Anti-SARS-CoV2 Monoclonal Antibodies

Efficacy, Indications, Perspectives

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Links of interest:

• With industry
  • Janssen: anti-HIV Vaccine (consultant fees)
  • Fondation de Mécénat MSD-Avenir: Research Program on cancers

• Member of:
  • Conseil d’Orientation de la Stratégie Vaccinale : Déc. 2021 –
  • Conseil Scientifique vaccins Covid-19: Juin 2020 –
  • Ansm: Expert Externe
Anti-SARS-CoV2 Monoclonal Antibodies

• anti-SARS-CoV2 Antibodies and Vaccines:
  • Neutralizing Ab and protection;
  • Vaccine Efficacy: Correlates of vaccinal protection and Results in Immune-suppressed patients

• Treatment with anti-SARS-CoV2 MAbs
  • anti-SARS-CoV2 monoclonal Abs and Reactivity against variants
  • Clinical Trials and real life efficacy
  • Regulatory Authorisations (ATU)

• Prophylaxis (PEP et PrEP) with anti-SARS-CoV2 MAbs
  • Vaccine Responses from Immune-suppressed persons
  • Clinical Trials Regulatory Authorisations (ATU)
  • Practical issues
Anti-SARS-CoV2 Monoclonal Antibodies
Immune Correlates of protection against severity?

➢ SARS-CoV2 et Spicule S

➢ Antibodies:
- in >95% infected subjects
- Low levels in A-symptomatics

➢ Neutralizing Abs = Anti-Spike (RBD)
- Directed against binding site RBD
- in convalescents, persist > 10 mois
- No/low cross-reactivity with CoronaVirus

➢ T cell mediated immunity : broader reactivity

Jiang HW et al. doi: https://doi.org/10.1101/2020.03.20.20039495 medRxiv;
Jiang S et al. Trends in Immunology, May 2020;
Kai-Wang To K et al. www.thelancet.com/infection 2020
Sun B et al.Emerg Microbes Infect. 2020; Ni L et al Immunity. 2020

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Protection conferred by Neutralizing Antibodies?

➢ Viral load, severity, clinical evolution correlated:
  ➢ Weakly to levels of IgG anti-S ou –RBD
  ➢ Moderately to Neutralizing Ab levels
  ➢ More strongly to the Kinetics of Neutralization:

\[ \text{High Neutralizers} \]

\[ \text{Discharged} \]

\[ \text{Deceased} \]
anti-SARS-CoV2 Monoclonal Antibodies

- **P Wang et al. BioRxiv 2020**

  anti-SARS-CoV2 human monoclonal Abs:

  - Isolated from convalescent B lymphocytes
  - Cloned and selected for their potent neutralizing activity
  - Reacting against the Spike RBD
  - Constant Fc region genetically-modified or not for
    - reducing Fc-mediated functions (ADE, ADCC..)
    - Increasing half-life (from 1 to 3-6 months)
  - Produced as pure mAbs
  - Used as:
    - Monotherapy
    - or combined cocktails of 2 MAbs

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**Anti-S Ab and Neutralizing Abs as Immune Correlates of Vaccine Efficacy?**

- Strongly correlated to disease severity and predictive of protection

- **1st correlate of protection:** A UK study post-AZ (Feng S, medRxiv 2021.06.21.21258528)

- **Primary Protection:** 80% / symptoms
  
  with **anti-S IgG = 264 BAU/mL** (binding antibody units)
  
  (95% CI 108, 806), WHO international standard (NIBSC code 20/136).

- Other Results ???

- Detection threshold for anti-S seropositivity = 30 BAU/mL

*(Khoury S, Nat.Med. 21)*
anti-SARS-CoV2 Mabs epitopes and reactivity against and Variants

P Wang et al. BioRxiv 2020
Neutralizing Efficacy of Mab cocktails / variants

anti-SARS-CoV2 Mabs and Variants

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P Wang et al. BioRxiv 2020

Chang Liu et al., Cell. 2021
# Clinical update | Emerging Therapeutics Evidence

<table>
<thead>
<tr>
<th>Asset class</th>
<th>Asset</th>
<th>Use case</th>
<th>Summary of results and workstream actions / implications</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAbs</td>
<td>LY-CoV555 (Bamlanivimab) and LY-CoV016 (Etesevimab)</td>
<td>Mild</td>
<td>New combination</td>
<td>Jan 26 – BLAZE-1 preliminary results (Ph3) demonstrate combination significantly reduced COVID-19-related hospitalizations and deaths in high-risk pts (70% reduction, p= 0.0004). Requires 1 hour infusion with dilution. In addition, initial results from BLAZE-4 looking at viral load, PD and PK demonstrate lower doses of combo are similar to higher doses used in BLAZE-1, with plans to explore lower doses. Strong efficacy data, await results on variant impact.</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 (Bamlanivimab)</td>
<td>PEP, PrEP</td>
<td>Mild</td>
<td>Jan 21 – BLAZE-2 preliminary results (Ph3 in mild pt) of 8 weeks follow-up showed significantly lower frequency of symptomatic COVID-19 in Bamlanivimab treatment arm vs placebo (odds ratio 0.43, p=0.0021). For sub-groups of nursing home residents’ results suggest 80 percent lower risk of contracting COVID-19. EUA update expected soon. Strong efficacy data but unlikely to be actionable for ACT-A given impact of variants on asset.</td>
</tr>
<tr>
<td></td>
<td>REGN-COV (Casirivimab/imdevimab)</td>
<td>PrEP/PEP</td>
<td>Mild</td>
<td>Jan 26 – REGN-COV preliminary Ph3 results for antibody cocktail, used as a passive vaccine for the prevention of COVID-19 in high risk pt resulted in 100% prevention of symptomatic infection and approx. 50% lower overall rates of infection, and associated with lower disease burden, no significance quoted, unclear of effect on variant. REGN-COV given as injection, not infusion. Strong efficacy data, await clinical results on variant impact (pre-clinical data demonstrates combo unaffected by UK and SA variant)</td>
</tr>
</tbody>
</table>

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1. Wang et al. (David Ho's lab) Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization, 26/1/21 [biorxiv](https://www.biorxiv.org/content/10.1101/2021.01.22.429371v1).
Anti-SARS-CoV2 Therapeutic monoclonal antibodies
First Phase II/III clinical trials: BLAZE-1 bamlanivimab + etesevimab

**BLAZE-1: AMBULATORY STUDY DESIGN**

**PHASE 2 PORTION**
- Bamlanivimab Monotherapy
  - 7000 mg (N = 101)
  - 2800 mg (N = 107)
  - 700 mg (N = 101)
  - Placebo (N = 100)
- Bamlanivimab + Etesevimab
  - 2800 mg + 2800 mg (N = 109)
  - Placebo (N = 56)

**Primary Endpoint:** Virology
**Population:** Mild-to-Moderate COVID-19

**Now Published**
- 2021 Jan 31, Nat Med, 223-237
- 2021 Jan, Online ahead of print

**PHASE 3 PORTION**
(Higher Risk Population)
- Bamlanivimab + Etesevimab
  - 2800 mg + 2800 mg (N = 517)
  - Placebo (N = 517)
- 700 mg + 1400 mg (N ~ 500)
  - Placebo (N ~ 250)

**Primary Endpoint:** Hospitalization or Death Through Day 29
**Population:** Mild-to-Moderate COVID-19 with Risk Factor(s)

**Presented Today**

**CROI 2021  Bi-Therapy Eli-Lilly**

- 2800+1400mg: N= 517
  - 71% reduction Hospitalisation
  - Réduction de CV (p<0.001)
- 1400+700mg: ...


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Extension Phase 3 BLAZE-1 bamlanivimab + etesevimab:

N = 769 patients high risk
Covid mild / moderate
n=511; placebo: n=258.

Results:
- 4 evts vs 15 in placebo = 87% RR (p<0.0001).
- 4 deaths: Placebo
- Reduction in VL CV

Figure 1: Time to COVID-19 related hospitalization
Randomized Study: Cocktail vs Placebo: 2 doses (2.4 & 8 mg)

- Inclusion Criteria
  - > 18 yo
  - Symptoms < 7d

- Primary End-points:
  - Ph2: Viral Load
  - Ph3: medical intervention Needs < D29

Cohorts 1 = 275 2 = 524
Age. 44 41
Obesity 42% 34%
>1 risk Fact. 64% 59%

Treatment benefits (medically attended visits in pts with Risk Factors)

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>RGN 2.4 (215)</th>
<th>RGN 8.0 (219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Risk factors</td>
<td>2.2%</td>
<td>3.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>&gt;1 risk factor</td>
<td>9.2%</td>
<td>2.2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- 75% reduction (p=0.001)

- Anti-viral efficacy if EARLY treatment = before host’s immune response

Significantly reduced viral load in both seronegative and overall populations

REGN-2002, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19
D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore,
13 534 patients dont :
- **594 Mabs** (MonoT Eli-L : 80%; Bi-T RGNR: 19.5%)
- Controles : contemporains, historiques
- Age median : 61 ans
- Facteurs de risque: médiane: 4/patient (Immunosuppression: 4.3%)
- Ambulatoires
- Formes Minimes /Modérées depuis <7j

Critère Primaire: Hospit. ou SAU:
- Mabs: 12.6% vs 18.4% controles RR = 0.69

Tolérance:
- SAE: 0.3%

➤ Standard of care aux USA
Treatment with anti-SARS-CoV2 Mabs: Early Access in France

- March 8th 21 (extension 8/6/21): **ATU "de cohorte"** for Eli-Lilly and Regeneron/Roche MAbs:
  - Indication: treatment of **confirmed COVID-19 symptomatic or not**
  - Treatment instaured asap after positive PCR: **within 5 days post first symptoms or post-1st positive PCR**
  - In patients > **12yo not requiring O2 for COVID-19 AND**:
Accès précoce aux anticorps monoclonaux en France

Extension de la population éligible pour les bithérapies intervenue le 8 juin 2021 qui peuvent être dorénavant utilisées chez les patients à partir de 12 ans

- 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 immunosuppresseur
  - Traitement par corticoïde >10 mg/jour d’équivalent prednisone pendant plus de 2 semaines
  - Traitement immunosuppresseur incluant rituximab
  - Infection par le VIH non contrôlée ou stade SIDA

- Les patients à risque de complications :
  - Obésité (IMC>30),
  - BPCO et insuffisance respiratoire chronique,
  - Hypertension artérielle compliquée,
  - Insuffisance cardiaque,
  - Diabète (de type 1 et de type 2),
  - Insuffisance rénale chronique,
  - 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 de 80 ans et plus
New Extension of therapeutic ATUc with anti-SARS-CoV2 Mabs 3/9/2021

- **RECOVERY** trial: 4000mg each Roche Mab as add-on:
  - Primary endpoint: death at D28, in seronegative patients (IgG anti-S) at randomisation
    - **reduction of mortality all causes by 20 %**
      - Deaths: 24% in group Ab vs 30%; RR: 0.80 (IC 95% : 0.70-0.91 ; p=0.001.

  - Italy: 6/8/21: early access in patients >12 yo hospitalized for COVID-19 and seroNEGATIVE for anti-SRAS-CoV-2 IgG,

- **Extension of Therapeutic ATUc**: Ansm 3/9/2021:
  - Patients hospitalized for COVID-19 AND seroNegatives (IgG anti-S) at entry:
    - with non invasive oxygénotherapy (conventional or high flow) for COVID-19
    - at high risk of severity in previous ATU indications
What’s next? SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

➢ A peculiar anti-SARS-CoV Monoclonal: developed from a SARS-CoV 2003 patient,
  ➢ cross-reacting with SARS-CoV2
  ➢ directed against a conserved epitope below the RBD
    = not affected by RBD mutations
Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

➢ COMET-ICE
Phase II/III trial

Table 1. Baseline Demographic and Disease Characteristics (ITT Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sotrovimab (N = 291)</th>
<th>Placebo (N = 292)</th>
<th>Total (N = 583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr, median (range)</td>
<td>53.0 (18-96)</td>
<td>52.5 (18-88)</td>
<td>53.0 (18-96)</td>
</tr>
<tr>
<td>≥65 yr – no. (%)</td>
<td>66 (23)</td>
<td>65 (22)</td>
<td>128 (22)</td>
</tr>
<tr>
<td>&gt;70 yr – no. (%)</td>
<td>33 (11)</td>
<td>32 (11)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Male gender – no. (%)</td>
<td>135 (46)</td>
<td>131 (45)</td>
<td>266 (46)</td>
</tr>
<tr>
<td>Body-mass index† – mean (SD)</td>
<td>32.0 (6.4)</td>
<td>32.1 (6.3)</td>
<td>32.1 (6.3)</td>
</tr>
<tr>
<td>Duration of symptoms‡ – no. (%)</td>
<td>167 (57)</td>
<td>171 (59)</td>
<td>338 (58)</td>
</tr>
<tr>
<td>≤3 days</td>
<td>123 (42)</td>
<td>121 (41)</td>
<td>244 (42)</td>
</tr>
<tr>
<td>Any risk factor for Covid-19 progress – no. (%)</td>
<td>291 (100)</td>
<td>290 (&gt;99)</td>
<td>581 (&gt;99)</td>
</tr>
</tbody>
</table>

Number of concurrent risk factors for Covid-19 progression – no. (%)

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2</td>
<td>170 (58)</td>
<td>338 (58)</td>
</tr>
<tr>
<td>1</td>
<td>168 (58)</td>
<td>66 (29)</td>
<td>177 (30)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>91 (31)</td>
<td>86 (29)</td>
<td>177 (30)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>30 (10)</td>
<td>35 (12)</td>
<td>66 (11)</td>
<td></td>
</tr>
</tbody>
</table>
Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab
Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

➢ COMET-ICE Phase II/III trial ➢ 85% Prevention of Hospitalizations or Deaths

Table 2. Summary of Efficacy Outcomes Through Day 29 (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Sotrovimab (N = 291)</th>
<th>Placebo (N = 292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized &gt;24 hours or death for any cause – no. (%)</td>
<td>3 (1)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Hospitalized &gt;24 hours for any cause</td>
<td>3 (1)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Death by any cause</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alive and not hospitalized – no. (%)</td>
<td>284 (98)</td>
<td>270 (92)</td>
</tr>
<tr>
<td>Missing – no. (%)</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Withdrew consent prior to dosing – no. (%)</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Other clinical outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Sotrovimab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency room visit, hospitalization, or death for any cause – no. (%)</td>
<td>6 (2)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Emergency room visit for any cause</td>
<td>2 (&lt;1)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Hospitalized for any cause</td>
<td>4 (1)†</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Death by any cause</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Percent reduction (97.24% CI), P value: 85% (44% to 96%); P = 0.002
Therapeutic anti-SARS-CoV2 Monoclonal antibodies: What’s next?

- **AZD7442:**
  - **Discovery:** Ongoing Phase III trial in hospitalized moderate patients < 9 days post-symptoms
  - **Clinical Primary endpoint:** D15

- **TACKLE Phase III,** randomised, blinded, placebo-controlled, multi-centre trial assessing:
  - **Safety and Efficacy** of 600mg IM dose of AZD7442 vs placebo for outpatients:
    - N= 903 randomised (1:1: AZD7442 : n = 452) or placebo (n = 451)
    - mild-to-moderate COVID-19 and **symptomatic for 7 days** or less and PCR+ < 3 days prior to D1.
    - 13% > 65 years, 90% = co-morbidities and high risk factors (cancer, diabetes, obesity, chronic lung disease or asthma, cardiovascular disease or immunosuppression)

  ➢ **Press release October 11th 2021**
  - **Primary efficacy endpoint = severe COVID-19 or death through D29.**
    - 50% reduction in risk of developing severe COVID-19 or death (18/407 events in AZD7442 vs 37/415 in placebo)
    - **Good safety profile**

  ➢ prespecified analysis of treatment **within 5 days of symptom**
    - 67% reduction in risk of developing severe COVID-19 or death vs placebo
      - 9/253 events in AZD7442 vs 27/251 in placebo

  ➢ **FDA submission for EUA:** early Oct 21
Can anti-SARS-CoV2 Mabs help protect Vaccine Non Responders?

Synthesis of current french datas

Kidney Transplants

From S Caillard, 29/06/21

Transplants and others

<table>
<thead>
<tr>
<th></th>
<th>Post-dose 2</th>
<th>Post-dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non Responders</td>
<td>Poor Responders</td>
</tr>
<tr>
<td>SOT (SFT) kidney</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>CLL (FILO)</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>CSH Allografts (SFGM-TC)</td>
<td>20%</td>
<td>18% (&lt;250 BAU)</td>
</tr>
<tr>
<td>Anti-CD20</td>
<td>&gt;35%</td>
<td>50%</td>
</tr>
</tbody>
</table>

➢ 1st dose: 6 - 18%
➢ 2nd dose: 8 - 59%

➢ 2 situations post complete vaccine scheme (2 or 3 doses):
  - **Total failure** = No Response (Ac anti-S <30 BAU/mL)
  - **Partial Failure** = Low Titers (Ab anti-S << 250 BAU/mL).
anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs : Clinical Trials

➢ PEP (Post-Exposure Prophylaxis): Prevention of symptoms:

• Bamlanivimab IV: in high risk contacts (non immunosuppressed) : OR : 0.43 p<0.01  
  (M Cohen, JAMA, 21)
  
  Not active on Delta  but  Etesimab and cocktail still active (Monotherapy)

• AZD7442 IM :  in about 75% in PCR-negative contacts  
  (communiqué de presse AZ 15/6/21)
anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs: Clinical Trials

- **PEP (Post-Exposure Prophylaxis):** Prevention of symptoms:
  - Casirivimab-Indevimab SC: in 81% PCR-negative contacts:

### Table 1. Demographic and Clinical Characteristics of the Seronegative Population at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>REGEN-COV (N=753)</th>
<th>Placebo (N=752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range) — yr</td>
<td>43.2 (12–87)</td>
<td>42.7 (12–92)</td>
</tr>
<tr>
<td>High risk of Covid-19 — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any high-risk factor</td>
<td>238 (31.6)</td>
<td>221 (29.4)</td>
</tr>
<tr>
<td>≥65 yr of age</td>
<td>76 (10.1)</td>
<td>55 (7.3)</td>
</tr>
<tr>
<td>BMI ≥35</td>
<td>99 (13.1)</td>
<td>104 (13.8)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>17 (2.3)</td>
<td>11 (1.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>58 (7.7)</td>
<td>45 (6.0)</td>
</tr>
<tr>
<td>Immunosuppressive disease</td>
<td>5 (0.7)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Receipt of immunosuppressive therapy</td>
<td>4 (0.5)</td>
<td>11 (1.5)</td>
</tr>
<tr>
<td>≥55 yr of age with cardiovascular disease, hypertension, or COPD</td>
<td>99 (13.1)</td>
<td>90 (12.0)</td>
</tr>
</tbody>
</table>
anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs: Clinical Trials

PEP (Post-Exposure Prophylaxis):
Casirivimab-Indevimab SC:

83.5% of participants = PCR negative at D0 and 73% = SeroNegative
Primary Prophylaxis (PrEP): Prevention of symptomatic Covid-19:

- **AZD7442**: (Press release 20/8/21):
  - Reduces risk of symptomatic COVID-19 by **77%** (IC 9: 46-90) / au placebo:
    - N= 5 197, 1 dose IM (n = 3 460) 300mg in 2 IM.
      - >75 % subjects at high risk of severe COVID-19 (Immunosuppressed, diabete, obesity, cardiopathy, BPCO, Chronic renal insuffisiency, chronic hepatitis).
  - Severe Covid: Gp AZD7442: N=0 / Placebo: N=3 with 2 deaths.
  - Good safety
Subjects at very high risk for severe Covid19 AND not responding adequately to Vaccines (complete scheme 2 or 3 doses) due to their immunodepression:

- Priority: Non Responders: seronegative (Ab anti-S <30 BAU) AND:
  - SOT recipients,
  - Allogénic CSH grafts recipients
  - Lymphoïd Hemopathies: CLL treated or not, NHL and myelomas under treatment (including CAR-T cell or bi-phenotypic Abs).
  - Anti-CD20 whatever the indication, or BTK inhibitors, azathioprine, cyclophosphamide, mycophenolate mofetil
  - Primary Immune Deficiency
  - Other indications: Oncology (some immunosuppressive treatments) or Hemodialysis

Any SeroNegative Vaccinated patient at high risk of severe COVID-19

- Inadequate Ab Response to Vaccine: Same patients with: anti-S IgG < 260 BAU (hypothetical threshold for protection currently available susceptible to modifications with future datas)
L’ANSM atteste de la forte présomption d’efficacité et de sécurité du médicament RONAPREVE (casirivimab et imdevimab) dans les indications thérapeutiques suivantes :

- Receveurs de greffes d’organes solides
- Receveurs d’une greffe allogénique de cellules souches hématopoïétiques
- Hémopathies lymphoïdes : leucémies lymphoïdes chroniques traitées ou non, lymphomes non hodgkiniens et myélomes sous traitement, y compris les patients receveurs de thérapie cellulaire génique de type CAR-T cell ou d’anticorps thérapeutiques bi-phénoméotypes
- Patients recevant un traitement par anticorps anti-CD20 ou inhibiteurs de BTK ou azathioprine, cyclophosphamide et mycophénolate mofetyl
- Sujets porteurs d’un déficit immunitaire primitif
- Patients séronégatifs après un schéma vaccinal complet ou non éligibles à la vaccination et qui présentent une immunodépression sévère et qui sont à haut risque de forme grave de COVID-19.

Dans le cadre d’une administration en prophylaxie post-exposition, les sujets cas-contact doivent avoir la confirmation d’un test RT-PCR négatif avant l’administration. Le casirivimab et l’imdevimab doivent être administrés simultanément dès que possible après l’exposition confirmée au SARS-CoV-2.

En contexte d’urgence, les patients tels que définis ci-dessus n’ayant pas reçu un schéma vaccinal complet ou une exposition à un patient COVID-19 dans les 7 jours après la dernière dose, peuvent également bénéficier de la prophylaxie post-exposition sans attendre le résultat de la sérologie.

Dans le cadre d’une administration en prophylaxie pré-exposition, le casirivimab et l’imdevimab doivent être administrés simultanément et de façon répétée toutes les 4 semaines dès lors qu’il existe un risque d’être exposé au SARS-CoV-2. Les patients doivent avoir la confirmation d’un test RT-PCR négatif avant chaque administration.

Cette indication est susceptible d’évoluer en fonction de l’état des connaissances scientifiques et du contexte épidémique. »
• in 12 yo in prophylaxis:

• **Post-ExposURE (PEP)**
  • Severely Immunosuppressed patients **Non or Weak Responders** to a complete scheme of vaccination or non éligible to vaccination with high risk of severe Covid-19 (Indications ANRS-MIE).
  • Cocktail of 2 MAbs in contacts **asap after negative PCR** or in emergency if uncomplete vaccination

• **Pre-Exposure (PrEP)**
  • Severely Immunosuppressed patients **Non Responders** to a complete scheme of vaccination or non éligible to vaccination with high risk of severe Covid-19 (Indications ANRS-MIE).
  • Cocktail of 2 MAbs **every 4 weeks as long as exposed**.
  • *Because of insufficient data, this authorization is not extended to Weak Responders*.

• Advice susceptible to be modified as a function of scientific and epidemiological data

• Estimated target Population: 130 000 immunosuppressed patients non-responding to a complete vaccination scheme
National Prospective Cohort for Primary and Post-Exposure Prophylaxis by anti-SARS-CoV2 MAbs

- **Co-PI:** Prs V Levy (Hématologie, Avicenne), G Blancho (Transplantation Rénale, Nantes), G Martin-Blondel (Infectiologie, Toulouse)

- **Promotion:** APHP : URC : Avicenne (ou Bichat)

- **Methodology:** Equipe URC AVC

- **Follow-up:** monthly:

- **Biostatistics & data Analysis:** F. Mentré (Equipe Inserm, Bichat).

- **Cohort "Sous l'égide de l'ANRS"
Anti-Covid19 anti-SARS-CoV2 Mabs

TREATMENT TO PREVENT DISEASE

• **Cocktails recommended** (or broad spectrum)

• Efficacy:
  - in high risk outpatients: 50 - 75%
  - In seronegative hospitalized patients: 20%

• Good safety profile

• Indications:
  - Prevention of disease in outpatients:
    - < 5 days post-symptoms or post-infection
    - Non O2-dependent
    - Immune deficiency or other High risk factors or > 80y
  - Prevention of severe disease or death in hospitalized
    - Seronegative, O2 dependent (non invasive)

PROPHYLAXIS

• **Cocktails recommended** (or broad spectrum)
  - ½ life: 1 month: Caserivimab+Indevimab
  - 3 months: AZD7442

• Efficacy: Pre and Post-Exposure: about 75%

• Indications:
  - Currently:
    - PEP: Caserivimab+Indevimab SC or IV for Non and Weak Responders to Vaccines
    - PrEP: Caserivimab+Indevimab SC for Non Responders

• Future?
  - PEP: Caserivimab+Indevimab SC ?
  - PrEP: AZD 7442 IM once a year (?)

➢ FUTURE? Respective indications of oral anti-viral drugs vs Mabs???
Anti-SARS-CoV2 MabTher Reacting group:

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