Can antimalarials be used to treat COVID-19?

This write-up summarises a rapid evidence review of antimalarials, chloroquine or hydroxychloroquine, to treat patients with COVID-19. The information may be revised as new evidence emerges.

Background

An article by Gao et al. titled "Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies" announced preliminary findings of 15 clinical trials from 10 hospitals in China on 19 February 2020.[1] The authors report that results from more than 100 patients have shown chloroquine, an antimalarial treatment, is efficacious in preventing exacerbation of pneumonia, improving lung imaging findings, promoting virus free conversion, and shortening the disease course. This led them to recommend chloroquine as a treatment option for COVID-19 in the Chinese National Health Commission Guidelines for Prevention, Diagnosis, and Treatment of Pneumonia caused by COVID-19.[2] Preliminary results of a clinical study by Gautret et al. published on 17 March 2020 also reported that hydroxychloroquine (an analog of chloroquine) is effective in treating COVID-19.[3]

Following these early positive findings, news of chloroquine poisoning from inappropriate use, including a report of a fatality, have surfaced in the U.S. and Nigeria.[4,5]

Clinical evidence

There is insufficient evidence to support the safety or efficacy of chloroquine or hydroxychloroquine for the treatment of COVID-19 at this time. Current literature consists of narrative reviews, laboratory studies and preliminary findings of clinical studies.

A review by Cortegiani et al. of six articles published in March 2020 on the efficacy and safety of chloroquine for COVID-19 treatment suggested there is sufficient preclinical evidence to justify clinical research on the topic and extrapolated the safety of chloroquine on its existing use in clinical practice for other indications. [6]

In the study by Gautret et al., 20 French patients above 12 years of age, who tested positive for COVID-19 and were treated with hydroxychloroquine alone or in combination with azithromycin. The authors found all patients treated with hydroxychloroquine and azithromycin, and 57.1% of patients treated with hydroxychloroquine alone, were virus free at day 6.[3]

The safety of chloroquine when used for other viral infections has also been reported:

- In Tricou et al. which examined chloroquine for the treatment of dengue virus infection, significantly more adverse events occurred in patients treated with chloroquine (18 patients with 33 adverse events in the treatment arm versus 6 patients in the placebo arm, Fisher's exact test p=0.01).[7] Approximately 51% of patients reported vomiting, one patient developed haematemesis and one patient developed anorexia with vomiting resulting in a low narrow pulse pressure.
- Adverse events such as headache, dizziness, nausea, and diarrhea were also reported in patients given chloroquine for the prevention of influenza in a study by Paton et al.[8]

Numerous trials assessing antimalarial treatments for COVID-19 have been registered and are in the planning or active recruitment stage with results anticipated in the near future.

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Table 1: Ongoing or planned studies for chloroquine or hydroxychloroquine in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
ChiCTR2000030054[9]	SC*, OL, RCT	Hydroxychloroquine and chloroquine	Standard treatment	Unknown
ChiCTR2000030031[10]	MC*, DB, RCT	Chloroquine	Placebo	Unknown
ChiCTR2000029992[11]	OL, SC*, RCT	Chloroquine and hydroxychloroquine	Standard treatment	Unknown
ChiCTR2000029988[12]	OL, SC*, RCT	Chloroquine	Standard treatment	Unknown
ChiCTR2000029975[13]	SA, SC*	Chloroquine aerosol inhalation	No comparison group	Unknown
ChiCTR2000029939[14]	SC*, RCT	Chloroquine	Standard treatment	Unknown
ChiCTR2000029935[15]	SA, OL, SC*	Chloroquine	No comparison group	Unknown
ChiCTR2000029899[16]	OL, MC*, RCT	Hydroxychloroquine	Chloroquine	Unknown
ChiCTR2000029898[17]	OL, MC*, RCT	Hydroxychloroquine	Chloroquine	Unknown
ChiCTR2000029868[18]	OL, MC*, RCT	Hydroxychloroquine	Standard treatment	Unknown
ChiCTR2000029803[19]	OL, SC, RCT	Hydroxychloroquine	Arbidol	Unknown
ChiCTR2000029741[20]	OL, SC*, RCT	Chloroquine	Lopinavir/Ritonavir	Unknown
ChiCTR2000029740[21]	OL, SC*, RCT	Hydroxychloroquine	Standard treatment	Unknown
ChiCTR2000029609[22]	OL, MC*	Mild-moderate: chloroquine or chloroquine plus lopinavir/ritonavir; Severe: chloroquine	Mild-moderate: lopinavir/ritonavir; Severe: lopinavir/ritonavir, placebo	Unknown
ChiCTR2000029559[23]	SC*, DB	Hydroxychloroquine	Placebo	Unknown
ChiCTR2000029542[24]	SC*, CS	Chloroquine	Standard treatment	Unknown
NCT04286503[25]	OL, MC*, phII, RCT	Carrimycin	Lopinavir/ritonavir or arbidol or chloroquine	February 2021
NCT04261517[26]	SC, OL, phIII, RCT	Hydroxychloroquine	Standard treatment	August 2020

Abbreviations: Abbreviations: DB; double blind, SA; single arm, OL; open label, MC; multicenter, SC; single centre, CS; cohort study, phIII, phase III; phIV; phase IV, RCT; randomised controlled trial
* Study sites in China

In addition, the World Health Organization (WHO) has also recently announced that it will be conducting a large, global trial (SOLIDARITY)[27] on the four most promising therapies identified to date to treat COVID-19, including chloroquine and hydroxychloroquine. The following countries are currently included in the trial: Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand, with more countries likely to be included over time. The trial completion date has not been released yet.

Recommendations from professional bodies

Several international professional bodies, acknowledging the lack of robust scientific evidence, have provided advice on the use of antimalarials for patients with COVID-19:

- WHO states there is no specific medicine to prevent or treat COVID-19 and those with the virus should receive appropriate care to relieve and treat symptoms while those with severe illness should receive optimised supportive care.[28]
- CDC has communicated there is no specific treatment for COVID-19 currently available. Some in-vitro or in-vivo studies suggest potential therapeutic activity against related coronaviruses, but there are no available data from randomised controlled trials to support recommendations of any investigational therapeutics for patients with confirmed or suspected COVID-19 currently.[29]
- The Working Group on Antibiotics Policy (Netherlands) suggests chloroquine may be used in the case of deterioration under initial therapy or very severe presentation through a compassionate use program. The workgroup however, maintains there are no clinical studies conducted to clearly conclude that a particular drug is effective and safe.[30]

Conclusion

There is a lack of high-quality evidence to conclude that chloroquine or hydroxychloroquine is effective and safe for the treatment of COVID-19. A single study published thus far involved a small number of patients and warrants further research in a larger population with longer term follow up. Several clinical trials are ongoing and are likely to report results in the months ahead which will determine whether antimalarials should be more widely used for COVID-19 treatment.

References

1. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Mar 16; 14(1):72-73. doi:10.5582/bst.2020.01047.
2. Chinese National Health Commission (NHC) Chinese clinical Guidance for COVID-19 Pneumonia diagnosis and Treatment. Accessed 23 March 2020 at: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/11/22/chinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment
3. Gautret et al. Hydroxychloroquine and azithromycin as a treatment of COVID019: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 17 March 2020. doi:10.1016/j.ijantimicag.2020.105949
4. Newsweek. (2020) Health officials warn against self-medicating with chloroquine for coronavirus after man dies from taking fish tank cleaner. 2020 Mar 24. Accessed 25 Mar 2020 at: https://www.newsweek.com/health-officials-warn-against-self-medicating-chloroquine-coronavirus-after-man-dies-taking-fish-1493874
5. Cable News Network. (2020) Nigeria records chloroquine poisoning after Trump endorses it for coronavirus treatment. 2020 Mar 23. Accessed 25 Mar 2020 at: https://edition.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html
6. Cortegiani A, Ingoglia G, Ippolito M et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-10. J Crit Care. 2020. Doi: 10.1016/j.jcrc.2020.03.005
7. Tricou V, Minh NN, Van TP et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLoS Negl Trop Dis. 2010 Aug 10;4(8):e475. doi: 10.1371/journal.pntd.0000785.
8. Paton NI, Lee L, Ooi EE et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis. 2011 Sep; 11(9):677-83. doi: 10.1016/S1473-3099(11)70065-2
9. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49869
10. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49806
11. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/historyversionpuben.aspx?regno=ChiCTR2000029992
12. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49218
13. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/historyversionpuben.aspx?regno=ChiCTR2000029975
14. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49612
15. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49607
16. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49536
17. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49482
18. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49524
19. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49428
20. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49263
21. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49317
22. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49145
23. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=48880
24. Chinese Clinical Trial Register. Accessed: 24 March 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=48968
25. ClinicalTrials.gov. Accessed: 24 March 2020 at: https://clinicaltrials.gov/ct2/show/NCT04286503?term=NCT04286503&draw=2&rank=1
26. ClinicalTrials.gov. Accessed: 24 March 2020 at: https://clinicaltrials.gov/ct2/show/NCT04261517?term=NCT04261517&draw=2&rank=1
27. World Health Organisation (WHO) News. Accessed: 24 March 2020 at: https://www.who.int/thailand/news/detail/20-03-2020-thailand-joins-the-who-solidarity-trial-global-testing-of-effective-treatments-of-covid-19-across-8-countries-an-aggressive-effort-to-save-lives-from-the-pandemic
28. World Health Organization (WHO) Clinical management of severe acute respiratory infection (SARI) when novel coronavirus (nCoV) infection is suspected. Interim Guidance. Accessed 24 March 2020 at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
29. Centers for Disease Control and Prevention (CDC) Information for Clinicians on Therapeutic Options for COVID-19 Patients. Accessed 23 March 2020 at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
30. Stichting Werkgroep Antibioticabeleid (SWAB) Urgent: Preliminary treatment options COVID-19 (infections with SARS-CoV-2). Accessed 23 March 2020 at: https://swab.nl/nl/article/urgent/493/voorlopige-behandelopties-covid-19-infecties-met-sars-cov-2