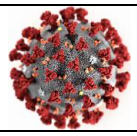
National COVID-19 Science Task Force (NCS-TF)	

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Contact persons : Alexandra Calmy and Oriol Manuel	
Comment on planned updates : Upon data indicating that drugs against have a significant impact on mortality	
Title : Impact of therapies against Covid-19 on mortality	
Questions : To present the therapies with a possible impact to reduce COVID-19-associated mortality	

Summary: Several drugs are emerging for the treatment of COVID-19, the most interesting being dexamethasone showing a reduction of Covid-19 caused mortality and Remdesivir demonstrating a reduction of hospital length of stay. The exact positioning in the disease management is still in progress and meta-analyses, as well as follow-up data from randomized trials, are still to come. In the meantime, it is reasonable to add both drugs in treatment options, at least for patients with severe pneumonia, hospitalized for oxygen supplementation (remdesivir) or mechanical ventilation (dexamethasone).

In comparative analyses, Switzerland has demonstrated so far one of the lowest, if not the lowest hospital Covid-19 caused mortality in an international context. In this context it is not yet possible to judge whether the impact of these treatments would be identical in Switzerland (as hospital mortality is lower), i.e. if they have the identical impact on mortality and/or hospital stay duration.

Larger comparative trials are being conducted elucidating the role of Remdesivir and anti-inflammatory drugs. Importantly, first trials are starting investigating newly developed drugs such as monoclonal antibodies or drugs interfering with the replication of SARS-CoV-2.

Policy brief on the reduction of mortality by drug therapies

Since the beginning of the pandemic, hundreds of clinical trials assessing therapeutic options for COVID-19 have been included in international registers. However, very few have been completed with the appropriate power to detect a significant effect on mortality.

A consortium, led among others by Cochrane France, Cochrane Ireland, Cochrane South Africa, the French National Institute of Health and Medical Research (Inserm) and the University of Milan, has established a living mapping and systematic review of COVID-19 studies and has entered the results of 30 randomized controlled clinical trials, 19 non-randomized studies and 201 observational studies (covid-nma.com, data extracted on 29 July 2020).

In addition, several so-called “mega-trials” including thousands of patients are currently ongoing worldwide. The most important ones are the following:

Recovery trial (https://www.recoverytrial.net/). A UK-based trial initially evaluating several therapeutic arms: lopinavir/ritonavir (LPVr), hydroxychloroquine (HQC), dexamethasone and azithromycin. Two additional arms were included later, i.e. tocilizumab and convalescent plasma. After interim analyses showing the lack of clinical benefit of HCQ and LPV/r and the significant clinical benefit of dexamethasone (see below), the current trial design includes azithromycin, tocilizumab, convalescent plasma, and a pediatric arm of dexamethasone. The trial has currently included more than 11,500 patients.

Solidarity trial (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). A WHO-sponsored trial with initially five arms: remdesivir, HCQ, LPV/r and LPVr + interferon beta, compared to the standard of care. The trial has currently enrolled more than 9000 patients in over 400 participating hospitals in 35 countries. An interim analysis has confirmed the lack of efficacy of the HCQ and LPVr arms. Accordingly, the new factorial design of the study includes: remdesivir, interferon beta, and a combination of remdesivir and interferon beta, compared to the standard of care.

ACTT trial (known as the "Adaptive COVID-19 Treatment *Trial" [https://www.niaid.nih.gov/clinical-trials/adaptive-covid-19-treatment-trial-actt])***.* A United States National Institution of Allergy and Infectious Diseases (NIH)-sponsored trial with also an adaptive design. The ACTT-1 trial compared remdesivir with placebo in more than 1000 patients. The preliminary results showed a shorter time to clinical improvement in the remdesivir arm (see below). The ACTT-2 trial is currently comparing remdesivir plus baricitinib (a JAK inhibitor).

In this policy brief, we focus on the evidence obtained by published randomized clinical trials for the drugs under investigation. Importantly, the internal validity of many randomized clinical trials is impaired by significant protocol changes during the trial, and the external validity is limited by the different healthcare settings, as evidenced by significant differences in mortality due to gender, age and comorbidity distribution, as well as the organization of care.

Drugs tested in randomized clinical trials

1. Dexamethasone

Steroids are currently recommended (with weak evidence) to treat acute respiratory distress outside of COVID-19. The Recovery trial included more than 6000 patients randomized to receive dexamethasone 6 mg daily for 10 days compared with only usual care (>4000 patients). Overall, the use of dexamethasone was associated with a 17% reduction in age-adjusted 28-day mortality (relative risk ratio [RR] 0.83 [0.74 to 0.92]; P=0.0007). This effect was higher in ventilated patients (RR 0.65 [0.48 to 0.88]; P=0.0003) and in those receiving oxygen only (RR 0.80 [0.67 to 0.96]; P=0.0021). There was no benefit among patients who did not require respiratory support at randomization (RR 1.22 [0.93 to 1.61]; P=0.14). Of note, the 28-day mortality rate was higher than that reported in the literature (41% in those who required ventilation, 25% in patients who required oxygen only, and 13% in those who did not require any respiratory intervention). For example, in the European RISC-19-ICU registry cohort, intensive care unit mortality was 24% (Wendel Garcia et al, EClinicalMedicine, published by The Lancet, July 6, 2020). In a multicenter, randomized, open label, randomized trial in COVID-19 patients with moderate and severe ARDS (CoDEX study), dexamethasone significantly increased the number of days alive and free of mechanical ventilation over 28 days (P=0.04). There was no impact of dexamethasone on all-cause day 28 mortality. Of note, the study was stopped early after the publication of the Recovery dexamethasone results.

A meta-analysis of pooled data from 7 randomized clinical trials using steroids for the treatment of COVID-19 has been published and confirms the effect on day-28 all-cause mortality of systemic corticosteroids in critically ill patients with COVID-19. Based on this, WHO

issued a strong recommendation for using systemic (intravenous or oral) corticosteroid therapy for 7 or 10 days in patients with severe and critical COVID-19. The overall results of the meta-analysis are driven primarily by the results of the Recovery trial (57% weight among the pool of studies).

2. Remdesivir

Remdesivir is a nucleotide analogue prodrug that inhibits the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA polymerase. In the ACTT-1 trial, patients randomized to receive remidesivir (200 mg daily loading dose, then 100 mg daily for 10 days) had a shorter recovery time than patients on placebo (11 days [9-12] vs. 15 days [13-19]; P<0.001). In the preliminary analysis, the hazard ratio (HR) for death at 14 days was 0.70 (0.47-1.04), which was not statistically significant. In the subgroup analysis, the effect of remdesivir on mortality was significant in patients requiring supplemental oxygen (HR 0.22 [0.08-0.59]), but not in those receiving invasive or non-invasive mechanical ventilation. Beigel et al report that a 28-day follow-up is available and will be published to complete the preliminary data (Beigel et al, New England Journal of Medicine, 22 May 2020)

In a trial enrolling 237 patients (158 in the remdesivir group and 79 in the placebo group), there were no differences in time to clinical improvement between arms: 21 days (13-28) in the remdesivir arm vs. 23 days (15-28) in the placebo arm. Due to the modest sample size, only 32 deaths were reported (15% in the remdesivir group and 13% in the placebo group).

A meta-analysis of all randomized clinical trials using remdesivir for the treatment of COVID-19 is currently ongoing. The Cochrane Review Consortium forest plots on all-cause mortality are available at: https://covid-nma.com/living_data/index.php#images2-13).

In recent guidelines from the Infectious Diseases Society of America on the treatment and management of patients with COVID-19 (Adarsh Bhimraj et al, www.idsociety.org/COVID19guidelines), the guideline panel suggests remdesivir rather than no remdesivir for the treatment of severe COVID-19 in hospitalized patients. However, additional data are needed to precisely understand the benefit of treatment based on disease severity at treatment initiation. The panel has added the following remark : "for consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen, rather than in patients on mechanical ventilation or extracorporeal mechanical oxygenation".

The BMJ Rapid Recommendations issued by the MAGIC group (Rochwerg B et al, BMJ 2020 Jul 30) suggest remdesivir rather than no remdesivir for the treatment of patients with severe COVID-19 infection (weak recommendation) and recommend that randomized controlled trials examining remdesivir in patients with COVID-19 should continue. In Switzerland, we recommend that all patients receiving remdesivir are followed-up in a prospective cohort study to evaluate the rate of progression to mechanical ventilation and/or death.

3. Hydroxychloroquine

HCQ inhibits SARS-CoV-2 through several mechanisms, including the inhibition of viral fusion and nucleic acid replication. In addition, HCQ also exerts immune modulating effects (inhibition of cytokine production and modulation of the expression of co-stimulatory molecules), which may be relevant in COVID-19 patients.

In the Recovery trial, mortality was not significantly different in patients receiving HCQ (418/1561; 26.8%) or the standard of care (788/3155; 22%; RR 1.09 [0.96-1.23]). In the Solidarity trial, unpublished data showed an increase in mortality in the HCQ arm vs. the

standard of care arm. A meta-analysis of both trials suggests an increase in mortality of HCQ, but publication of data is still pending.

4. Lopinavir/ritonavir

LPVr inhibits SARS-CoV-2 protease. In the Recovery trial, mortality was not significantly reduced in the LPVr arm (353/1596; 22.1%) vs. the standard of care arm (719/3376; 21.3%; RR 1.04 [0.91-1.18]). In the Solidarity trial, unpublished data showed no reduction in mortality in the LPVr arm vs. the standard of care arm. In a Chinese trial (Cao B et al, New England Journal of Medicine, DOI: 10.1056/NEJMoa2001282), the only published randomized clinical trial results publicly available to date, 28-day mortality was numerically lower in the LPV/r group compared with the standard of care group for both the intention-to-treat population (19.2% vs. 25.0%; difference, −5.8% [95%, CI −17.3 to 5.7]) and the modified intention-to treat population (16.7% vs. 25.0%; difference, −8.3% [95% CI −19.6 to 3.0]). Results of LPVr used as a treatment were discouraging and the use of LPV/r to treat COVID-19 is no longer recommended outside of clinical trials.

5. Interferon

In an open randomized clinical trial, 86 patients received LPV/r, ribavirin, and interferon beta-1b (three doses of 8 Mio units) were compared to 41 patients receiving LPVr alone. The combination group had a significantly shorter viral clearance (7 days vs. 12 days). No patient died during the trial.

As mentioned, interferon B1a is currently being tested in the Solidarity trial.

6. Tocilizumab

Tocilizumab is an anti-human IL-6 receptor monoclonal antibody. Several randomized clinical trials on the use of tocilizumab in patients with COVID-19 are ongoing. A press release on 27 April 2020 reported that a French randomized clinical trial had observed that patients receiving tocilizumab had a significant reduction in mortality, but the trial has not yet been published. Guaraldi et al published the results of a retrospective observational cohort study of 179 patients treated with tocilizumab plus standard of care vs. 222 patients who received only standard of care (Lancet Rheumatology 2020). After adjustment for gender, age, recruiting center, duration of symptoms, and the Sepsis-related Organ Failure Assessment score, tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted HR 0·61 [95% CI 0·40–0·92]; P=0·020). New infections occurred in 24 (13%) of 179 patients treated with tocilizumab vs. 14 (4%) of 365 patients treated with standard of care alone (P<0·0001). On 29 July 2020, Roche pharmaceuticals provided an update of the phase III COVACTA trial of tocilizumab in hospitalized patients with severe COVID-19-associated pneumonia. The COVACTA trial did not meet either its primary endpoint of improved clinical status, or the secondary endpoint of reduced patient mortality at week 4 (19.7% vs 19.4% in the placebo arm, with a difference of 0.3% (7.6%, 8.2%), P=0.94).

7. Convalescent plasma

In an open label, multicenter, randomized clinical trial, 103 patients received convalescent plasma (n=52) or standard of care (n=51) (JAMA, published online 3 June 2020). Clinical improvement up until day 28 occurred in 51.9% of patients treated in the convalescent plasma group vs. 43.1% of control patients (difference, 8.8% [95%CI, −10.4% to 28.0%]; HR, 1.40 [95%CI, 0.79-2.49]; P=0.26). There was also no significant difference in mortality (15.7% vs. 24.0%; odds ratio, 0.65 [0.29-1.46]; P=0.30). Several trials assessing

convalescent plasma are ongoing. Clinical data are currently insufficient to recommend either for or against the use of convalescent plasma.

8. Other drugs

Several compounds are currently under investigation in clinical trials, including antivirals (favipiravir, ivermectin, nitazoxanide) and immunomodulatory drugs (e.g., infliximab, anakinra, ruxolitinib, baricitinib, eculizumab). No robust data including mortality as the primary endpoint are currently available from these trials.

In summary, several drugs are emerging for the treatment of COVID-19, the most interesting being dexamethasone showing a reduction of Covid-19 caused mortality and Remdesivir demonstrating a reduction of hospital length of stay. The exact positioning in the disease management is still in progress and meta-analyses, as well as follow-up data from randomized trials, are still to come. In the meantime, it is reasonable to add both drugs in treatment options, at least for patients with severe pneumonia, hospitalized for oxygen supple-mentation (remdesivir) or mechanical ventilation (dexamethasone).

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