Les vaccins contre la Covid-19 : un état des lieux

Groupe Vaccination et Prévention de la SPILF

4 février 2022 – PARIS

Quatrième dose vaccinale, plasma de convalescents, anticorps monoclonaux : quel bilan des dispositifs pour les immunodéprimés ?

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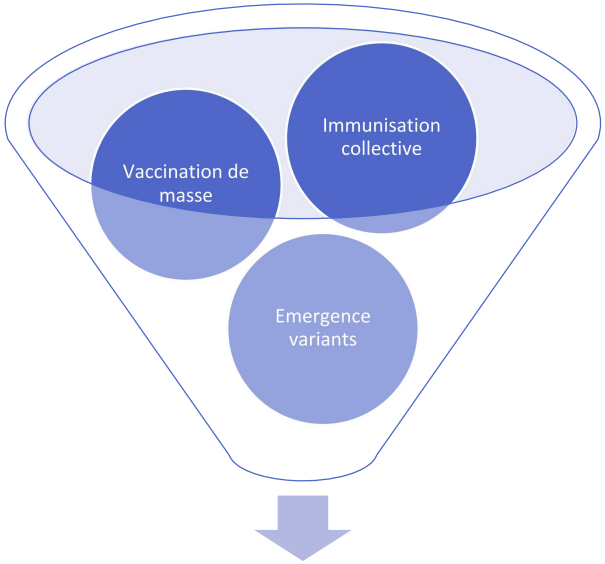
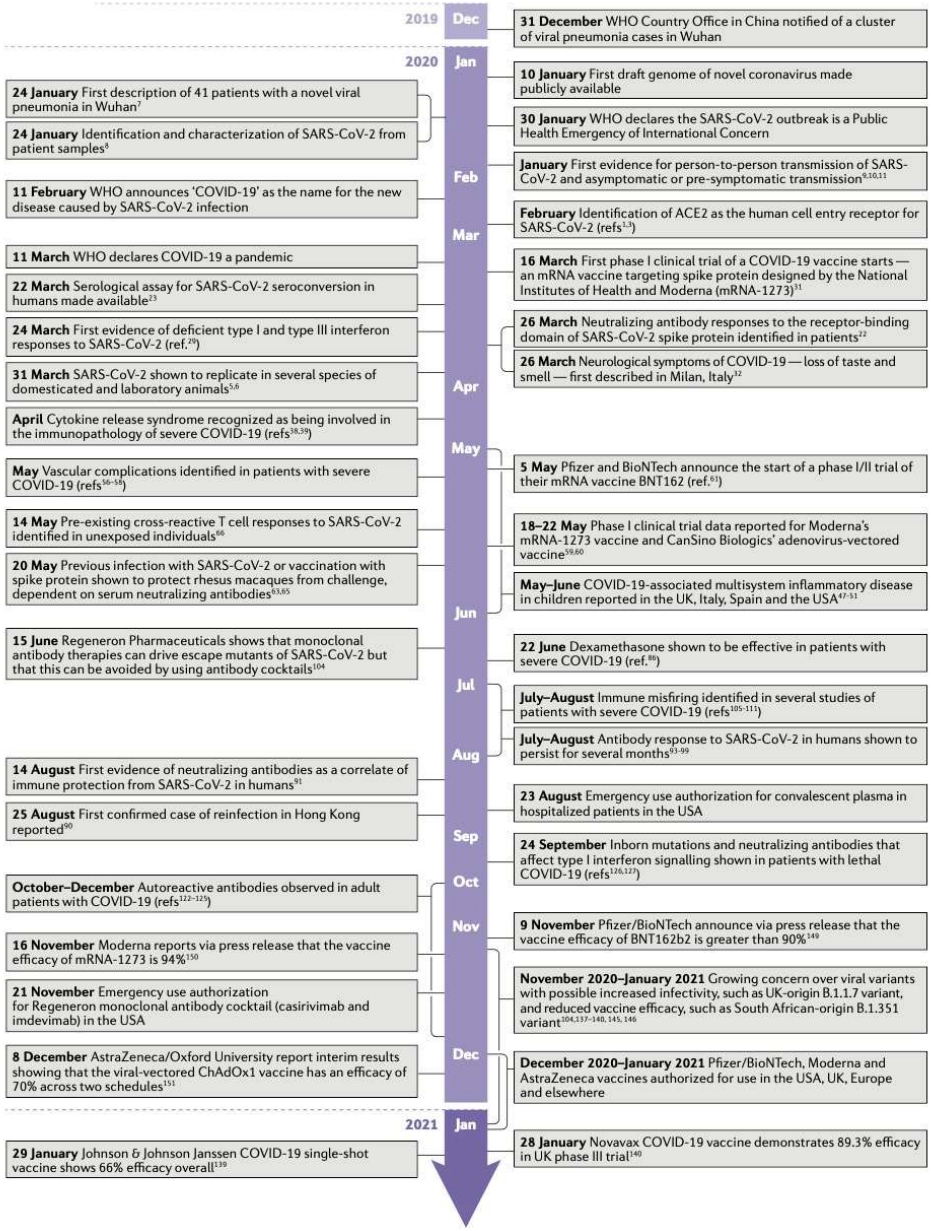
Quel bilan des dispositifs pour les immunodéprimés ??



Hyper-sélection populations susceptibles/prédisposées

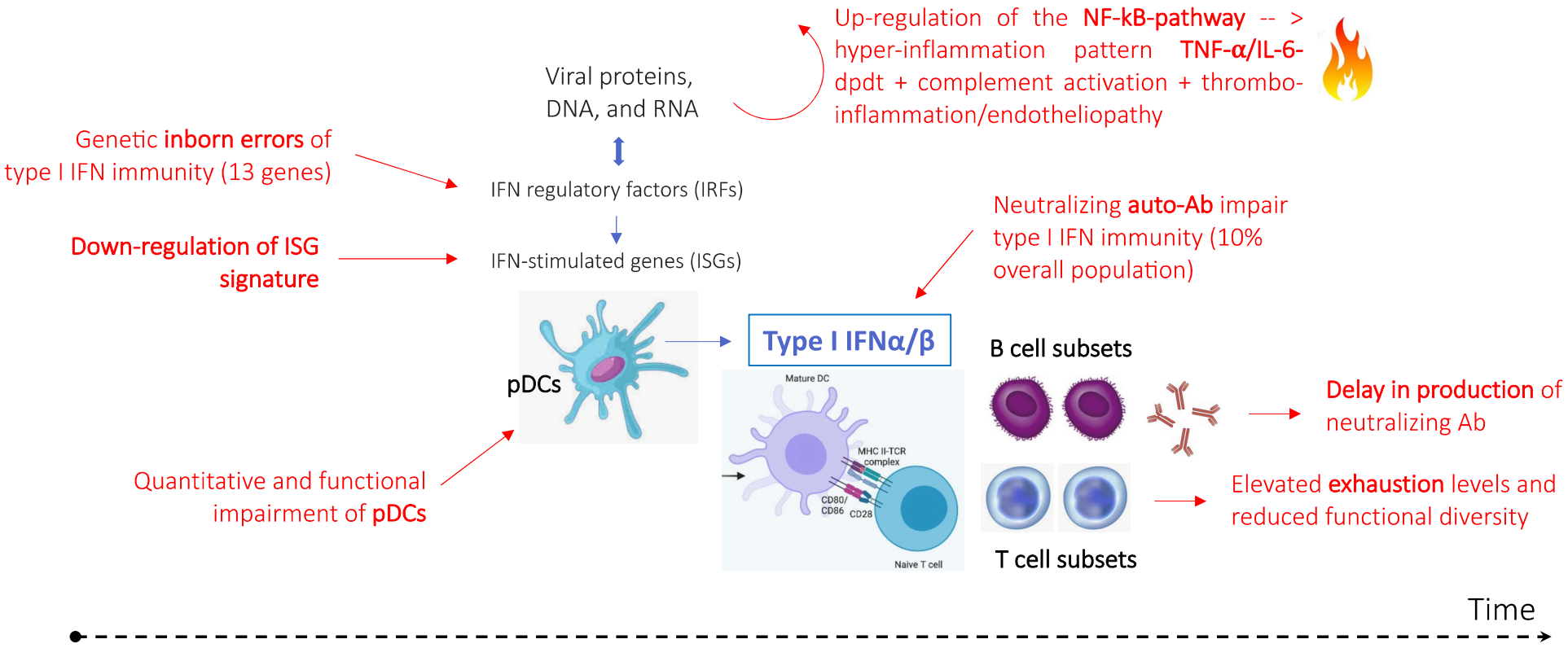
---- > Faire un **état de situation** en tenant compte:

de l'hétérogénéité des populations d'immunodéprimés
de la dynamique des données médico-scientifiques disponibles
de la situation épidémiologique changeante
de l'accessibilité aux traitements

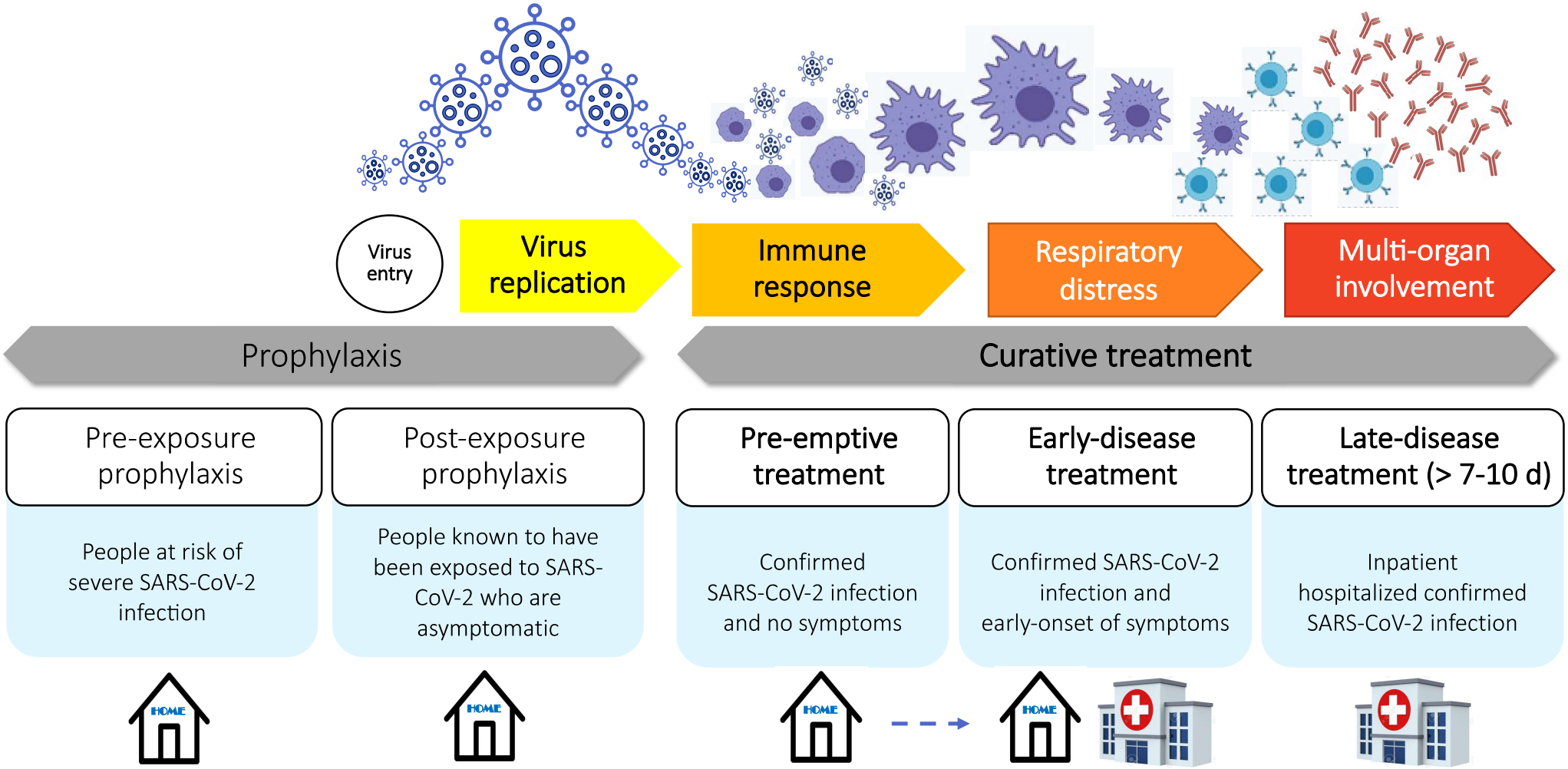


Carvalho, T., Krammer, F. & Iwasaki, A. The first 12 months of COVID-19: a timeline of immunological insights. *Nat Rev Immunol* **21,** 245–256 (2021). https://doi.org/10.1038/s41577-021-00522-1

Multifaceted disease -- > “viral sepsis”



--- > highly variable clinical spectrum


Virus entry
Virus replication
Immune response
Respiratory distress
Multi-organ involvement
Prophylaxis
Curative treatment
Pre-exposure prophylaxis
People at risk of severe SARS-CoV-2 infection
Post-exposure prophylaxis
People known to have been exposed to SARS-CoV-2 who are asymptomatic
Pre-emptive treatment
Confirmed SARS-CoV-2 infection and no symptoms
Early-disease treatment
Confirmed SARS-CoV-2 infection and early-onset of symptoms
Late-disease treatment (> 7-10 d)
Inpatient hospitalized confirmed SARS-CoV-2 infection
HOME

A TRES HAUT RISQUE DE FORME GRAVE
Immunodéprimés profonds
faiblement ou non répondeurs à la vaccination
(BAU <260/mL)

- Patients atteint d'un cancer solide
- Receveurs d'une transplantation d'organe solide
- Receveurs d'une greffe allogénique de CSH +/- GvHD
- Hémopathies lymphoïdes : LLC traitées ou non, LH et LMNH, MM sous traitement y compris les patients receveurs de thérapie cellulaire génique et type CAR-T cell ou d'anticorps thérapeutiques bi-phénotypiqes
- Patients recevant un traitement par Ac anti-CD20 ou inhibiteurs de BTK ou azathioprine, cyclophosphamide et mycophénolate mofétil
- Sujets porteurs d'un déficit immunitaire primitif

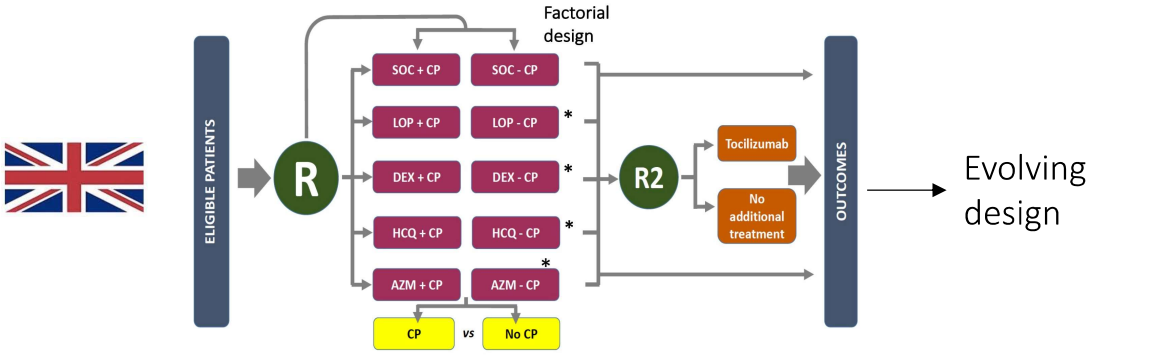
Patients à risque de complication

Immunosenescents > 80 ans

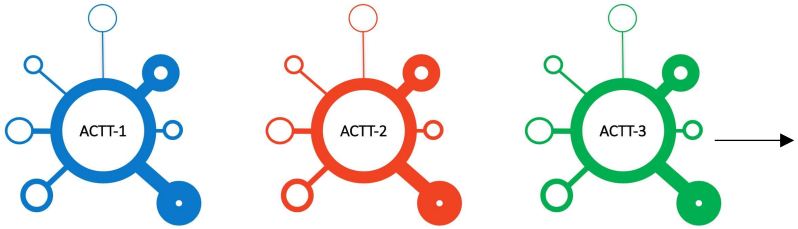
- Obésité morbide (IMC > 30 kg/m^2),
- BPCO et IRC,
- HTA compliquée,
- Insuffisance cardiaque,
- Diabète (type 1 et 2),
- Insuffisance rénale chronique,
- Autres pathologies chroniques ???

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

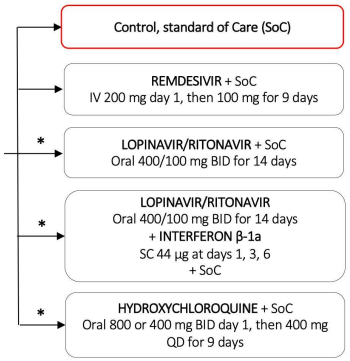


Evolving design



ACTIV-1 to 6

World Health Organization



Pro

⇢ sufficiently powered data to conclude to futility on raw/critical efficacy endpoints

⇢ open adaptive platform = flexibility to stop or start arms

⇢ gaining insights through key secondary endpoints : safety PK, pathogen kinetics, imagery, biocollections for ancillary studies

Cons

⇢ Heterogeneity of recruitment

⇢ **difficulty for properly stratifying**

⇢ **Evolving SoC comparator** and progression in medical management

⇢ double-blinding/placebo design not always possible

Data in hospitalized COVID-19 patients

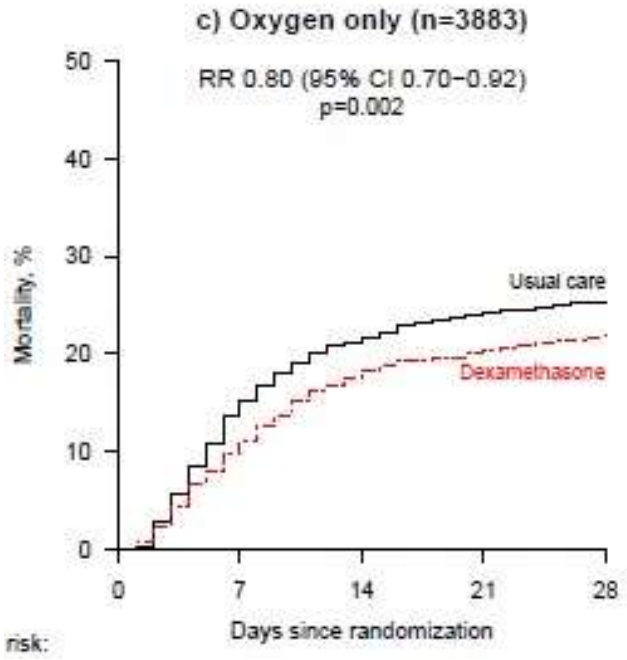
Corticosteroids:

The first effective treatment to decrease mortality (20% in patients on oxygen therapy, RR:0.80 [0.70- 0.92])

Dexamethasone 6mg/d

Other steroids? (methyprednisolone?)

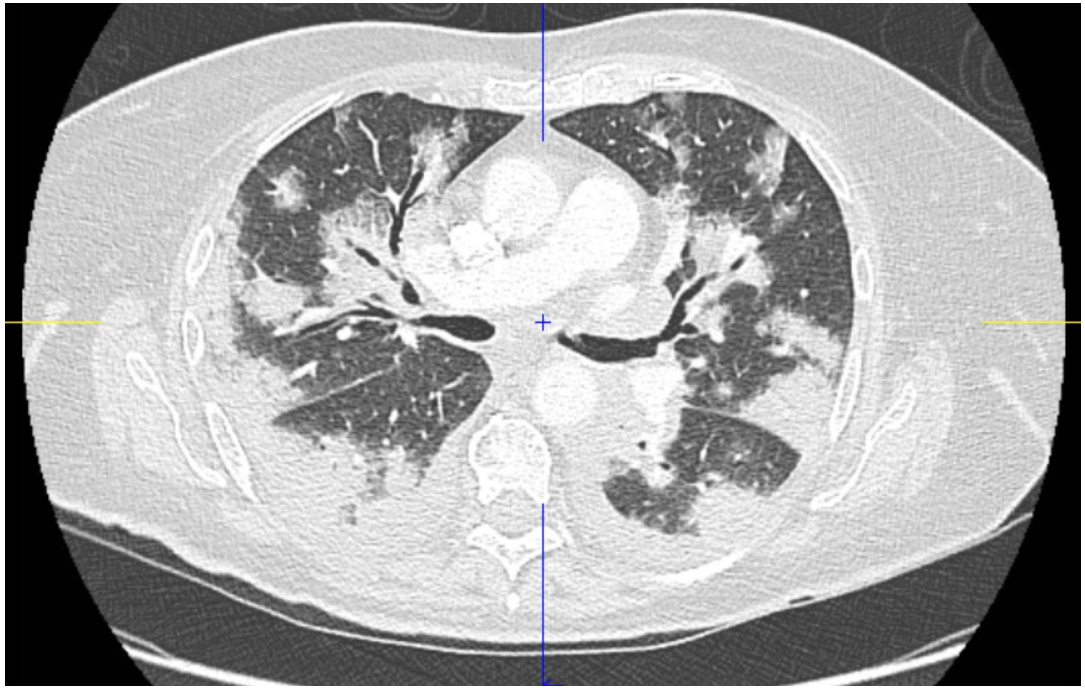
Other anti-inflammatory drugs?



Horby P and the Recovery Collaborative Group, New Engl J Med June 2020

One fits all ???? Challenging the “anti-inflammatory package” without antivirals

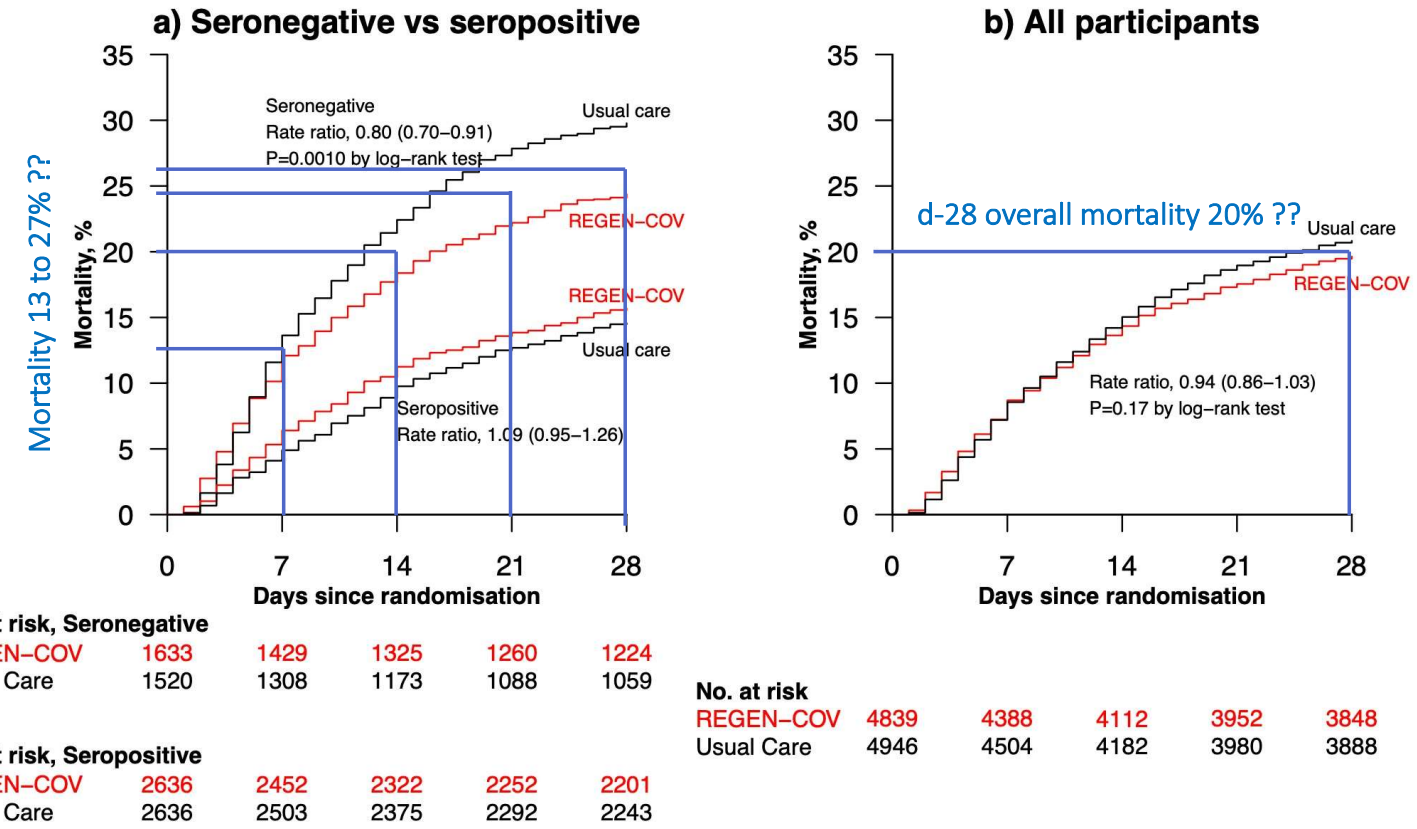
Agressive B-cell malignancy (on-goingR-CHOP)
D+9 after onset of symptoms
ICU-High flow oxygen
SARS-CoV-2 PCR in NP swab: pos. Ct 20
SARS-CoV-2 viremia: pos. Ct 28
SARS-CoV-2 serology: neg.
Ferritinémia: 2583 μg/L (N < 388)
D-Dimer: 2137 μg/L (N < 500)
Fibrinogen: 7.8 g/L (N < 3.5)
C-RP: 425 mg/L (N < 10)
Total Lc count: 0.1 G/L
IgG: 2.3 g/L (N > 7 g/L)
CT-scan: 25-50%



DXM + TCZmAb ???

? -- > Hémopathies lymphoïdes/CAR T-cells
? -- > LAM/allo-HSCT < 12 mois
? -- > Sd myélodysplasique
? -- > TOS
? -- > Anti-CD20

Effect of allocation to casirivimab+indevimab on 28-day mortality



RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. [Preprint.] medRxiv 2021:2021.06.15.21258542

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Increased (v) (1)	Increased (v) (2, 3)	Increased (v) (4, 5)	Community
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Increased (v) (6)	Increased (v) (7)	Increased (v) (5)	Community
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Increased (v) (8)	Increased (v) (9-11)	Increased (v) (10, 12)	Community
Omicron	B.1.1.529	South Africa and Botswana	(x)	November 2021	Unclear (v) (13-15) a	Increased (v) (16)	Reduced (v) (17-23) b	Dominant

x: A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

a: The observed increased growth rate may be due to increased inherent biological transmissibility, contextual factors such as transmitting in population groups with increased contact rates, or escape from immunity which increases the size of the susceptible population.

b: Preliminary studies show reduced risk of hospitalisation, but more data from EU/EEA countries is required to determine if this effect is observed across population groups (e.g. by age, vaccination and prior infection status). Conclusive evidence on mortality risk is not yet available.

https://www.ecdc.europa.eu/en/covid-19/variants-concern

Shifting the needs

From « *general population at risk* » to immuno-suppressed patients

Omicron surge and immunocompromised patients

- High-risk heterogeneous population
- Lower vaccine efficacy
- Longer viral excretion (sometimes several months) and more likely to transmit the virus
- Combination therapy not all targeting the spike protein could provide a benefit in terms of:
  - Clinical efficacy---- > to be prioritized in clinical trials
  - Mutation prevention
- Adaptation due to drug diffusion index (PK/PD) mays be required in immunocompromised patients

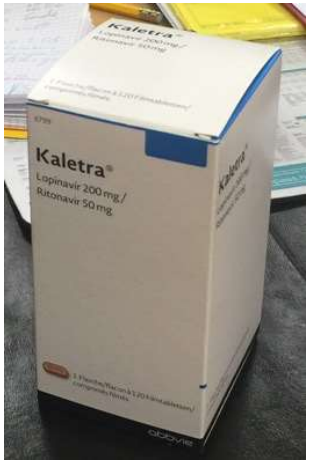
Weigang S et al. Nature communications 2021

Gaps in the evidence generated by registrational trials in the immunocompromised setting

	Published	Age	Symptom onset/setting	**Vaccinated**	**Inclusion of Immunocompromised**	Inclusion period or VoCs if investigated
Molnupiravir [(a)]	YES (MSD) NO? (India)	≥18	up to 5 days outpatient	**NO**	**Active cancer** (1.8%)	33% delta, 12% mu, 45% UNK
Nirmatrelvir/r	NO	≥18	up to 5 days outpatient	**NO**	**YES BUT *?**	16/07/21 – 26/10/21 97% delta
Sotrovimab [(b)]	YES	>18	Up to 5 days Hospitalized	**NO**	**NO**	27/08/20 – 04/03/21
Convalescent plasma [(C)]	YES	**≥ 18**	Hospitalized Critically ills	**NO**	**YES** 127/1973 (6.4%)	09/03/20 – 18/01/21

(*) “poorly represented [chronic lung disease, CVD], immunosuppressive disease …] making difficult to conclude on the relevance of the results in these subpopulations“

[(a)] *A. Jayk Bernal et al, NEJM, December 16, 2021, 10.1056/NEJMoa2116044*
[(b)] *Anil Gupta et al, NEJM, November 18, 2021, 10.1056/NEJMoa2107934*
[(c)] *REMAP-CAP COVID-19 Convalescent Plasma Randomized Clinical Trial, JAMA. 2021;326(17):1690-1702. 10.1001/jama.2021.18178 Published online October 4, 2021.*



March 2020

June 1, 2021

From repositioned drugs to specific human monoclonal antibodies in just a year…

- mAbs currently approved or under conditional/provisional authorization or "accessible" through emergency use authorization (EUA) in various countries (as of January 26, 2022)

  Bamlanivimab [LY-CoV555] + Etesevimab [LY-CoV16] – IV

  Casirivimab [REGN10933] + Indevimab [REGN10987] (REGN-CoV-2) – IV, SC

  *Sotrovimab [VIR-7831] – IV

  Regdanvimab [CT-P59] – IV

  #Tixagevimab + Cilgavimab [AZD7442 (AZD8895+AZD1061)] – IV, IM

  *Target site ≠ spike
  #Long-acting Ab (Ab recycling mechanism) extending half-life of 90 days on average. Phase I study: estimated residual protection of 83% at 6 months

Omicron brings its own challenges

Decreased efficacy to all monoclonal known antibodies

Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against SARS-CoV-2 Variants in Vitro.*

Monoclonal Antibody or Antiviral Drug	SARS-CoV-2 Variant					
	SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (A)	SARS-CoV-2/UT-HP127-1Nf/Human/2021/Tokyo (Alpha/B.1.1.7)	hCoV-19/USA/MD-HP01542/2021 (Beta/B.1.351)	hCoV-19/Japan/TY7-503/2021 (Gamma/P.1)	hCoV-19/USA/WI-UW-5250/2021 (Delta/B.1.617.2)	hCoV-19/Japan/NC928-2N/2021 (Omicron/B.1.1.529)
Neutralization activity of monoclonal antibody — ng/ml†						
LY-CoV016, etesevimab	18.19±9.10	150.38±83.51	>50,000	>50,000	15.37±9.78	>50,000
LY-CoV555, bamlanivimab	4.69±1.43	2.65±1.30	9554.88±926.53	1601.65±896.02	641.73±324.79	>50,000
REGN10987, imdevimab	3.05±0.93	1.87±1.60	2.17±1.30	1.04±0.68	3.95±1.78	>50,000
REGN10933, casirivimab	2.79±1.87	2.74±1.84	757.13±287.91	187.69±128.88	2.89±1.78	14,110.70±1782.13
COV2-2196, tixagevimab	1.92±0.28	1.34±0.67	18.98±1.42	6.56±1.56	4.05±2.60	1299.94±406.58
COV2-2130, cilgavimab	7.70±2.20	3.60±1.62	10.03±3.05	4.00±2.70	12.76±2.93	443.87±167.96
S309, sotrovimab precursor	27.33±3.24	44.91±22.76	100.98±22.27	28.38±1.86	111.43±58.22	373.47±159.49
LY-CoV016 plus LY-CoV555	12.60±1.91	15.26±3.98	>10,000	2545.04±625.72	10.28±3.33	>10,000
REGN10987 plus REGN10933	3.53±0.66	1.55±0.78	5.18±1.45	2.11±0.48	1.91±0.79	>10,000
COV2-2196 plus COV2-2130	3.42±0.92	1.94±0.34	10.30±1.17	1.79±0.87	5.50±2.75	255.86±45.31
Viral susceptibility to drug — μM‡						
GS-441524§	1.04±0.32	0.83±0.19	0.63±0.20	0.91±0.33	1.12±0.20	1.28±0.42
EIDD-1931¶	0.51±0.14	0.95±0.17	0.60±0.21	0.41±0.13	0.83±0.41	0.43±0.08
PF-00835231‖	18.45±7.35	10.56±5.85	14.20±4.34	9.40±3.28	14.81±5.24	12.71±3.00

Kinoshita K et al., New Eng J Med, January 27th, 2022

04/02/2022 – PrEP et post-expo négative (ANSM – DGS)

PRE-EXPOSITION

Immunodéprimés profonds*
Et faiblement ou non répondeurs après un schéma vaccinal complet conformément aux recommandations en vigueur

EVUSHELD /6 mois
AAP plateforme spécifique

POST-EXPOSITION

Immunodéprimés profonds*
Et faiblement ou non répondeurs après un schéma vaccinal complet conformément aux recommandations en vigueur

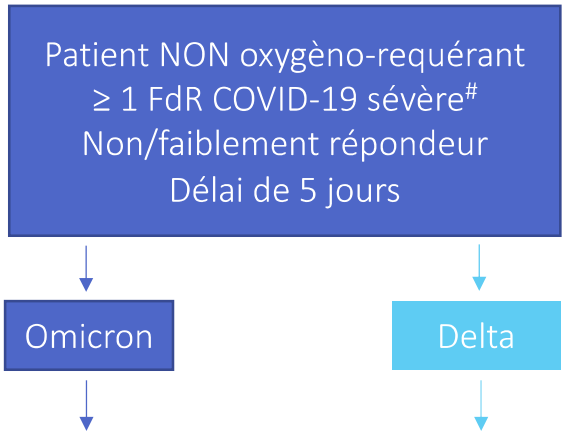
EVUSHELD
AAC e-Saturn

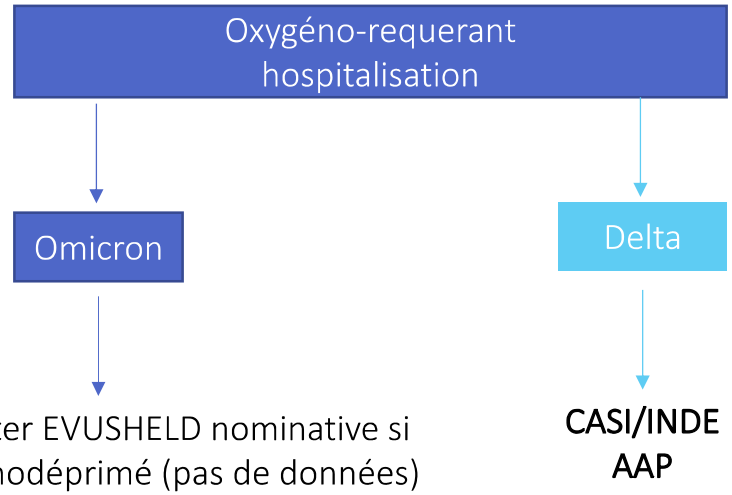
WARNING

FdR CV x2

Contre-indications Evusheld:
antécédent d'infarctus du myocarde récent, insuffisance coronaire symptomatique, syndrome coronaire aigu

04/02/2022 – Infection/maladie





ou Inclusion dans les **ESSAIS CLINIQUES (i.e.; Discovery)**

Ou tenter Sotrovimab ATU compassionelle ANSM (?)

Discuter plasma de convalescent hyper-immun en cas de lymphodepletion-B/hypogamma profonde

1. ≥ 80 ans ;
2. Immunodéprimés :
   * Chth en cours,
   * TOS,
   * Allogreffe de CSH,
   * Lupus systémique ou vasculaire avec traitement IS,
   * Traitement par CC > 10 mg/jour d'équivalent prednisone >2 semaines,
   * Traitement IS --- > lymphodépletion B;
3. Les patients à risque de complications :
   - Obèse (IMC > 30 kg/m²),
   - BPCO/IRC,
   - HTA compliquée,
   - Insuffisance cardiaque,
   - Diabète (I et II),
   - IRC,
   - Autres pathologies chroniques, cas/cas
   - Femmes enceintes ? ---- > Cas/cas

Evolutif en fonction de l'état des connaissances scientifiques et du contexte épidémio

MALADIES INFECTIEUSES ÉMERGENTES

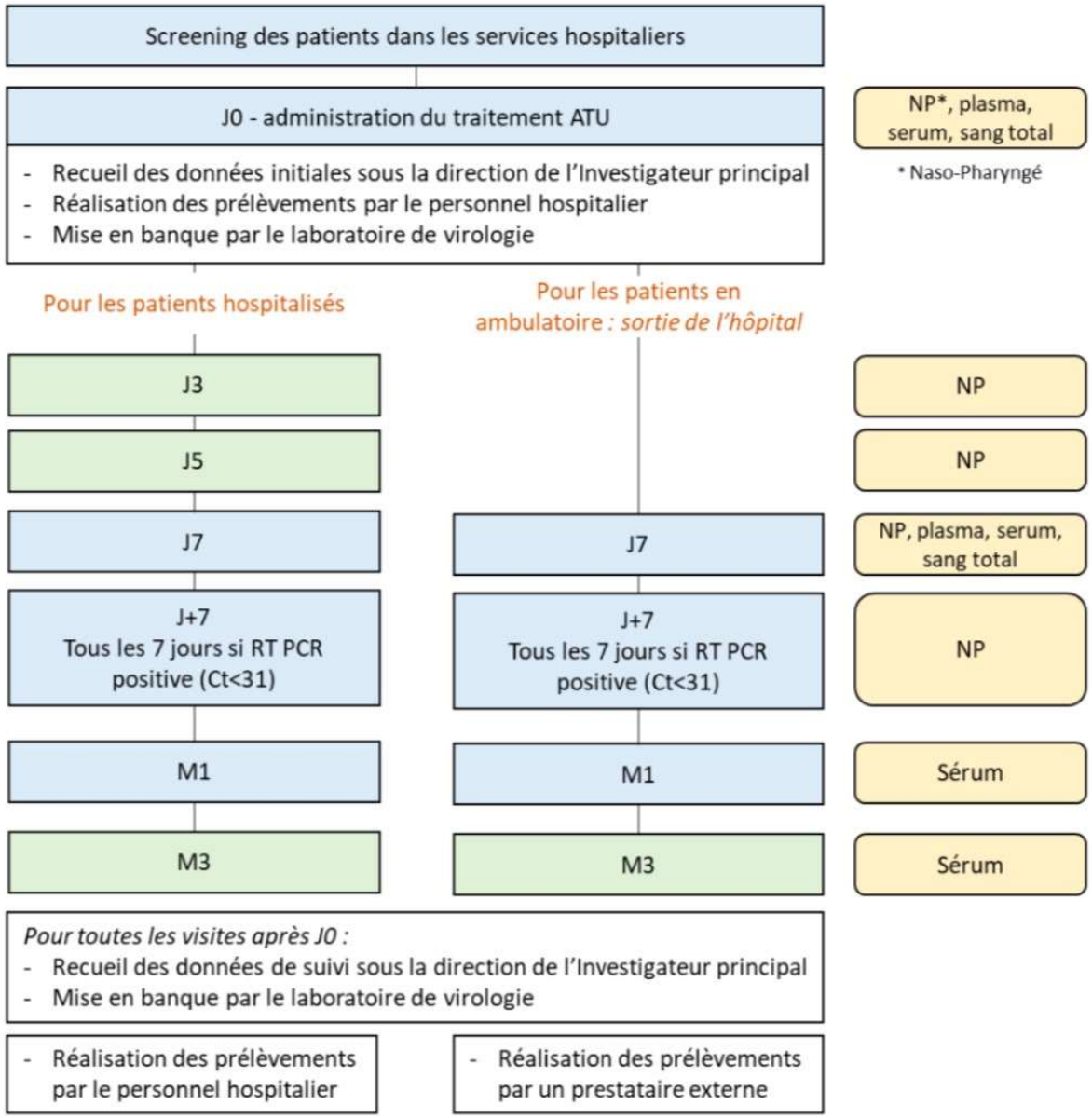
ANRS 0003S COCOPREV

Prévention des complications de la COVID-19 chez les sujets à haut risque infectés par le SARS-CoV-2 éligibles aux traitements relevant d'une ATU de cohorte. Une cohorte prospective.

Objectifs

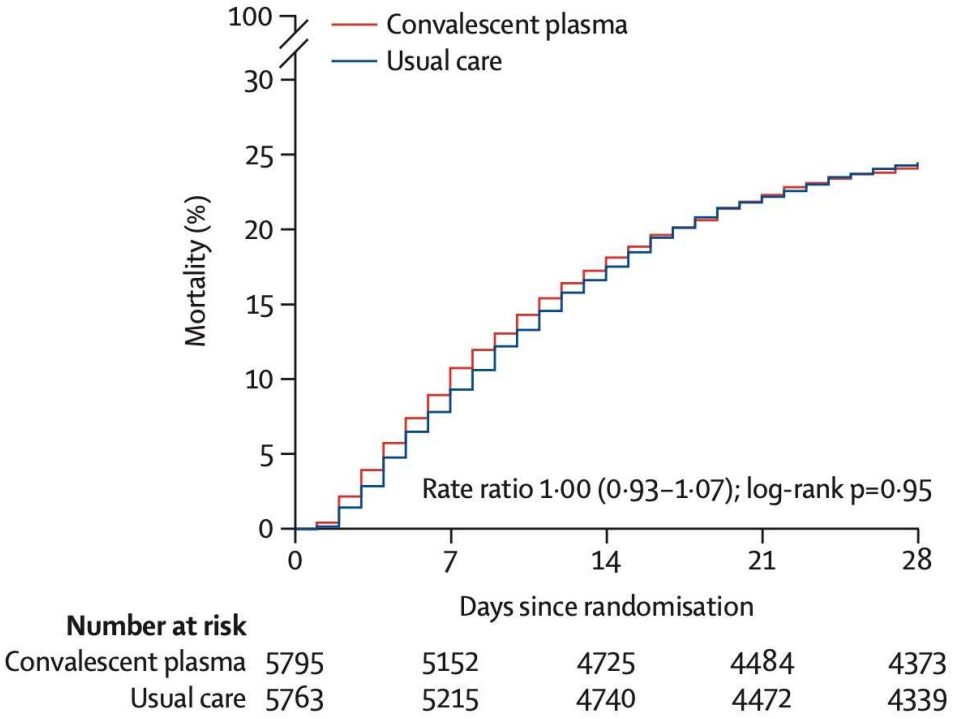
- **Objectif principal**
  - Evaluer l'évolution clinique des patients infectés par le SARS-CoV-2 à haut risque de complications traités dans le cadre d'une ATU de cohorte délivrée par l'ANSM

- **Objectifs secondaires**
  - Evaluer l'évolution virologique et ses déterminants
  - Evaluer les complications secondaires et leurs déterminants
  - Evaluer la tolérance au traitement
  - Evaluer le risque d'émergence de variant résistant
  - Evaluer la faisabilité de la prévention précoce des complications secondaires
  - Evaluer la réponse immunologique après traitement et ses déterminants

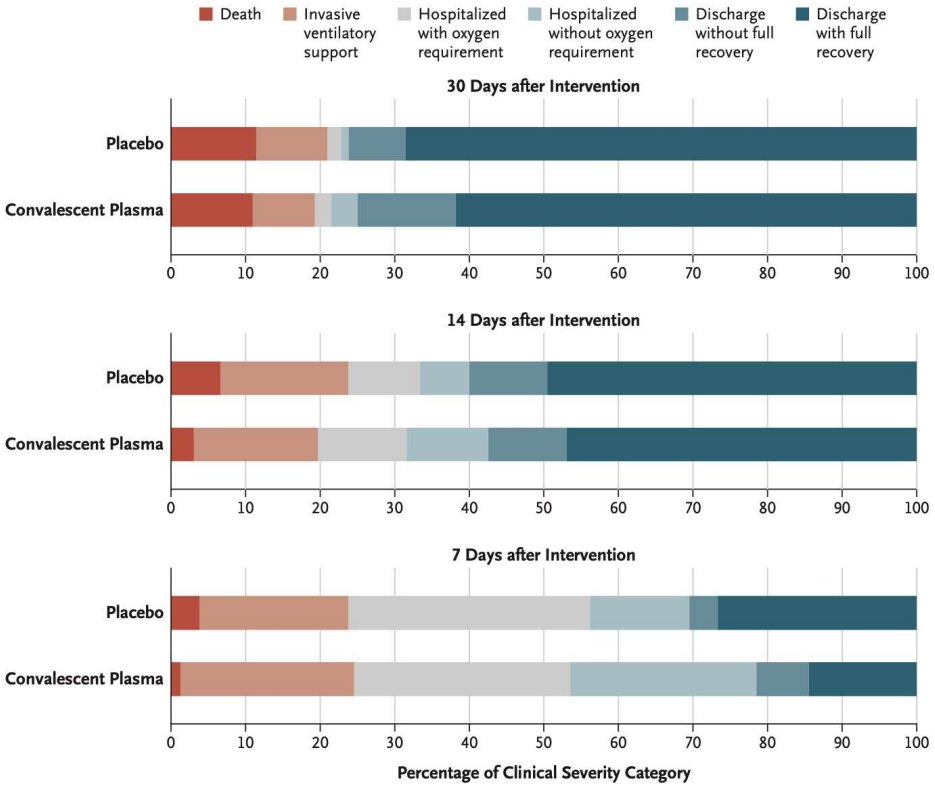


Hyper-immune convalescent plasma for COVID-19: the right patients at the right time?

Hospitalized with SARS-CoV-2 pneumonia

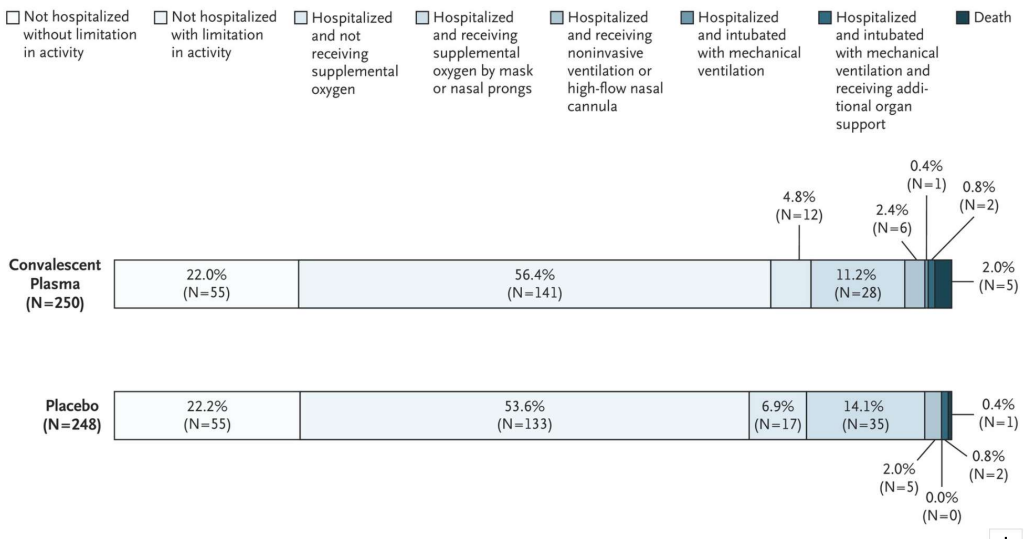


RECOVERY collaborative group, Lancet 2021; 397: 2049-2059



Simonovitch VA et al., N Engl J Med 2021; 384:619-629 DOI: 10.1056/NEJMoa2031304

Early convalescent plasma for High-Risk Outpatients with Covid-19



Characteristic	Convalescent Plasma (N=257)	Placebo (N=254)
Eligibility risk factor — no. (%)		
Age ≥50 yr	155 (60.3)	155 (61.0)
Body-mass index ≥30‡	152 (59.1)	150 (59.1)
Hypertension	105 (40.9)	111 (43.7)
Current or former tobacco use	81 (31.5)	71 (28.0)
Diabetes mellitus	76 (29.6)	66 (26.0)
COPD or asthma	56 (21.8)	68 (26.8)
Coronary artery disease	28 (10.9)	23 (9.1)
Immunosuppression	33 (12.8)	17 (6.7)
Chronic lung disease	16 (6.2)	15 (5.9)
Chronic kidney disease	16 (6.2)	12 (4.7)
Congestive heart disease	9 (3.5)	11 (4.3)
Currently pregnant	3 (1.2)	3 (1.2)
Organ transplant recipient	5 (1.9)	0

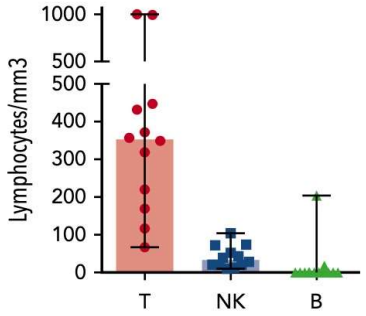
Korley FK et al., N Engl J Med 2021; 385:1951-1960 DOI: 10.1056/NEJMoa2103784

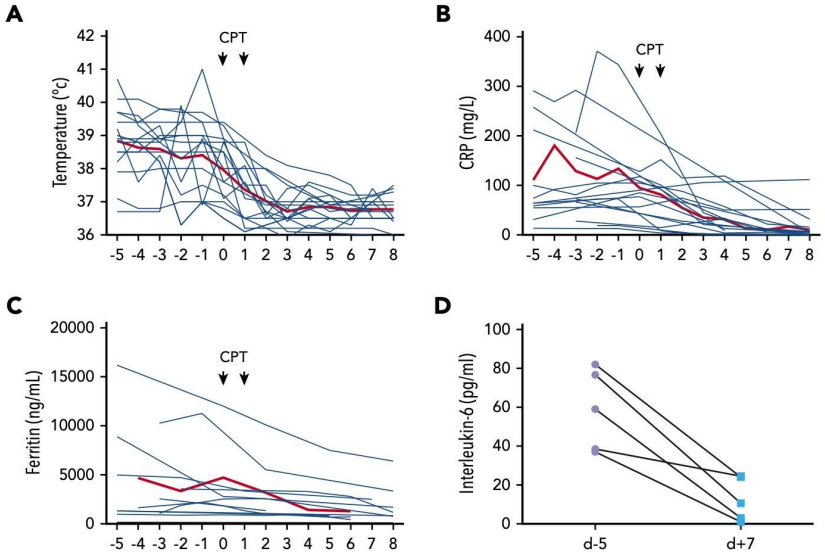
Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

blood® 12 NOVEMBER 2020 | VOLUME 136, NUMBER 20

KEY POINTS

- **As a proof of concept, COVID-19 convalescent plasma represents an interesting approach in B-cell–depleted patients with protracted COVID-19.**
- **COVID-19 convalescent plasma induces a decrease in temperature and inflammatory parameters within 1 week associated with oxygen weaning.**





Hueso T, et al. Blood 2020

Characteristics	Data
Age, median (range), y	58 (35-77)
Females/males, n	5/12
Hematological malignancies	15 (88)
Diffuse large B-cell lymphoma	4 (28)
Mantle cell lymphoma	3 (20)
Follicular lymphoma	3 (20)
Chronic lymphocytic leukemia/Richter syndrome	3 (20)
Marginal zone lymphoma	1 (6)
Waldenström macroglobulinemia	1 (6)
Nonhematological malignancies	2 (12)
Multiple sclerosis	1 (6)
Common variable immune deficiency	1 (6)
Disease status	
Complete response	11 (65)
Partial response	3 (18)
Progressive disease	2 (12)
Not attributed	1 (5)
Last chemotherapy	
R-chemotherapy*	6 (35)
Rituximab/obinutuzumab maintenance	7 (42)
Other†	3 (18)
Not attributed	1 (5)
Previous treatment with anti-CD20 therapy	15 (88)
Cycles of anti-CD20 therapy, median (range)	7 (4-18)
Gammaglobulinemia, median (range), g/L‡	3.5 (1.8-14)
Time between COVID-19 symptoms onset and last anti-CD20 therapy, median (range), mo	4 (3-6)
COVID-19 severity (WHO score)	
4	5 (29)
5-6	10 (59)
≥7	2 (12)
Previous COVID-19–specific treatments	11 (65)
Steroids	8 (72)
Hydroxychloroquine	5 (45)
Tocilizumab	4 (36)
Remdesivir	3 (27)
Lopinavir-ritonavir	2 (18)
Time from COVID-19 symptoms onset to CPT, median (range), d	56 (7-83)
Oxygen weaning (NIV or nasal prong)	10 (100)
Time for oxygen weaning after CPT, median (range), d	5 (1-45)
Length of hospital stay after CPT, median (range), d	7 (2-14)
Overall survival	16 (94)

Early high-titer plasma therapy to prevent severe Covid-19 in older adults

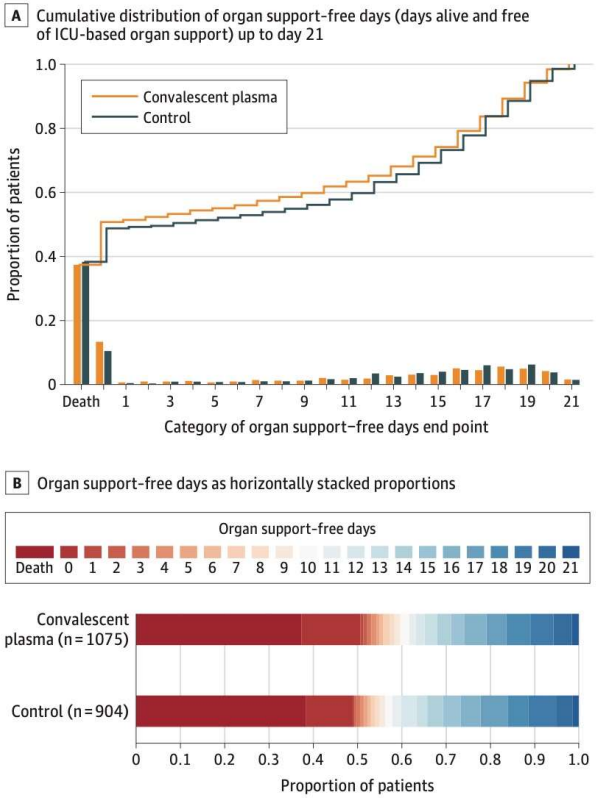
65-74 y within 72h after mild COVID-19 symptoms

Dose-dependent IgG effect in convalescent plasma infusions.

Plasma with IgG titers of 1:3200 or higher reduced the risk of severe respiratory disease by 73%

Libster R et al. N EngJ Med 2021

Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19

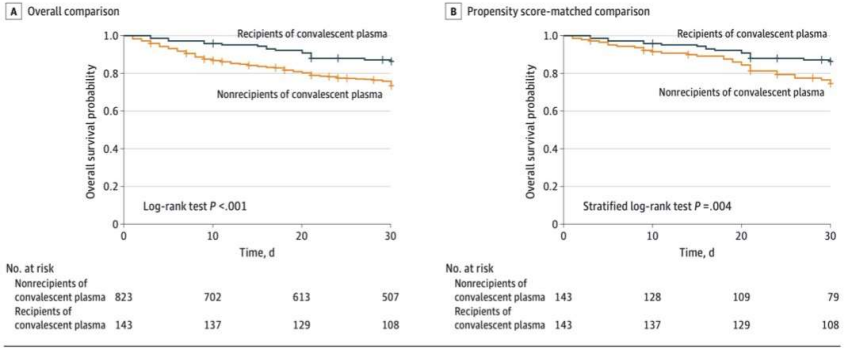


In the small number of participants (n = 126) with immunodeficiency at baseline, convalescent plasma demonstrated potential benefit (posterior probability of superiority of 89.8%)

Writing Committee for the REMAP-CAP Investigators
JAMA. 2021;326(17):1690-1702. doi:10.1001/jama.2021.18178 Published online October 4, 2021

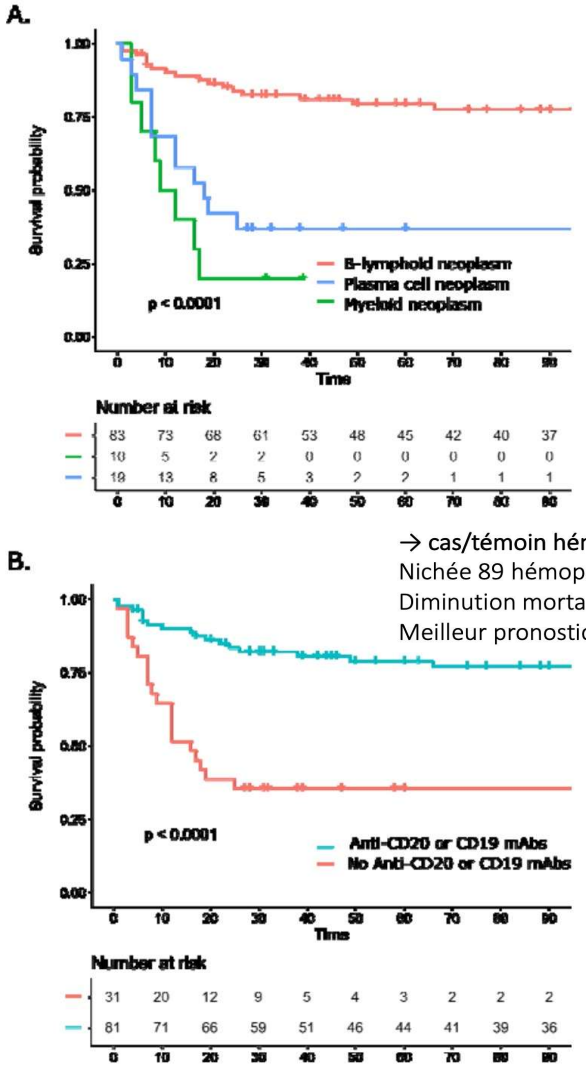
JAMA Oncology | Original Investigation

Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19



The crude mortality rate 13.3% CPT *vs.* 24.8% non CPT (HR, 0.60; 95% CI, 0.37-0.97; *P* = .03)

Thompson MA et al JAMA Oncol. 2021;7(8):1167-1175



→ cas/témoin hémopathies malignes
Nichée 89 hémopathies lymphoïdes B
Diminution mortalité 63% (95%CI=31%-80%)
Meilleur pronostic sous-gp ayant reçu RTXM

Hueso T, et al. Leukemia 2022

Polyclonal hyper-immun: cibles multiples (Ac anti-mb, anti-NCC, anti-S, etc…)

RCPs plasmathérapie

Hospitalisés O_2-requérent

Lymphodépletion B/ hypogamma :

- LH/LMNH, LLC, CAR T
- Maladies auto-inflammatoires sous anti-CD20
- ? moindre efficacité myélome ?

Transplantation organe solide (rein)

Gestion : tps d'infusion (800 mL), hypervolémie, TRALI/ADE

EFS
ÉTABLISSEMENT FRANÇAIS DU SANG
Du donneur aux patients

VOUS ÊTES GUÉRI DU COVID-19

votre plasma peut aider d'autres patients !

L'Établissement français du sang redémarre la collecte de plasma issus de donneurs convalescents COVID à partir du 25 janvier afin de traiter certains patients atteints de formes graves sans autre alternative thérapeutique.

Les conditions pour participer à ce type de don de plasma sont :

- **Avoir un schéma vaccinal initial complet**
- **Avoir eu un test COVID positif à compter du 01/01/2022, ou avant cette date à condition d'avoir la certitude d'une infection par le variant Omicron (PCR avec typage viral)**
- **Etre à plus de 14 jours après la disparition de signes cliniques (s'il y en a eu) ou être à plus de 14 jours du test positif**

Si vous remplissez ces conditions et que vous souhaitez faire un don de plasma, merci d'envoyer un mail à l'adresse suivante :

aura.coviplasm@efs.sante.fr

Indiquez vos coordonnées et le site sur lequel vous pourriez réaliser votre don : Clermont-Ferrand, Grenoble, Lyon ou Saint-Etienne.

L' EFS vous contactera rapidement pour déterminer votre aptitude et fixer un rendez-vous

QU'EST-CE QUE LE DON DE PLASMA PAR APHÉRÈSE ?

C'est une technique de prélèvement sanguin qui permet de recueillir entre deux et quatre fois plus de plasma que lors d'un don de sang classique. Grâce à une machine automatique, les différents composants du sang sont séparés pour isoler votre plasma. Une fois recueilli, vos globules rouges, globules blancs et plaquettes vous sont rendus par la même aiguille.
Le composant plasma, sera ensuite préparé pour devenir un produit sanguin qui sera transfusé au malade.
Le don de plasma dure entre 30 et 60 minutes.

La 4ème dose….pour les transplantés d’organe solide

Assessment of 4 Doses of SARS-CoV-2 Messenger RNA–Based Vaccine in Recipients of a Solid Organ Transplant

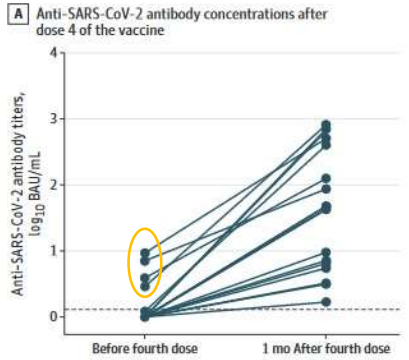
Nassim Kamar, MD, PhD; Florence Abravanel, PharmD, PhD; Olivier Marion, MD; Raphaelle Romieu-Mourez, MSc; Chloé Couat, MSc; Arnaud Del Bello, MD; Jacques Izopet, PharmD, PhD

Jama Netw Open 2021 Nov 1;4(11):e2136030

- case series, n=37 SOT recipients
- 4th dose of BNT162b2 vaccine

dose 1 — dose 2 — dose 3 — dose 4

1 month — 57d (SD, 17d) — 65d (SD, 9d)



4 we after dose 4:

At inclusion, after 3 doses:

weak response (range, 1-9 BAU/mL), n=5 (13,5%) → response (range, 87-402 BAU/mL), 5/5

no response, n=31 (83,8%) → response (range, 1,7-658 BAU/mL), 13/31 (41,9%)

no response, n=31 (83,8%) → no response 18/31 (58,2%)

Assessment of 4 Doses of SARS-CoV-2 Messenger RNA–Based Vaccine in Recipients of a Solid Organ Transplant

JAMA Network Open™

Nassim Kamar, MD, PhD; Florence Abravanel, PharmD, PhD; Olivier Marion, MD; Raphaelle Romieu-Mourez, MSc; Chloé Couat, MSc; Arnaud Del Bello, MD; Jacques Izopet, PharmD, PhD *Jama Netw Open* 2021 Nov 1;4(11):e2136030

- case series, n=37 SOT recipients
- 4th dose of BNT162b2 vaccine

4ème dose = permet une « faible » réponse humorale

Qui profite de cette 4ème dose ?

→ *les patients faiblement répondeurs après 3 doses (versus non répondeurs)*

→ *parmi les non répondeurs après 3 doses :*

- *les greffés rénaux*
- *les « vieux greffés » (moins immunodéprimés)*
- *Les moins lymphopéniques*

Table. Clinical and Biological Characteristics of Solid Organ Transplant Recipients According to Humoral Response 1 Month After 3 Doses of mRNA-Based Vaccine

Characteristic	All patients (N = 37)	Patients seronegative before dose 4[a]		P value
		Remained seronegative (n = 19)	Became seropositive (n = 13)	
Gender, No. (%)				
Male	20 (54.0)	12 (63.2)	6 (46.2)	.26
Female	17 (46.0)	5 (26.3)	7 (53.8)	
Age, mean (SEM), y	60 (14)	58 (16)	60 (14)	.76
Type of organ transplant, No. (%)				
Kidney	25 (67.6)	11 (57.9)	13 (100)	.03
Heart	5 (13.5)	4 (21.1)	0	
Liver	4 (10.8)	4 (21.1)	0	
Pancreas	3 (8.1)	0	0	
Rejection in the year before vaccination, No.	0	0	0	NA
Time between vaccine and transplant, mean (SD), mo	109 (84)	79 (66)	161 (97)	.007
Lymphocyte count before dose 4, mean (SD), per mm^3	1193 (711)	947 (427)	1431 (866)	.04

pas de différence ttt IS, paramètres immuno autres que [Ly]

Neutralizing antibody titers and cellular response were low in both groups

Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

Alejo et al. *Transplantation* 2021

Age, y	Sex	Organ(s)	Time since transplant, y	Antimetabolite	Initial vaccine series	Post-D2 titer	D3	Post-D3 titer	Post-D3 titer	D4	Post-D4 titer	Post-D4 titer
44	F	Kidney	4	Yes	Moderna	Negative	Pfizer	Negative	0.22 E	Pfizer	Negative	0.92 E
65	F	Kidney	0.5	Yes	Moderna	Negative	Moderna	Negative	0.06 E	Moderna	Negative	0.06 E
44	M	Kidney	3	Yes	Pfizer	Negative	Pfizer	Negative	0.09 E	J&J	Negative	0.4 R
63	M	Liver	11	Yes	Pfizer	Negative	J&J	Negative	0.46 R	Pfizer	High	54.9 R
57	M	Kidney	15	Yes	J&J	Negative	Moderna	Negative	0.97 E	Moderna	High	286.9 R
53	M	Kidney	21	Yes	Pfizer	Negative	Pfizer	Negative	(self-report)	J&J	High	343 R
61	F	Kidney	8	Yes	Pfizer	Negative	Moderna	Low	2.75 R	Moderna	High	>2500 R
49	F	Kidney	1	Yes	Moderna	Negative	Pfizer	Low	7.3 R	Pfizer	High	82.9 R
52	F	Kidney-Pancreas	20	Yes	Moderna	Negative	Pfizer	High	504.4 R	Pfizer	High	845 R
54	M	Liver	1	Yes	Pfizer	Low	Moderna	High	125.7 R	Moderna	High	>2500 R
69	M	Heart	16	Yes	Pfizer	Negative	Moderna	High	8.37 E	Moderna	High	>2500 R
68	M	Heart	2	Yes	Pfizer	Negative	Moderna	High	>250 R	Moderna	High	402.9 R
43	F	Pancreas	1	Yes	Pfizer	Negative	Moderna	High	4.72 E	Moderna	High	5.27 E
58	M	Kidney	3	Yes	Moderna	Low	Moderna	High	6.93 E	Moderna	High	4.16 E
42	F	Liver	5	No	Moderna	Negative	Pfizer	High	11.39 E	Pfizer	High	8.75 E
73	F	Kidney-Liver	18	Yes	Pfizer	Low	Moderna	High	4.45 E	Moderna	High	1691 R
67	F	Kidney	11	Yes	Moderna	Low	Pfizer	High	9.19 E	Pfizer	High	>2500 R
64	M	Liver	21	No	Moderna	Low	Pfizer	High	7.21 E	Pfizer	High	>2500 R

D, dose; E, EUROIMMUN assay (parameters: low-positive, ≥1.1 and <4; high-positive, ≥4 AU); F, female; J&J, Johnson & Johnson; M, male; R, Roche assay (parameters: low-positive, ≥0.8 and <50; high-positive, ≥50 U/mL).

time from D3 to D4: 28d (IQR, 21-30)

The 3 participants with persistently negative titers post-D4 were KTR <5 y posttransplant on tacrolimus+MMF+CTC(2/3)

Au final, pour discuter…

4ème dose de primovaccination déja has been…..
… The place to be : rappel 1 + 1 (faut suivre…)
--- > optimisation réponse secondaire et maturation d'affinité

En pratique, sur le terrain : retard+++ de rappel dans les cohortes d'immunodéprimés:

- Transplantation de CSH
- CAR T-cells
- Hémopathies lymphoïdes
- RTXM

COV-POPART

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Systematic review

Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review

Simon Galmiche [1], Liem Binh Luong Nguyen [1], Eric Tartour [2], Xavier de Lamballerie [3], Linda Wittkop [4], Paul Loubet [5], Odile Launay [6,*]

Et les anticorps monoclonaux dans tout ça ?

- *le seuil de 264 BAU/mL est-il encore adapté à l'heure du variant omicron ?*

https://solidarites-sante.gouv.fr/IMG/pdf/cosv_-_recommandations_pour_la_protection_des_personnes_severement_immunodeprimees_-_19_novembre_2021.pdf