www.guidelines.ch - SARS-CoV-2 - Specific antiviral Treatment (preliminary document)
Autor: SSI Guidelines, Co-Autoren: Prof Dr med Enos Bernasconi , Benedikt Huttner , Nicolas Mueller
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SARS-CoV-2 - Specific antiviral Treatment (preliminary document)

Introduction - Important Note

Work in progrss - prelimary status

- The present guideline is a preliminary summary of available evidence provided by a collaborative group of experts from SSI (see "References")
- The guideline is developed and endorsed in collaboration with the Swiss Society of Intensive Care Medicine
- The information is to be considered as a decision aid, not a recommendation
- The information will change rapidly - SSI Experts will adapt as quickly as possible
- All treatment discussed here are experimental or off-lable use. Consider with caution.

Indication for antiviral therapy - who should be approached

Who should be considered, and when?

- General comment: Limited resources will require a triage
- Decison multidisciplinary team
- Admission to ICU: Follow Criteria Swiss Society Intensive Care Medicine

Indication for treatment

- Documentation of infection with SARS CoV2 in nasopharyngeal swab or BAL
  AND
- Hospitalization
  AND
- Presence of one or more risk-factor
  - Age >65
  - Cardiovascular disease
  - Diabetes
  - chron. resp illness
  - cardiopathy
  - Immunosuppressed patients (comment PV: do we have the evidence?)

When should treatment be innitiated

- Patients with advanced presentation (can develop during hospitalization)
  - pulmonary infiltrates (usually bilateral)
  - tachypnea (>25/min)
  - Oxygen saturation <90% (or PaO2 <10kPa)
- Patient not improving on its own, regardless of age and risk factors

Proposed therapeutic approach

Current recommendation (SSI) for starting patient for whom treatment is indicated

Given the lack of an established therapy, any recommendation to be used with caution. Discuss the lack of evidence with patients and document at least oral consent in chart.

Proposed first line therapy (experimental)

- Kaletra® 200/50mg, 2-0-2 Tabl[1][2]
  OR
- Plaquenil 200mg 1-0-1[3]
  - first loadinig dose 2 Tabl[4]
- Duration: 5 (-10) d (stop after cliical improvement)
- Consider Compassionate use Programm Remdesivir for specific patients (see indication)

⇒SSI-expert group opinion

- WHO guidelines strongly recommend not to give any antiviral COVID19 therapy outside of a clinical trial
- The combination of Kaletra and Plaquenil is an expert opinion and did not reach consensus within the SSI. Monitor side effects and respect contra-indication prior to administration.

Additional options and considerations (with ICU-team)

- Tocilizumab (Actemra)Currently, protocols and trials are being developed. Update to follow[5]
  - Patients with respiratory / radiological deterioration
  - to be discussed in refractory/severe hypoxemia if otherwise optimized (ventilation/proning)
  - interdisciplinary approach with intensive care team
  - Practical recommendation
    - Baseline IL-6 and D Dimer
    - Quantiferon and hepatitis B status
- Preemptive or prophylactic antibitic therapy not recommended
- Further references summarized in "SARS-CoV-2 treatment 14 March 2020"

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[1] Kaletra can be given in nasogastric tube: Liquid: 10 ml 1x/24h Exclude HIV-infection to avoid suboptimal monotherapy

[2] Low evidence, weak recommendation (SSI expert group)

[3] Very weak evidence for recommendation (SSI expert group)

[4] Dose recommended based on first chineese experience (Yao CID, 2020)

[5] Currently, protocols and trials are being developed. Update to follow.

Remdesivir-Therapy (compassionate use programm)

Indication / Limitation to receive use acess to remdesivir

⇒ Due to the global request for drug supply, indictions include patient in Gilead compassionate use are limited

Inclusion criteria

- Confirmed SARS-CoV-2-Infection (positive PCR)
- mechanical ventilation

Exclusion criteria

- Multi organ failure
- Vasopressor support
- ALT > 5 X ULN
- eGFR <30 mL/min, Dialysis or CVVHD
- No other experimental antivirals against COVID-19

Procedure to include a patient for the compassionate programm

- Order Remdesivir (GS-5734) for compassionate use online (Gilead USA)
    - Case by case definition by Gilead USA
    - process to receive drug lasts at least 48hrs
- If substance is provided: inform Gilead CH: olivier.schorr@gilead.com and corinna.oberle@gilead.com

Treatment regimen within compassionate use programm

- Stop Kaletra / Plaquenil treatment
- Remdesivir, given in saline infusion i.v. (over 30')
    - 200mg on day 1 (loading dose)
    - 100mg every 24hrs (maintenance dose)
    - Duration 5-10 days (see protocol)

Antiviral treatments to be considered

Remdesevir (GS-5734)

- Safety: >175 patients treated in a phase III trial (PALM trial, Ebola) (Mulangu, NEJM 2019). 1 SAE (death due to cardiac arrest)
- In vitro data: Antiviral with broad-spectrum activity against coronaviruses including SARS-CoV-2 (Sheahan, Sci Transl Med 2017; Wang, Cell Res 2020; Agastini, mBio 2018)
- Animal data: Mouse model against SARS-CoV (Sheahan, Sci Transl Med 2017): Recuced viral load in early tx / clinical sy improved
- Successfully used in the prevention and treatment of monkeys infected by the MERS coronavirus (De Wit, PNAS 2020)
- Superior to lopinavir/ritonavir in a mouse model (decrease in respiratory symptoms /viral load (Sheahan, Nat Commun 2020)

Human data

- Case report of a patient with pneumonia successfully treated with remdesivir (Holshue, NEJM, 2020) (very low evidence)
- 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.(Midgley, medRxiv, 2020)
- 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

- Safey: HIV-drug with Well-known profile, contraindications and interactions (CYP3A4 inhibitor)
- Its administration should not impede on the prescription of another necessary medication
- In vitro activity against coronaviruses: inferior to remdesevir, controversial/inconsistent results (Biochem Biophys Res Commun 2004;318(3):719-725; Chu, Thorax 2004). Unknown mechanism of action
- Animal data: Combined with IFN, no clinical or virological effect in MERS mouse models (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 treatment vs 21 ctrl), PEP in HCW superior, 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 (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 (retrospecitve): 75 matched patients: reduction in mortality (2.3% vs 16%) among treated (median of 5.5 d after sy 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 with bilateral pneumonia died after 5 days of treatment. Concomitant treatment with IFN, alpha2b and prednisone. Pathology : microvesicular steatosis / portal alterations (DD: 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 treatment group, retrospective, n=201, unclear monotherapy vs combination (low to very low evidence).
    - Multiple RCTs in China lopinavir/ritonavir in combination with various treatments: results pending.
    - Dose: Kaletra mostly given at a regular dose (400/100 mg bid), 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)
- Safety 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)
- Dosing Consideration:
    - 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)
    - 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 (n=23), 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:

Tocilizumab (anti-Il-6)

- 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)

Other

- Anakinra (IL-1 antagonist): No evidence.
- Irinotecan, etoposide: No evidence.
- 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 trialsTenofovir: 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

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

References / Authors / Links

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Source document prepared by the team of the national center for new Infections (NAVI):

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Authors

Author group from NAVI / SSI: names to be added.