Azithromycin in the treatment of adult patients with COVID-19

Updated: 5 May 2020
(first publication: 9 April 2020)

ITALIAN MEDICINES AGENCY

Considering the absence of proven effective therapies for COVID-19, it is deemed essential to provide clinicians with useful elements to guide the prescription and to define, for each medicine used, a risk/benefit balance for the individual patient.

Classification Azithromycin (500mg tablets or 200mg/5ml powder for oral suspension) is an antibiotic of the macrolide family, authorized for the treatment of upper and lower respiratory tract infections, odontostomatological infections, skin and soft tissue infections, non-gonococcal urethritis, soft ulcers. The indicated dosage is 500 mg per day for 3 consecutive days.	
Why do some sources indicate that this medicine is useful in the treatment of COVID-19?	***Rationale*** The antibacterial property of macrolides derives from their interaction with the bacterial ribosome and the consequent inhibition of protein synthesis. There is evidence that macrolides exert beneficial effects in patients with inflammatory lung disease in addition to their ability to inhibit the replication of pathogenic bacteria. In vitro and in vivo studies have shown that macrolides mitigate inflammation and modulate the immune system; in particular, they have been shown to cause the downregulation of cell surface adhesion molecules, to reduce the production of proinflammatory cytokines, to stimulate phagocytosis by alveolar macrophages and to inhibit the activation and mobilization of neutrophils. The mechanism whereby macrolides exert these anti-inflammatory and immunomodulatory effects is not well known.
What evidence of efficacy and safety is available?	***Clinical studies*** ***Studies assessed as of 2 April 2020*** A retrospective analysis of 408 patients with pneumococcal bacteraemia identified over 10 years from microbiological isolation showed a reduction in hospital mortality in patients treated with a macrolide combined with a beta lactam (route of administration, dosage and duration of treatment are not known) compared to those treated without a macrolide. The authors highlight the numerous methodological limitations of the comparison and highlight that a prospective study is much needed. No conclusions can be drawn regarding the reason for this difference; the possibility of an effect going beyond the antibacterial one is still hypothetical. In a RCT versus placebo, clarithromycin administered intravenously for 3 days, in addition to the remaining antibiotic therapy, in 200 patients with ventilator-associated pneumonia and sepsis, reduced mechanical ventilation time but had no impact on mortality. A post hoc analysis of the data of one RCT (LARMA trial) on 235 patients in ARDs with Acute Lung Injury (ALI) showed that the 47 patients who had taken a macrolide (it is not known by which administration route, dose and duration) showed a reduction in mortality at 3 months compared to those

	taking other antibiotics. Also in this case we are dealing with preliminary data associated with a high number of confounders, which do not allow to draw any conclusions. Macrolides, due to possible anti-inflammatory and antiviral effects, have been studied in patients with severe viral respiratory infections (RVI), but with inconsistent results. In an open-label RCT of hospitalized influenza patients (n=107), early combination therapy with clarithromycin, naproxen and oseltamivir was associated with reduced mortality and length of hospital stay compared to oseltamivir monotherapy. On the other hand, in a multicenter observational study (n=733), macrolides were **not** associated with improved survival in critically ill patients with influenza A (H1N1) pdm09. In one RCT, in which 50 adult patients hospitalized for influenza virus infection were randomized to receive oseltamivir and azithromycin or oseltamivir plain, both for 5 days, pro-inflammatory cytokines decreased more rapidly in the oseltamivir-azithromycin group, but without any difference between the two groups as for viral clearance. In a retrospective observational study conducted in Saudi Arabia of 349 patients with MERS, no difference in 90-day mortality and viral clearance was observed between patients who took macrolides during hospitalization compared to those who did not. Also in this case the data are to be considered preliminary due to the methodological limits of the type of study. Regarding COVID-19, the only evidence currently available concerns the preliminary results of a very recent study, carried out in France on patients hospitalized with COVID-19, asymptomatic, symptomatic with disorders affecting the upper respiratory tract or symptomatic with disorders of the lower respiratory tract with unspecified characteristics. This was a single-arm study where 20 patients were administered hydroxychloroquine as compared to a control cohort of 16 patients who refused to take hydroxychloroquine plus others who were not taking the drug. In some patients of the hydroxychloroquine group, upon clinical judgment, azithromycin (6/20 patients) was added for the prevention of bacterial superinfections. In this preliminary analysis, the authors observed a higher rate of viral clearance (primary outcome of the study) in patients treated with azithromycin and hydroxychloroquine than in those treated with hydroxychloroquine plain. However, the strength and reliability of the data are questioned by important methodological flaws: non-randomized study, low overall sample size (n=36), extremely small number of subjects exposed to azithromycin (n=6), relatively high number - 6/26 - of lost to follow-up). Finally, a very recent report relating to a small French study showed that out of 11 patients with COVID-19 hospitalized consecutively and treated with hydroxychloroquine plus azithromycin according to the same dosage regimen used by Gautret et al., one patient died, 2 were transferred in the ICU, one patient had to stop treatment due to prolongation of the QT interval. Of the 10 surviving patients, 8 were still positive for SARS-CoV2 5-6 days after starting treatment.

	Update as of 5 May 2020 Six retrospective studies (most of them not officially published) on the emergency use of HCQ, plain or in combination with azithromycin, show some safety signs which should be taken into account. 1. In a first international multicenter study on a cohort of 956,374 rheumatic patients with prevalent use of HCQ, the comparison between those in whom incident azithromycin use was detected (323,122 cases) and those who accidentally added amoxicillin (351,956 cases) shows that the combination of HCQ + azithromycin is associated with an increased risk of cardiovascular mortality at 30 days [HR 2.19 CI: 1.22-3.94]. 2. A second multicenter study conducted in the USA reports the results of a retrospective analysis on 362 male patients hospitalized for SARS-CoV-2 infection and exposed to HCQ (97 pts.), HCQ + azithromycin (113 pts.) Or not exposed to HCQ (158 pts.). The analysis shows that HCQ, with or without azithromycin, does not reduce the risk of evolution towards mechanical ventilation and, on the contrary, an increased risk was reported of overall mortality [HR 2.61; 95% CI: 1.10-6.17; P = 0.03] in patients treated with HCQ plain compared to patients not treated with HCQ. Furthermore, in the subgroup of mechanically ventilated patients, no difference in mortality was observed between patients exposed and non-exposed to HCQ. 3. A third retrospective observational study on 84 consecutive adult patients admitted for COVID-19 in a New York hospital and treated with HCQ + azithromycin evaluated the QTc changes after 4.3 + 1.7 days of treatment, showing that 11% of patients reached QTc values> 500 ms, a value associated with a high risk of life-threatening arrhythmia. No case of *torsades de pointes* (TdP) was found in the above case studies. 4. A fourth retrospective observational study stems from the FDA Adverse Event Reporting System (FAERS) and considers AEs of HCQ/CQ plain, azithromycin plain, HCQ/CQ + azithromycin, amoxicillin plain, HCQ/CQ + amoxicillin. Amoxicillin serves as control (antibiotic with similar indications to azithromycin, but which does not prolong QTC). This is necessary since the AE detection system does not have the denominator represented by the use of each drug and does not allow a comparison of absolute numbers. 13.3 million reports were analyzed, HCQ or CQ does not appear to be associated with a safety signal related to TdP/QT prolongation when used plain. Azithromycin plain or in combination with HCQ/CQ is associated with a potential safety signal. 5. A fifth French study included all COVID-19 patients admitted to intensive care and treated with HCQ (200 mg x2 for 10 days) with or without azithromycin (250 mg per day for 5 days) after checking for contraindications/warnings including a QTc interval not > 460 ms. The QTc interval was monitored daily with ECG. From 16 to 29 March 2020, 40 patients were included in the analysis (75% ventilated, 63% on vasoactive drugs), HCQ plain was taken by 18 patients (45%), the remaining 22 took HCQ + azithromycin (55%); 50% of patients also took other QTc-prolonging drugs. No patient developed severe ventricular arrhythmias, but the QTc interval

	increased in over 90% of cases and, in particular, 6 of the 18 patients (33%) who took HCQ + azithromycin developed an increase in QTc> 500 ms, compared with 1 in 22 (5%) of those treated with HCQ plain (P = .03). This result is not transferable outside the intensive care setting. 6. A further observational study involving 90 patients, including 37 treated with HCQ and 53 with HCQ + azithromycin, admitted to Beth Israel Deaconess Medical Center in Boston, showed that in both groups a QTc interval ≥ 500 msec was observed in approximately 20% of cases and prolongations ≥ 60 msec from baseline in 13% in the combination group versus 3% of HCQ plain. In a patient of the HCQ + azithromycin group, *torsade de pointes* were observed following QT prolongation. The studies presented are all retrospective observational studies, with a series of different limits and characteristics. The study 1 is of significant size and methodologically robust, observes a substantially out-of-hospital reality, but does not include COVID patients; studies 2, 3, 5 and 6 have a very limited number, refer to different hospital settings and observe COVID patients. Study 3 is a collection of spontaneous reports of AE with the limitations that such collection presents and does not include COVID patients. No study allows to draw definitive conclusions and all suggest the urgent need for randomized studies. In anticipation of this, owing to the uncertainties in terms of benefit, it is considered useful to underline the potential risk of QT interval prolongation induced by the combination of HCQ with azithromycin, in particular in the presence of known risk factors or in hospital settings.
For which patients is it possibly recommended?	***Guidelines for therapeutic use*** **The lack of a solid rationale and the absence of efficacy evidence in the treatment of COVID-19 patients does not allow to recommend the use of azithromycin, plain or in combination with other medicines, with particular reference to hydroxychloroquine, beyond any case of bacterial superinfection.** **The use of azithromycin for indications other than those registered can only be considered in the context of randomized clinical trials.** **Uses not foreseen by the authorized indications and not recommended fall within the prescriber's responsibility and cannot be attributed to the NHS.**

What are the recommendations of international organizations?	**EMA**: As part of an information note published on 24 April regarding the potential risks associated with the use of QC and HCQ, the European Medicines Agency reminds prescribers and patients that the combination with azithromycin may cause an exacerbation of the same adverse reactions. **FDA**: On 25 April, the US Agency warns that it is aware of reports of serious heart rhythm problems in patients (hospitalized and not) with COVID-19 treated with HCQ or CQ, often in combination with azithromycin and other medicines prolonging the QT interval, especially in patients with renal insufficiency. Such adverse reaction reports include ventricular tachycardia or fibrillation or *torsades de pointes* and include some fatal cases. **WHO**: The use of high doses of HCQ or CQ can be associated with adverse events seriously negative for health. Antibiotics should not be used as a means of preventing or treating COVID-19.
What are the major risks in terms of adverse reactions and pharmaceutical interactions?	***Warnings and main interactions (from data sheet):*** The main warnings reported in the technical data sheet concern: - Severe hepatic insufficiency - Prolongation of the QT interval In particular, when evaluating the risk-benefits of azithromycin, the risk of prolongation of the QT interval should be taken into account for patients: ▪ with congenital or documented prolongation of the QT interval; ▪ treated with other active ingredients prolonging the QT interval, such as class IA (quinidine and procainamide) and class III (amiodarone and sotalol) antiarrhythmics, cisapride and terfenadine, antipsychotic medicines such as pimozide, antidepressants such as citalopram, fluoroquinolones such as moxifloxacin, levofloxacin and chloroquine and hydroxychloroquine. ▪ with alterations of electrolytes, especially in cases of hypokalemia and hypomagnesemia; ▪ with clinically relevant bradycardia, cardiac arrhythmia or severe heart failure. The Italian Society of Cardiology has created an algorithm relating to pharmaceutical interactions for COVID-19 and QT interval: https://www.sicardiologia.it/public/SIC-Covid-e-QT.pdf The main interactions related to medicines used for COVID-19 (from the Liverpool Drug Interaction group) are: https://www.covid19-druginteractions.org/ ▪ Atazanavir (potential effect on Q/T interval) ▪ Lopinavir / Ritonavir (potential effect on Q/T interval) ▪ Chloroquine (potential effect on Q/T interval) ▪ Hydroxychloroquine (potential effect on Q/T interval)

Ongoing studies in Italy	**Please refer to the appropriate section on AIFA website:** https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19
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