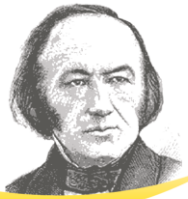
JEUDI 26 NOVEMBRE 2020
UFR Médecine Paris 7 Diderot,
site Xavier-Bichat - Paris 18ème

63ème journée Claude-Bernard



Immunomodulateurs et COVID-19

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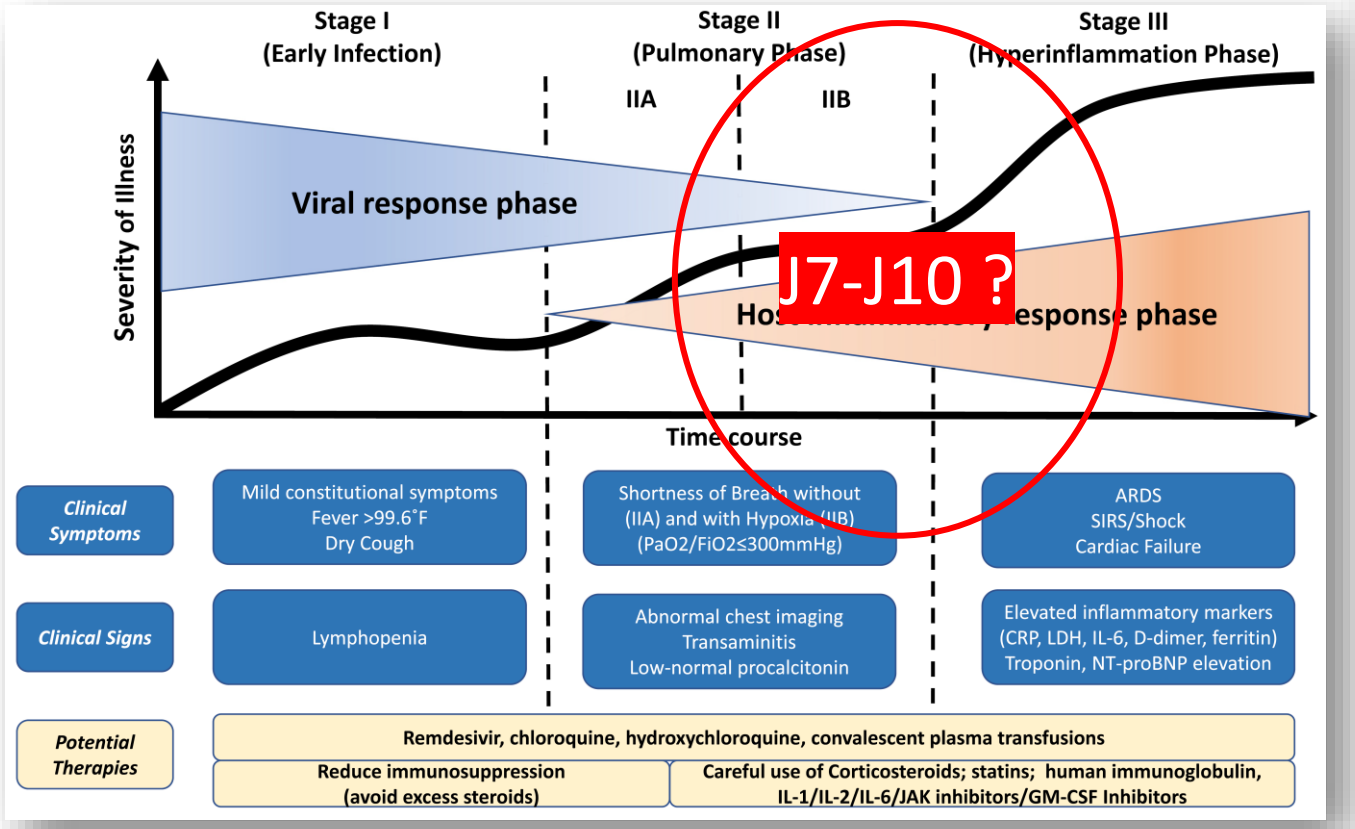
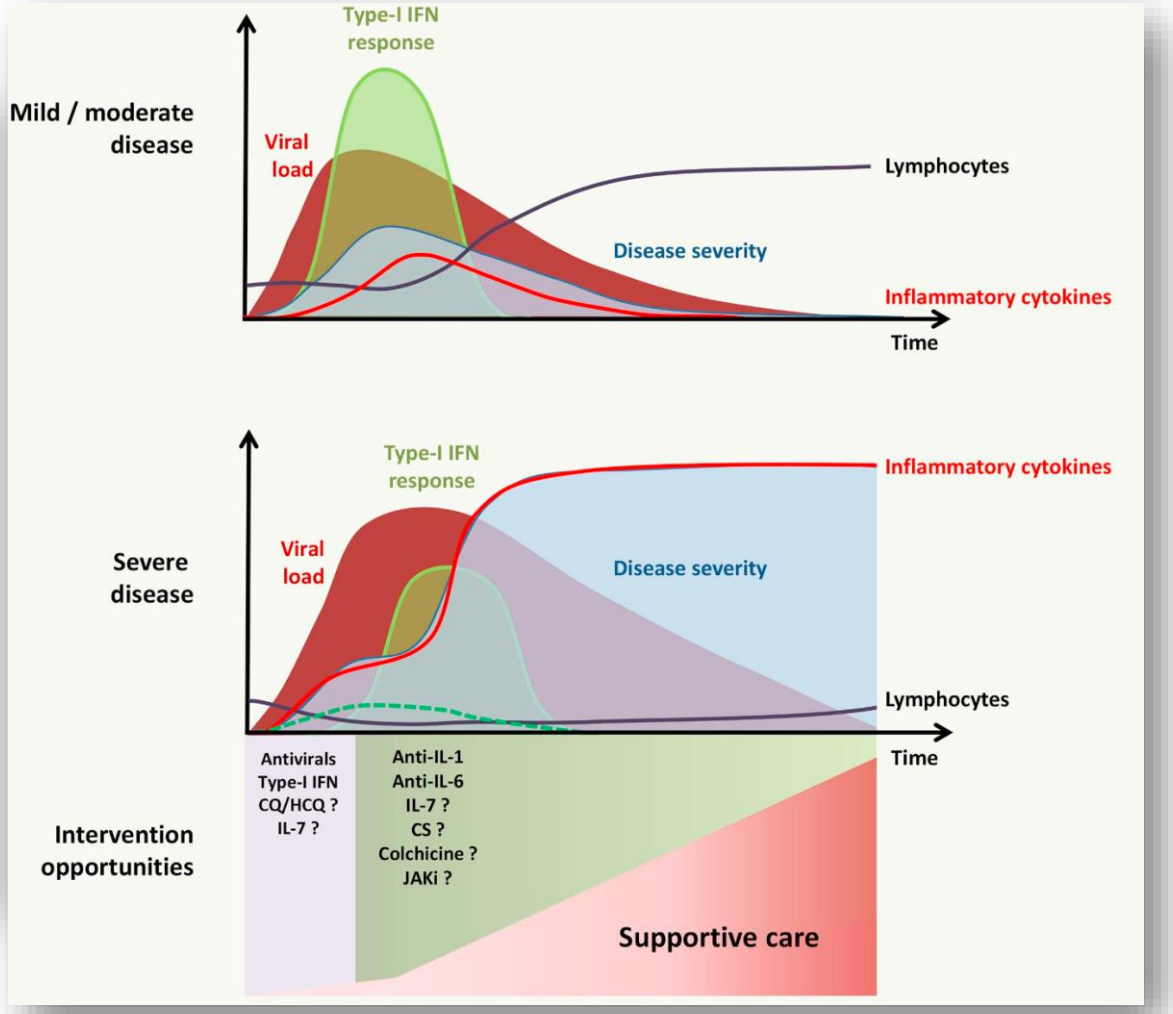
Liens d’intérêt

- Pfizer
- MSD
- Novartis
- Eumédica
- Gilead
- Correvio

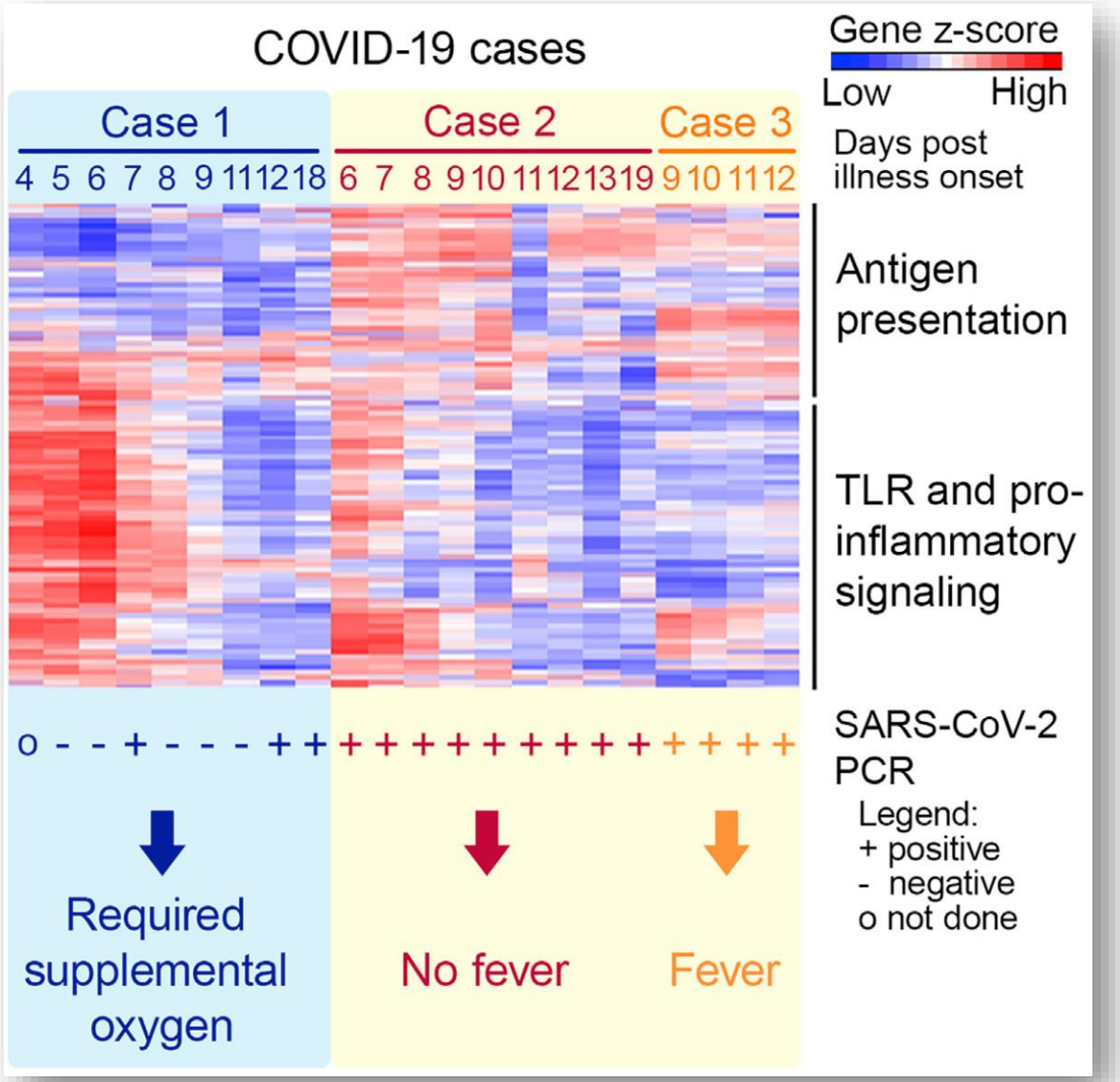
COVID-19 grave : une maladie inflammatoire ?



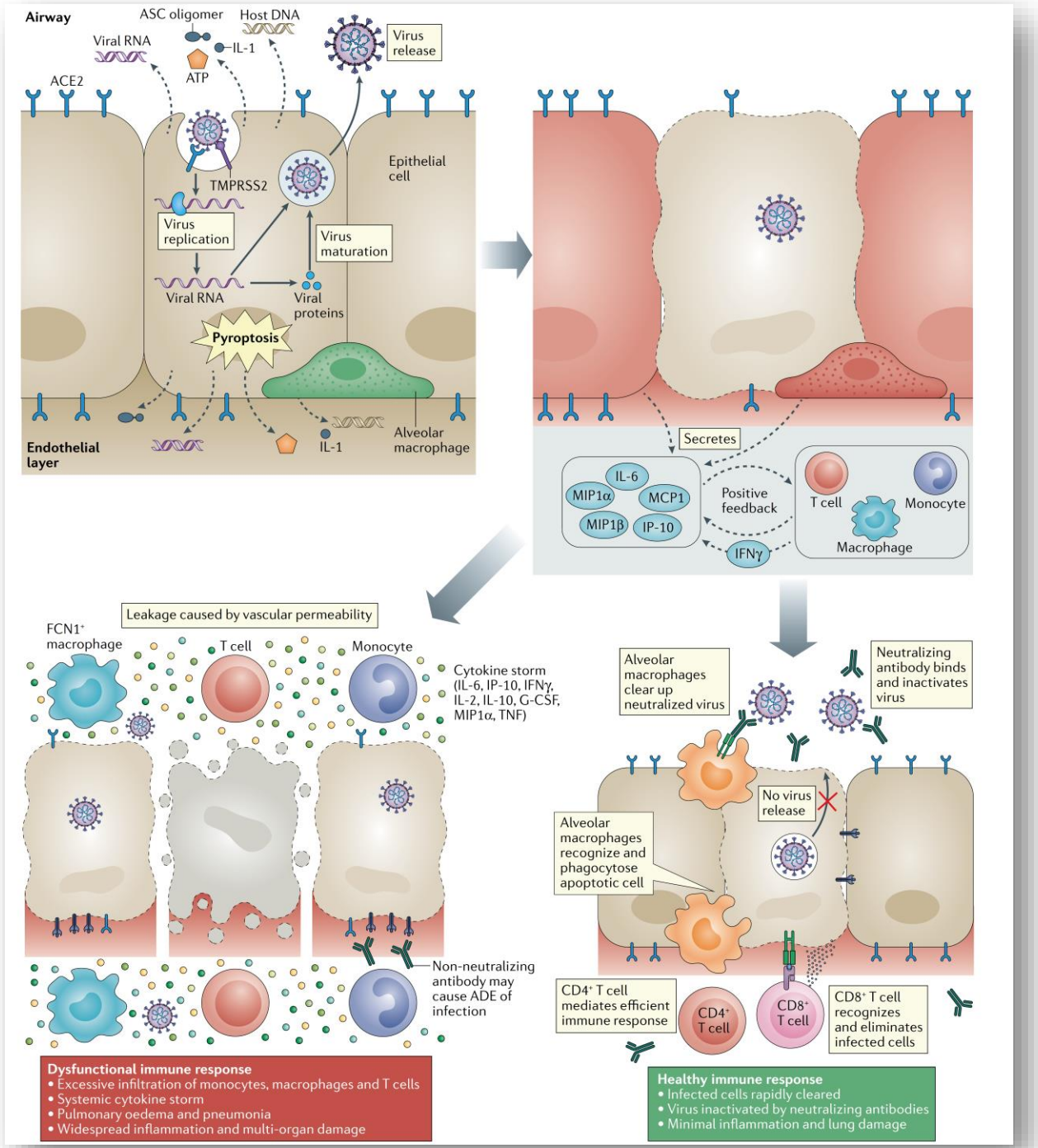
Siddiqui HK et al. J Heart Lung Transplant. 2020



Jamillou Y et al. Autoimmunity Reviews. 2020

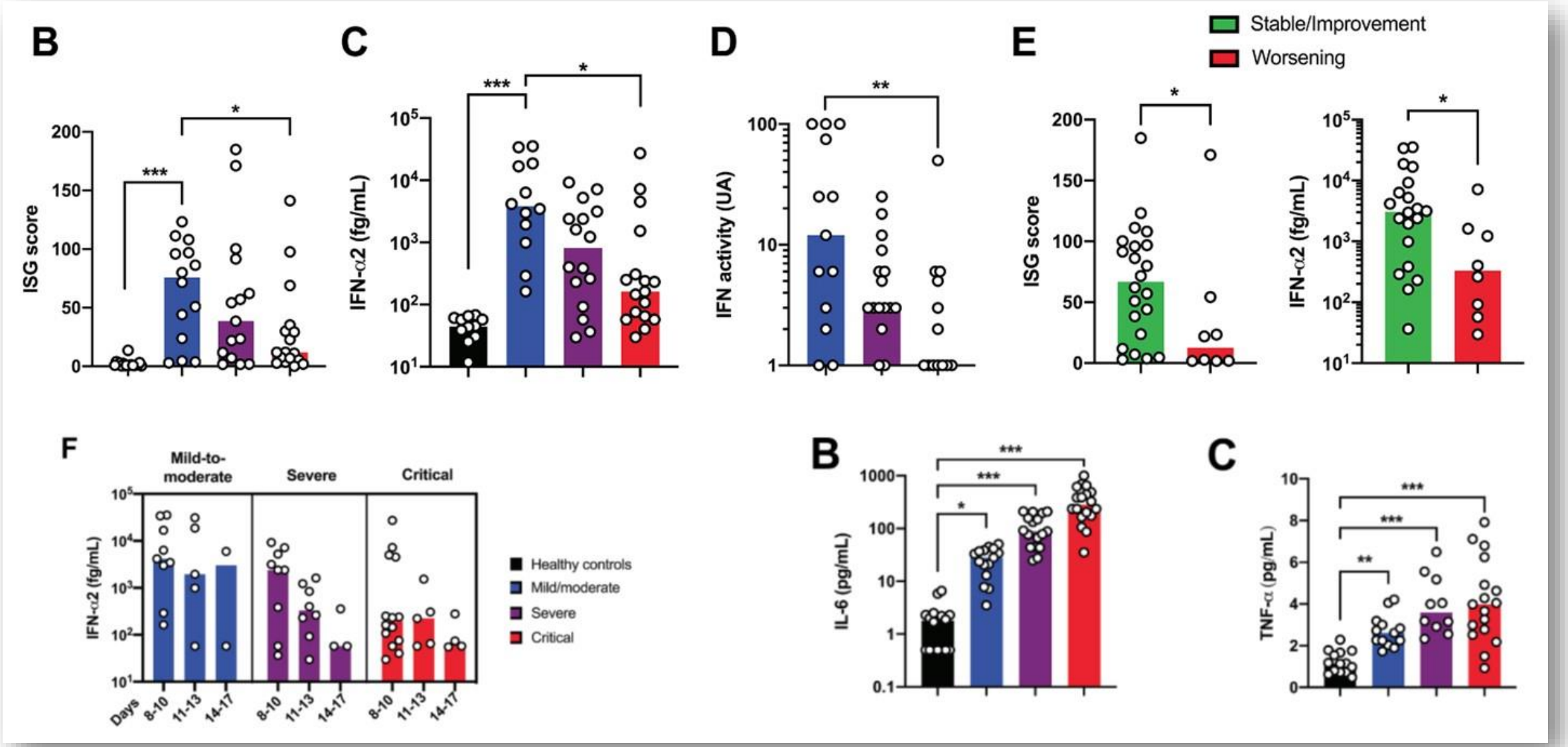


Ong EZ et al. Cell Host and Microbe. 2020

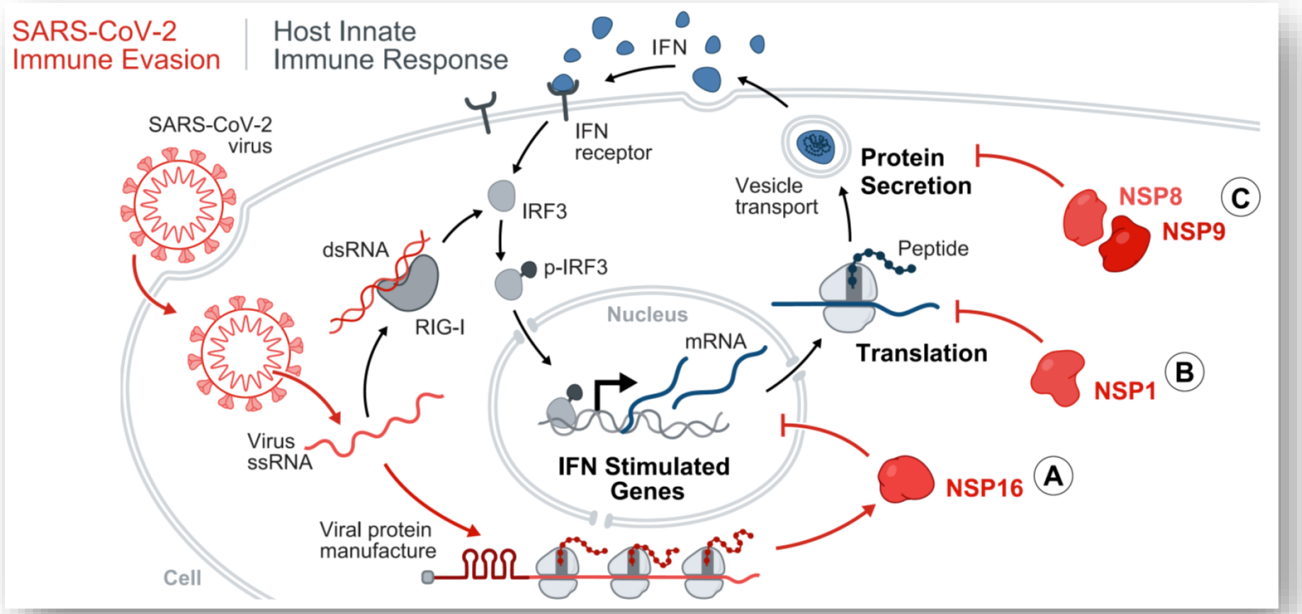


Tay MZ et al. Nature Reviews Immunology. 2020

Défaut interféron type 1/augmentation (excès ?) IL pro-inflammatoires

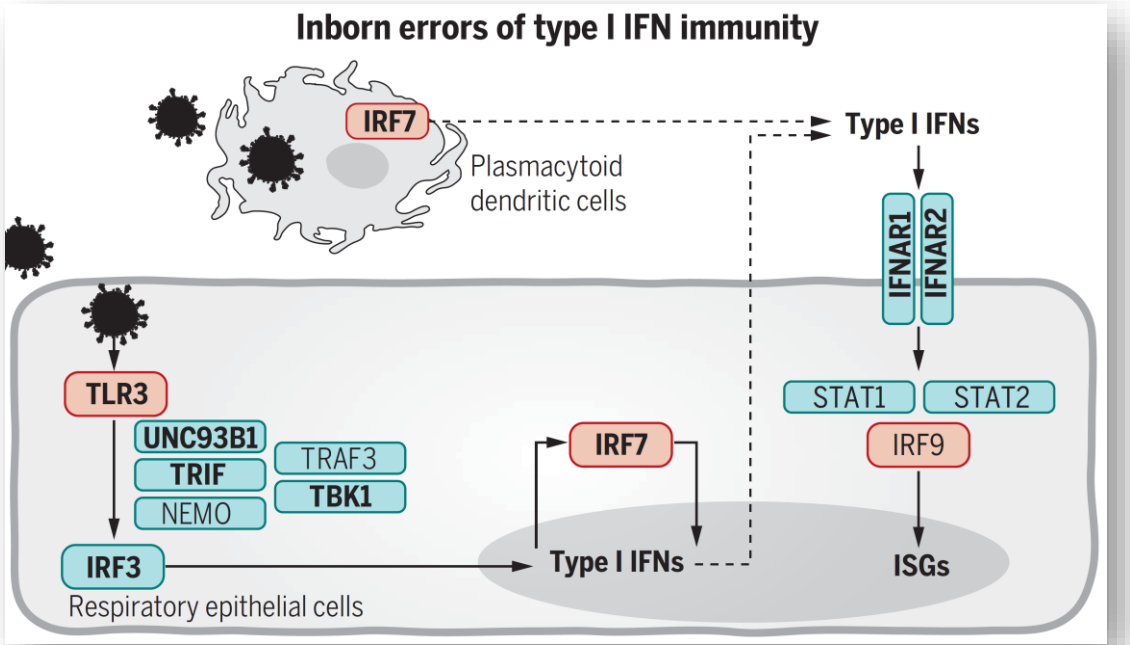


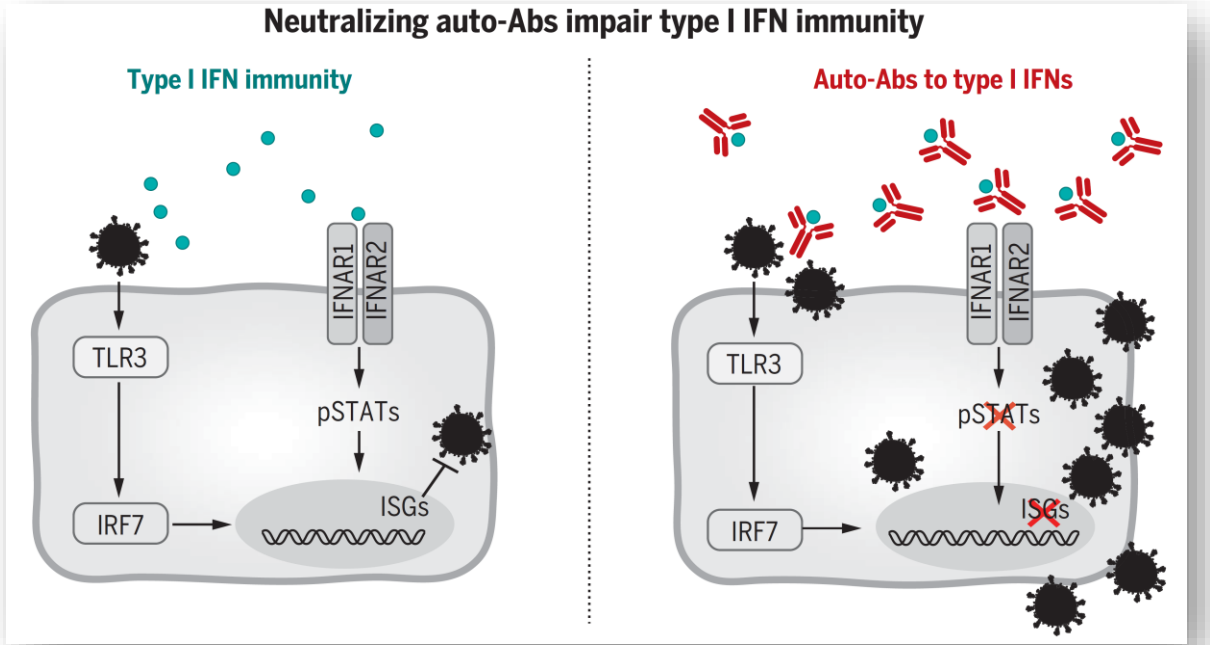
Hadjadj J et al. Science. 2020



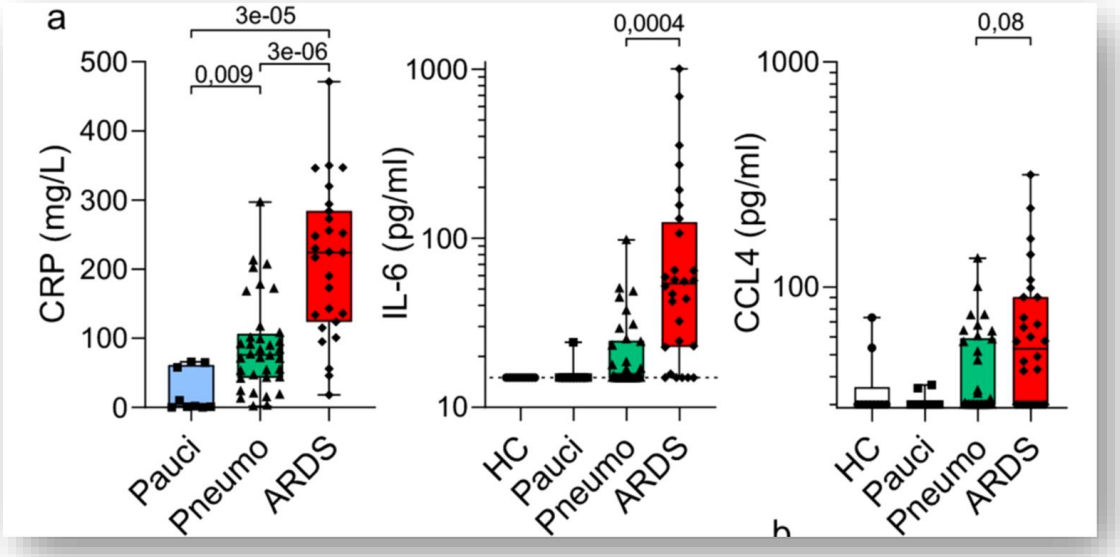
Les trois raisons du « déficit » des IFN de type 1 :

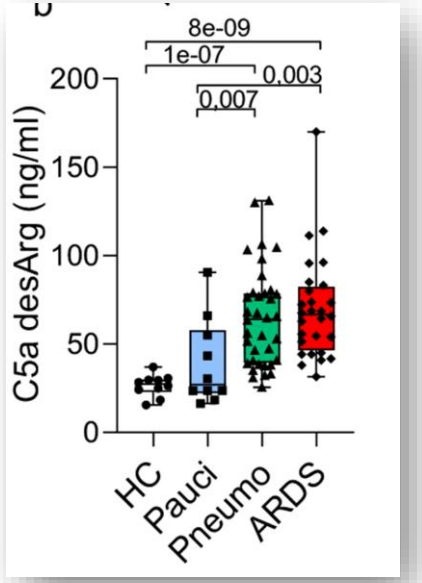
- **une inhibition par le virus** *(Banerjee AK et al. Cell. 2020)*
- **un déficit génétique** (*Zhang Q et al. Science. 2020*)
- **une présence d'auto-Ac** (*Bastard P et al. Science. 2020*)

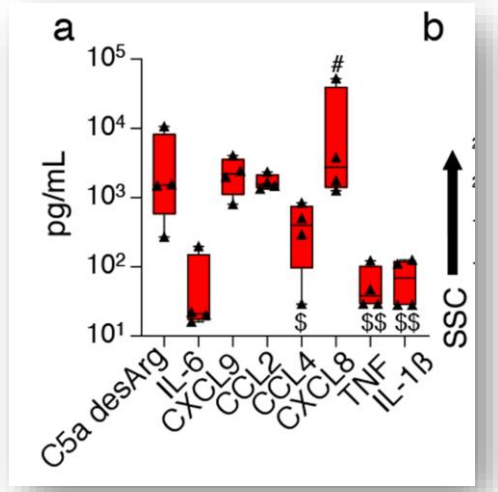




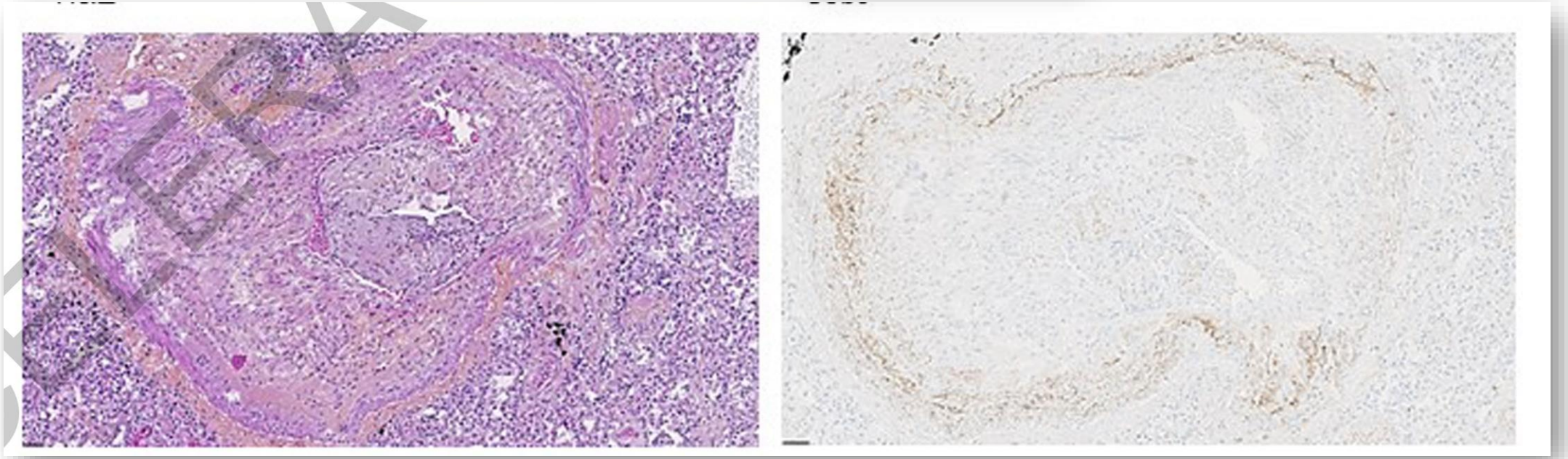
Lien inflammation/thrombose : le complément (C5a)



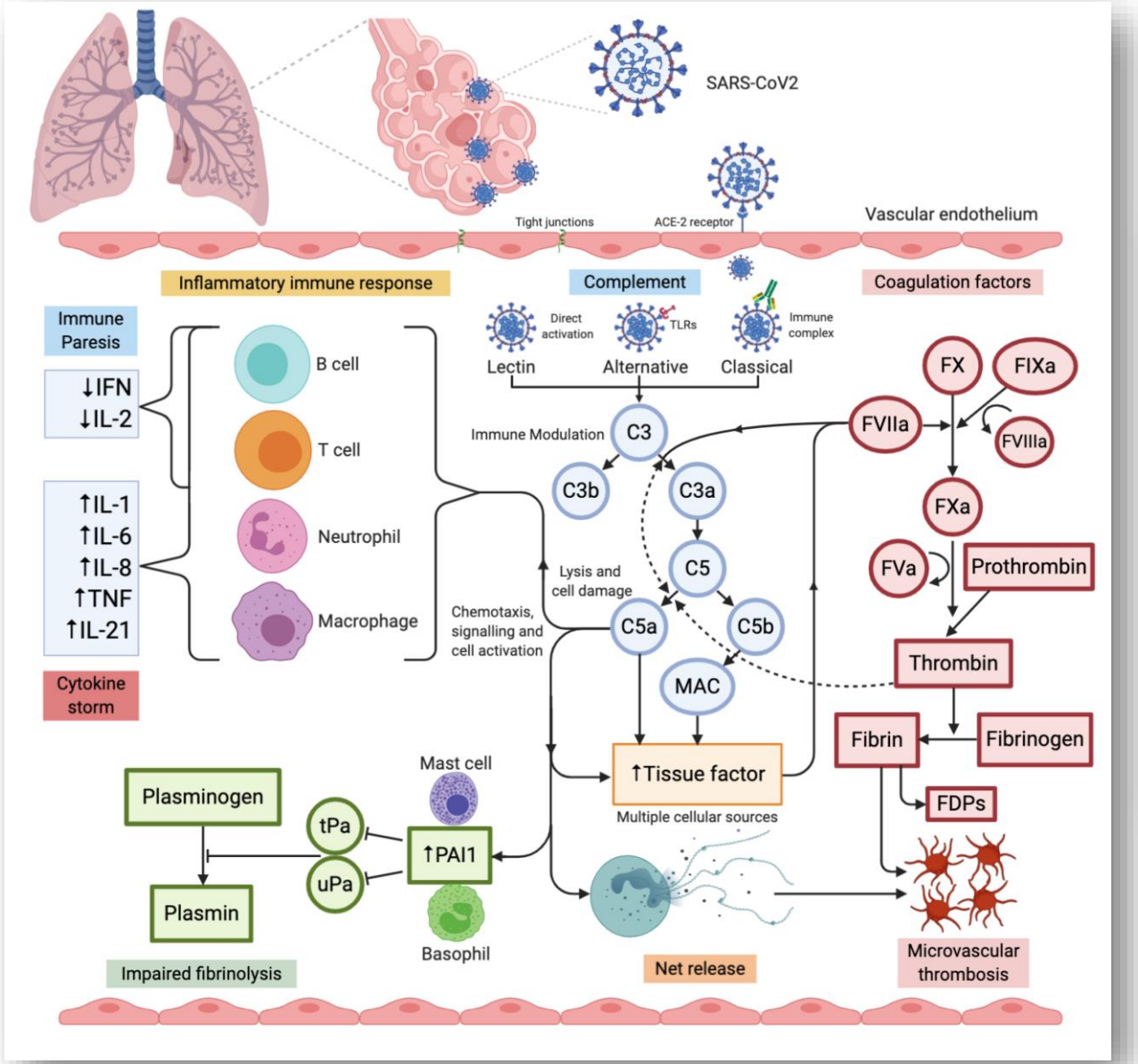




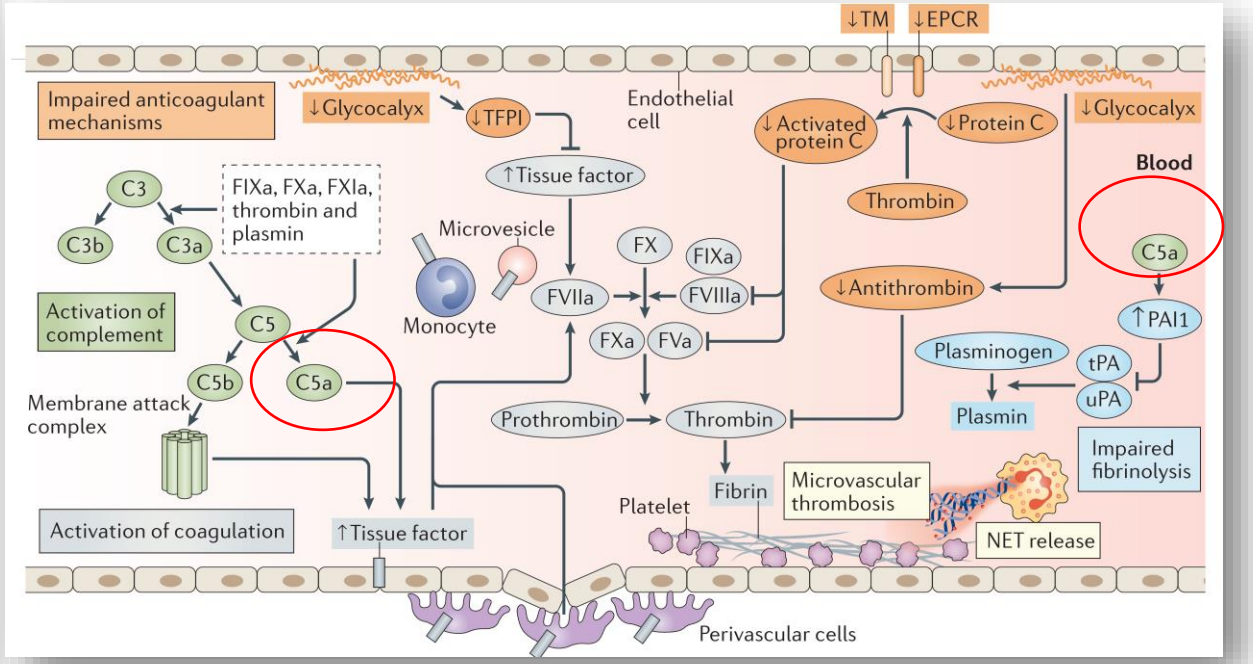
Carveli J et al. Nature. 2020



Lien inflammation/thrombose : le complément



Chauhan AJ et al. JTH. 2020



van der Poll T et al. Nature Reviews Immunol. 2017

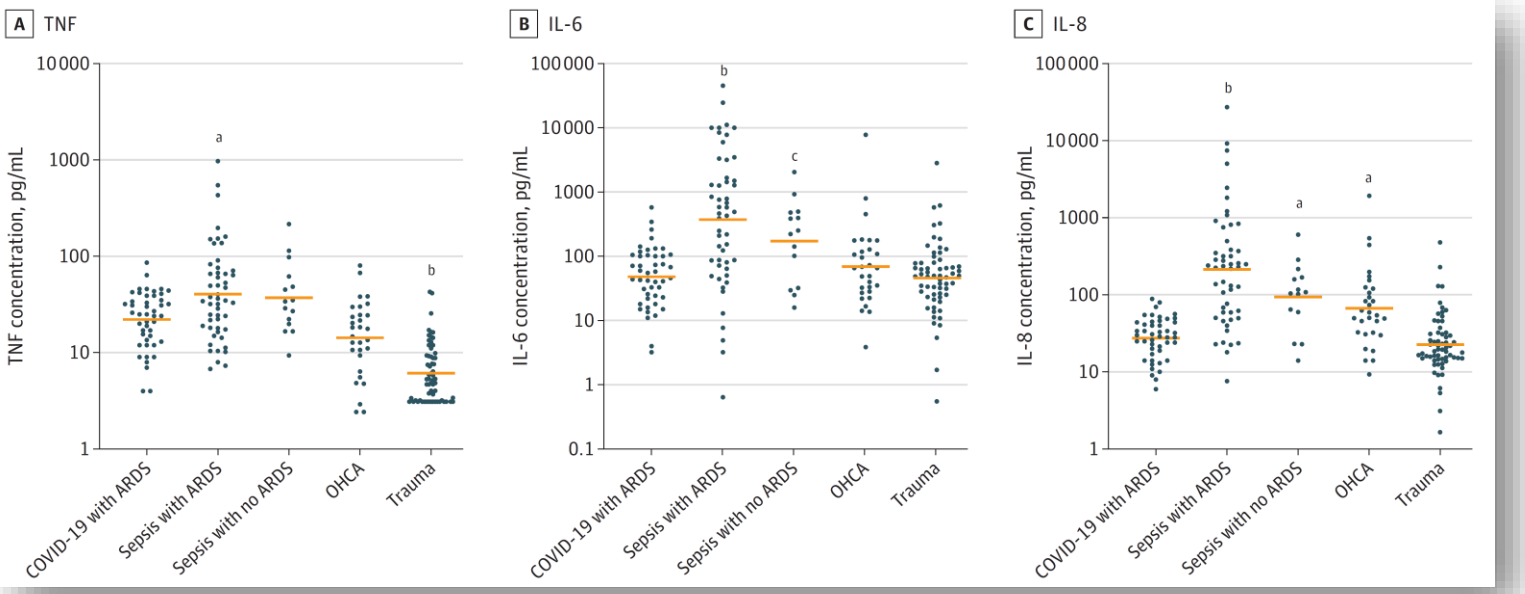
« L'orage cytokinique » est il vraiment le problème?

Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS[a]

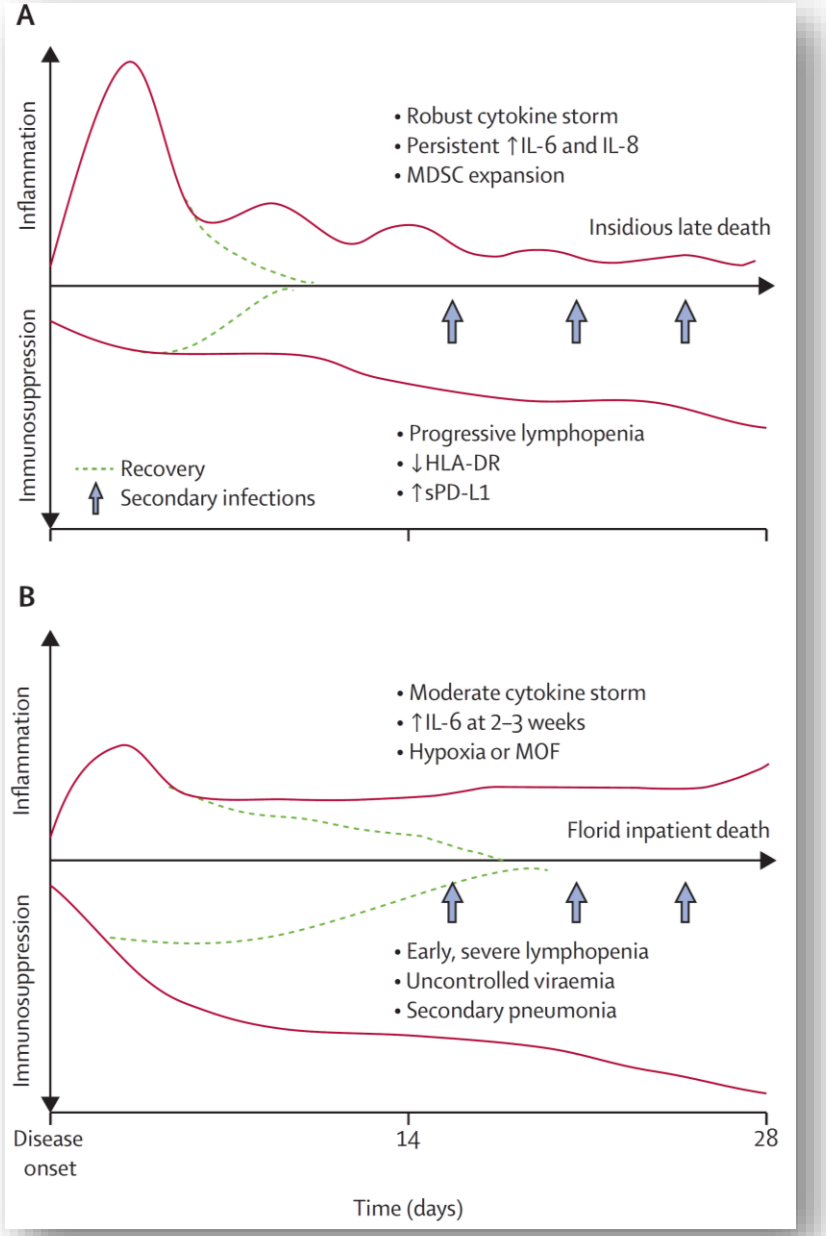
	Total population		Severe disease		
COVID-19	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	Measurement platform
Zhou et al[4]	191	7 (5-11)	54[b]	11 (8-14)	CL
Wu et al[1]	123	7 (6-9)	84[c]	7 (6-11)	CL
Mo et al[5]	155	45 (17-96)	85[d]	64 (31-165)	CL
Qin et al[2]	452	21 (6-47)	286[e]	25 (10-55)	CL
Cummings et al[6]	NR	NR	237[f]	26 (11-69)	CL

	Total population		Hypoinflammatory		Hyperinflammatory		
ARDS	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	Measurement platform
ALVEOLI[7]	521	238 (94-741)[f]	386	154 (67-344)	135	1525 (584-3802)	ELISA
FACTT[8]	884	130 (46-411)[f]	638	86 (34-216)	246	578 (181-2621)	ELISA
SAILS[9]	720	443 (173-1513)[f]	451	282 (115-600)	269	1618 (517-3205)	ELISA

Sinha P et al. JAMA Internal Med. 2020



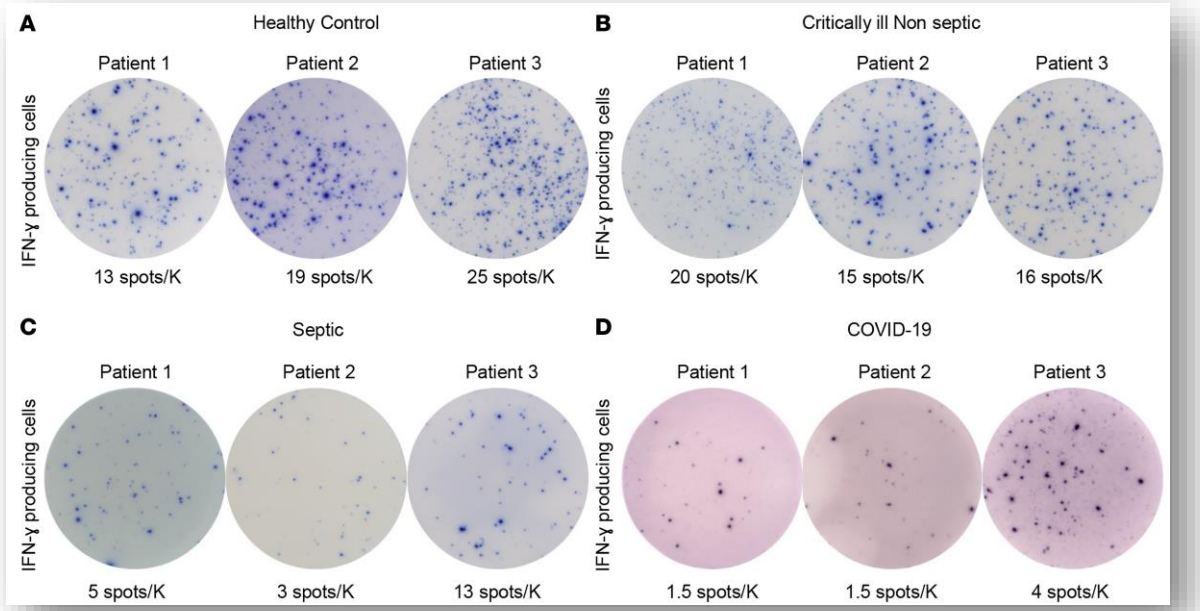
Kox M et al. JAMA. 2020



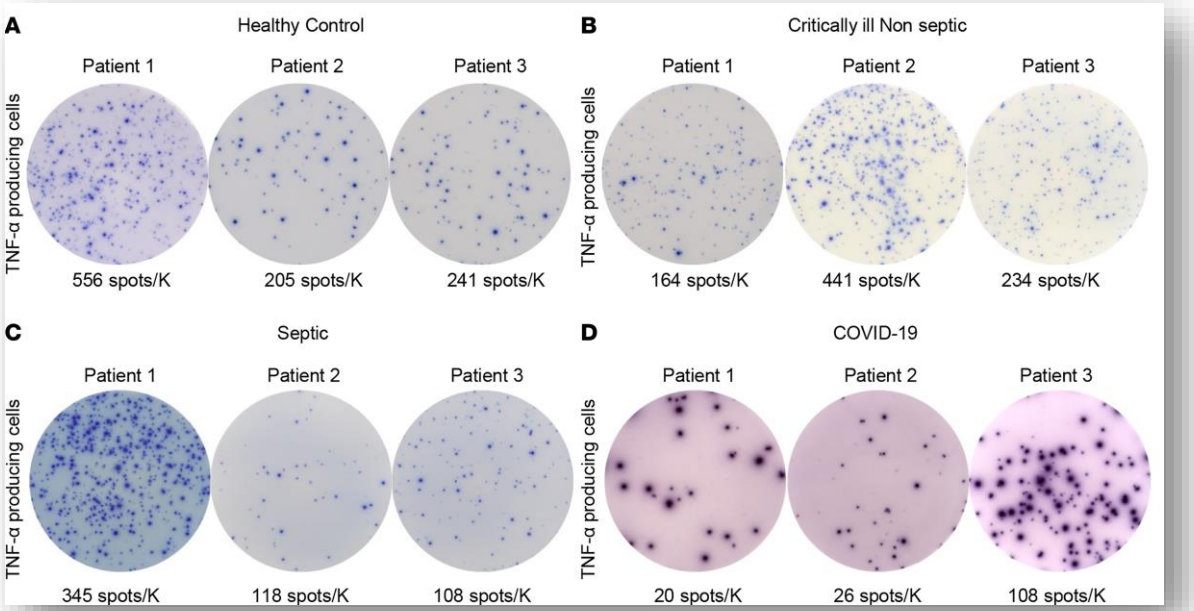
Remy KE et al. Lancet. 2020

Sachant que les patients sont « immunodéprimés »

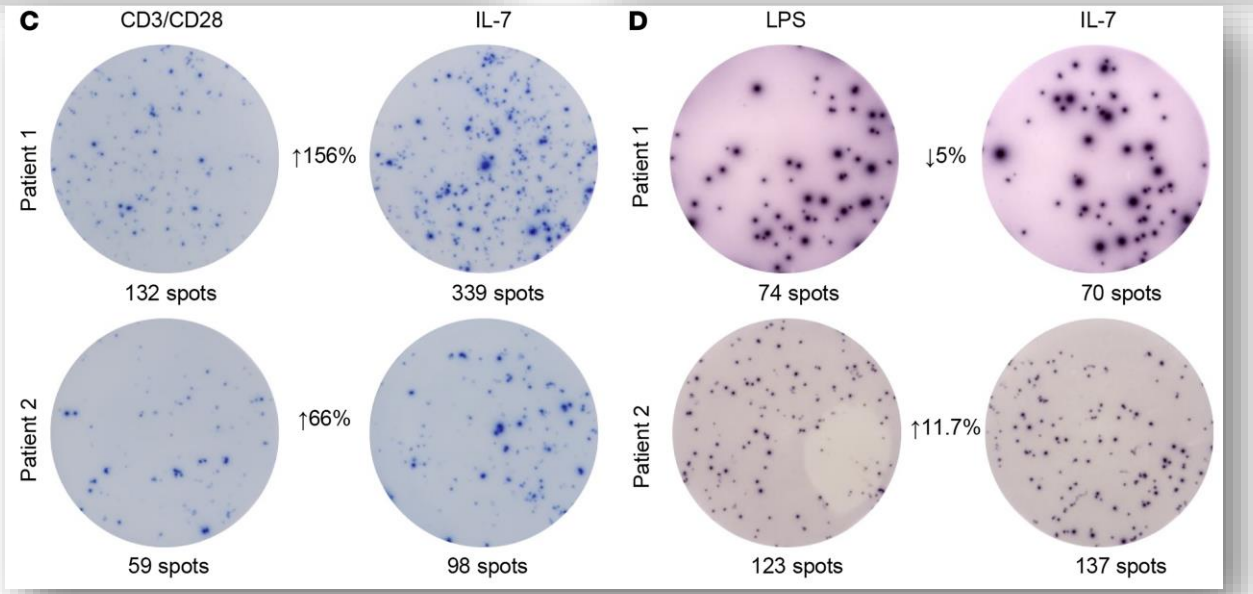
Elispot IFN γ



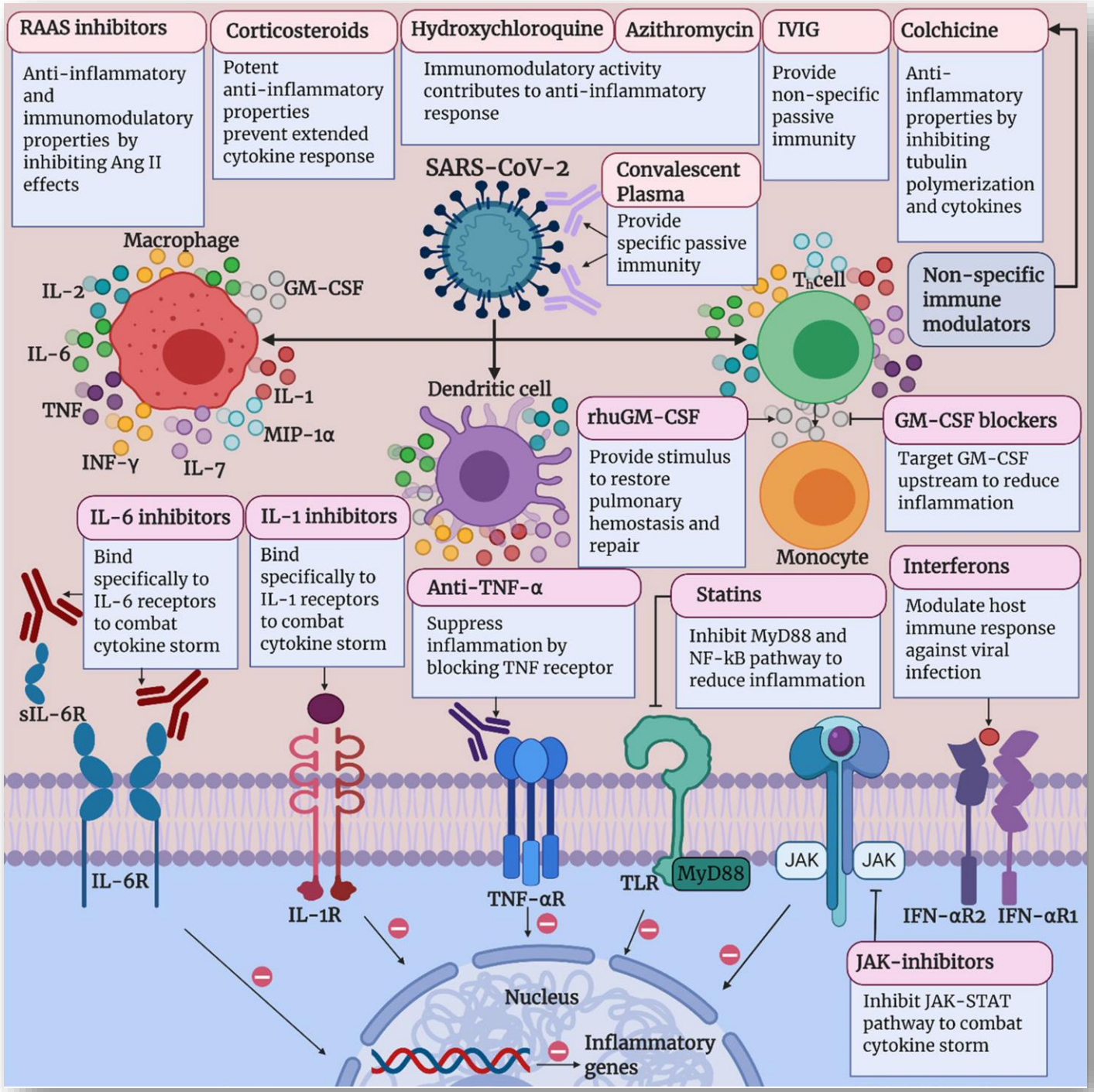
Elispot TNFα



Restauration IFN γ avec IL7



Remy KE et al. JCI. 2020



Inhibiteurs Bruton Tyrosine Kinase (acalabrutinib)

Anticorps anti C5a

Anticorps anti C5

Risk JG. Drugs 2020

L'immunomodulation polyvalente tout terrain : les corticoïdes

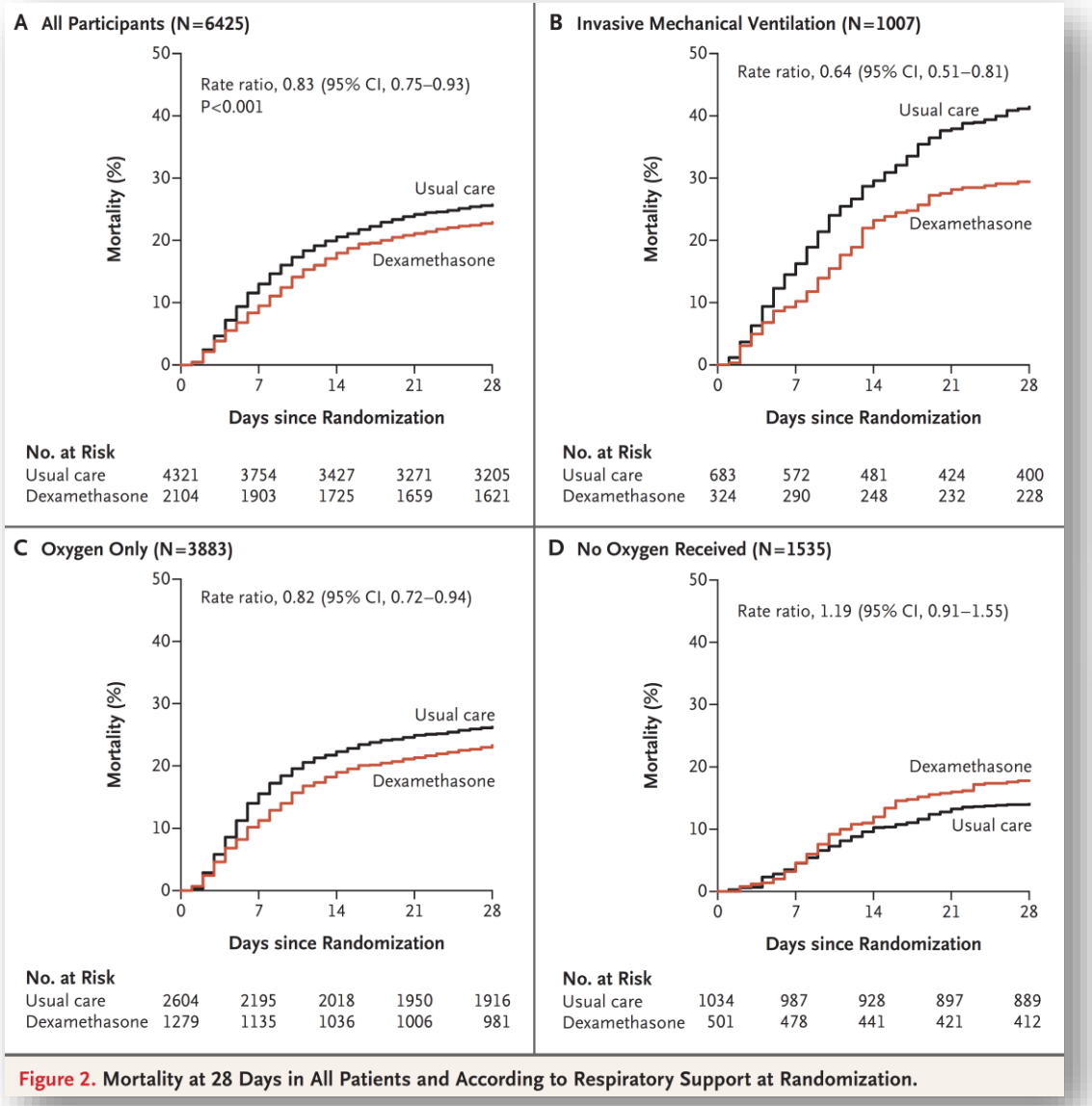


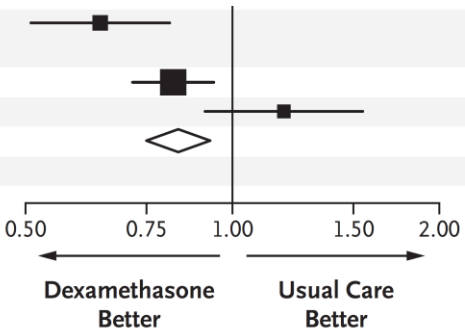
Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

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)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

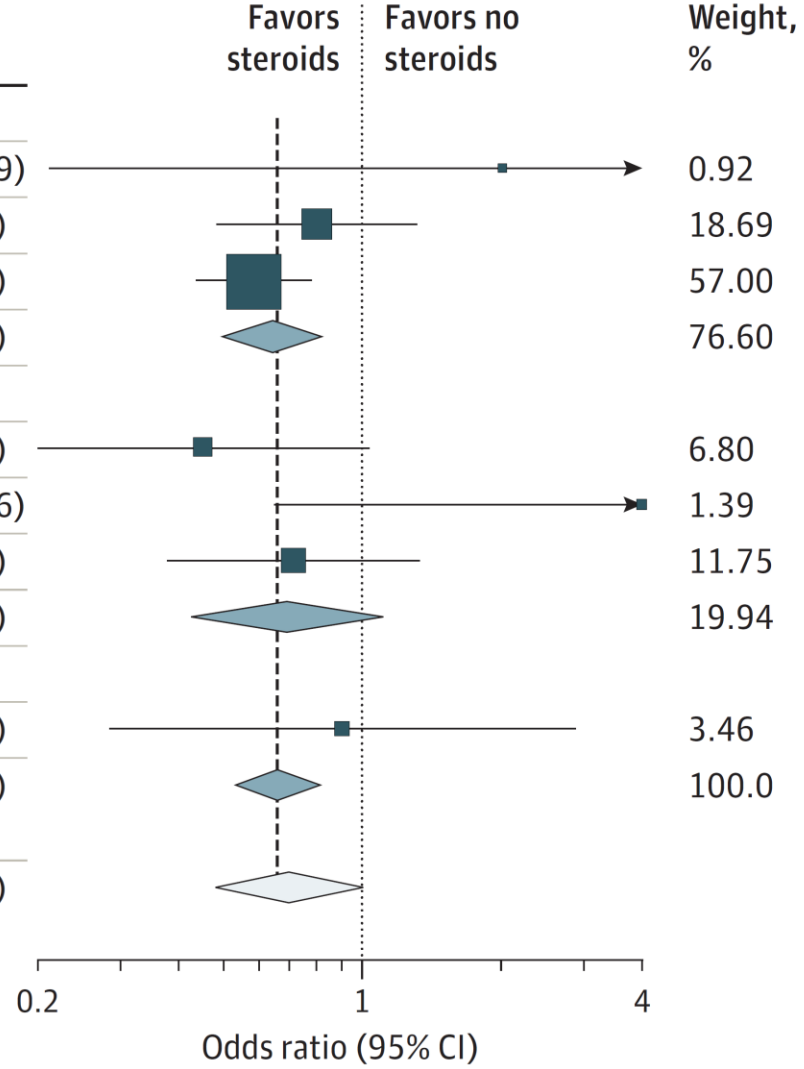
Chi-square trend across three categories: 11.5



Recovery. NEJM. 2020

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)	



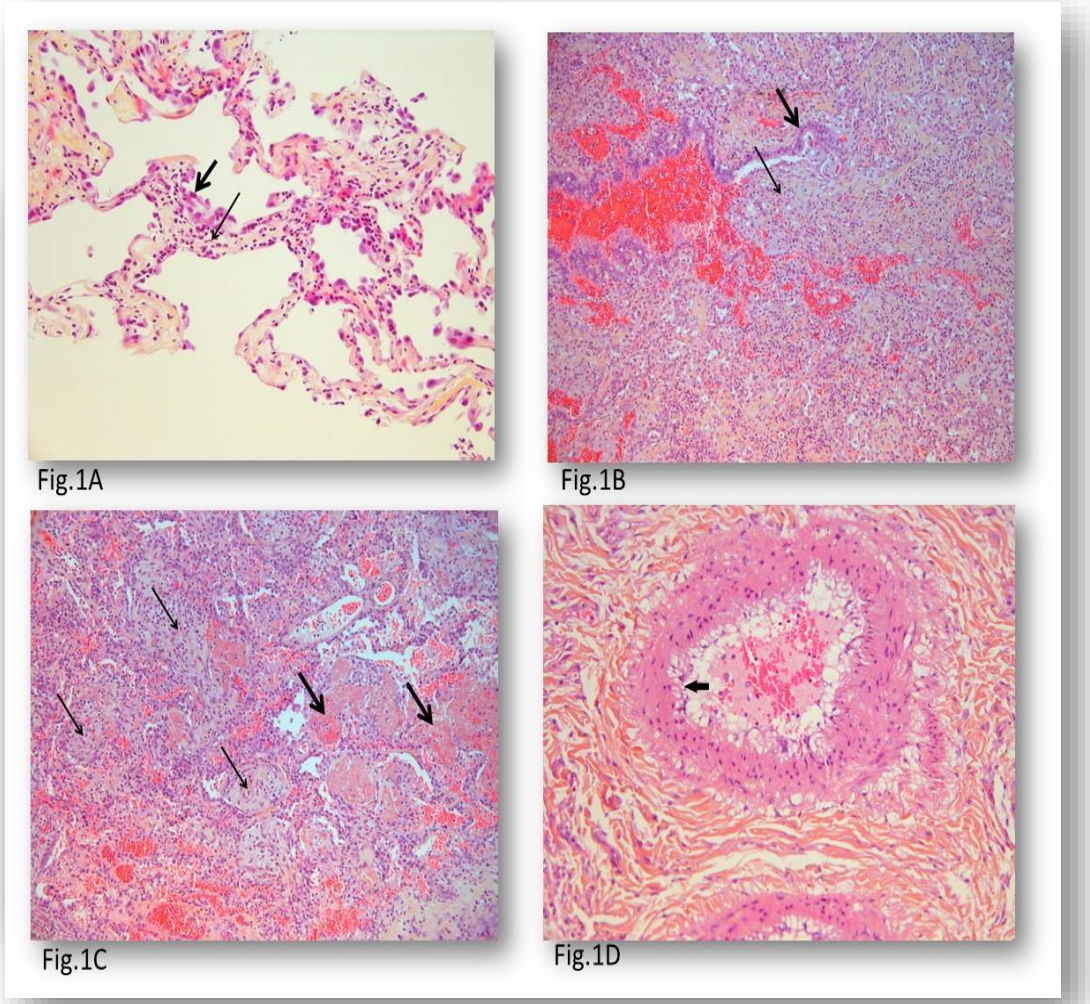
React working group. JAMA. 2020

A mettre en perspective avec « l'ARDS » : quelle est la bonne dose chez les malades les plus sévères ?

Dexa 20mg 5 jours puis 10 mg 5 jours

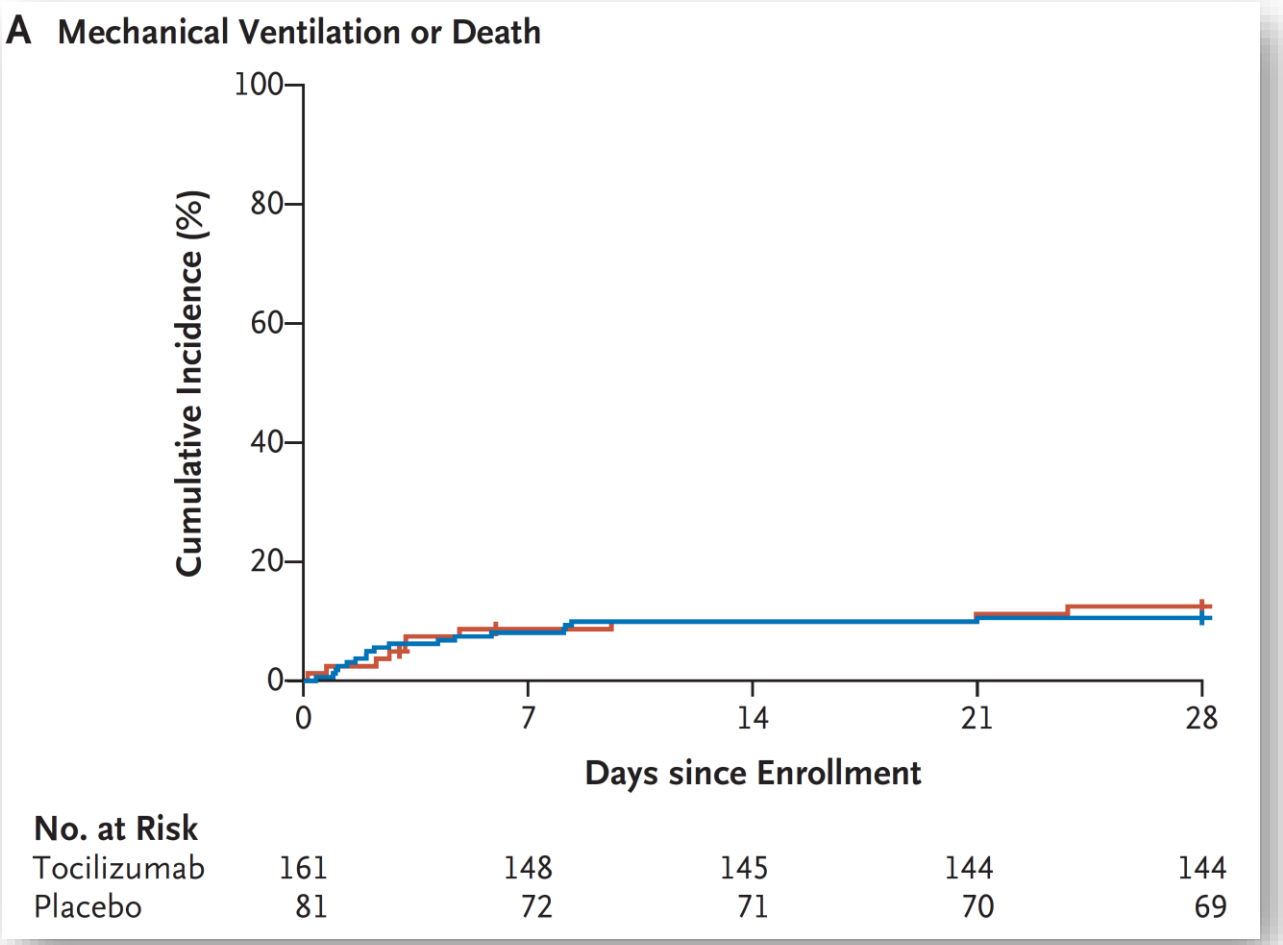
	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	−15·3% (−25·9 to −4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	−12·5% (−22·4 to −2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	−12·5% (−22·9 to −1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	−5·3 (−8·4 to −2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	−5·9 (−9·1 to −2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (−5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (−8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (−4·0 to 9·8)	0·41

Villar J et al. Lancet Respir Med. 2020



Copin MC et al. ICM. 2020

Immunomodulation ciblée. Toci « précoce » : aucun bénéfice



Inclusion

- Clinique, au moins 2 parmi : fièvre dans les 72h, infiltrats pulmonaires, O2 pour Sat>92%
- Biologique, au moins 1 parmi : CRP>50 mg/L, ferritine > 500 ng/mL, D-dimères > 1000 ng/mL, LDH >250 UI/L
- Exclusion si O2 > 10 L/min

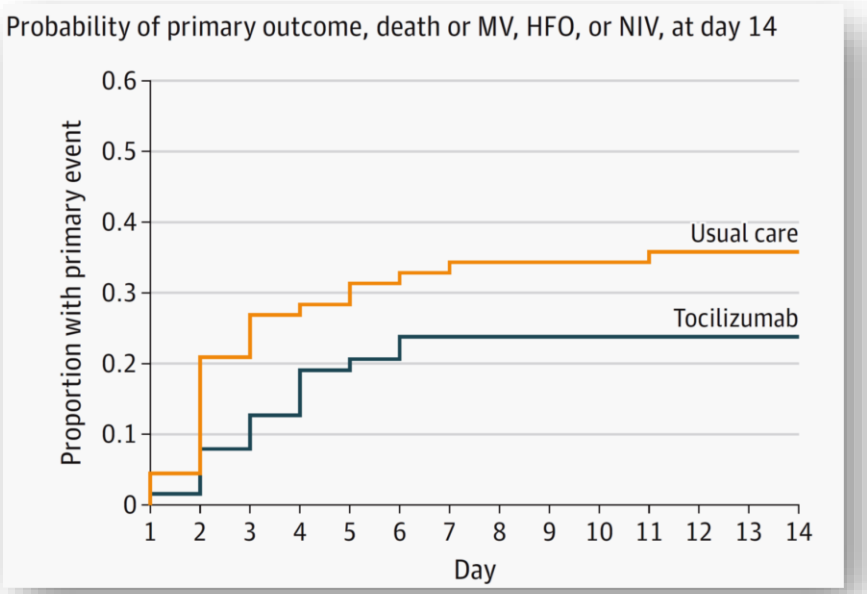
En médiane

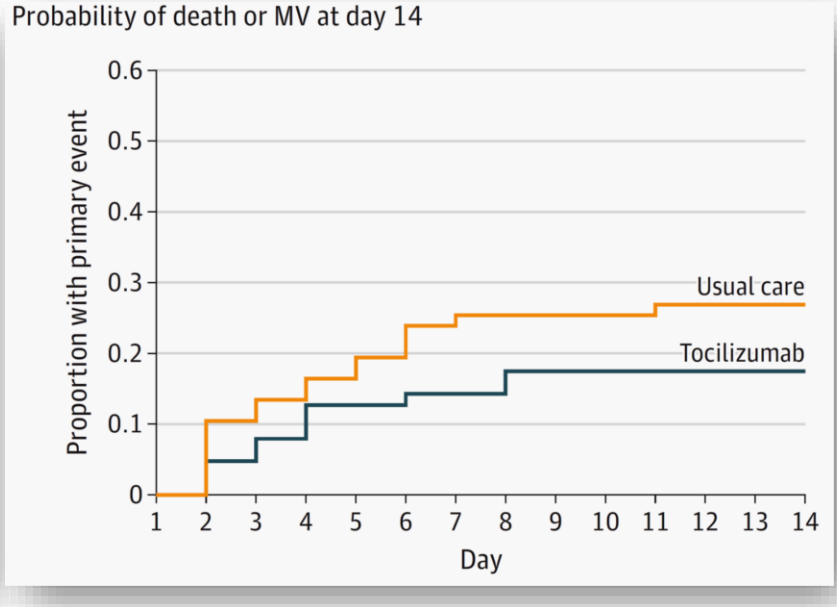
- CRP : 110 mg/L
- Ferritine 708ng/mL
- D-dimères 884 ng/mL
- LDH 340 UI/L
- IL 6 : 24,4 pg/mL

NB: pas de corticoïdes ! Effet « pur »

Stone JH et al. NEJM. 2020

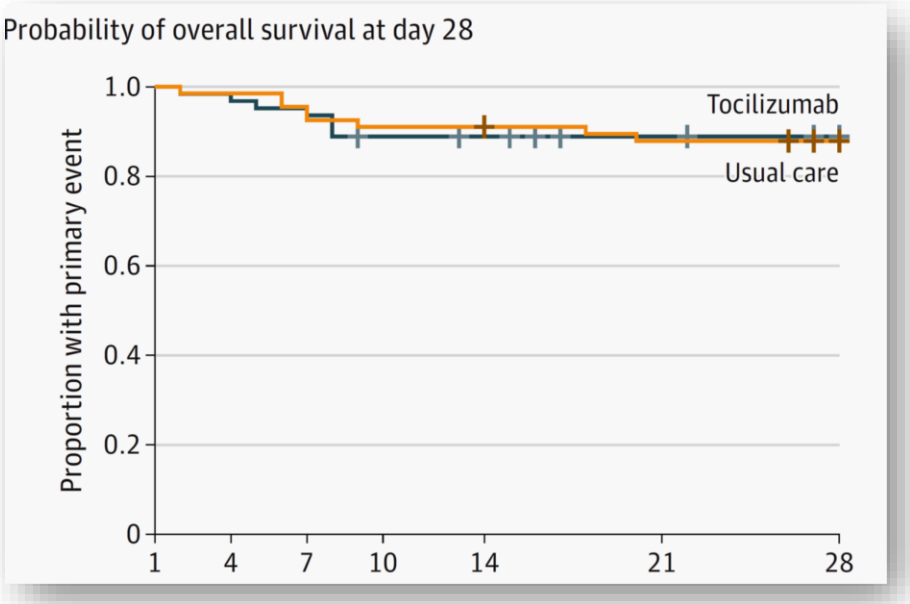
Corrimuno : COVID-19 « modérée à sévère »

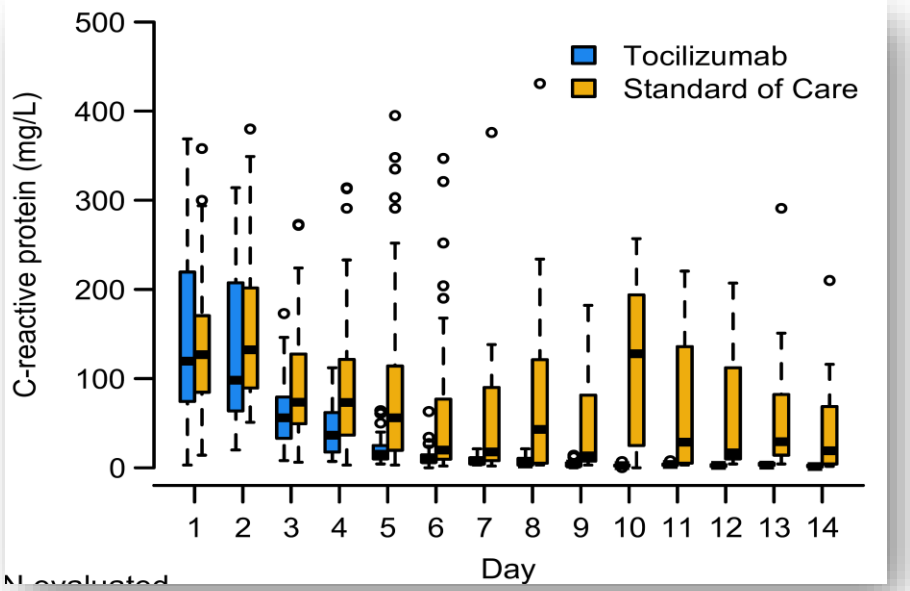




Patients > 3L d'O2
≥ stade 5 échelle OMS
Mais pas en réa
Donc ce n'est pas sévère !

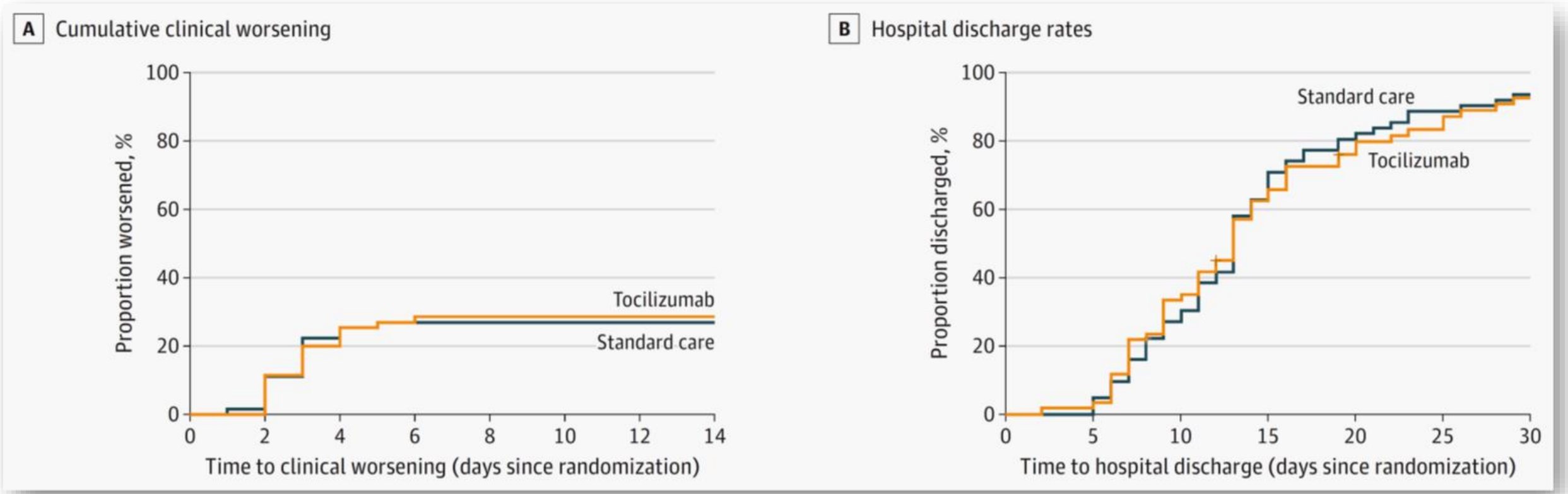
Antico > 90%
Cortico 33% toci vs 61% SOC





Hermine O et al. JAMA Int Med. 2020

Toci chez les malades sévères



200<PaO2/FiO2<300 mmHg
Optiflow et CPAP Venturi possible

Aggravation clinique J14 :

- **Réa**
- **DC**
- **PaO2/FiO2<150 mmHg**

Salvarani C et al. JAMA Int Med. 2020

Immunomodulation ciblée plus large : qu'en attendre ?

Update on CALAVI Phase II trials for Calquence in patients hospitalised with respiratory symptoms of COVID-19

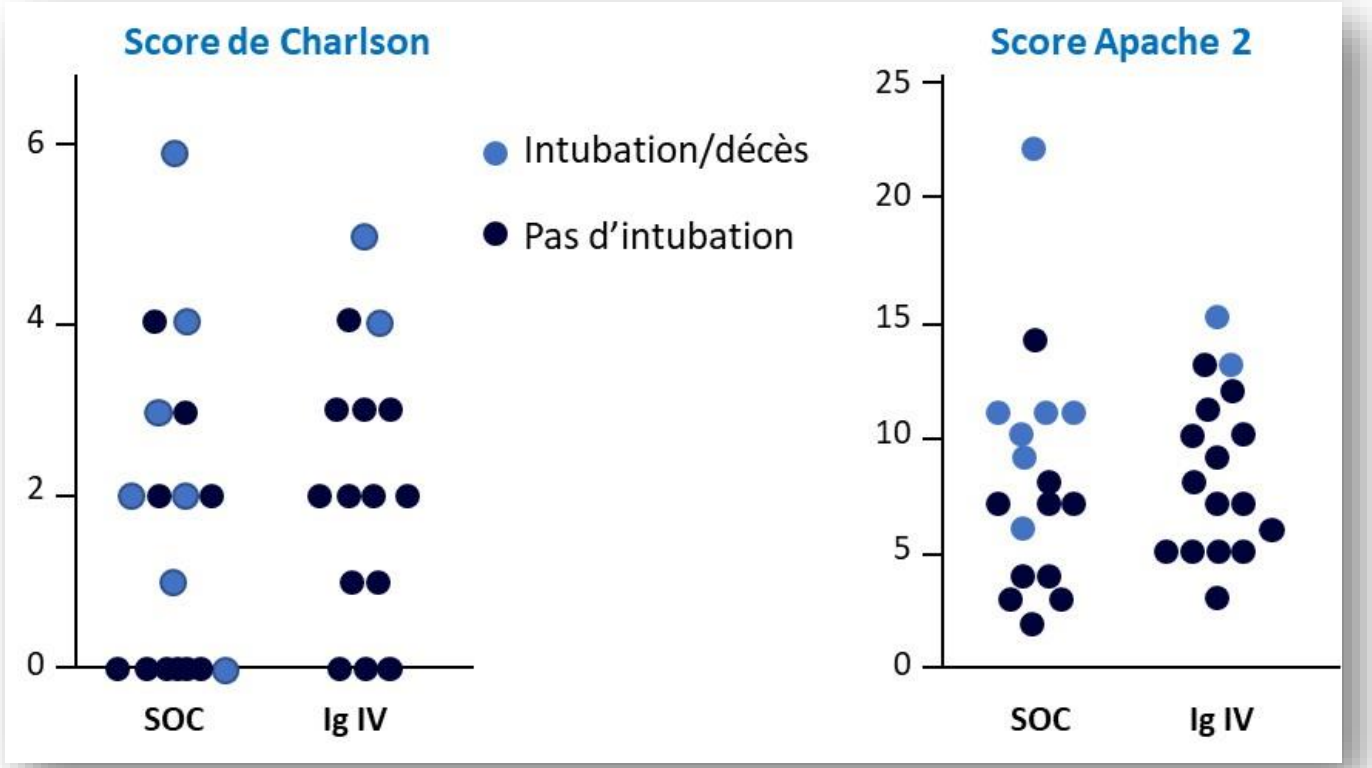
PUBLISHED
12 November 2020

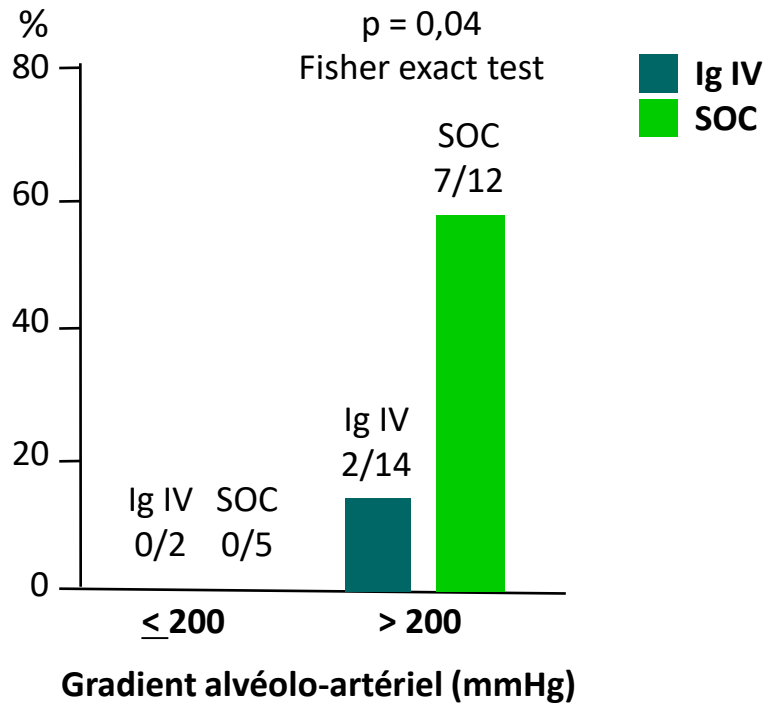
12 November 2020 07:00 GMT

CALAVI did not meet the primary endpoint of increasing the proportion of patients who remained alive and free of respiratory failure

- Multiples essais JAK-inhibiteurs
- Essai phase 2 Ac anti C5a peu concluant mais sûreté validée. Force en cours en France
- A revisiter avec les cortico ?? ++
- Quid de l'IL 7 ?

Ig polyvalentes ? Un bénéfice possible pour les malades les plus graves





- Essai randomisé en ouvert, SOC vs SOC + Ig polyvalente
- O_2 ≥ 4 l/min pour SpO_2 ≥ 90 %, exclusion si intubé
- Ig IV polyvalentes : 0,5 g/kg/j x 3 jours, avec **40 mg de méthylprednisolone 30 minutes avant chaque injection**

Sakoulas G, IDWeek 2020, Abs. 71

Conclusion : « One Size Does Not Fit All »

- Pour l'instant seuls les corticoïdes ont prouvé leur efficacité
- Sur le versant inflammatoire/ARDS
  - Dose ? Timing idéal ?
- Que faire si échec/rebond ?
- Les thérapeutiques ciblées généralisées sont un échec
- A personnaliser ? De manière séquentielle ? Cibler vaisseau/thrombose ?
- Quid de l'impact sur la réplication virale ?
- Place de la stimulation immunitaire ? Interférons ? Précocement ? IL7 ?