Anti viral agents for COVID-19 a short review

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Chloroquine and Hydroxychloroquine

- Chloroquine and hydroxychloroquine appear to **block viral entry** into cells.
- These agents also have **immunomodulatory** effects through ***attenuation of cytokine production***.
- Hydroxychloroquine has in vitro activity with a lower EC50 for SARS-CoV-2 compared with chloroquine after 24 hours.

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

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Author information

Keywords: COVID-19, SARS-CoV-2, 2019-nCoV, pneumonia, chloroquine

The efficacy and safety of **chloroquine or hydroxychloroquine** have been tested in the treatment of **COVID-19** associated pneumonia in *more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo.*

Results

- from more than **100 patients** have demonstrated that chloroquine phosphate is **superior** to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course.
- **Severe adverse reactions** to chloroquine **were not noted** in the aforementioned patients.

However, the clinical trial design and outcomes **data have not yet been presented** or published for peer review, preventing validation of these claims.

ELSEVIER

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In Press, Journal Pre-proof

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret [a, b, $], Jean-Christophe Lagier [a, c, $], Philippe Parola [a, b], Van Thuan Hoang [a, b, d], Line Meddeb [a], Morgane Mailhe [a], Barbara Doudier [a], Johan Courjon [e, f, g], Valérie Giordanengo [h], Vera Esteves Vieira [a], Hervé Tissot Dupont [a, c], Stéphane Honoré [i, j], Philippe Colson [a, c], Eric Chabrière [a, c], Bernard La Scola [a, c], Jean-Marc Rolain [a, c], Philippe Brouqui [a, c], Didier Raoult [a, c]

- A **nonrandomized French study** of **36** patients (20 in the HCQ and 16 in the control group) reported improved **virologic clearance with HCQ 200** mg, every 8 hours compared with control patients receiving ***standard supportive care***.
- *Virologic clearance at day 6*, measured by nasopharyngeal swabs, was **70% vs 12.5%** for the HCQ and control groups, respectively (P = .001).
- The authors also reported that **addition of azithromycin** to HCQ in 6 patients resulted in superior viral clearance (**100%**) compared with HCQ monotherapy (57%).

Dosing of chloroquine to treat COVID-19 has consisted of **500mg orally once or twice daily**. However, a paucity of data exists regarding the optimal dose to ensure the safety and efficacy of chloroquine.

Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. Published online March 4, 2020.

HCQ dosing recommendations for SLE generally are 400mg daily.
However, a physiologically based pharmacokinetic modeling study recommended that the optimal dosing regimen for **HCQ in COVID-19** treatment is a loading dose of **400 mg twice daily for 1 day followed by 200 mg twice daily**.

Yao X, Ye F, ZhangM, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2). Clin Infect Dis. Published online March 9, 2020.

Use of chloroquine and

hydroxychloroquine in **pregnancy**

is generally considered **safe**.

FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems

Does not affect FDA-approved uses for malaria, lupus, and rheumatoid arthritis

We suggest **not using hydroxychloroquine** in **hospitalized patients** given the lack of clear benefit and potential for toxicity. In June 2020, FDA revoked its emergency use of these agents in patients with **severe COVID-19**, noting that the known and potential benefits no longer outweighed the known and potential risks.

US FDA. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. June 15, 2020.

Lopinavir/Ritonavir and Other Antiretrovirals

- demonstrated in vitro activity against **other novel coronaviruses** via inhibition of 3-chymotrypsin-like protease.
- **No published** SARS-CoV-2 in vitro data exist for lopinavir/ritonavir.
- The timing of administration during the **early peak** viral replication phase (**initial 7-10 days**) appears to be important because ***delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes***.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 7, 2020 VOL. 382 NO. 19

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

Cao and colleagues reported the results of an open-label RCT comparing the efficacy of **lopinavir/ritonavir vs standard care** in 199 patients with COVID-19. Importantly, **the median time from symptom onset to randomization was 13 days** (interquartile range [IQR], 11-16), with no between-group difference.

RESULTS

- Treatment with lopinavir–ritonavir **was not associated** with a difference from standard care in the time to **clinical improvement** and **viral clearance**.
- **Gastrointestinal adverse events** were more common in the lopinavir–ritonavir group.
- In hospitalized adult patients with severe Covid19, **no benefit was observed** with lopinavir–ritonavir treatment beyond standard care.

Atazanavir

- has an inhibitory potency against the SARS-CoV-2 coronavirus-like proteinase.
- Atazanavir showed to be effective in the treatment of COVID-19 by presenting overall high binding affinities among tested antivirals for six proteins of SARS-CoV-2.

Ribavirin

- Ribavirin, a guanine analogue, inhibits viral RNA-dependent **RNA polymerase**.
- Its activity against other n-CoVs makes it a candidate for COVID-19 treatment.
- its in vitro activity against SARS-CoV was limited and required **high concentrations** to inhibit viral replication, necessitating **high-dose** (1.2 g to 2.4 g every 8 hours) and combination therapy.
- The high doses used in the SARS trials resulted in **hemolytic anemia** in **more than 60%** of patients.

Oseltamivir

- has no documented in vitro activity against SARSCoV-2.
- This agent **has no role** in the management of COVID-19 once influenza has been excluded.

TheCOVID-19 outbreak in China initially occurred **during peak influenza** season so a large proportion of patients received empirical oseltamivir therapy until the discovery of SARS-CoV-2 as the cause of COVID-19.

Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. Published online February 7, 2020.

Umifenovir (Arbidol)

- is a more promising repurposed antiviral agent with a unique mechanism and **inhibiting membrane fusion** of the viral envelope.
- The agent is currently approved in **Russia and China for influenza** and is of increasing interest for treating COVID-19 based on in vitro data.

A nonrandomized study of **67 patients** withCOVID-19 showed that treatment with **umifenovir** for a median duration of **9 days** was associated with **lower mortality** rates**(0%[0/36] vs 16%[5/31])**and higher discharge rates compared with patients who did not receive the agent.

Wang Z, Yang B, Li Q,Wen L, Zhang R. Clinical Features of 69 cases with coronavirus disease 2019 inWuhan, China. Clin Infect Dis. Published online March 16, 2020.

Remdesivir

- remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several CoVs, including SARS-CoV-2
- In murine lung infection models with MERS-CoV, remdesivir **prevented lung hemorrhage**
- ***reversible aspartate aminotransferase and alanine transaminase elevations occurred***.
- The current dose under investigation is a single 200-mg loading dose, followed by 100-mg daily infusion.

In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; remdesivir-treated animals had lower virus levels in the lungs and **less lung damage** than the control animals.

Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature. 2020; Published online ahead of print.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt,

Method

- Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support.
- Patients received a 10-day course of remdesivir.

Results

- During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated.
- A total of 25 patients (47%) were discharged, and 7 patients (13%) died.

FDA has issued an emergency use authorization for remdesivir for hospitalized **children and adults** with severe COVID-19 (SpO2 ≤94 percent on room air, requiring supplemental oxygen, mechanical ventilation, or ECMO).

US FDA. Remdesivir letter of EUA. https://www.fda.gov/media/137564/download (Accessed on May 01, 2020).

- The pharmacokinetics of remdesivir in the setting of **renal impairment are uncertain**, and it is prepared in a cyclodextrin vehicle that ***accumulates in renal and may be toxic***; thus, remdesivir **is not recommended in patients with an eGFR <30 mL/min**.
- ***Remdesivir should not be used with hydroxychloroquine or chloroquine*** because of potential drug interactions.

US FDA. Remdesivir letter of EUA. https://www.fda.gov/media/137564/download (Accessed on May 01, 2020).

Overall, available data suggest there is likely some clinical benefit to remdesivir.

- **remdesivir reduced time to recovery from severe COVID-19**
- **remdesivir reduces mortality remains uncertain.**

https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-management-in-hospitalized-adults?

The suggested **adult dose is 200 mg *intravenously*** on ***day 1*** **followed by 100 mg daily for 5 days total** (with ***extension to 10 days*** if there is no clinical improvement and in patients on mechanical ventilation or ECMO).

US FDA. Remdesivir letter of EUA. https://www.fda.gov/media/137564/download (Accessed on May 01, 2020).

Remdesivir is not recommended in patients with an **alanine aminotransferase ≥5** times the upper limit of normal (and *should be discontinued if it rises above this level during treatment* or if there are other signs of liver injury).

US FDA. Remdesivir letter of EUA. https://www.fda.gov/media/137564/download (Accessed on May 01, 2020).

Recommendation for Prioritizing Limited Supplies of Remdesivir

- Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).

Last Updated: July 24, 2020

Favipiravir

- is a prodrug of a purine nucleotide, inhibits the RNA polymerase.
- Most of favipiravir's preclinical data are derived from its influenza and Ebola.
- A loading dose is recommended (2400mg to 3000mg BID × 2 doses) followed by a maintenance dose (1200mg to 1800mgBID).

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

Chang Chen, MD[1,2,#], Jianying Huang, MD[1,3,#], Zhenshun Cheng, MD[4], Jianyuan Wu, PhD[1,3], Song Chen, MD[5], Yongxi Zhang, MD[6], Bo Chen, PhD[1,3], Mengxin Lu, MD[5], Yongwen Luo, MD[5], Jingyi Zhang, MD[7], Ping Yin, PhD[8], Xinghuan Wang, MD[1,3,5,9,*]

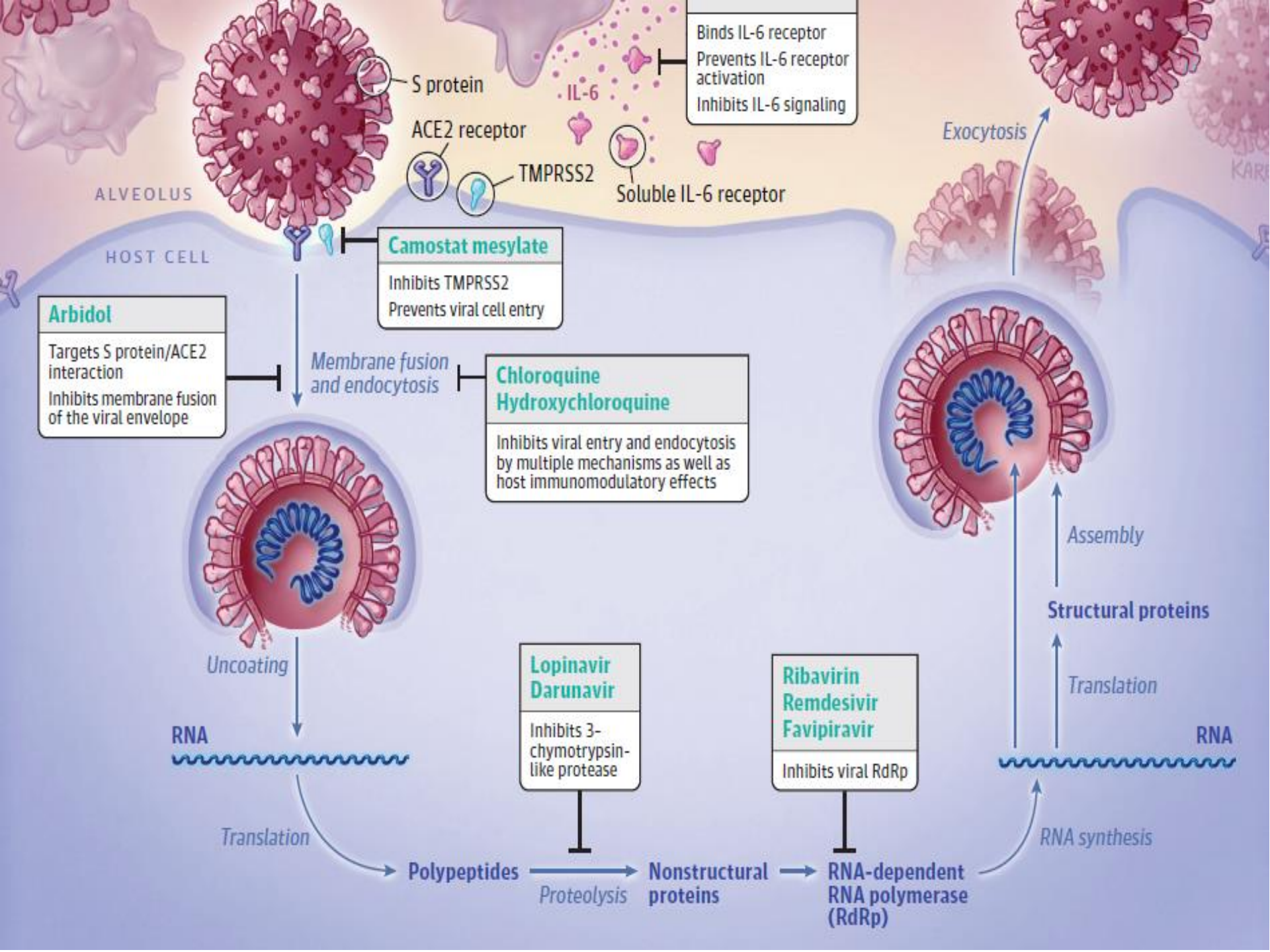
In a prospective, randomized, multicenter
study, favipiravir (n = 120) was compared with Arbidol
(n = 120) for the treatment of moderate and severe COVID-19 infections.

RESULTS

- Differences in clinical recovery at day 7 were observed in patients with **moderate infections** (71.4%favipiravir and 55.9%Arbidol, P = .019)
- **No significant differences** were observed in the **severe or severe and moderate** (combined) arms.
- for severe patients, clinical recovery rate was 0 (0/9) in the arbidol group and 5.56% (1/18) in the favipiravir group (P=0.4712)

- In a study of patients with **non-severe disease** (***including oxygen saturation >93 percent***), use of **favipiravir** was associated with **faster rates of viral clearance** (***median time to clearance 4 versus 11 days***) and more ***frequent radiographic improvement*** (in 91 versus 62 percent by day 14) ***compared with lopinavir-ritonavir***

experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020.


Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
S protein
IL-6
ACE2 receptor
TMPRSS2
Soluble IL-6 receptor
Exocytosis
ALVEOLUS
HOST CELL
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Assembly
Structural proteins
Uncoating
Translation
RNA
Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease
Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp
Translation
Polypeptides
Proteolysis
Nonstructural proteins
RNA-dependent RNA polymerase (RdRp)
RNA synthesis
RNA