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New coronavirus : SARS-CoV-2
Specific antiviral treatment

1. Introduction

The new coronavirus SARS-CoV-2 can cause severe pneumonia.

No specific validated treatment currently exists. Patient management consists of symptomatic treatment and supportive care (resuscitation measures) including oxygen administration and treatment of secondary bacterial infections and other complications, which are sometimes serious, such as myocarditis or acute respiratory distress syndrome (ARDS). Admission to the intensive care unit is sometimes needed.

Some experimental treatments known to be active against coronaviruses may have an effect on SARS-CoV2, but very little clinical data is available to this day. More than 80 clinical randomized trials are ongoing, mostly in China, but no results have been made public at the present time. The aim of this document is to review the available literature and develop recommendations based on clinical evidence.

2. Antiviral treatments to be considered: existing literature

A) Remdesevir (GS-5734)

- *Safety profile*:
  Administered to more than 175 patients treated in a phase III trial (PALM trial) against Ebola virus disease caused by the *Ebola Zaire* virus (Mulangu, NEJM 2019).
  Security data: 1 severe adverse effect (SAE) attributed to remdesevir (death due to cardiac arrest): hypotension. No other severe adverse effects.

- *In vitro data*:
  Antiviral with broad-spectrum activity against coronaviruses including SARS-CoV-2: adenosine analog, chain terminator (Sheahan, Sci Transl Med 2017; Wang, Cell Res 2020; Agastini, mBio 2018).

- *Animal data*:
  Mouse model against SARS-CoV (Sheahan, Sci Transl Med 2017): In early treatment, it reduces lung viral load and improves clinical symptoms and respiratory function.

  Superior to lopinavir/ritonavir in a mouse model: decrease in respiratory symptoms and viral load (Sheahan, Nat Commun 2020). The mouse model offers a limited understanding of the pathology of coronaviruses in humans.

Successfully used in the prevention and treatment of monkeys infected by the MERS coronavirus (De Wit, PNAS 2020).

- *Human data :*
  Case report of a patient with pneumonia successfully treated with remdesivir (Holshue, NEJM, 2020) (very low evidence).

  (Midgley, medRxiv, 2020) Case series non peer-reviewed: 3/12 patients treated by remdesevir, not randomized, uncontrolled: no death, no clear temporal association between treatment administration and clinical improvement or viral shedding. (very low evidence).

  Only IV available formulation.

- *Accessibility*:
  Supply difficulty: as of March 7 2020, only provided by Gilead for patients requiring mechanical ventilation and without heart disease or need for vasopressors under MEURI.

B) Lopinavir/ritonavir

- *Security profile*:
  Well-known security profile with well described contraindications and interactions (CYP3A4 inhibitor). Its administration should not impede on the prescription of another necessary medication.
  Validated by Swissmedic for the treatment of HIV infected patients.

- *In vitro data*:
  In vitro activity against coronaviruses, but inferior to remdesevir and controversial/inconsistent results (Biochem Biophys Res Commun 2004;318(3):719-725; Chu, Thorax 2004).

  Unknown mechanism of action.

- *Animal data*:
  In association with IFN, no effect on the respiratory illness or viral load in mouse models infected with MERS (Sheahan, Nat Commun 2020).

- *Human data:*

  - *Clinical data for MERS and SARS*:

  *MIRACLE trial treatment for MERS in combination with IFN (Arabi, Trials 2020): ongoing, no data yet.

  *Case reports against MERS: uncontrolled, in combination with other treatments. Patient survived (Kim, Antivir Ther 2016), patient died (Spanakis, Int J Antimicrob Agents 2014) (very low evidence).

  May be useful as PEP in combination with ribavirine (?): small trial (22 in the treatment group vs 21 in the control (no treatment) group), showed efficiency as PEP for HCW

exposed to MERS, but exposure history not clear and 40% had adverse effects (Park J Hosp Infect 2019) (very low evidence).

*Case reports against SARS: uncontrolled study, 3 patients treated, all had other concomitant treatments, all developed altered liver function tests (the differential diagnosis of this adverse effect was a viral illness) (Chau, Hepatology, 2004).
In combination with ribavirine, possible efficacy in patients with severe SARS infection (open label and before/after study): less ARDS/deaths (2.4% vs 29%, respectively) amongst patients also treated with lopinavir/ritonavir (Chu, Thorax 2003) (quality of evidence very low given the observational design, observed difference unlikely).

Against SARS, in a retrospective study of 75 matched patients: reduction in mortality (2.3% vs 16%) among those treated a median of 5.5 days after symptom onset, sometimes in combination with ribavirine. No reduction in mortality in patients undergoing salvage therapy (Chan, HK Med J 2003) (low to very low evidence given the observational design, despite matching).

- *Clinical data for SARS-CoV-2*:

Case report of survival in a patient with SARS-CoV2 pneumonia, but late administration after evidence of clinical improvement (Lim, JKMS 2020) (very low evidence).

*° Case report of 1 patient with bilateral pneumonia who died after 5 days of treatment. Concomitant treatment with IFN, alpha2b and prednisone. Pathology showed microvesicular steatosis and portal alterations with a differential diagnosis of medication toxicity vs viral illness (Xu et al, Lancet 2020) (very low evidence).

Young, JAMA 2020*:* Singapore, 5 oxygen-dependent patients treated with lopinavir/ritonavir: 3 improved, 2 worsened and developed respiratory failure (very low evidence).

^`Wang Bio Science Trends, 2020: treatment of 4 patients with lopinavir/ritonavir in combination with umifenovir and Chinese medicine, developed pneumonia but no deaths (very low evidence because uncontrolled case reports and combination with other treatments).

*Chen, J Med Virol 2020: 9 patients with pneumonia, good outcome, combination of multiple antiviral agents (very low evidence because retrospective study, no randomization).

*^`Chen Chinese J of Infectious Diseases: in combination with IFN-alpha2b: 52 lopinavir/ritonavir + 34 arbidol, 48 without treatment: no effect on clinical progress at 7 days or on viral shedding (retrospective study, no randomization, low to very low evidence).

*°Zhou, Lancet, 2020: Retrospective observational study, 41 patients treated with lopinavir/ritonavir: no difference in survival or viral shedding, concomitant treatments, late administration of treatment with a median of 14 days (very low evidence because retrospective study, no randomization).

*`Wu, JAMA 2020: Less ARDS in the antiviral treatment group, retrospective study of 201 patients, no clear description of the treatment (monotherapy vs combination?) (low to very low evidence).

*°`Multiple RCTs in China lopinavir/ritonavir in combination with various treatments: results pending.

*: In association with IFN

^: association with Arbidol (unifenovir)

° association with steroids: methylprednisolone

` association with other treatments (Chinese medicine, IVIG)

- *Dose*:
  In the above-mentioned trials, lopinavir/ritonavir was given at a dose of 400/100 mg twice daily (i.e. 2 tablets of 200/50 twice daily); a double dose was suggested by some groups (no evidence reported).

  Suggested treatment duration is 5 to 10 days (very low evidence).

C) Chloroquine

- *In vitro data*:
  In vitro antiviral activity against SARS-CoV-2 (alkalization) (Wang, Cell Res 2020).

- *Security profile:*
  Well-known security profile and contraindications (hemolytic anemia, porphyrin, glucose-6-phosphate dehydrogenase [G6PD] deficiency).

  Most common adverse effects of short-term use are QTc prolongation, gastrointestinal side effects, pruritis, hypoglycemia and cytopenia (rare). Visual disturbances and cardiomyopathies are described with longer treatment duration.

  Validated by Swissmedic for other indications (no special authorization necessary).

- *Animal data*:
  Bernard, Antivir Chem Chemother 2006;17(5):275284: no effect on mice infected with SARS.

- *Clinical data*:
  A Chinese study raised the notion of an apparent efficacy, but data not available (Gao, Bio Sci Trends 2020) (very low evidence).

  CAVEAT CHIKV: In vitro activity, but increases the viral load in non-human primates, no effect on viral load in humans who have a possible delay in the immune response (Roques, Viruses 2018).

- *Pharmacokinetics, dosage and schema*:
  Sufficient plasma concentrations can be achieved: effective concentration (EC) 50%

chloroquine: inhibitory concentration of 1 uM, which corresponds to 352 µg/L L or 352 ng/mL.

Can be achieved with the recommended dose for the treatment of malaria, i.e. an initial loading dose of 1.5 g chloroquine base divided into 600 mg at H0, and 300 mg at H6, H24 and H48. In patients with malaria, blood levels were higher than that of controls (Tan-Ariya, Transac Royal Soc Trop Med Hyg 1995; Na-Bangchang, Br J Clin Pharmac 1994).

Given that 200 mg of chloroquine sulfate (hydroxychloroquine - Plaquenil®) is equivalent to 155 mg of chloroquine base, an equivalent dose will be achieved with 4 tablets of Plaquenil® 200 mg at H0, then 2 tablets at H6, H24 and H48. These doses were used for the treatment of malaria.

A dose of 600 mg of chloroquine base (or 4 tablets of hydroxychloroquine 200 mg) is suggested by some teams (absence of evidence).

Other schemas:
Hydroxychloroquine 200 mg twice daily (absence of evidence) or chloroquine base 500 mg twice daily (very low evidence). Duration of treatment 5 to 10 days (very low evidence)

D) Other treatments: (very low evidence)

- Protease inhibitors

- Atazanavir may be more active due to its conformation. No in vitro data (very low evidence).
- Ongoing randomized controlled trial of darunavir/cobicistat, no in vivo or in vitro studies for SARS-CoV-2.

- Interferon:

- Multiple in vitro studies (very low evidence).
- IFN-alpha: many types. In vivo animal studies against SARS-CoV: Prophylaxis > PEP (Haagmans et al., Nat Med 2004).
  MERS case series: 8 patients, 6 of whom died (Al Ghamdi BMC Infect Dis 2016) (very low evidence).
  Retrospective observational study of 349 patients with MERS showed no effect on mortality (Arabi, CID, 2019) (very weak evidence).
- IFN-beta: case series of 23 cases of which 18 died (Al Ghamdi, BMC Infect Dis 2016) (very low evidence).
  Retrospective observational study of 349 patients with MERS showed no effect on mortality (Arabi, CID, 2019) (very low evidence).
  In non-human primate animal models, disease course was less severe and the lung viral load was lower in necropsied animals (Chan, J infect Dis 2015) (very low evidence)
- Often given in combination with lopinavir/ritonavir (see paragraph entitled « lopinavir/ritonavir ») (very low evidence).

- Immunomodulators:

A. Tocilizumab

- Monoclonal antibody against the interleukin-6 receptor: 21 patients, retrospective, observational, non-controlled study, non-peer-reviewed: concomitant administration with other non-controlled treatments: no deaths (very low evidence).
- Used by Italian teams who report a benefit in patients with elevated inflammatory markers. Data only reported by the press (very low evidence).

B. Anakinra (IL-1 antagonist): No evidence.
C. Irinotecan, etoposide: No evidence.
D. Ruxolitinib: Ongoing RCT, no evidence.

- Camostat mesylate: commercialized in Japan for the treatment of pancreatitis: Blocks the entry of SARS-CoV-2 in cells in in vitro models (Hoffman, Cell, 2020) (very low evidence).

- Nitazoxanide: In vitro activity against MERS and SARS-CoV-2 (Wang, Cell research, 2020) (very low evidence).

- Monoclonal antibodies:
- Still experimental
- Not available (Regeneron?)
- Efficacy in the mouse model (MERS) (Widjaja, Emerg Microbes Infect 2019)

- Brincidofovir, TMPRSS-2 inhibitor (no data at present time)

- Anti-influenza agents:
- No data on anti-coronavirus activity, including the broad-spectrum antiviral favipiravir
- Umifenovir: ongoing randomized controlled trial, in vitro activity
- Favipiravir, oseltamivir, baloxavir: ongoing randomized controlled trials

- Tenofovir: no data available, but security profile established

- Chinese medicine: ongoing randomized controlled trial

- NK lymphocyte infusion, mesenchymal cell infusion: ongoing randomized controlled trial

- Vitamin C: ongoing randomized controlled trial

3. Treatment combinations

No preclinical or clinical data are currently available regarding the combination of lopinavir/ritonavir with chloroquine and/or remdesevir.

A concomitant administration of chloroquine and lopinavir/ritonavir can increase the QTc (www.hivdruginteractions.org, very low evidence).

Given the possible interactions reported by the manufacturer of remdesevir, its "compassionate" use should not be associated with lopinavir/ritonavir.

Clinical and pre-clinical data on combination treatment of lopinavir/ritonavir with ribavirin, interferon, Chinese medicine or steroids exists but is of weak to very weak quality.

4. Treatments not recommended by WHO

- Ribavirin (clinical deterioration and adverse effects such as hemolytic anemia).
- Steroids (except for patients who develop septic choc or ARDS) as they lead to increased viral shedding in viral diseases i.e MERS (Stockman et al. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343); ongoing randomized controlled trial in China. The timing of the administration of steroids for the prevention of ARDS following an episode of viral pneumonia remains to be determined (Villars, Lancet 2020).
- Mycophenolate mofetil (Chan, JID 2015).

5. Summary

- *Remdesevir*:

Possible benefit, but uncertain given the very limited preclinical data (low degree of certainty). Good security profile *a priori*. Intravenous administration possible.
Resources: no cost involved as treatment is on "compassionate" grounds, major supply problem. The competition with another molecule would pose a problem if several randomized controlled trials are conducted in parallel (currently not the case).

Practically:
First line treatment, if available, in case of severe infection because it can be administered intravenously (but Gilead decided as of March 7, 2020 to only release the medication in case of respiratory failure requiring mechanical ventilation in the absence of cardiac conditions, organ failure and need for vasopressors).

Dosage and duration: 200mg IV as loading dose followed by 100mg once daily for up to 10 days.

Obtain a signed informed consent before ordering the medication from the manufacturer. Inform patients that some of their clinical data will be anonymously shared with the pharmaceutical company.

Fill the online order on Gilead's platform: https://rdvcu.gilead.com/. Inform the pharmacy of the order (Cyril Stucki or on call pharmacist) who will inform the cantonal pharmacist (tel: 022 546 51 82 or pharmacien.cantonal@etat.ge.ch) of treatment arrival (formulaire de déclaration pour l'importation de médicaments selon l'article 49 de l'OAMed). Once you obtain the approval of the cantonal pharmacist, inform Gilead to release the medication.

A clinical assessment follow up form must be filled daily and sent to Remdesivir_CDM@gilead.com

- *Lopinavir/ritonavir:*

Possible benefit, but uncertain according to preclinical data (low degree of certainty; very indirect data, not always coherent, possible publication bias). Good security profile, but several interactions (possible interaction, but also competition with other potentially useful treatments: should not impede on the administration of a necessary treatment).
Can be given to neonates, children and pregnant or breast-feeding women.
Resources: acceptable cost; feasibility: its equity is to be evaluated by international health authorities to ensure that there is a sufficient stock to treat patients currently on this treatment for a valid indication without alternative therapies.

Practically:
- Dose and duration: Lopinavir 200mg/ritonavir 50mg, 2 tablets twice daily for 5 to 10 days.

- Given the uncertain level of evidence, its use must not impede on other necessary or potentially more useful treatments. It should not be used in case of contraindication with another necessary medication.
- Use with caution due to the potential cardiac side effects of the medication such as arrhythmia and QTc prolongation and given the risk of SARS-CoV-2 induced myocarditis. An ECG should be done at baseline and during treatment with lopinavir/ritonavir.
- As of March 13, 2020, the Swiss reserve of lopinavir/ritonavir is limited.
- In case of use, explain to the patient that the use of lopinavir/ritonavir for the treatment of SARS-CoV-2 is off-label. Document informed consent in the medical chart.
- Available in syrup form and can be administered via NG tube (tablets must not be crushed), an alternative to intravenous remdesevir.
- Check for contraindications and follow the recommendations (https://www.hiv-druginteractions.org/checker or http://www.covid19-druginteractions.org/).
- Always do a baseline HIV test to make sure the patient is seronegative.

- *Chloroquine:*

Possible benefit, but uncertain according to available preclinical data (low degree of certainty), very low evidence according to clinical data, side-effects and contraindications known. Resource: inexpensive; feasibility: possible
Access: hydroxychloroquine available, equity is to be evaluated by international health authorities to ensure that there is a sufficient stock to treat patients currently on this treatment for a valid indication without an alternative.

Practically:
- Hydroxychloroquine Plaquenil® 200 mg: 4 tablets at H0, 2 tablets at H6, H24 et H48 or a single dose of 4 tablets at H0.
- Evidence concerning the dosage and the efficacy is very uncertain. Last line of treatment.
- In case of use, explain to the patient that the use of chloroquine for the treatment of SARS-CoV-2 is off-label. Document informed consent in the medical chart.
- Do not use in case of major contraindications. Test for G6PD deficiency before initiating this treatment. Discontinue the medication in case of adverse effects.
- Use with caution due to the potential cardiac side effects of the medication such as QTc prolongation and given the risk of SARS-CoV-2 induced myocarditis.
  Monitor QTc while on treatment.

- *Conclusion*:

No strong recommendations on specific treatment can be made at the present time given the very uncertain benefit of the treatments discussed here. The evidence for the administration of each of these treatments is low, if not very low, and the risk/benefit ratio must be carefully assessed for each patient.

In the absence of proof of efficacy, the widespread use of any of these treatments cannot be recommended, particularly amongst patients without risk factors and with a mild illness (e.g. young patients with no comorbidities presenting with upper respiratory tract infection symptoms). The discussion should be reserved for patients with risk factors and for severe cases.

Special population: currently no evidence of a more severe disease course in pregnant women (scarce data, case series, low evidence).

6. Timing of administration and target population

Similar to other viral illnesses, antiviral treatment must be administered as early as possible to try to limit viral replication. The serious consequences of the viral illness (ARDS) are due to the direct cytopathogenic effect of the virus and to the secondary immune dysregulation manifested by overactivation of T cells and increased cytotoxicity of CD8 cells (Xu et al, Lancet 2020).

Treatment should be considered:

- As soon as possible in an immunosuppressed patient (e.g. immunosuppressant, immunomodulatory treatment, steroids, HIV)
- Among patients presenting with a lower respiratory tract infection **and** risk factors (age ≥ 65 years, comorbidities such as diabetes, cardiovascular illness, chronic respiratory illness, cancer) in the absence of clinical improvement at the time of diagnosis of COVID-19.

At the present time, there are no strong arguments for the treatment of young patients (<60-65 years) without comorbidities presenting a non-serious illness.

7. WHO clinical management recommendations March 13, 2020

On the 13th of March 2020, the WHO published updated recommendations for the treatment of suspected and confirmed cases of COVID-19. This document states that there is currently insufficient evidence to recommend any specific anti-COVID-19 treatment for confirmed cases.

A strong recommendation has been emitted for the use of experimental anti-COVID-19 treatment only in the setting of randomized trials and after approval from local authorities. If clinical trials are not available, those treatments should be used in the context of MEURI: Monitored Emergency Use of Unregistered and Investigational Interventions.

8. Conclusion and recommandation

Currently, routine use of anti-viral treatments for patients infected with the SARS-CoV-2 are not recommended at HUG for the following reasons: the efficacy and benefit from these treatments remain very uncertain, the national Swiss stock of lopinavir/ritonavir is limited and reserved for the treatment of people living with HIV, and the WHO currently recommends the use of experimental anti-COVID-19 drugs only in the setting of randomized controlled trials.

Discussion with Gilead is ongoing to establish a clinical trial aiming to asses Remdesevir's efficacy. In the meantime, compassionate use of remdesivir can be discussed with the manufacturer on a case by case basis within the context of MEURI: Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions.

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