Hydroxychloroquine and azithromycin combination therapy for COVID-19

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

COVID-19 Evidence Review Group

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Version 1

Rapid Evidence Review

What is the evidence base for combination therapy with hydroxychloroquine and azithromycin in the treatment of COVID-19?

Prepared by the COVID -19 Evidence Review Group

24th March 2020

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

One French trial involving 42 patients who were hospitalised with confirmed COVID-19 reported higher rates of virological cure in patients treated with hydroxychloroquine compared to a control group. More pronounced viral suppression was observed in a small subgroup (n=6) of patients incidentally treated with azithromycin to prevent bacterial superinfection**.** The comparative efficacy of hydroxychloroquine/azithromycin (Hyd/Az) combination versus single-agent hydroxychloroquine treatment is unclear and unproven by this study. The reported aims of this study did not include an investigation of the efficacy of combination therapy compared with single-agent therapy. No detail was provided on how patients were selected for combination therapy. There was a high level of attrition and loss-to-follow up. The evidence for combination therapy arising from this study could be more appropriately described as a small case-series rather than a comparative study. Both hydroxychloroquine and azithromycin are known to prolong the QT interval. Though the combination of chloroquine and azithromycin has been investigated for the treatment of malaria, the potential for increased risk of torsades de pointes and ventricular arrhythmia cannot be out-ruled.

Conclusion

Our review finds that the evidence on comparative efficacy is insufficient to conclude whether combination therapy is more beneficial than hydroxychloroquine alone. Importantly each of these drugs alone are known to prolong QT interval and the more serious ventricular arrhythmia, Torsades de Pointes has also been reported.

Rapid Evidence Review

A rapid critical appraisal of a study by Gautret et al, reporting the use of hyrdroxychloroquine/azithromycin (Hyd/Az) combination therapy for COVID-19, was conducted by the Evidence Review Group (1). Additional searches of guidelines, clinical trial registers, Pubmed, Google Scholar and other online resources were also conducted (See Appendix).

Critical appraisal of hyrdroxychloroquine/azithromycin (Hyd/Az) combination study by Gautret et al

Study design:

An open-label, non-randomised clinical trial, co-ordinated by the IHU Méditerranée Infection in Marseille, aimed to assess the effect of hydroxychloroquine on SARS-CoV-2 infected patients, compared with a control group (1). An investigation of the efficacy of combination therapy with Hyd/Az was not reported as an original aim of the study, nor is this aim evident in the trial listing on the EU clinical trials register. Thirty-six patients who were hospitalised with confirmed COVID-19 were included in the study if they were aged >12 years with documented SARS-CoV-2 carriage in nasopharyngeal sample at admission. Exclusions included known relevant allergies or contraindications to the study drug, breastfeeding and pregnancy. It is not clear if all hospitalised patients meeting the inclusion criteria were included in the study, or if patients were otherwise identified for study recruitment. The control group consisted of patients in other centres who did not receive hydroxychloroquine, and patients in the Marseille centre who refused the treatment or had exclusion criteria. Again, it is unclear if all patients in other centres were included in the control group or if specific selection criteria were applied. The primary endpoint was virological clearance at day 6 post-inclusion.

Results:

Forty-two patients met the inclusion criteria for the study, 26 of whom received hydroxychloroquine sulfate 200mg three times daily for ten days, and 16 were controls. Six hydroxychloroquine-treated patients (23%) were reported as lost to follow-up (three due to transfer to an intensive care unit, one due to death, one due to nausea and one due to patient decision to discharge from hospital). None of the control patients were lost to follow up. Among hydroxychloroquine patients, six patients received azithromycin (500mg on day one, followed by 250mg per day for the next four days) to prevent bacterial super-infection. The criteria for selecting patients for combination treatment with Hyd/Az were not reported. It was not reported if any of the control patients received azithromycin. Hydroxychloroquine patients were older than control patients (51.2 years vs 37.3 years). Two (10%) of the hydroxychloroquine patients and four (25%) of the control patients were

asymptomatic. An intention-to-treat analysis was not undertaken, as the patients who were lost-to-follow-up were not included in the efficacy analyses. At day six post-inclusion, the authors reported that 70% (14/20) of the hydroxychloroquine-treated patients were virologically cured compared with 12.5% (2/16) in the control group (p=0.001). The patients who were lost-to-follow-up were not included in the efficacy analyses. Under the assumption of treatment failure among those who are lost-to-follow-up, 54% (14/26) were virologically cured. All six patients treated with Hyd/Az were virologically cured at 6 days however one patient who met the primary outcome of virological clearance at day 6 tested positive again at low titre at day 8. A difference was observed between hydroxychloroquine-treated patients and controls, and between single-drug hydroxychloroquine-treated patients and the Hyd/Az-treated patients from day three post-inclusion.
No safety outcomes were reported.

Limitations:

Limitations of this study include its non-randomised design, small patient numbers, absence of information on the methods of patient selection and recruitment to the treatment arms and criteria for Hyd/Az combination therapy, and the post-hoc nature of the analysis comparing single-agent hydroxychloroquine therapy with Hyd/Az combination therapy. The proportion of hydroxychloroquine-treated patients who received Hyd/Az combination treatment (23%), is equivalent to the proportion of hydroxychloroquine- treated patients patients who were lost-to-follow-up. This level of attrition limits the conclusions which can be made on the comparative efficacy of combination vs single-agent therapy.

Commentary:

Despite the limitations of this study, this data adds to the growing evidence base of studies demonstrating an improvement in outcomes in hydroxychloroquine-treated patients infected with SARS-CoV-2. The study does not provide a robust insight into the potential efficacy of Hyd/Az combination treatment compared with hydroxychloroquine alone.

Safety considerations

Both hydroxychloroquine and azithromycin are known to cause QT prolongation. The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsades de pointes and ventricular arrhythmia(2). A number of articles have quantified this risk and a 2013 Danish study which compared azithromycin (five days) versus no antibiotic estimated the rate ratio of cardiovascular death to be 2.85 (95% CI 1.13 to 7.24) (3). An expert consensus published by a multicentre collaboration group of the Department of Science and the Technology of Guangdong Province and Health Commission of Guangdong Province, relating specifically to the use of chloroquine phosphate, was published on 20th February (4). The panel recommended avoiding concurrent administration of other drugs

known to prolong the QT interval such as macrolide antibiotics, which would include azithromycin (4). However, it should be noted that a number of studies have been published reporting the efficacy and safety of azithromycin-chloroquine combination in the treatment of malaria (5-7). CredibleMeds is a specialist database on drugs which cause QT abnormalities. On March 19th 2020 CredibleMeds published an update to highlight that both hydroxychloroquine and azithromycin alone can cause QT prolongation and chloroquine. Hydroxychloroquine and azithromycin are on the CredibleMeds' list of drugs known to cause Torsades de Pointes.

Clinical/scientific rationale for the use of azithromycin in viral illness

Studies have reported the in vitro activity of azithromycin against Zika virus, including a study originating from the same centre and involving some of the same authors as the Gautret et al study. In the case of the Ebola virus, a study by Madrid et al, failed to reproducibly demonstrate in vivo efficacy of azithromycin in animal models (8).

Relevant evidence from other sources

Treatment Guidelines:
Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium (19 March 2020) recommends that the observations reported in the Gautret et al study are still too preliminary to recommend systematic administration of hydroxychloroquine and azithromycin concomitantly, taking into account some significant risks of interaction. It further advises that in case antibiotics must be provided, consider to add azithromycin (given its possible synergistic effect with hydroxychloroquine) BUT with a particular caution for interaction and QTc prolongation (daily ECG or cardiac monitoring). Combination therapy with Hyd/Az is not referred to in the most recent guidelines published by the WHO (13 March 2020), the Chinese Preventive Medicines Association (Tentative Sixth Edition) and the Italian Society of Infectious and Tropical Diseases (13 March 2020).

Clinical Trial Registers:
A search of the following clinical trial registers did not yield any further evidence relevant to the review question: EU clinical trials register, clinicaltrials.gov, ChinaXiV.org, Chinese clinical trial registry.

References

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8. Madrid PB, Panchal RG, Warren TK, Shurtleff AC, Endsley AN, Green CE, et al. Evaluation of Ebola Virus Inhibitors for Drug Repurposing. ACS Infectious Diseases. 2015;1(7):317-26.

Technical Appendix

Search strategy 23rd March 2020

Database	Key terms	Number of results
Google Scholar	SARS-CoV-2 macrolide	19
	SARS-CoV-2 azithromycin	31
PubMed	(SARS-Cov-2) OR COVID-19) OR "Coronavirus"[MeSH Terms])	12504
	(SARS-Cov-2) OR COVID-19) OR "Coronavirus"[MeSH Terms]) AND (hydroxychloroquine OR chloroquine) AND azithromycin	0
	Azithromycin AND (chloroquine OR hydroxychloroquine)	104
ChinaXiV	(Covid-19) OR Title:(coronovirus)	20
	AND Category:(azithromycin)	0
Clinicaltrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2	128
EU clinical trials register	COVID-19	9