Scientific update on COVID-19

Updated on July 22nd 2021
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Questions:
- What drug showed clinical efficacy?
- What drugs did not show proven benefits?
COVID-19 Treatment

- **Dexamethasone** is the first drug to show life-saving efficacy in patients infected with COVID-19
- More data from clinical trials are needed

### Classes of treatment

<table>
<thead>
<tr>
<th>Anti viral effect</th>
<th>Monoclonal antibody</th>
<th>Immunomodulatory effect</th>
<th>Passive immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hydroxy)chloroquine</td>
<td>Anti-C5a IFX-1</td>
<td>Corticosteroids</td>
<td>Convalescent plasma</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>IL-1 R Antagonist</td>
<td>INFβ-1a</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>IL-6 R Antagonist</td>
<td>Janus Kinase (JAK) inhibitor</td>
<td></td>
</tr>
<tr>
<td>Remdesivir</td>
<td>LY CoV 555/016</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>REG CoV2</td>
<td></td>
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</tr>
</tbody>
</table>
What targets for treatment?

- **Protease inhibitor:** LPVr
- **Polymerase inhibitor:** RDV
- **Immune modulatory effect:** CQ
- **Neutralizing antibodies:** CP
- **IL-1 receptor antagonist:** ANK
- **Anti C5a:** TCZ
- **Neutralizing antibodies:** CP
- **Convalescent plasma:** CP
- **Corticosteroids:** CT
- **Hydroxychloroquine:** HCQ
- **Vilobelimab:** IFX-1
- **Interferon beta 1a:** INFβ-1a
- **Tocilizumab:** TCZ
- **Remdesivir:** RDV
Hydroxychloroquine (HCQ)

- Systematic review of randomized controlled trials (RCTs), using standard Cochrane methods, academic study, UK
- **Inclusion criteria**: RCTs testing chloroquine or hydroxychloroquine in people with COVID-19, people at risk of COVID-19 exposure, and people exposed to COVID-19
- **Data collection**: Two review authors independently assessed eligibility of search results, extracted data from the included studies, and assessed risk of bias using the Cochrane “Risk of bias” tool
- **Outcomes**: Death due to any cause, negative PCR for SARS-CoV-2 on respiratory samples at D14 from enrolment, proportion admitted to hospital, progression to mechanical ventilation, length of hospital admission, time to clinical improvement, time to negative PCR for SARS-CoV-2 on respiratory samples, any adverse events...

- 953 records identified through database searching
- 860 records after duplicated removed
- 860 records screened
- 257 full text articles assessed for eligibility
- 14 studies included in qualitative synthesis
- 243 full articles full not included in qualitative synthesis
- 88 full-text articles excluded
- 122 ongoing studies
- 12 studies included in quantitative synthesis (meta-analysis)
Anti viral effect

Hydroxychloroquine (HCQ)

- HCQ makes little or no difference to death due to any cause, compared with no HCQ; RR: 1.09, 95% CI [0.99:1.19]; 8040 participants; 9 trials

- HCQ may make little or no difference to the likelihood of a negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment; RR: 1, 95% CI [0.91:1.10]; 213 participants; 3 trials

- HCQ probably results in little to no difference in progression to mechanical ventilation; RR: 1.11, 95% CI [0.91:1.37]; 4521 participants; 3 trials

MV: mechanical ventilation

Singh B et al. Cochrane Database syst Rev Feb 2021
# Lopinavir/ritonavir (LPVr)

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (Primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao</td>
<td>Randomized, controlled, open-label</td>
<td>LPVr vs. SoC (Hospitalized)</td>
<td>N= 199</td>
<td>Time to clinical improvement</td>
<td>LPVr group not associated with a difference in time to clinical improvement HR: 1,31 95% CI[0,95-1,80]</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>Randomized, controlled, open-label</td>
<td>LPVr + SoC vs. SoC (Hospitalized)</td>
<td>N= 5 040</td>
<td>28-day all-cause mortality</td>
<td>LPVr + SoC group: 364/1616 (23%) vs. SoC group 767/3424 (22%); RR: 1,03 95% CI[0,91-1,17], p=0,60</td>
</tr>
<tr>
<td>Schoergenhofer</td>
<td>Experimental</td>
<td>One group (Hospitalized)</td>
<td>N= 8</td>
<td>LPVr plasma concentration</td>
<td>Approximately 2-fold higher than HIV patients receiving the same dose (7.1 µg/mL) 60 to 120-fold higher concentrations are required to reach the assumed LPV EC50</td>
</tr>
</tbody>
</table>

No virological data on some studies
### Lopinavir/ritonavir (LPVr)

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (Primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLIDARITY (WHO)</td>
<td>Multicenter, randomized, open-label, non-placebo-controlled</td>
<td>LPVr vs. control (Hospitalized)</td>
<td>N= 2 791</td>
<td>All-cause mortality</td>
<td>LPVr group: 148/1399 (9,7%) vs. placebo group: 146/1372 (10,3%); rate ratio: 1,00; 95% CI[0,79-1,25]; p= 0,97</td>
</tr>
</tbody>
</table>
| Zhang            | Systematic review and meta-analysis         | LPVr vs. control specified (Hospitalized) | N= 4 023     | ARDS and Mortality rate          | ARDS rate: LPVr group 15,6% vs. control group 24,2%; p= 0,49  
Mortality rate: LPVr group 6,2% vs. control group 5,5%; p= 0,93 |
| DISCOVERY*       | Multicenter, randomized, open-label, superiority-controlled | LPVr + SoC vs. SoC (Hospitalized) | N= 150       | D15 clinical status              | LPVr vs. control; adjusted odds ratio: 0,83; 95% CI[0,55-1,26]; p= 0,39 |

* Discovery study is included in Solidarity study

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No virological data on some studies
Ivermectin (IVM)

- Systematic review of randomized controlled trials (RCTs), academic study, USA/Peru/Brazil
- **Inclusion criteria:** RCTs assessing ivermectin effects on COVID-19 adult patients, hospitalized and non-hospitalized, irrespective of severity
- **Data collection:** Two investigators independently screened titles and abstracts, data extracted from five databases and preprints, and assessed risk of bias using the Cochrane “Risk of bias” 2.0 tool
- **Outcomes:** all-cause mortality, length of hospital stay, and adverse events (AE), SARS-CoV-2 clearance on respiratory samples, clinical improvement, need for mechanical ventilation, and severe adverse events (SAE)

256 records identified through database searching
265 records after duplicated removed
265 records screened
253 records excluded
12 full-text articles assessed for eligibility
10 RCTs included in systematic review
2 records excluded
1 no control group
1 sole outcome of no interest (duration of fever)
Ivermectin (IVM)

- IVM did not have effect on all-cause mortality compared with controls; RR: 0.37, 95% CI [0.12:1.13]; 425 participants; 5 trials

- IVM did not have effect on length of stay compared with controls; Mean difference: 0.72, 95% CI [-0.862:2.29]; 176 participants; 3 trials

- IVM did not have effect on adverse events compared with controls; RR: 0.95, 95% CI [0.79:1.07]; 425 participants; 5 trials

- No effect of IVM on severe adverse events in comparison to the controls; RR: 1.39, 95% CI [0.36:5.30]; 425 participants; 5 trials
Remdesivir (RDV)

- Systematic review and meta-analysis of randomized controlled trials (RCTs), academic study, USA

- **Inclusion criteria:** English-language, RCTs reporting on remdesivir for treatment of adults with confirmed or suspected COVID-19. Studies were eligible if they compared remdesivir *versus* placebo, standard care, or another agent

- **Data collection:** Two investigators; one abstracted data (study information, population, disease severity, intervention...), a second reviewer verified data. The Cochrane Risk of Bias Tool and Grading of Recommendations Assessment, Development and Evaluation (GRADE) method were used

- **Outcomes:** all-cause mortality, percentage of patients who recovered, and serious adverse events (SAE)
Remdesivir (RDV)

- Ten-day course of remdesivir probably results in little to no reduction in **mortality** compared with controls; RR: 0.93, $95\%$ CI [0.82:1.06]; 3635 participants; 4 trials

- Ten-day course of remdesivir may result in a small reduction in the **proportion of patients receiving mechanical ventilation (MV)** compared with controls; RR: 0.71, $95\%$ CI [0.56:0.90]; 887 participants; 3 trials

- Ten-day course of remdesivir probably reduces **serious adverse events (SAE)** by a moderate amount compared with controls; RR: 0.75, $95\%$ CI [0.63:0.90]; 880 participants; 3 trials
Corticosteroids (CT) - 1

- Randomized, controlled, open-label, multi center (176 hospitals), academic study, UK (RECOVERY)
- **Inclusion criteria**: age ≥ 9yo (age changed during the study)), SARS-CoV-2 infection (clinically suspected or laboratory confirmed), pregnant or breast-feeding women were eligible
- **Primary outcome**: all-cause mortality within 28 days after randomization
- **Secondary outcome**: time until discharge from hospital, invasive mechanical ventilation (including ECMO) or death (among patients not receiving invasive mechanical ventilation at randomization)
- **6 425** participants; **4 321 usual care alone group, 2 104 DXM group (2:1)**

**11 303 patients recruited**
- **9 355** underwent randomization
- **1 948** excluded
- **357** did not have dexamethasone available
- **1 707** not considered suitable for randomization to dexamethasone

**2 104 to the DXM group**
- **1 withdrew consent**
- **95 proceeded to second randomization**
- **2 104 included in the 28-day intention to treat analysis**

**4 321 to usual care alone group**
- **6 withdrew consent**
- **276 proceeded to second randomization**
- **4 321 included in the 28-day intention to treat analysis**
## Corticosteroids (CT) - 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DXM (N=2 104)</th>
<th>Usual care (N=4 321)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥ 70 yr – no (%)</strong></td>
<td>963 (45)</td>
<td>1817 (42)</td>
</tr>
<tr>
<td><strong>Female sex – no (%)</strong></td>
<td>766 (36)</td>
<td>1572 (36)</td>
</tr>
<tr>
<td><strong>Coexisting conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>521 (25)</td>
<td>1025 (24)</td>
</tr>
<tr>
<td>Heart disease – no (%)</td>
<td>586 (49,1)</td>
<td>1171 (27)</td>
</tr>
<tr>
<td>Chronic lung disease – no (%)</td>
<td>415 (20)</td>
<td>931 (22)</td>
</tr>
<tr>
<td><strong>SARS-CoV-2 test result</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive – no (%)</td>
<td>20 (18-22)</td>
<td>18 (18-20)</td>
</tr>
<tr>
<td><strong>Respiratory support received</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oxygen – no (%)</td>
<td>501 (24)</td>
<td>1034 (24)</td>
</tr>
<tr>
<td>Oxygen only – no (%)</td>
<td>1279 (61)</td>
<td>2604 (60)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation – no (%)</td>
<td>324 (15)</td>
<td>683 (16)</td>
</tr>
</tbody>
</table>
• **Day 28 mortality**: 482/2104 (22.9%) DXM group vs. 1110/4321 (25.7%) usual care group, risk ratio 0.83 CI_{95%}[0.75-0.93]

• **Discharged from hospital within 28 days**: 1413/2104 (67.2%) DXM group vs. 2745/4321 (63.5%) usual care group, risk ratio 1.10 CI_{95%}[1.03-1.17]

• **Invasive mechanical ventilation or death**: 456/1780 (25.6%) DXM group vs. 994/3638 (27.3%) usual care group, risk ratio 0.92 CI_{95%}[0.84-1.01]

• **Limits**: Preliminary report, patients without confirmed SARS-CoV-2 positive PCR included, age of inclusion changed during the study, absence of viral load follow-up
Corticosteroids (CT) - 2

- Prospective Meta-analysis, academic study, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

**Objective:** estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality

**Primary outcome:** all-cause mortality at 28 days after randomization

**Secondary outcome:** investigator-defined serious adverse events

- 1703 included participants; 678 (40%) **corticosteroid group** (systemic dexamethasone, hydrocortisone, or methylprednisolone); 1025 (60%) **usual care or placebo group**

16 Trials identified
13 Found via database searches
3 Found via other sources

16 Screened after duplicates removed
7 Excluded
3 Wrong interventions
3 Not yet recruiting
1 ineligible population

9 Trial investigators contacted for participation
2 Excluded
1 No response
1 Declined participation due to ongoing recruiting for trial

7 Trial included in quantitative synthesis (meta-analysis)

Sterne et al. JAMA Sep 2020
Corticosteroids (CT) - 2

- 222/678 deaths among patients randomized to corticosteroids group vs. 425/1025 deaths among patients randomized to usual care or placebo; OR: 0.66 IC$_{95\%}$ [0.53-0.82]; $p < 0.001$ fixed-effect meta-analysis

- Association with mortality: DXM: 0.64 IC$_{95\%}$ [0.5-0.82]; $p<0.001$ (3 trials), HC: 0.69 IC$_{95\%}$ [0.43-1.12]; $p=0.13$ (3 trials), mPred: 0.91 IC$_{95\%}$ [0.29-2.87]; $p=0.87$ (1 trial)

- Limits: risk of selective reporting or of publication bias, missing outcome data, trials only recruited adults, effect of corticosteroids on children remains unclear

DXM: dexamethasone  
HC: hydrocortisone - mPred: methylprednisolone
# Corticosteroids (CT) - 3

<table>
<thead>
<tr>
<th>Author</th>
<th>CT</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fadel R</td>
<td>mPred</td>
<td>Multi-center, quasi-experimental</td>
<td>mPred vs. no mPred</td>
<td><strong>N=213</strong> Moderate to severe COVID-19, Median time to CT initiation from admission: 2 days (1-4)</td>
<td>Escalation of care from ward to ICU</td>
<td>SoC group 31 (44,3%) vs. mPred group 32 (27,3%) OR: 0,47, 95% CI[0,25-0,88], p= 0,017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New requirement for MV</td>
<td>SoC group 26 (36,6%) vs. CT group 26 (21,7%) OR: 0,47, 95% CI[0,25-0,92], p= 0,025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>SoC group 21 (26,3%) vs. CT group 18 (13,6%) OR: 0,45, 95% CI[0,22-0,91], p= 0,024</td>
</tr>
<tr>
<td>Nelson B</td>
<td>mPred</td>
<td>Case-control study</td>
<td>mPred vs. control</td>
<td><strong>N=117</strong> Requiring MV Median time from symptom onset to admission: 7 days (3–8)</td>
<td>D28 ventilator-free after admission</td>
<td>mPred group 6,2 vs. control group 3,14, p=0,044</td>
</tr>
</tbody>
</table>

mPred: methylprednisolone
MV: mechanical ventilation
## Corticosteroids (CT) - 4

<table>
<thead>
<tr>
<th>Author</th>
<th>CT</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prado Jeronimo</td>
<td>mPred</td>
<td>Parallel, double-blind, placebo-controlled, randomized</td>
<td>mPred vs. placebo</td>
<td>N=416 Suspected COVID-19 hospitalized patients Median time from illness onset to randomization: 13 days (9–16)</td>
<td>D28 mortality</td>
<td>mPred group 72/194 (37,1%) vs. placebo group 76/199 (38,2%) HR: 0,924 95%CI[0,669-1,275]; p= 0,629</td>
</tr>
<tr>
<td>Tomazini</td>
<td>DXM</td>
<td>Multicenter, randomized, open-label</td>
<td>DXM + SoC vs. SoC</td>
<td>N= 299 Receiving MV, Median time since symptom onset: DXM group: 9 days (7-11) vs. SoC group 10 days (6-12)</td>
<td>Ventilator-free days during the first 28 days</td>
<td><strong>Study interrupted</strong> DXM + SoC group 6,6 IC95% [5-8,2] vs. SoC group 4,0 95%CI[2,9-5,4]; p= 0,04</td>
</tr>
</tbody>
</table>

**mPred:** methylprednisolone - **DXM:** dexamethasone  
**MV:** mechanical ventilation
## Immunomodulatory effect

### Corticosteroids (CT) - 5

<table>
<thead>
<tr>
<th>Author</th>
<th>CT</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dequin</td>
<td>HC</td>
<td>Multicenter randomized double-blind</td>
<td>HC vs. placebo</td>
<td>N=149 Critically ill, acute respiratory failure Median durations of symptoms prior to randomization: HC group 9 days (7-11,5) vs. placebo group 10 days (8-12)</td>
<td>D21 treatment failure</td>
<td>Study stopped early HC group 32/76 (42,1%) vs. placebo group 37/76 (50,7%) p= 0,29</td>
</tr>
<tr>
<td>Angus</td>
<td>HC</td>
<td>Multicenter, open label trial</td>
<td>HC vs. placebo</td>
<td>N=384 Admitted in ICU for respiratory or cardiovascular organ support</td>
<td>D21 respiratory and cardiovascular organ support–free</td>
<td>Study stopped early No treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions</td>
</tr>
</tbody>
</table>

**HC**: hydrocortisone
**IL-6 Receptor Antagonist**

- Prospective meta-analysis, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
- **Inclusion criteria:** clinical trials, hospitalized COVID-19 patients, administration of IL-6 antagonists compared with usual care or placebo
- **Data collection:** systematic searches of ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform. Search terms employed included IL-6, IL-6 antagonist, tocilizumab, sarilumab, COVID-19, SARS-CoV-2. Bias assessed using version 2 of the “Cochrane Risk of Bias”. GRADE approach used to assess certainty of the evidence
- **Outcomes:** all-cause mortality at 28 days after randomization

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**72 Records identified**
- 3 duplicate records identified and removed

**69 Records Abstracts/Titles screened for eligibility**
- 38 Records ineligible/excluded
  - 11 Not RCTs
  - 11 Ineligible Intervention/Control
  - 4 Trials terminated/withdrawn
  - 4 No response from investigators
  - 4 Did not commence recruitment
  - 1 Ineligible population
  - 1 Anti-IL6 arm dropped from trial
  - 1 No usual care alone arm
  - 1 Recruitment ongoing (anticipated end date June 2021)

**31 eligible trials invited to participate in prospective meta-analysis**
- 4 trials not included in meta-analysis

**27 Studies included in quantitative synthesis (meta-analysis)**
IL-6 Receptor Antagonist

- **D28 all-cause mortality tocilizumab**: 960/4299 (22%) tocilizumab group vs. 1023/3749 (25%) usual care or placebo group; OR: 0.83, 95% CI [0.74:0.92]; p<0.001, 8048 participants; 19 trials.

- **D28 all-cause mortality sarilumab**: 473/2073 (26%) sarilumab group vs. 139/753 (25%) usual care or placebo group; OR: 1.08, 95% CI [0.86:1.36]; p=0.52, 2826 participants; 9 trials

- **D28 all-cause mortality overall IL-6 Receptor antagonist**: 1407/6449 (22%) IL6 group vs. 1158/4481 (25%) usual care or placebo group; OR: 0.86, 95% CI [0.79:0.95]; p=0.003
**Vilobelimab (IFX-1)**

- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria**: age ≥ 18yo, severe pneumonia (PaO₂/FiO₂ between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive ventilation
- **Primary outcome**: Day 5 PaO₂/FiO₂ percentage change from the baseline
- **Secondary outcome**: Day 28 mortality
- **30 participants**: **15 control group, 15 IFX-1 treated group (1:1)**

172 patients assessed for eligibility
142 not included
141 did not meet inclusion criteria
1 declined participation

30 enrolled

15 randomly assigned IFX-1 group
15 received at least one dose of treatment
3 received seven infusions
3 received six infusions
3 received five infusions
5 received less than five infusions
15 completed the study up to day 28
2 died
13 recovered

15 randomly assigned control group
15 received allocated best supportive care
15 completed the study up to day 28
4 died
11 recovered
Vilobelimab (IFX-1)

- **Day 5 PaO₂/FiO₂ percentage change**: no differences; IFX-1 group (17%) vs. control group (41%); difference –24% 95% CI[–58–9], p=0.15

- **D28 mortality**: IFX-1 group 13%; 95% CI[0–31] vs. control group 27%; 95% CI[7–49]; HR=0.65 95% CI[0.1–4.14]

- **Limits**: patient heterogeneity, open label study, very low number of participants (15 in each group)

### Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IFX-1 (N=15)</th>
<th>Control (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) - yr</td>
<td>58 (9)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>11 (73)</td>
<td>11 (73)</td>
</tr>
</tbody>
</table>

#### Coexisting conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>IFX-1 (N=15)</th>
<th>Control (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension – no (%)</td>
<td>6 (40)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>4 (27)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Obesity – no (%)</td>
<td>2 (13)</td>
<td>4 (27)</td>
</tr>
</tbody>
</table>

#### Respiratory support

<table>
<thead>
<tr>
<th>Support</th>
<th>IFX-1 (N=15)</th>
<th>Control (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubated at randomization – no (%)</td>
<td>8 (53)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Oxygen mask – no (%)</td>
<td>6 (40)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Nasal cannula – no (%)</td>
<td>1 (7)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Vlaar APJ et al. Lancet Rheumatol Sep 2020
**LY-CoV555 and LY-CoV016 - 1**

- **LY-CoV555** (bamlanivimab): potent antispike neutralizing MAb
- **LY-CoV016** (etesevimab): potent antispike neutralizing MAb
- Randomized, double-blind, placebo-controlled, multicenter, USA (BLAZE-1)
- **Inclusion criteria**: age ≥ 18yo, not hospitalized, ≥ 1 mild or moderate COVID-19 symptoms, first positive SARS-CoV-2 viral infection ≤ 3 days prior to start of the infusion
- **Primary outcome**: effect of LY-CoV555 monotherapy and combination therapy with LY-CoV555 and LY-CoV016 compared with placebo on SARS-CoV-2 log viral load from baseline to day 11 (±4 days)
- **577 participants**: 101 **LY-CoV555 700 mg** group, 107 **LY-CoV555 2800 mg** group, 101 **LY-CoV555 7000 mg** group, 112 **LY-CoV555 2800 mg + LY-CoV016 2800 mg** group, 156 **placebo** group

**Diagram**:
- 613 Adults with symptomatic SARS-CoV-2 infection screened for eligibility
- 21 Excluded
- 592 Randomized
- 101 included Efficacy analysis population
- 107 included Efficacy analysis population
- 101 included Efficacy analysis population
- 112 included Efficacy analysis population
- 156 included Placebo
- 100 included Primary analysis
- 103 included Primary analysis
- 95 included Primary analysis
- 102 included Primary analysis
- 146 included Primary analysis

**Notes**:
- **MAb**: Monoclonal Antibody
- **MAb**: Monoclonal Antibody
- **Gottlieb RL et al. JAMA Jan 2021**
## LY-CoV555 and LY-CoV016 - 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LY-CoV555</th>
<th>LY-CoV555 + LY-CoV016</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>700 mg N=101</td>
<td>7000 mg N=101</td>
<td></td>
</tr>
<tr>
<td>Age (y) – median (IQR)</td>
<td>39 (31-58)</td>
<td>46 (34-55)</td>
<td>46 (35-57)</td>
</tr>
<tr>
<td>Female sex – no (%)</td>
<td>63 (62.4)</td>
<td>58 (57.4)</td>
<td>58 (51.8)</td>
</tr>
<tr>
<td>BMI (kg/m²) – median (IQR)</td>
<td>28.8 (25.1-35.4)</td>
<td>27.8 (24.7-32.3)</td>
<td>29.2 (25.9-34.2)</td>
</tr>
<tr>
<td>Duration of symptoms (days) , median (IQR)</td>
<td>5 (3-6)</td>
<td>4 (2-7)</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>SARS-CoV-2 Ct – mean (SD)</td>
<td>23.8 (6.5)</td>
<td>23.4 (6.8)</td>
<td>23.8 (7.8)</td>
</tr>
<tr>
<td><strong>COVID-19 severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild – no (%)</td>
<td>83 (82.2)</td>
<td>70 (69.3)</td>
<td>92 (82.1)</td>
</tr>
<tr>
<td>Moderate – no (%)</td>
<td>18 (17.8)</td>
<td>31 (30.7)</td>
<td>20 (17.9)</td>
</tr>
</tbody>
</table>

---

Monoclonal
antibody

Gottlieb RL et al. *JAMA* Jan 2021
LY-CoV555 and LY-CoV016 - 1

- **D11 change from baseline SARS-CoV-2 viral load:** -3.72 700 mg group vs. -4.08 2800 mg group vs. -3.49 7000 mg group, -4.37 combination treat group, -3.80 placebo group

- **Compared with placebo, differences in the change in log viral load at D11:** 700 mg group 0.09; 95% CI [-0.35 - 0.52], p = 0.69, vs. 2800 mg group -0.27; 95% CI [-0.71 - 0.16], p = 0.21, vs. 7000 mg group 0.31; 95% CI [-0.13 - 0.76], p = 0.16 vs. combination treatment -0.57 95% CI, [-1.00 - -0.14], p = 0.01

- **Limits:** small patient population, trial originally designed as a safety and biomarker study

- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**
LY-CoV555 and LY-CoV016 - 2

- **LY-CoV555** (bamlanivimab): potent antispike neutralizing MAb
- **LY-CoV016** (etesevimab): potent antispike neutralizing MAb
- Randomized, double-blind, placebo-controlled, multicenter, USA (BLAZE-1)
- **Inclusion criteria**: age ≥ 12yo, not hospitalized, ≥ 1 mild or moderate COVID-19 symptoms, first positive SARS-CoV-2 viral infection ≤ 3 days prior to start of the infusion
- **Primary outcome**: Day-29 Covid-19–related hospitalization (acute care for ≥ 24 hours) or death from any cause
- 1035 participants; 518 LY-CoV555 + LY-CoV016 group, 517 placebo group (1:1)

**Eligibility Assessment**

- 1087 Patients were assessed for eligibility
  - 38 screened but did not undergo randomization
  - 32 Did not meet eligibility criteria
  - 2 Withdrew
  - 2 Were withdrawn by physician
  - 1 Was missing
  - 1 Had other reason

**Randomization**

- 1049 Underwent randomization

**Infusion**

- 518 assigned to LY-CoV555 + LY-CoV016
  - 492 Completed 29-day treatment period
  - 26 Did not complete the 29-day treatment period, did not yet transition to follow-up period, or the trial site did not update the disposition status at time of data lock
  - 2 Were lost to follow-up

- 517 assigned to placebo
  - 481 Completed 29-day treatment period
  - 36 Discontinued placebo
  - 1 Was lost to follow-up

**Outcome Analysis**

- 1035 Underwent randomization and underwent infusion
- 1035 included in the analysis of the primary outcome (hospitalization or death from any cause)

**Monoclonal antibody**

- MAb: Monoclonal Antibody

**References**

- Dougan M et al. *NEJM* Jul 2021
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LY-CoV555 + LY-CoV016</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 518</td>
<td>N= 517</td>
</tr>
<tr>
<td>Age (y) – mean (SD)</td>
<td>54,3 (17,1)</td>
<td>53,3 (16,4)</td>
</tr>
<tr>
<td>BMI (kg/m²) – median (IQR)</td>
<td>34,14</td>
<td>33,90</td>
</tr>
<tr>
<td>Median days from symptom onset to randomization — no (range)</td>
<td>4 (0–29)</td>
<td>4 (0–13)</td>
</tr>
<tr>
<td>SARS-CoV-2 viral load (Ct) – mean</td>
<td>23,98</td>
<td>23,97</td>
</tr>
</tbody>
</table>

**Risk of severe Covid-19**

<table>
<thead>
<tr>
<th></th>
<th>LY-CoV555 + LY-CoV016</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>High – no/total no (%)</td>
<td>493/518 (95,2)</td>
<td>490/517 (94,8)</td>
</tr>
<tr>
<td>Low – no/total no (%)</td>
<td>25/518 (4,8)</td>
<td>27/517 (5,2)</td>
</tr>
</tbody>
</table>

**COVID-19 severity**

<table>
<thead>
<tr>
<th></th>
<th>LY-CoV555 + LY-CoV016</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild – no (%)</td>
<td>397 (76,6)</td>
<td>403 (77,9)</td>
</tr>
<tr>
<td>Moderate – no (%)</td>
<td>121 (23,4)</td>
<td>114 (22,1)</td>
</tr>
</tbody>
</table>
LY-CoV555 and LY-CoV016 - 2

- **Day-29 Covid-19–related hospitalization or death from any cause**: 11/518 (2.1%) LY-CoV555 and LY-CoV016 group vs. 36/517 (7%) placebo group. Absolute risk difference: -4.8%; 95% CI[-7.4 -2.3], relative risk difference: 70%, p<0.001

- **Death**: 0/518 LY-CoV555 and LY-CoV016 group vs. 10/517 (2%) placebo group. Of these 10 deaths, 9 were deemed to be Covid-19–related by trial staff who were unaware of the trial-group assignments

- **Limits**: low number of participant receiving immunosuppressive agents, study limited to the United States

- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**

Dougan M et al. NEJM Jul 2021
LY-CoV555

- **LY-CoV555** = LY3819253 = bamlanivimab; potent antispitake neutralizing MAb
- ACTIV-3/TICO (Therapeutics for Inpatients with COVID-19) platform, therapeutic agents platform trial
- **Inclusion criteria**: hospitalized patients, documented SARS-CoV-2 infection, duration of Covid-19 symptoms < 12 days
- **Primary outcome**: time to sustained recovery, time to hospital discharge
- **Secondary outcome**: death from any cause, safety
- **314 participants**: 163 LY-CoV555 group, 151 placebo group (1:1)

326 participants enrolled

169 assigned LY-CoV555

- 6 not infused (5 randomized October 13)

157 assigned Placebo

- 6 not infused (3 randomized October 13)

163 in mITT analysis

Availibility of Ordinal Outcome

- Day 1: 163
- Day 3: 162
- Day 5*: 161
- Day 7: 153

151 in mITT analysis

Availibility of Ordinal Outcome

- Day 1: 151
- Day 3: 151
- Day 5*: 150
- Day 7: 146

* Primary measure of efficacy in stage 1
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LY-CoV555 (N=163)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) — median (IQR)</td>
<td>63 (50-72)</td>
<td>59 (48-71)</td>
</tr>
<tr>
<td>Female sex — no (%)</td>
<td>66 (40)</td>
<td>71 (47)</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m² — no (%)</td>
<td>81 (50)</td>
<td>83 (55)</td>
</tr>
<tr>
<td>Duration of symptoms (days), median (IQR)</td>
<td>7 (5-9)</td>
<td>8 (5-9)</td>
</tr>
<tr>
<td>Coexisting conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension requiring medication — no (%)</td>
<td>82 (50)</td>
<td>72 (48)</td>
</tr>
<tr>
<td>Diabetes requiring medication — no (%)</td>
<td>54 (33)</td>
<td>36 (24)</td>
</tr>
<tr>
<td>Renal impairment — no (%)</td>
<td>24 (15)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Noninvasive ventilation or high-flow device — no (%)</td>
<td>30 (18)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Invasive ventilation or ECMO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Associated medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remdesivir — no (%)</td>
<td>60 (37)</td>
<td>66 (44)</td>
</tr>
<tr>
<td>Glucocorticoid — no (%)</td>
<td>80 (49)</td>
<td>74 (49)</td>
</tr>
</tbody>
</table>
**LY-CoV555**

- **Time to sustained recovery**: 71/87 (82%) Ly-CoV555 group vs. 64/81 (79%) placebo group, rate ratio 1.06 Cl$_{95\%}$[0.77-1.47]
- **Time to hospital discharge**: 143/163 (88%) Ly-CoV555 group vs. 136/151 (79%) placebo group, rate ratio 0.97 Cl$_{95\%}$[0.78-1.20]
- **Death**: 9/163 (6%) Ly-CoV555 group vs. 5/151 (3%) placebo group, hazard ratio 2.00 Cl$_{95\%}$[0.67-5.99]; p=0.22
- **Safety** (composite outcome): 49/163 (30%) Ly-CoV555 group vs. 37/151 (25%) placebo group, hazard ratio 1.25 Cl$_{95\%}$[0.81-1.93]; p=0.31
- **Limitation**: inability to make definitive statements about the safety (small sample size, short follow-up duration)
LY-CoV555 and REGN-COV2

- LY-CoV555 = bamlanivimab;
- REGN-COV2 = casirivimab and imdevimab

**Inclusion criteria**: adults (>18 years), mild-to-moderate COVID-19 infection, no supplemental O₂, received NmAb infusion (LY-CoV555 or REGN-COV2), not hospitalized, first onset symptoms ≤ 10 days

- **Primary outcome**: hospitalization with a COVID-19 diagnosis between one and 30 days after the index date
- **Secondary outcome**: length of inpatient stay for hospitalized patients, post-index ER/clinic visits, and post-index death

- **707** received NmAb (533 LY-CoV555, 154 REGN-COV2), **1709** control group

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NmAb (N=707)</th>
<th>Control (N=1709)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) – mean (SD)</td>
<td>59.8 (15.9)</td>
<td>58.1 (15.2)</td>
</tr>
<tr>
<td>BMI ≥ 35 kg/m² – no (%)</td>
<td>232 (32.8)</td>
<td>306 (17.9)</td>
</tr>
<tr>
<td>Duration of symptoms before infusion (days) – mean (SD)</td>
<td>6.15 (2.76)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Coexisting conditions**

| Chronic pulmonary disease – no (%)                        | 96 (13.6)    | 240 (14.0)      |
| Diabetes without complications – no (%)                  | 132 (18.7)   | 278 (16.3)      |
| Diabetes with complications – no (%)                     | 27 (3.8)     | 115 (6.7)       |
| Renal disease – no (%)                                    | 40 (5.7)     | 129 (7.5)       |
| Congestive heart failure – no (%)                         | 22 (3.1)     | 95 (5.6)        |
LY-CoV555 and REGN-COV2

- **Hospitalization rate**: 41/707 (5.8%) NmAb group vs. 195/1709 (11.4%) control group; *p*<0.0001

- **Length of inpatient stay (days)**: 5.2 ± 4.6 NmAb group vs. placebo group 7.4 ± 8.1; *p*=0.02

- **ER visits within 30 days post-index**: 57/707 (8.1%) NmAb group vs. 210/1709 (12.3%) placebo group; *p*=0.003

- **Hospitalisation-free survival**: longer NmAb group vs. control group; unadjusted HR: 0.5 Cl95%[0.35-0.69]; *p*<0.0001

- **Limitations**: retrospective study using electronics medical record (EMR)

- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**

Hospitalizations for COVID-19 in patients who received a NmAb infusion and controls (censored at 30 days)
REGN-COV2

- **REGN-COV2**: antibody cocktail containing two SARS-CoV-2 neutralizing antibodies (casirivimab and imdevimab)
- Randomized, double-blind, placebo-controlled, multicenter, phase 1–3 study
- **Inclusion criteria**: age ≥ 18yo, not hospitalized, positive SARS-CoV-2 antigen or molecular test, symptom onset ≤ 7 days before randomization, O₂ saturation ≥93% (room air)
- **Primary outcome**: D7 viral load (VL) average change
- **Secondary outcome**: safety
- 275 participants; 90 REGN-COV2 high dose group, 92 REGN-COV2 low dose group, 93 placebo group (1:1:1)
## REGN-COV2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>REGN-COV2 (N=182)</th>
<th>Placebo (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) - median (IQR)</td>
<td>43,0 (35,0–52,0)</td>
<td>45,0 (34,0–54,0)</td>
</tr>
<tr>
<td>Female sex - no (%)</td>
<td>98 (54)</td>
<td>43 (46)</td>
</tr>
<tr>
<td>BMI (kg/m²) - mean (SD)</td>
<td>30,51 (6,87)</td>
<td>29,73 (7,15)</td>
</tr>
<tr>
<td>Days from symptom onset to randomization - median (range)</td>
<td>3,0 (0–8)</td>
<td>3,0 (0–8)</td>
</tr>
<tr>
<td>Positive baseline qualitative RT-PCR - no (%)</td>
<td>147 (81)</td>
<td>81 (87)</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/mL) - mean (SD)</td>
<td>5,02 (2,50)</td>
<td>4,67 (2,37)</td>
</tr>
<tr>
<td>Baseline serum C-reactive protein (mg/L) - Mean (SD)</td>
<td>11,7 (24,4)</td>
<td>21,5 (43,5)</td>
</tr>
<tr>
<td>At least one risk factor for hospitalization - no (%)</td>
<td>118 (65)</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Age &gt; 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromise</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**REGN-COV2**

- **Time-weighted average change in viral load from day 1 through day 7**: $-1.74 \pm 0.95\% \text{CI}[−1.95 - -1.53]$ REGN-COV2 group vs. $-1.34 \log_{10} \text{cp/mL} \pm 0.95\% \text{CI}[−1.60 - -1.08]$ placebo group

- **Viral load difference vs. placebo at day 7**: $-0.41 \log_{10} \text{cp/mL} \pm 0.95\% \text{CI}[−0.71 - -0.10]$

- **Safety**: Grade 3 or 4 event: 1/176 (0.56%) REGN-COV2 group vs. 1/93 (1.07%) placebo group, Event that led to infusion interruption 1/176 (0.56%) REGN-COV2 group vs. 1/93 (1.07%) placebo group, none led to death

- **Limits**: interim analysis

- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**
**Anakinra (ANK)**

- **Anakinra**: recombinant human IL-1 receptor antagonist
- Multicenter, open-label, Bayesian randomized clinical trial, France (CORIMUNO-ANA-1)
- **Inclusion criteria**: positive SARS-CoV-2 RT-PCR or chest CT scan typical of COVID-19 pneumonia, mild-to-moderate, severe, or critical pneumonia (O₂ flow of >3 L/min via mask or nasal cannula and WHO-CPS score ≥5 points)
- **Coprimary outcome**: proportion of patients who had died or needed NIV or MV (WHO-CPS score of >5 points) at D4, survival with no need for MV or NIV at D14
- **116** participants; **59 ANK group, 57 usual care group (1:1)**

**Flowchart**

- **153 patients screened**
  - 37 excluded
    - 19 included in another CORIMUNO trial
    - 2 did not meet inclusion criteria
    - 2 errors in the inclusion process
    - 14 unspecified reason

- **116 eligible for randomisation**
  - **59 randomly assigned to ANK group**
  - **57 randomly assigned to UC group**

- **59 received assigned treatment**
- **57 received usual care**

- **59 analysed for primary outcome**
- **55 analysed for primary outcome**

---

MV: mechanical ventilation  
NIV: non-invasive ventilation  
UC: usual care
## Anakinra (ANK)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Anakinra (N=59)</th>
<th>Usual care (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) - median (IQR)</td>
<td>67,0 (55,5–74,3)</td>
<td>64,9 (59,5–78,3)</td>
</tr>
<tr>
<td>Female sex - no (%)</td>
<td>16 (27)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>BMI (kg/m²) - median (IQR)</td>
<td>27,4 (24,9-32,0)</td>
<td>26,8 (24,7-31,5)</td>
</tr>
<tr>
<td>Coexisting conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cardiac disease - no (%)</td>
<td>22 (37%)</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Diabetes - no (%)</td>
<td>19 (32%)</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Chronic kidney disease (stage 1 to 3) or dialysis - no (%)</td>
<td>5 (8%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ flow (L/min) - median (IQR)</td>
<td>5,0 (4,0–7,0)</td>
<td>6,0 (4,0–9,0)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min) - median (IQR)</td>
<td>28,0 (24,0–32,0)</td>
<td>28,0 (23,0–36,0)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L) - median (IQR)</td>
<td>121,0 (77,0–198,0)</td>
<td>120,0 (87,0–191,5)</td>
</tr>
<tr>
<td>Time from symptoms onset to randomization (days) - median (IQR)</td>
<td>10,0 (8,0–13,0)</td>
<td>10,0 (7,0–13,0)</td>
</tr>
</tbody>
</table>

Anakinra (ANK)

- **WHO-CPS score of >5 points** at D4: 21/59 (36%) anakinra group vs. 21/55 (38%) usual treatment group, median posterior ARD: –2.5%, 90% CI[−17.1 - 12.0]

- **Survival with no need for MV or NIV at D14**: 28/59 (47%) anakinra group vs. 28/55 (51%) usual treatment group, median posterior HR: 0.97, 90% CI[0.62 - 1.52]

- **Overall mortality at D90**: 16/59 (27%) anakinra group vs. 15/55 (27%) usual treatment group, median posterior HR: 0.97, 95% CI[0.46 - 2.04]

- **Limits**: not blinded trial, usual care may differed among centers, small sample size

- **Study stopped early for futility**
Interferon beta 1a - 1

- **SNG001**: inhaled nebulized Interferon beta 1a (INFβ-1a)
- Randomized, double-blind, placebo-controlled, phase 2, multicenter, academic trial, UK (SG016)
- **Inclusion criteria**: age ≥ 18 yo, hospitalized patients, COVID-19 symptoms, positive SARS-CoV-2 RT-PCR
- **Exclusion criteria**: inability to use a nebulizer, pregnant and breastfeeding women,
- **Primary outcome**: clinical condition change (WHO Ordinal Scale for Clinical Improvement)
- **Secondary outcome**: change in Breathlessness, Cough And Sputum Scale score, safety and tolerability
- **101** participants; **50 SNG001** group, **51 placebo** group (1:1)

116 patients assessed for eligibility
15 excluded
1 of childbearing potential
1 had confirmation of SARS-CoV-2 infection >24 h
13 were negative for SARS-CoV-2 infection

101 randomly assigned
51 assigned to placebo
50 received intervention
1 withdrew consent
50 assigned to SNG001
48 received intervention
2 withdrew consent

14 withdrawn
5 withdrew consent
2 lost to follow-up
2 due to investigator’s decision
2 for other reasons
2 due to a fatal serious adverse reaction
1 due to a non-serious adverse reaction

36 completed follow-up at D28
50 included in ITT analysis
43 included in the per-protocol analysis

39 completed follow-up at D28
48 included in the ITT analysis
43 included in the per-protocol analysis

SoC: standard of care
IMV: invasive mechanical ventilation
STR: steroids
### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SNG001 (N=50)</th>
<th>Placebo (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) – mean (SD)</td>
<td>57.8 (14.6)</td>
<td>56.5 (11.9)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>27 (56)</td>
<td>31 (62)</td>
</tr>
</tbody>
</table>

#### Coexisting conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>SNG001 (N=50)</th>
<th>Placebo (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension – no (%)</td>
<td>18/26 (69)</td>
<td>11/27 (41)</td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>3/26 (12)</td>
<td>9/27 (33)</td>
</tr>
<tr>
<td>Cardiovascular disease – no (%)</td>
<td>5/26 (19)</td>
<td>8/27 (30)</td>
</tr>
<tr>
<td>Chronic lung condition – no (%)</td>
<td>11/26 (42)</td>
<td>12/27 (44)</td>
</tr>
</tbody>
</table>

#### Severity of disease at baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>SNG001 (N=50)</th>
<th>Placebo (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitation of activities — no (%)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hospitalised (no oxygen therapy) – no (%)</td>
<td>11 (23)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Oxygen by mask or nasal prongs – no (%)</td>
<td>36 (75)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Non-invasive ventilation or high-flow oxygen – no (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Interferon beta 1a - 1

- **Clinical condition change (D15 or D16 OSCl improvement):** 36/48 (75.0%) SNG001 group vs. 35/50 (70%) placebo group; OR: 2.32; 95% CI[1.07-5.04], p=0.033

- **D14 BCSS score:** difference between SNG001 group and placebo group: -0.8; 95% CI[-1.5;-0.1], p=0.026

- **Safety:** serious adverse events considered either unlikely be related to study treatment or not related to study treatment

- **Limits:** limited sample size, OSCl: new tool at the time of the study, nebulizer not suitable for ventilated patients, follow-up limited at 28 days
Interferon beta 1a - 2

- Randomized, open-label, non-placebo-controlled, international trial, WHO, SOLIDARITY
- **Inclusion criteria**: patients aged $\geq 18$ yo, hospitalized with definite COVID-19, not already receiving any of the study drugs, no allergy nor contraindications to any of them
- **Exclusion criteria**: significant contraindication to any one of the study drugs
- **Primary outcome**: all-cause mortality
- **Secondary outcome**: initiation of mechanical ventilation and hospitalization duration
- 4127 patients underwent randomization; 2063 INF group, 2064 control group (1:1)

4 127 underwent randomization between INF and control

2 063 Were assigned to receive INF
2 064 Were assigned not to receive INF

13 Had no or unknown consent to follow-up
14 Had no or unknown consent to follow-up

2050 Were included in the intention-to-treat analyses
- 1756 Died or left the hospital
- 65 Entered trial before Sept.; still an inpatient in late Sept.
- 30 Entered trial before Sept.; not yet reported on in late Sept.
- 199 Entered trial in or after Sept.; not reported on in late Sept. (entry ended Oct. 16)

2050 Were included in the intention-to-treat analyses
- 1819 Died or left the hospital
- 56 Entered trial before Sept.; still an inpatient in late Sept.
- 21 Entered trial before Sept.; not yet reported on in late Sept.
- 154 Entered trial in or after Sept.; not reported on in late Sept. (entry ended Oct. 16)
## Interferon beta 1a - 2

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (N= 11 266)</th>
<th>INF (N= 2 050)</th>
<th>Control (N=2 050)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 yr – no (%)</td>
<td>3995 (35)</td>
<td>720</td>
<td>697</td>
</tr>
<tr>
<td>50-69 yr – no (%)</td>
<td>5125 (45)</td>
<td>934</td>
<td>973</td>
</tr>
<tr>
<td>≥ 70 yr – no (%)</td>
<td>2146 (19)</td>
<td>396</td>
<td>380</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>6985 (62)</td>
<td>1303</td>
<td>1278</td>
</tr>
<tr>
<td><strong>Co existing conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>2768 (25)</td>
<td>489</td>
<td>537</td>
</tr>
<tr>
<td>Heart disease – no (%)</td>
<td>2337 (21)</td>
<td>427</td>
<td>456</td>
</tr>
<tr>
<td>Chronic lung disease – no (%)</td>
<td>635 (6)</td>
<td>114</td>
<td>109</td>
</tr>
<tr>
<td><strong>Respiratory support</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No supplemental O(_2) at entry</td>
<td>3204 (28)</td>
<td>482</td>
<td>490</td>
</tr>
<tr>
<td>Supplemental O(_2) at entry</td>
<td>7146 (63)</td>
<td>1429</td>
<td>1430</td>
</tr>
<tr>
<td>Already receiving ventilation</td>
<td>916 (8)</td>
<td>139</td>
<td>130</td>
</tr>
</tbody>
</table>
Interferon beta 1a - 2

- **All-cause mortality**: 243/2050 (12.9%) INFβ-1a group vs. 216/2050 (11%) placebo group; rate ratio: 1.16; 95% CI[0.96-1.39]; p=0.11
- **Initiation of mechanical ventilation**: INFβ-1a group: 209/1911 (10.9%) vs. control group 210/2475 (10.9%)
- **Time to discharge**: INFβ-1a did not reduced hospitalization duration

Study stopped for futility on 16th October
Baricitinib (JAK inhibitors)

- Double-blind, randomized, placebo-controlled, multicenter, academic study, Adaptive Covid-19 Treatment Trial 2 (ACTT-2)

- **Inclusion criteria**: hospitalized patients aged ≥ 18yo, positive SARS-CoV-2 RT-PCR test, lower respiratory tract infection (radiographic infiltrates, SpO₂ ≤94% (room air), requiring supplemental O₂, mechanical ventilation, or ECMO)

- **Exclusion criteria**: significant contraindication to any one of the study drugs

- **Primary outcome**: time to recovery

- **Secondary outcome**: clinical status at day 15, D28 mortality, adverse events

- **1033 patients** underwent randomization; 515 Baricitinib + RDV group, 518 control group (1:1)

- Immunomodulatory effect

- 1067 Patients assessed for eligibility
  - 34 excluded
    - 29 ineligible owing to meeting exclusion criteria or not meeting inclusion criteria
    - 5 eligible but were not enrolled

- 1033 Underwent randomization
  - 515 assigned to receive baricitinib + RDV
    - 508 Received infusion
    - 507 Received tablet
    - 7 did not receive any treatment
  - 518 assigned to receive placebo + RDV
    - 509Received infusion
    - 509 Received tablet
    - 9 enrolled but did not receive any treatment

- 66 discontinued intervention (deaths and discharges excluded)
  - 31 Were receiving tablets
  - 5 Were receiving infusions
  - 33 Were receiving both trial products
  - 84 Discontinued participation in trial early
    - 23 Died
    - 40 Were lost to follow-up

- 515 included in the ITT population
  - 507 included in the as-treated population
    - 8 excluded from as-treated population owing to not receiving at least 1 tablet

- 110 Discontinued participation in trial early
  - 36 Died
  - 41 Were lost to follow-up
  - 16 Withdrew

- 94 Discontinued intervention (deaths and discharges excluded)
  - 39 Were receiving tablets
  - 13 Were receiving infusions
  - 50 Were receiving both trial products

- Kalil AC et al. NEJM Dec 2020
# Baricitinib (JAK inhibitors)

## Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (N= 1033)</th>
<th>Baricitinib + RDV (N= 515)</th>
<th>Placebo + RDV (N= 518)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – Mean – yr (SD)</td>
<td>55,4 (15,7)</td>
<td>55,0 (15,4)</td>
<td>55,8 (16,0)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>652 (63,1)</td>
<td>319 (61,9)</td>
<td>333 (64,3)</td>
</tr>
<tr>
<td>BMI – Mean – kg/m² (SD)</td>
<td>32,2 (8,3)</td>
<td>32,2 (8,2)</td>
<td>32,3 (8,4)</td>
</tr>
<tr>
<td>Time from symptom onset to randomization – Median – days (IQR)</td>
<td>8 (5–10)</td>
<td>8 (5–10)</td>
<td>8 (5–11)</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate – no (%)</td>
<td>706 (68,3)</td>
<td>358 (69,5)</td>
<td>348 (67,2)</td>
</tr>
<tr>
<td>Severe – no (%)</td>
<td>327 (31,7)</td>
<td>157 (30,5)</td>
<td>170 (32,8)</td>
</tr>
<tr>
<td><strong>Score on ordinal scale – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Hospitalized, not requiring supplemental O₂, requiring ongoing medical care (Covid-19–related or otherwise)</td>
<td>142 (13,7)</td>
<td>70 (13,6)</td>
<td>72 (13,9)</td>
</tr>
<tr>
<td>5. Hospitalized, requiring supplemental O₂</td>
<td>564 (54,6)</td>
<td>288 (55,9)</td>
<td>276 (53,3)</td>
</tr>
<tr>
<td>6. Hospitalized, receiving NIV or high-flow O₂ devices</td>
<td>216 (20,9)</td>
<td>103 (20,0)</td>
<td>113 (21,8)</td>
</tr>
<tr>
<td>7. Hospitalized, receiving invasive MV or ECMO</td>
<td>111 (10,7)</td>
<td>54 (10,5)</td>
<td>57 (11,0)</td>
</tr>
</tbody>
</table>

NIV: Non invasive ventilation
MV: mechanical ventilation

Kalil AC et al. NEJM Dec 2020
Baricitinib (JAK inhibitors)

• **Time to recovery** (median days): 7 days Baricitinib + RDV group vs. 8 days RDV group; RR: 1,16 95% CI[1,01-1,32]; p = 0,03

• **Clinical status at day 15**: Baricitinib + RDV group: 30% higher odds of improvement; OR: 1,3 95% CI[1,0-1,6]

• **D28 mortality**: Baricitinib + RDV group: 5,1% 95% IC[3,5-7,6] vs. RDV group: 7,8% 95% IC[5,7-10,6], Hazard ratio: 0,65; 95% CI[0,39-1,09]

• **Serious adverse events**: Baricitinib + RDV group: 81/515 (16%) vs. RDV group: 107/518 (21%) between-group difference: −5.0; 95% CI[−9,8:-0,3]; p=0.03
Tofacitinib (JAK inhibitors)

- Double-blind, randomized, placebo-controlled, multicenter, industrial study, Brazil, STOP-COVID
- **Inclusion criteria:** aged ≥ 18yo, positive SARS-CoV-2 RT-PCR test, Covid-19 pneumonia on radiographic imaging, hospitalized patient for less than 72 hours
- **Exclusion criteria:** use of noninvasive or invasive MV or ECMO on the day of randomization
- **Primary outcome:** D28 occurrence of death or respiratory failure
- **Secondary outcome:** All-cause mortality
- 289 patients underwent randomization; 144 tofacitinib group, 145 placebo group (1:1)

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**Diagram Details:**
- 533 Patients assessed for eligibility
  - 244 excluded
  - 289 Underwent randomization
  - 144 Were assigned to receive tofacitinib
    - 142 Received Tofacitinib
      - 20 Discontinued Tofacitinib
    - 12 Did not receive tofacitinib
  - 145 Were assigned to receive placebo
    - 142 Received placebo
      - 15 Discontinued placebo
    - 3 Did not receive placebo
- 144 Were included in the primary analysis
- 142 Were included in the safety analysis
- 145 Were included in the primary analysis
  - 142 Were included in the safety analysis

---

MV: Mechanical Ventilation

Guimarães PO et al. NEJM Jul 2021
## Tofacitinib (JAK inhibitors)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N= 289)</th>
<th>Tofacitinib (N= 144)</th>
<th>Placebo (N= 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – Mean – yr (SD)</td>
<td>56 (14)</td>
<td>54 (14)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Female sex – no (%)</td>
<td>101 (34,9)</td>
<td>50 (34,7)</td>
<td>51 (35,2)</td>
</tr>
<tr>
<td>BMI – Median – kg/m² (IQR)</td>
<td>29,7 (26,7-32,9)</td>
<td>29,4 (26,8-33,2)</td>
<td>29,7 (26,4-32,7)</td>
</tr>
<tr>
<td>Time from symptom onset to randomization – Median – days (IQR)</td>
<td>10 (7–11)</td>
<td>10 (7–12)</td>
<td>9 (7–11)</td>
</tr>
<tr>
<td>Time from Covid-19 diagnosis to randomization – Median – days (IQR)</td>
<td>5 (2–8)</td>
<td>5 (2–8)</td>
<td>4 (2–8)</td>
</tr>
<tr>
<td>Hospitalization in the ICU at randomization – no (%)</td>
<td>54 (18,7)</td>
<td>28 (19,4)</td>
<td>26 (17,9)</td>
</tr>
<tr>
<td>Score on ordinal scale – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Hospitalized, not requiring supplemental O₂, requiring ongoing medical care (Covid-19–related or otherwise)</td>
<td>71 (24,6)</td>
<td>34 (23,6)</td>
<td>37 (25,5)</td>
</tr>
<tr>
<td>5. Hospitalized, requiring supplemental O₂</td>
<td>181 (62,6)</td>
<td>91 (63,2)</td>
<td>90 (62,1)</td>
</tr>
<tr>
<td>6. Hospitalized, receiving NIV or high-flow O₂ devices</td>
<td>37 (12,8)</td>
<td>19 (13,2)</td>
<td>18 (12,4)</td>
</tr>
</tbody>
</table>

NIV: Non invasive ventilation
MV: mechanical ventilation

Guimarães PO et al. NEJM Jul 2021
Tofacitinib (JAK inhibitors)

- **D28 cumulative of death or respiratory failure**: 26/144 (18.1%) Tofacitinib group vs. 42/145 (29%) placebo group; RR: 0.63; 95% CI[0.41-0.97]; p = 0.04
- **D28 all causes mortality**: 4/144 (2.8%) Tofacitinib group vs. 8/145 (5.5%) placebo group; HR: 0.49; 95% CI[0.15-1.63]
- **Proportional odds of having a worse score on the eight-level ordinal scale with Tofacitinib vs. control**: D14: 0.60; 95% CI[0.36-1.00], D28: 0.54; 95% CI[0.27-1.06]
Convalescent plasma (CP) - 1

- Randomized, controlled, open-label, multicenter trial, academic study, UK, (Randomized Evaluation of COVID-19 Therapy) RECOVERY

- **Inclusion criteria**: Hospitalized patients of any age, clinically suspected or laboratory confirmed SARS-CoV-2 infection, no medical contraindications to join the trial

- **Primary outcome**: all-cause mortality

- **Secondary outcome**: time to discharge from hospital, in patients not receiving MV at randomization; receipt of invasive MV (including ECMO) or death

- **11 558** patients underwent randomization; **5795 CP group**, **5763 usual care group** (1:1)

---

- **16 287 patients recruited**
- **13 127 eligible for randomization to CP**
- **11 558 randomized between convalescent plasma and usual care**
- **5 795 allocated convalescent plasma**
- **5 763 allocated usual care**
- **23 withdrew consent**
- **16 withdrew consent**
- **912 included in second randomization**
- **1125 included in second randomization**
- **5 795 included in 28-day intention-to-treat analysis**
- **5 763 included in 28-day intention-to-treat analysis**
## Convalescent plasma (CP) - 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CP (N= 5 795)</th>
<th>Usual care (N=5 763)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 yr – no (%)</td>
<td>3 705 (64)</td>
<td>3 748 (65)</td>
</tr>
<tr>
<td>70-79 yr – no (%)</td>
<td>1 310 (23)</td>
<td>1 281 (22)</td>
</tr>
<tr>
<td>≥ 80 yr – no (%)</td>
<td>780 (13)</td>
<td>734 (13)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>3 643 (63)</td>
<td>3 787 (66)</td>
</tr>
<tr>
<td><strong>Co existing conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>1 535 (26)</td>
<td>1 569 (27)</td>
</tr>
<tr>
<td>Heart disease – no (%)</td>
<td>1 267 (22)</td>
<td>1 309 (23)</td>
</tr>
<tr>
<td>Chronic lung disease – no (%)</td>
<td>1 385 (24)</td>
<td>1 328 (23)</td>
</tr>
<tr>
<td><strong>Median number of days since symptom onset</strong></td>
<td>9 (6–12)</td>
<td>9 (6–12)</td>
</tr>
<tr>
<td><strong>Median number of days since admission to hospital</strong></td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td><strong>Respiratory support received</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen only – no (%)</td>
<td>5 051 (87)</td>
<td>4 993 (87)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation – no (%)</td>
<td>302 (5)</td>
<td>315 (5)</td>
</tr>
</tbody>
</table>
Convalescent plasma (CP) - 1

- **28-day mortality**: 1388/5795 (24%) CP group vs. 1408/5763 (24%) usual care group; rate ratio: 1,00; 95% CI[0,93-1,07]; p= 0,95

- **Discharge alive within 28 days**: CP group: 3822/5795 (66%) vs. usual care group 3822/5763 (10,9%); rate ratio: 0,99; 95% CI[0,94-1,03]; p= 0,57

- **Invasive MV or death**: CP group: 1568/5493 (29%) vs. usual care group 1568/5448 (29%); rate ratio: 0,99; 95% CI[0,93-1,05]; p= 0,79

- Meta–analysis of mortality in RECOVERY and other trials: mortality rate ratio: 0,98 ; 95% CI[0,91-1,06]; p= 0,63
Convalescent plasma (CP) - 2

- Observational, multicenter, academic study, France
- **Inclusion criteria:** B-cell immunodeficiency with prolonged COVID-19 symptoms, positive SARS-CoV-2 RT-PCR from respiratory samples, no SARS-CoV-2 seroconversion
- 17 patients treated with 4 units of COVID-19 convalescent plasma

### Characteristics (N=17)

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [range] - yr</td>
<td>58 [35-77]</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>15 (88)</td>
</tr>
<tr>
<td>Non - Hematological malignancies</td>
<td>2 (12)</td>
</tr>
<tr>
<td>COVID-19 severity (WHO score), n (%)</td>
<td></td>
</tr>
<tr>
<td>4 – no (%)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>5-6 – no (%)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>7 – no (%)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Time between COVID-19 symptoms onset and CPT (days), median [range]</td>
<td>56 [7-83]</td>
</tr>
<tr>
<td>Time for oxygen weaning after CPT (days), median [range]</td>
<td>5 [1-45]</td>
</tr>
<tr>
<td>Overall survival, n (%)</td>
<td>16 (94)</td>
</tr>
</tbody>
</table>

- **Clinical symptoms:** 16/17 patients experienced amelioration of SARS-CoV-2 within 48 hours CP
- **SARS-CoV-2 RNAemia:** 9/9 patients witnessed a decreased below sensitivity threshold
1. What drug showed clinical efficacy?
   • Dexamethasone is the first drug to show life-saving efficacy in patients infected with COVID-19

2. What drugs did not show proven benefits?
   • No proven benefits have been reported with (hydroxy)chloroquine, ivermectin nor lopinavir/ritonavir treatment
Contacts

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