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SHORT PAPER

Azithromycin and COVID-19: Prompt early use at first signs of this infection in adults and children, an approach worthy of consideration

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Abstract

The devastating effects of the coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have led to urgent attempts to find effective therapeutic agents for inpatient and outpatient treatment of COVID-19. Initial enthusiasm for the combination of hydroxychloroquine and azithromycin has abated. However, as a result of positive clinical experience with azithromycin used alone during the first few days of the flu-like illness caused by this coronavirus, we recommend formal clinical trials using azithromycin early in the course of a COVID-19 infection. There is one clinical trial initiated, the individually randomized, telemedicine-based, "Azithromycin for COVID-19 Treatment in Outpatients Nationwide" based at the University of California San Francisco. This placebo-controlled trial is designed to determine the efficacy of a single 1.2-g dose of oral azithromycin to prevent COVID-19 patient progression to hospitalization. We recommend formal clinical trials of azithromycin in its prepackaged form at the first sign of COVID-19 infection in adults and children, using an initial adult dose of 500 mg followed by 250 mg per day for 4 days, a total cumulative dose of 1.5 g, and for children 5 to 18 years of age, 10 mg/kg on the first day followed by 5 mg/kg for 4 days.

KEYWORDS

azithromycin, COVID-19, hydroxychloroquine, macrolide, SARS-CoV-2

1 | INTRODUCTION

Numerous clinical trials, including some utilizing inexpensive, widely available drugs, are under way against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus now that COVID-19 has become a pandemic. There was initial enthusiasm for using hydroxychloroquine (HCQ) based on a French study which demonstrated a dramatic decrease in the nasopharyngeal viral load, with 93% of the subjects being negative by day 8.[1]

This study was done on 80, mildly affected, hospitalized patients. Each had been given a combination of 200 mg of HCQ three times a day for 10 days, in addition to azithromycin, 500 mg on the first day, followed by 250 mg daily for the next 4 days. Both the clinical and virologic outcomes were positive. In patients who did not receive HCQ, viral clearance occurred in 12.5% of them; in those treated with HCQ alone viral clearance was 70%. However, in those treated with HCQ combined with azithromycin, viral clearance was 100%. Azithromycin alone was not studied.

A follow-up retrospective study from this French group evaluated 1061 patients, 46.4% male, mean age 43.6 years, with an age range of 14 to 95 years. It reported a favorable clinical outcome with a virologic cure in 973 of the 1061 patients within 10 days when using a combination of HCQ and azithromycin.[2] Other studies involving hospitalized patients have been less encouraging.[3] Unfortunately, HCQ is also associated with a high risk of significant cardiac and other adverse effects that include an occasional severe cutaneous adverse drug reaction called generalized pustular figurate erythema.[3-5]

2 | DISCUSSION

An approach we have advocated since the inception of the pandemic is having a 5-day course of azithromycin ready for personal and family use at the first sign of COVID-19. One of us (R. M. S.) has successfully treated more than 50 patients with flu-like symptoms without virologic testing, including children and one 82-year-old male physician in addition to two women, 80 and 65 years of age, each of whom were documented to be SARS-CoV-2 positive. The treatment approach consisted of a 5-day course of azithromycin, marketed as a 5-day packaged regimen at a dose of 500 mg the first day and 250 mg for the remaining 4 days. Clinical improvement occurred in all patients within 24 to 48 hours of starting the antibiotic. There were neither complications nor hospitalizations. Its use would have been precluded; however, if there had been a history of liver disease, heart disease, or allergies to azithromycin, erythromycin, or any other macrolides.

Azithromycin is a macrolide antibiotic used for acne vulgaris and for skin, respiratory and other infections.[6] It is one of the most commonly prescribed antibiotics in the United States. It has shown in vitro activity against Zika and Ebola viruses and in vivo activity in the prevention of severe respiratory tract involvement in viral infections, probably owing to its immunomodulatory action.[7-9] Azithromycin inhibits protein synthesis and experimentally reduces inflammation and viral replication, possibly because cytokines and viruses are both made of proteins and utilize cellular ribosomes for protein translation. In addition, inhibiting virus production may reduce viral transmission to others, an important additional benefit.

Azithromycin is widely used and is generally considered a safe medication. There are, however, occasional adverse effects.[10] As with almost all antibiotics, diarrhea, nausea, vomiting, and headache may ensue, as may occasional urticaria and other skin eruptions. Serious side effects are uncommon; however, they may include cardiac arrhythmias, especially in the elderly and in those with preexisting QT interval prolongation, bradycardia, low serum potassium or magnesium, and in individuals who are taking certain antiarrhythmic drugs.[5,10] In the search for a safe, effective treatment for individuals with early mild or moderate COVID-19, however, azithromycin is one of the most promising.[11]

There are numerous clinical trials underway with azithromycin, although usually not by itself but in combination with HCQ, with 19 listed for the United States alone on the ClinicalTrials.gov U.S. governmental website.[12] A particularly innovative upcoming study is the individually randomized telemedicine-based clinical trial "Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION)" based at the University of California San Francisco (ClinicalTrials.gov Identifier: NCT04332107), in collaboration with the Bill and Melinda Gates Foundation, Pfizer, and Stanford University.[11] It is officially titled "Azithromycin for Prevention of Disease Progression in Patients with Mild or Moderate COVID-19." Its plan for patients 18 years and older is for an individually randomized, placebo-controlled trial to determine the efficacy of a single 1.2 g dose of oral azithromycin for prevention of COVID-19 progression to hospitalization.

3 | CONCLUSIONS

A number of therapeutic agents are being explored globally against the COVID-19 infection. Efforts to stop this pandemic should involve many approaches,[13,14] including drug therapy and the use of air cleansing devices.[15] There are encouraging anecdotal results of favorable clinical experiences using azithromycin alone early in the course of a COVID-19 infection. The outcome of the innovative University of California San Francisco ACTION clinical trial using a single 1.2-g course of azithromycin could prove significant.

We also encourage formal clinical trials with the prepackaged preparation of azithromycin administered at the first sign of a COVID-19 infection over a 5-day period with 500 mg the first day and 250 mg for the remaining 4 days, for a total of 1.5 g for adults over 18 years of age, and for children 5 to 18 years of age, 10 mg/kg on the first day, and 5 mg/kg for the following 4 days. Since COVID-19 patients may have a myriad of clinical signs and symptoms, some atypical, laboratory confirmation of COVID-19 is recommended. Patients should be examined carefully for coinfections with nosocomial respiratory pathogens, such as multidrug-resistant *Candida auris* and azithromycin-sensitive *Mycoplasma pneumoniae*, which may increase morbidity.[14,16]

This plan for the early treatment of adults and children is a potentially efficient, cost-effective, readily available, easy-to-use, relatively safe, therapeutic option for most patients with early symptomatic COVID-19. In addition, it has the potential to contain the global pandemic, reduce concerns about a worldwide economic depression,[17] and normalize people's lives.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Each author has made substantial contributions to analysis and interpretation of data, has been involved in drafting the manuscript or revising it critically, and has given final approval of the version to be published.

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