COVID-19: Principales options thérapeutiques en course

COVID-19: Main therapeutic options

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Introduction

The rapid spread of SARS-CoV-2, a novel *Coronavirus* that emerged in late 2019 and the resulting COVID-19 disease has been labled a Public Health Emergency of International Concern by the World Health Organistaion. The development of a specific antiviral treatment that stops *Coronavirus,* SARS-CoV-2, is now a global emergency.

To date, there are more than 600 clinical trials registered on "ClinicalTrials.gov" about treatment of COVID-19. However, to date, no treatment has demonstrated its effectiveness in curative or preventive treatment of SARS-CoV-2 infection with a sufficient level of scientific evidence. We propose to summarize the main therapeutic options being tested currently against SARS-CoV-2.

A literature review was performed using PubMed to identify relevant English-language articles published. We included clinical trials and review articles. Search terms included *Coronavirus*, *2019-nCoV*, *SARS-CoV-2*, *SARS-CoV*, *MERS CoV*, and *COVID-19* in combination with treatment.. Additional relevant articles were identified from the review of citations referenced and expert panel consensus supports. Active clinical trials were identified using the disease search term *Coronavirus infection* on ClinicalTrials.gov.

Treatment approach and mechanism-of-action:

An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in the treatment of related viral infections. The SARS-CoV-2 belongs to *Betacoronavirus* which also contains severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). The main drugs tested on SRAS-CoV and MERS-CoV were ribavirin, interferon and lopinavir/ritonavir. But the efficacy of several drugs remains controversial (1,2). The *figure 1* by K Kupferschmidt and J Cohen shows the action lines of attack of molecules tested against the SARS-CoV-2 (3).

Hydroxychloroquine and chloroquine:

Chloroquine (C) and its metabolite hydroxychloroquine (HC), widely-used antimalarial and auto-immune disease drugs, have recently been reported as a potential broad spectrum antiviral drug (1). Those are alkaloids belonging to the quinoleine group. They may inhibit the *Coronavirus* through a series of steps. They block virus infection by increasing endosomal pH required for virus/cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV (1,4). It represses nucleic acid replication, virions assembly, new virus particle transport, viral release

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and other processes to achieve it antiviral effects (5). It can be incorporated into nascent viral RNA chains and resulting in premature termination of RNA synthesis (1). Yao et al showed that HC decreased the viral replication in a dose related way. The simulated HC concentration in lung tissue was much higher than in plasma where the lung to plasma ratio with time reached a ratio of 400 (6). In addition, HC and C have immunomodulating effects and can suppress the increased of immune factors. In a pilot prospective Chinese study, Chun et al enrolled 30 patients with confirmed COVID-19. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 patients (86.7%) in the HC group and 14 patients (93.3%) cases in the control group ($p>0.05$). The median duration of hospitalization to virus nucleic acid clearance in the samples was comparable in the two groups. However these results are limited by the small sample size (7). In a French study, patients with COVID-19 were treated by HC. A significant viral clearance at day 6-post inclusion compared to controls was noted. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day 7, and 93% at Day 8. Virus cultures from patient respiratory samples were negative in 97.5% patients at Day 5. Despite of study's limitations including a small sample size, limited long-term outcome follow-up of the study, Gautret et al had concluded that COVID-19 patients should be treated with HC and azithromycin to cure their infection and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world (8,9).

The results of Chinese clinical trials conducted to test the efficacy and safety of C in the treatment of COVID-19 associated pneumonia in more than 10 hospitals showed that C has superior than the absence of treatment. Besides, the conclusion was that C reduced the duration of the disease, reversed the viral load, improved the signs on the chest imaging and reduced the pulmonary exacerbations (10). C and HC can induce gastrointestinal side effects. More serious side effects like heart rhythm disturbances, retinopathy or methemoglobinenia may also occur. However, at the recommended doses for a limited duration, side effects seem to be infrequent in the above studies and HC seems to be less toxic.

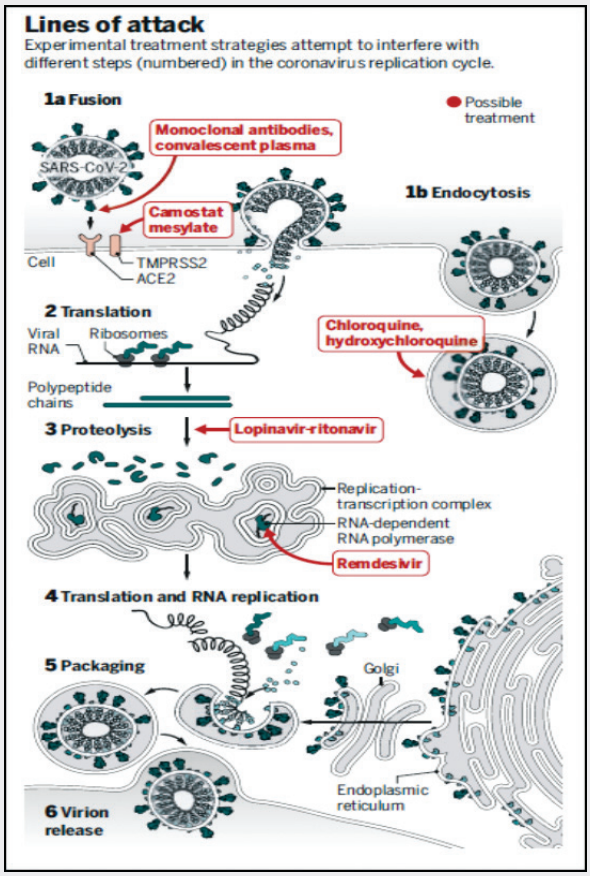

Figure 1. (by K Kupferschmidt and J Cohen, Science 2020) . Action lines of attack of drugs tested against the SARS-CoV-2.

Antiviral therapies:

Remdesivir:

Remdesivir (or GS-5734) is monophosphate derivative of a nucleoside analogue of adenosine, previously developed in infection with the *EBOLA* virus and was well tolerated (11). Its activity has been demonstrated in vitro and in vivo on both SARS-CoV and MERS-CoV viruses (12-14). Remdesivir acts as an RNA-dependent RNA polymerase inhibitor (RdRp), targeting the viral genome replication process. The RdRp is the protein complex CoVs use to replicate their RNA-based genomes. It is incorporated into the RNA strands of the virus. Wang reviewed the impact of different drugs on viral loads, cytotoxicity, and infection rates, using Vero E6 cells (a cell line originating

from African green monkey kidney epithelial cells). He found low potency of most of these drugs for inhibiting SARS-CoV-2. Remdesivir and chloroquine were the two drugs that needed the lowest concentrations to block viral infection (1). In a cohort of patients hospitalized for severe Covid-19 who had an oxygen saturation of 94% or less, remdesivir was provided with compassionate-use. Clinical improvement was observed in 36 of 53 patients (68%). However, authors concluded that measurement of efficacy will require ongoing randomized, placebo controlled trials of remdesivir therapy (15). Remdesivir currently has no Marketing Authorization. It is used either in randomized therapeutic trials in patients infected with the SARS-CoV-2 virus, or on a compassionate basis for severe COVID-19 disease.

Lopinavir/ritonavir

Lopinavir/ritonavir are antiretroviral protease inhibitors used in combination for the treatment of HIV infection since 2000.

The main side effects of this drug are gastrointestinal adverse events including nausea, vomiting, and diarrhea (16). Ritonavir is added to Lopinavir to increase Lopinavir half-life via inhibition of cytochrome P450 and acts only as pharmacokinetic enhancer (17). Lopinavir acts against the viral 3-chymotrypsin-likeprotease and has been reported with promising results against SARS-CoV and MERS-CoV (18-20). In a China randomized, controlled, open label, trial (Lopinavir trial for suppression of SARS-CoV-2 in China) was initiated to investigate the efficacy and safety of oral Lopinavir/ritonavir for SARS-CoV-2 infection in 199 adult patients with severe COVID-19. A group of 99 patients receivied lopinavir/ritonavir 400 mg/100 mg twice daily for 14 days and a group of 100 patients received standard therapy. The results showed no difference in clinical improvement and in Mortality at 28 days between the two groups (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). However, these two groups were very heterogeneous in terms of severity and in terms of the time for inclusion of patients compared to the date of onset of symptoms. In a post hoc subgroup analysis, the difference in mortality at day 28 between the two groups was observed to be greater among patients treated within 12 days after the onset of symptoms than among those treated later (rate difference was −8.0 (−25.3 to 9.3) according to Hodges–Lehmann estimate) (21). Finally, the authors concluded that no benefit was observed with Lopinavir/ritonavir beyond standard care in adult patients hospitalized with severe covid-19. Gastrointestinal adverse events were more common in lopinavir–ritonavir group (21).

Ribavirin

Ribavirin is a nucleoside analogue of guanosine used to treat the hepatitis C virus. This molecule tested in combination with other drugs and doesn't show significant efficacy on SARS-CoV-2 infection, with significant side effects as anemia (22-24).

Immunomodulatory therapies

Quin et al have shown that infection with SARS-CoV-2 leads to a dysregulation of the immune response. Severe cases trend to show a high neutrophil / lymphocyte ratio and increased expression of proinflammatory cytokines (25).

Tocilizumab is a monoclonal antibody that inhibits the interleukin-6 receptor (IL-6). It is a molecule used in the treatment of rheumatoid arthritis and is currently the subject of numerous therapeutic trials in patients infected with SARS-CoV-2. This IL-6 can be an important link in the chain of inflammatory reaction observed during COVID-19. Indeed, a retrospective study with a small number of patients showed a beneficial effect on the inflammatory storm in severe COVID-19 (26).

Interferon alfa and beta were a broad-spectrum antiviral agents through interaction with toll-like receptors and inhibit viral replication (27). However, several side effects are observed with these. Interferon-alfa and beta both demonstrated an anti-SARS-CoV-1 activity *in vitro* (28,29). Interferon-beta displayed potent activity in reducing MERS-CoV replication (30). In a comparative therapeutic trial against MERS-CoV, remdesivir and IFNb have superior antiviral activity to lopinavir/ritonavir in vitro (31).

Convalescent plasma transfusion In the treatment of SARS-CoV infection, the early administration of convalescent plasma (CP) was associated with a significant reduction of mortality compared with placebo or notherapy (32). In a laboratory test, the COVID-19 virus was found in the

bronchoalveolar lavage fluid of a severely sick patient, and it could be neutralized by sera from several patients (33). For the treatment of the COVID-19, the National Health Commission of China prompted convalescent patients to donate blood. Plasma from convalescence should be collected within two weeks after recovery to certify a high neutralization antibody titer. However, the difficulty in obtaining plasma during convalescence limits its clinical application. The efficacy and safety of convalescent plasma therapy in patients with COVID-19 infection should be further evaluated in well-designed clinical trials (33). Several trials using recovered plasma are currently underway.

In Tunisia, April 10th, 2020, the national authority for health evaluation and accreditation (INEAS) in partnership with other experts proposed the use of hydroxychloroquine or chloroquine in combination with azithromycin for patients with moderate or severe COVID-19 disease (34). Clinical trials using these therapeutic options for Tunisian patients will begin very soon.

Preventive therapies

The structure of SARS-CoV-2 S protein has been identified, and it should be helpful for rapid design and development of vaccines (35). The majority of the vaccines that are being developed for coronaviruses target the spike glycoprotein or S protein (33). Several efforts toward developing an effective SARCoV-2 vaccine are under development in many countries,

Conclusion

Among the drugs currently being tested, Hydroxycloroquine and Remdesivir seem to be the most efficient drugs in COVID-19 disease. Identifying effective antiviral agents to combat the COVID-19 disease is urgently needed.

To accelerate the results, two global megatrials of promising *Coronavirus* treatments have been launched: Solidarity by WHO (36) and Discovery by European center for disease prevention and control (37). The objective of both of them is similar: try to provide the best treatment option to cure COVID-19 based on a satisfactory level of scientific evidence.

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