July 4th update

COVID-NMA

- Summary of Main Results -

Introduction

This is the 4th Summary of Main Results report from the COVID-NMA initiative. It provides an overview of the results as of **July 4th, 2022**, summarizing the evidence regarding treatment of hospitalized Covid-19 patients for which there is high or moderate certainty.

Since March 2022, the COVID-NMA initiative has focused its scope on vaccines, immunomodulators, and antivirals (results for other interventions up to that date are still available on the website), updating the results every two weeks. Therefore, the most up to date results are available on covid-nma.com, and the list ofstudies pending data extraction is available here. Feel free to get in touch with us using our contact form and to disseminate this document on twitter (@Covid-NMA).

Updates since the previous report

Since the previous report (updated on June 3rd) there have been the following changes:

- There is one new comparison, **Camostat Mesilate** vs placebo, for which the certainty of evidence for clinical improvement (day 28) is moderate. probably results in little to no difference on clinical improvement around 28 days.
- There is now moderate certainty regarding the effect of **Anakinra** on clinical improvement and the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 60 days. The current evidence therefore indicates that, in hospitalized patients, Anakinra probably reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 28 days and around 60 days, as well as slightly increasing the likelihood of clinical improvement around 28 days. It probably results in little to no difference in the likelihood of clinical improvement around day 60 and in the risk of adverse events.
- There is now moderate certainty regarding the effect **Tocilizumab** on the risk of adverse events, which are probably little to no different than in standard care/placebo. Tocilizumab is likely to reduce the risk of all-cause mortality (around 28 days) in hospitalized patients, although it probably results in little to no difference on clinical improvement around 28 days.
- In the summary table below, the order of the outcomes (columns) has been modified to match that of the summary of findings on the covid-nma.com website: viral negative conversion now appears after all-cause mortality (D60).

Continues on next page…

What is the current evidence regarding treatment of hospitalized Covid-19 patients?

Updated on July 4th, 2022

Pharmacologic treatments in hospitalized patients

Critical outcomes of interest: Clinical improvement (around day 28 or day 60), WHO Clinical Progression Score ≥ 7 (around day 28 or day 60), all-cause mortality (around day 28 or day 60), viral negative conversion (around day 7), adverse events and serious adverse events.

For most pharmacological treatments in hospitalized patients, the certainty of the evidence is still low or very low. Below is a summary of pharmacological interventions that have **results in favor of a beneficial effect** so far compared with placebo or standard care. We only highlight outcomes of moderate and high certainty; other outcomes are of low or very low certainty.

- **Anakinra** (a monoclonal antibody) probably reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 28 days and around 60 days in hospitalized patients, as well as slightly increasing the likelihood of clinical improvement around 28 days. It probably results in little to no difference in the likelihood of clinical improvement around day 60 and in the risk of adverse events. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Baricitinib** (a kinase inhibitor) reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death, around 28 days) in hospitalized patients, although it results in little to no difference in clinical improvement around 28 days. It is likely to reduce the risk of all-cause mortality (around 28 days and around 60 days). It probably does not increase the risk of adverse events but probably decreases the risk of serious adverse events.
- **Casirivimab + Imdevimab (REGN-COV2)** (Monoclonal antibody combination) probably reduces the risk of all-cause mortality (around 28 days), although the likelihood of clinical improvement around 28 days and around 60 days probably is not improved. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Corticosteroids** probably increase clinical improvement (around 28 days) slightly and reduce the risk of all-cause mortality (around 28 days) in hospitalized patients. We pooled together oral and intravenous corticosteroids of participants with various disease severity. Of note, the largest study (the RECOVERY trial) found in subgroup analysis that “differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization”, and that “the use dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.”
- **Tocilizumab** (a monoclonal antibody) is likely to reduce the risk of all-cause mortality (around 28 days) in hospitalized patients, although it probably results in little to no difference on clinical improvement around 28 days. It probably results in little to no difference in the risk of adverse events. It is one of the interventions that have been authorized in the EU to treat Covid-19.

For the treatments below there are outcomes with moderate or high certainty indicating **uncertainty of benefit or harm**

- **Remdesivir** (an anti-viral), which is one of the interventions recommended by the NIH and which has been authorized in the EU to treat COVID-19, we found that the risk estimate for all-cause mortality (around 28 days) and its wide confidence interval (RR 0.91, 95% CI 0.74 to 1.11) point to uncertainty of benefit or harm.

For the treatments below there are outcomes with moderate or high certainty indicating **no evidence of beneficial effects** (e.g. clinical improvement or reduction in mortality) or an increase in the risks of negative effects (e.g. serious adverse events) compared with placebo or standard care:

- **Auxora** (an immunomodulator) probably results in little to no difference in the risk of adverse events and probably decreases the risk of serious adverse events.

- **Bamlanivimab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around day 60.
- **Camostat Mesilate** (an anti-viral) probably results in little to no difference on clinical improvement around 28 days.
- **Canakinumab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around 28 days and in little to no difference in the risk of adverse events.
- **Convalescent plasma** probably results in little to no difference on clinical improvement around 28 days or all-cause mortality (around 28 days).
- **Lopinavir + Ritonavir** (an anti-viral) probably results in little to no difference on viral negative conversion (around day 7), clinical improvement (around 28 days) or all-cause mortality (around 28 days).
- **Ruxolitinib** (a kinase inhibitor) probably results in little to no difference in the risk of adverse events.
- **Sotrovimab** (a monoclonal antibody) probably results in little to no difference in clinical improvement around day 60. Furthermore, it probably increases the risk of serious adverse events. While the NIH recommends this intervention for outpatients, it has not been recommended for hospitalized patients. Similarly, this intervention has been authorized in the EU to treat COVID-19, but only in patients who do not require supplemental oxygen and are at increased risk of the disease becoming severe.

For another intervention authorized by the European Medicines Association (Ritonavir alone) we have not yet identified randomized controlled trials reporting its effectiveness.

Summary table on next page…

Summary Table: Pharmacologic treatments in hospitalized patients

(Updated on July 4th , 2022)

Legend:

Moderate/**High** certainty of benefit
Moderate/**High** certainty of little or no difference
Moderate/**High** certainty of harm

Treatment (vs standard care or placebo)	Treatment effectiveness							Adverse events	
	Clinical improvement (D28)	**Clinical improvement (D60)**	**WHO progression score (level ≥7) (D28)**	**WHO progression score (level ≥7) (D60)**	**All-cause mortality (D28)**	**All-cause mortality (D60)**	**Viral negative conversion (D7)**	**Adverse events**	**Serious adverse events**
Anakinra	1.10 (1.00-1.20)	0.94 (0.79 - 1.11)	0.64 (0.42 - 0.98)	0.54 (0.3 - 0.96)	low certainty	low certainty	low certainty	1.02 (0.94-1.10)	low certainty
Auxora		very low certainty	very low certainty	very low certainty	very low certainty	very low certainty		1.04 (0.87 - 1.25)	0.68 (0.47 - 0.99)
Bamlanivimab (LY-CoV555)		0.98 (0.90 - 1.07)	low certainty		low certainty	low certainty		low certainty	low certainty
Baricitinib	**1.02 (1.00 - 1.05)**		**0.87 (0.78 - 0.97)**		0.75 (0.58 - 0.98)	0.69 (0.56 - 0.86)		0.96 (0.88 - 1.05)	0.77 (0.64 - 0.94)
Camostat Mesilate	1.03 (0.94 - 1.13)		low certainty		low certainty		very low certainty	very low certainty	very low certainty
Canakinumab	1.05 (0.96-1.14)		low certainty		low certainty	very low certainty		1.02 (0.86-1.21)	low certainty
Casirivimab + Imdevimab (REGN-COV2)	1.02 (0.99 - 1.04)	1.04 (0.97 - 1.12)	low certainty		0.93 (0.86 - 1.01)	low certainty			
Convalescent plasma	1.00 (0.97-1.02)	low certainty	low certainty	very low certainty	0.97 (0.92 - 1.02)	very low certainty	very low certainty	low certainty	low certainty
Corticosteroids	**1.05 (1.02 – 1.09)**		very low certainty		**0.91 (0.85-0.98)**	very low certainty	very low certainty	low certainty	very low certainty
Lopinavir + Ritonavir	0.99 (0.90 - 1.09)		low certainty	very low certainty	1.02 (0.92-1.12)	low certainty	1.05 (0.88 - 1.25)	low certainty	very low certainty
Remdesivir	low certainty		low certainty		0.91 (0.74-1.11)	very low certainty	low certainty	very low certainty	very low certainty
Ruxolitinib	low certainty		low certainty		low certainty			1.01 (0.85 - 1.19)	low certainty
Sotrovimab		1.05 (0.97 - 1.15)	low certainty		low certainty	low certainty		low certainty	2.03 (1.32 - 3.13)
Tocilizumab	**1.05 (1.00-1.11)**	very low certainty	low certainty		**0.88 (0.81-0.94)**	low certainty		1.03 (0.95 - 1.12)	very low certainty

All values are RR (95% CI). Bolded results have a high level of certainty, while non-bolded results have a moderate level of certainty. Last updated: July 4th 2022. Click on the treatment to access the corresponding site at covid-nma.com.

Acknowledgements

This work received some funding from the Agence Nationale de la Recherche (ANR), the World Health Organization (WHO), Cochrane France, Center of Research in Epidemiology and StatisticS (CRESS), Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu), the French Ministry of Higher Education and Research, the French Ministry of Health, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris Cité, Centre national de la recherche scientifique (CNRS), the Federal Ministry of Education and Research, Germany and the European Union's Horizon 2020 Research and Innovation Programme under agreement No. 101037867