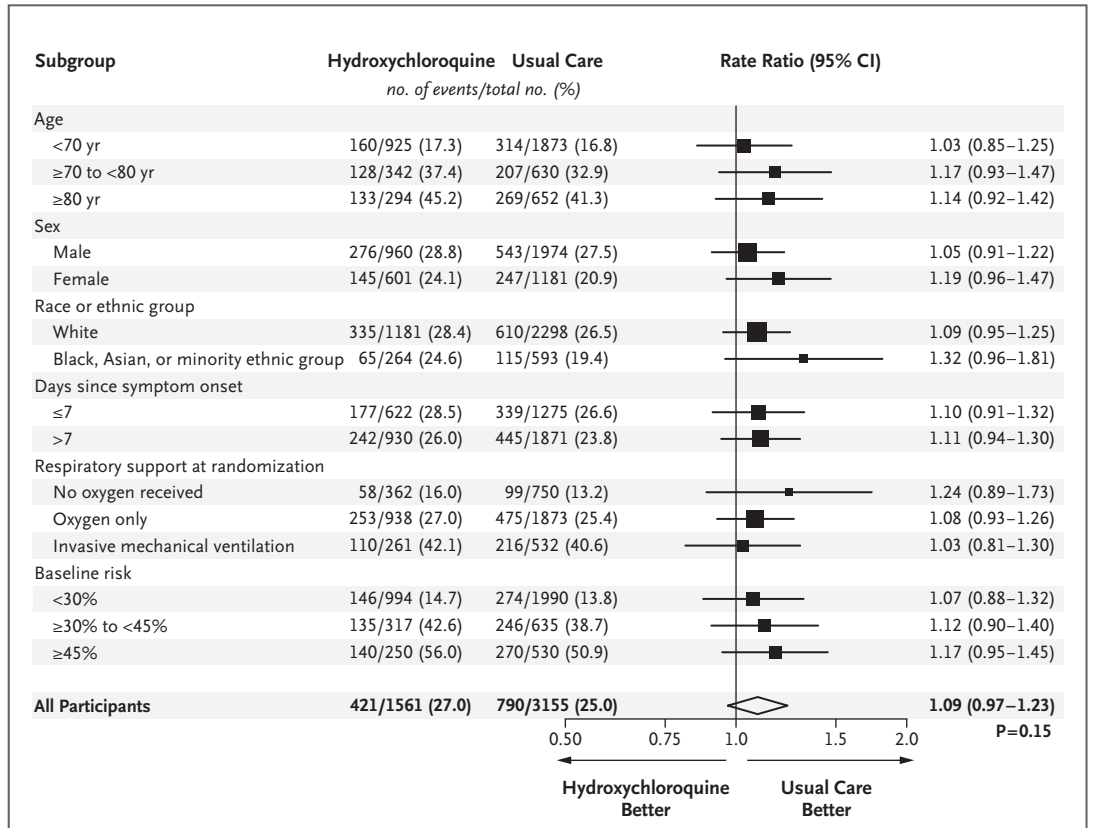


Table 2. Primary and Secondary Outcomes.

Outcome	Hydroxychloroquine (N=1561)	Usual Care (N=3155)	Rate or Risk Ratio (95% CI)
	no./total no. (%)		
Primary outcome: 28-day mortality	421/1561 (27.0)	790/3155 (25.0)	1.09 (0.97–1.23)*
Secondary outcomes			
Discharge from hospital in ≤28 days	931/1561 (59.6)	1983/3155 (62.9)	0.90 (0.83–0.98)*
Invasive mechanical ventilation or death†	399/1300 (30.7)	705/2623 (26.9)	1.14 (1.03–1.27)‡
Invasive mechanical ventilation	128/1300 (9.8)	225/2623 (8.6)	1.15 (0.93–1.41)
Death	311/1300 (23.9)	574/2623 (21.9)	1.09 (0.97–1.23)

Horby et al. NEJM 2020

2.3.2 Anti-IL6 : Tocilizumab

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pa_{O_2}:Fi_{O_2} <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

Tocilizumab plus standard of care vs Standard of care

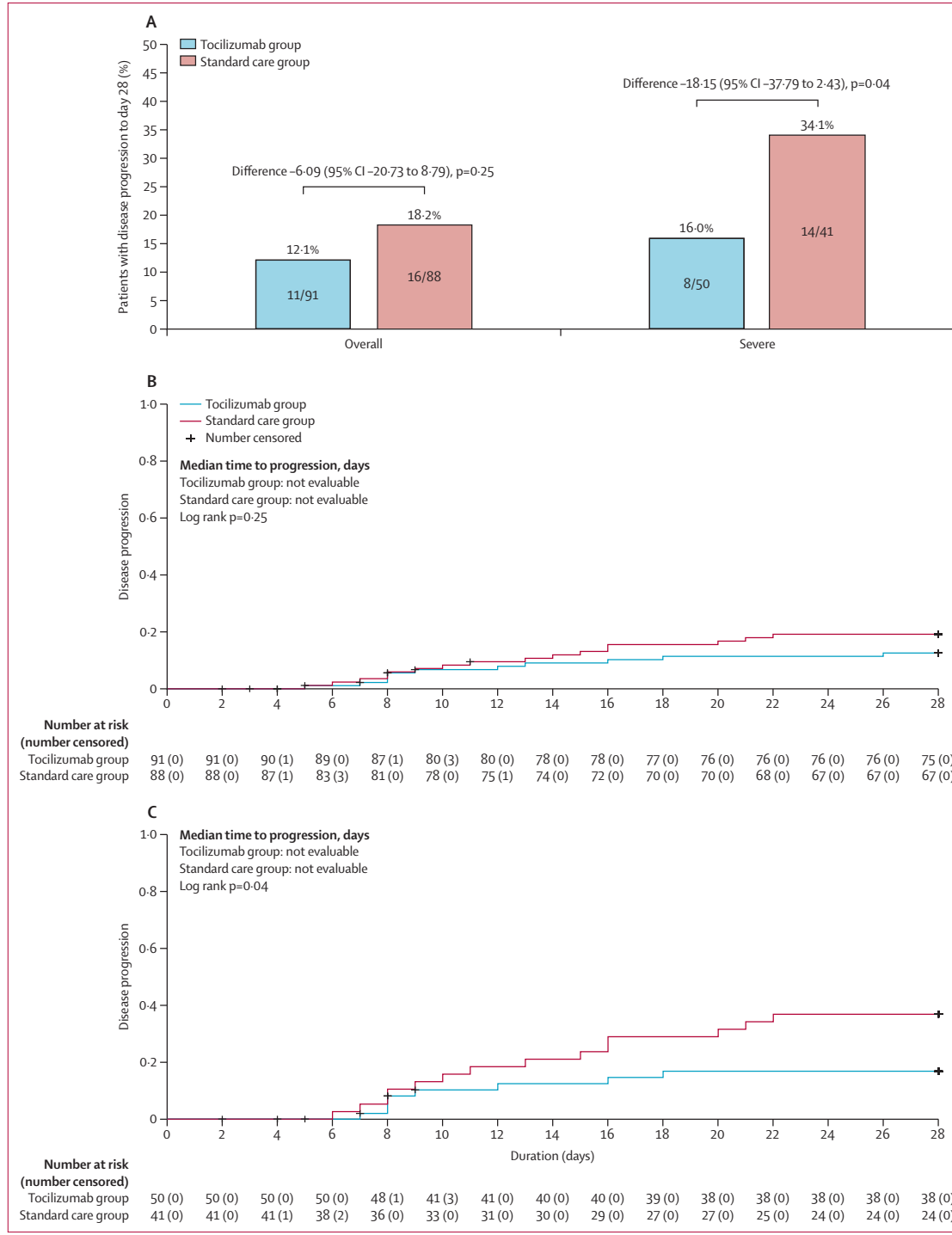
	Tocilizumab group (n=91)	Standard care group (n=88)
Sex		
Female	15 (16%)	12 (14%)
Male	76 (84%)	76 (86%)
Age, years		
Median (IQR)	56 (47–63)	54 (43–63)
18–60 years	62 (68%)	58 (66%)
>60 years	29 (32%)	30 (34%)
Body-mass index, kg/m²	27·0 (4·4)	26·8 (4·6)
Comorbidities		
Type 2 diabetes	31 (34%)	43 (49%)
Hypertension	36 (40%)	34 (39%)
Chronic obstructive pulmonary disease	1 (1%)	3 (3%)
Respiratory, thoracic, and mediastinal disorders	4 (4%)	3 (3%)
Renal and urinary disorders	4 (4%)	4 (5%)
Cardiac disorders	15 (16%)	12 (14%)
Laboratory measures		
IL-6, pg/mL	115·5 (245·6)	85·2 (232·2)
C-reactive protein, mg/L	110·7 (107·2)	88·1 (81·1)
Ferritin, ng/mL	920·6 (755·2)	692·7 (501·6)
Disease severity		
Moderate	41 (45%)	47 (53%)
Severe	50 (55%)	41 (47%)
Received other medicines during the study		
All patients		
Remdesivir	39 (43%)	36 (41%)
Corticosteroids	83 (91%)	80 (91%)
Moderate COVID-19		
Remdesivir	18/41 (44%)	21/47 (45%)
Corticosteroids	35/41 (85%)	42/47 (89%)
Severe COVID-19		
Remdesivir	21/50 (42%)	15/41 (37%)
Corticosteroids	48/50 (96%)	38/41 (93%)

(Table 1 continues in next column

	Tocilizumab group (n=91)	Standard care group (n=88)
(Continued from previous column)		
Respiratory support		
All patients		
Supplemental oxygen	81 (89%)	80 (91%)
Non-invasive bilevel positive airway pressure ventilation	28 (31%)	20 (23%)
Mechanical ventilation	5 (5%)	4 (5%)
Intensive care unit	64 (70%)	54 (61%)
Moderate COVID-19		
Supplemental oxygen	32/41 (78%)	39/47 (83%)
Non-invasive bilevel positive airway pressure ventilation	5/41 (12%)	6/47 (13%)
Mechanical ventilation	0	0
Intensive care unit	24/41 (59%)	22/47 (47%)
Severe COVID-19		
Supplemental oxygen	49/50 (98%)	41/41 (100%)
Non-invasive bilevel positive airway pressure ventilation	23/50 (46%)	14/41 (34%)
Mechanical ventilation	5/50 (10%)	4/41 (10%)
Intensive care unit	40/50 (80%)	32/41 (78%)

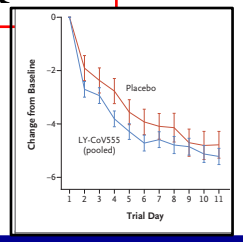
Data are n (%) or mean (SD) unless otherwise stated.

Table 1: **Baseline demographics and clinical characteristics (modified intention-to-treat population)**



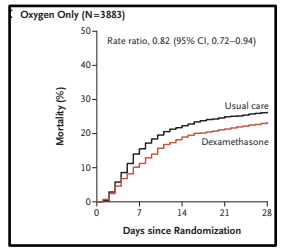
Soin et al. Lancet 2021

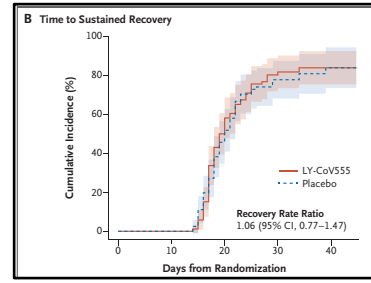
BAMLAVINIMAB
→Accélère clairance virale
ATU de cohorte
70-80 ans ou FDR



CCT à domicile
Méthylprednisone 1mg/kg 48h
Baisse de 50% toutes les 48h
J10

DEXAMETHASONE
→Augmente la survie
Phase 3 n=6425 +/- TOCI





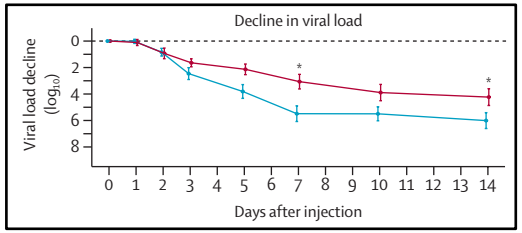
Inefficacité du BAMLAVINIMAB
H°

J0 PCR +
+ 50 ans FDR

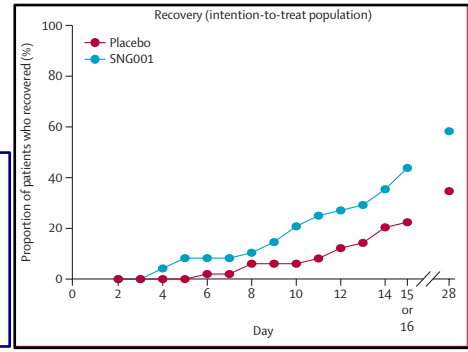
J5
À domicile
O2>3l/mn ou FR>22
CRP>50
TDM>25% parenchyme

J8
Hospitalisé pour COVID
O2>6l/mn

Peginterferon
Phase 2 n=60
→ Accélère clairance virale



IFN-β en intra-nasal
Phase 2 n=101
→ Accélère la rémission



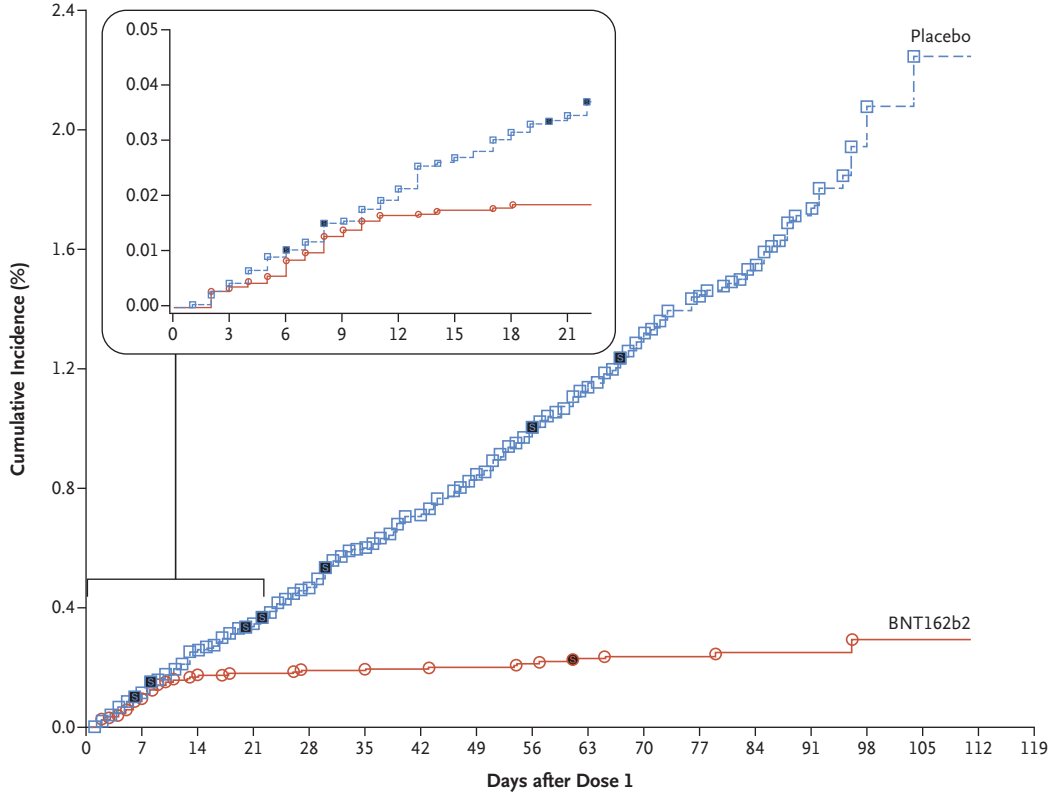
COVERAGE
IFN-β en intra-nasal
Phase 3: Obj diminue taux H°?

Cibler les patients qui bénéficieraient d'un traitement précoce → QFM

MINISTÈRE
DES SOLIDARITÉS
ET DE LA SANTÉ
Liberté
Égalité
Fraternité

Conclusion

- Peu d'avancées thérapeutiques malgré l'amélioration des connaissances physiopathologie
- Corticothérapie + Ventilation
- Espoirs: IFN+++
- Meilleure Immunothérapie COVID préventive **Vaccination**



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)