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Azithromycin and COVID-19 History and Review

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Author: Frank Valentin, MD
03-28-2020

Azithromycin:

Molecular Formula: $C_{38}H_{72}N_2O_{12}$

Disclosure:

The following article is with the intent to inform the community about azithromycin and not to be used for medical purposes. Please seek medical attention if you think you have flu or flu-like symptoms before ingesting antibiotics.

Introduction:

Azithromycin is part of a family of antibiotics called macrolides. It is an azalide antibiotic.

The first macrolide was called Erythromycin discovered in 1949 at Eli Lilly by McGuire who isolated erythromycin, from the metabolic products of a strain of the actinomycete *Saccharopolyspora erthraea*, formerly known as *Streptomyces erythreus*, found in soil samples collected from the Philippines by the Filipino Scientist Abelardo Aguilar.

Azithromycin was discovered by a team of Croatian scientist at Pliva in the 1980s and marketed 8 years later in Central and Eastern Europe under the brand name **Sumamed**. In 1991, azithromycin gained FDA approval and was brought to the US market by Pfizer under the brand name of Zithromax.

Indication:

The indications for these antibiotics is for Gram-positive bacteria (cocci and bacilli).

For out-patient therapy of CAP (Community Acquired Pneumonia, pharyngitis or skin-structured infections, also used for gastrointestinal infection, and STDs.

Dosage:

The Loading dose is of 500 mg, given on the first day and then 250 mg on day 2-5. This is general statement, dosing varies according to medical criteria and on the disease the patient is presenting.

Mechanism of Action:

Macrolides are bacteriostatic agents that inhibit protein synthesis by binding reversible to 50S ribosomal subunit of sensitive microorganisms, inhibit the translocation step, wherein a new synthesized peptidyl tRNA molecule moves from the receptor site on the ribosome to the peptidyl donor site.

Pharmacokinetics:

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Distribution: The drug is widely distributed and rapidly absorbed and their in no blood brain barrier distribution.

Elimination: The form is non-renal.

Untoward Effects:

Cholestasis Hepatitis

-GI Toxicity

-Prolonged QT Syndrome

-Transient Auditory Impairment

Drug-Drug Interactions:

(Parent Drug) Erythromycin inhibit the cytochrome enzymes, in this case, the antibiotic inhibits the CYP 3A4, therefore patients taking the following medication should be aware of these effects:

1. Carbamazepine
2. Corticosteroids
3. Cyclosporine
4. Digoxin
5. Theophylline
6. Warfarin

Azithromycin has perhaps the most benign safety profile of the current marketed macrolide agents. Indeed, only 0.7% of subjects receiving azithromycin discontinued therapy due to adverse events, compared with 2.6% of subjects receiving comparator drugs. (1)

Azithromycin is primarily eliminated unchanged, and does not interact with the cytochrome P450 system.

Interestingly, there still are anecdotal reports of toxicity when azithromycin is used with lovastatin, warfarin, cyclosporine, disopyramide and theophylline.

Drug-Vitamin Interaction

Vitamin B1 and B12: Although in short-term antibiotic therapy it is not significant effect, in long-term antibiotic therapy, calcium supplementation may be needed (as well as folic acid, vitamin B12)

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Clinical Trial and COVID-19

Clinical Trials that are recruiting participants are

Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-Cov-2 Virus (Coalition-I)

Description of Trial: COALITION I study aims to compare standard of care, hydroxychloroquine plus azithromycin and hydroxychloroquine monotherapy for treatment of hospitalized patients with COVID-19.

COALITION I will recruit 630 patients with infection by COVID-19 (210 per arm). Ordinal endpoint of status at 15 days will be the primary endpoint.

- I. Experimental Arm: Hydroxychloroquine after randomization, Hydroxychloroquine [400mg 2x/day, 12/12h] for **07 days**.
- II. Experimental Arm: Hydroxychloroquine + azithromycin After randomization, Hydroxychloroquine [400mg 2x/day, 12/12h] + azithromycin [500mg 1x/day]) for **07 days**.
- III. No intervention: Control, Standard Treatment Protocol for 2019-nCoV infection.

Clinical Trial is set to end August 30, 2020

Safety and Efficacy of Hydroxychloroquine Associated with Azithromycin in SARS-CoV2 Virus (Alliance Covid-19 Brasil II)

This clinical trial will start recruiting 440 patients starting this next Monday March 25, 2020. The responsible party is Hospital Israelita Albert Einstein, and is a phase 3 clinical trial. Its description is will evaluate the effectiveness and safety of the use of hydroxychloroquine combined with azithromycin compared to hydroxychloroquine monotherapy in the clinical evolution by the ordinal scale of 7 points in adult patients hospitalized with pneumonia caused by infection by the SARS-CoV2 virus in Brazil.

1. Intervention Group: Hydroxychloroquine + azithromycin. After randomization, Hydroxychloroquine [400mg 2x/day, 12/12h] + azithromycin [500mg 1x/day]) for **10 days**. Standard treatment is according to the treatment protocol for 2019-nCoV infection.
2. Active Control Group: Hydroxychloroquine. After randomization, Hydroxychloroquine [400mg 2x/day, 12/12h] for **10 days**. Standard treatment is according to the treatment protocol for 2019-nCoV infection.

Clinical Trial will end on August 30, 2020.

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Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID-19 (ProPAC-COVID).

This clinical study will take place in Denmark it is a phase 4 clinical trial that will start recruitment of 226 participants in a randomized and the trial is set to start on April 1, 2020 and will end on March 31, 2020. The aim of the study is to investigate whether the treatment can shorten hospitalization, reduce the risk of non-invasive ventilation, admittance to Intensive Care Units and death.

The third clinical trial that involved Azithromycin:

Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACT COVID19)

This clinical trial is taking place in Canada by the Population Health Research Institute. Its description is that consists of two parallel trials evaluating azithromycin and chloroquine therapy (ACT) versus usual care in outpatients and inpatients who have tested positive for COVID-19. The trial is an open-label, parallel group, randomized controlled trial with an adaptive design. Adaptive design features include adaptive intervention arms and adaptive sample size based on new and emerging data, it is to expected to recruit 1500 participants. It is set to start April 1, 2020 and end on December 31, 2020.

There are very promising clinical trial to start this week, but the majority of them have a timeline of 6 to 12 months. After clinical trials end, there is a time to collect and analyze correctly the data of the trial before its use.

Currently Azithromycin is not labeled for use against COVID-19, so for people not diagnosed with COVID-19, this is not a prophylaxis.

We must be careful with the information published over the internet, not to promote like with plaquenil, the usage of medication not labeled for COVID-19 as if it were labeled for, and create a shortage of these medications for people who have conditions for which the medication is labeled.

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