Ivermectin-based Combination Therapy Reduces Mortality Rate of COVID-19 Patients in Tlaxcala Mexico

By TrialSite Staff February 10, 2021

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A team of Mexican investigators sponsored by the health authorities of the Mexican state of Tlaxcala just completed and published the results of the use of a combination, Ivermectin-based therapy to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico. The study team employed a non-randomized trial using a combined therapy of Ivermectin, Azithromycin, Montelukast and Acetylsalicylic acid to find that out a total of 481 patients tested positively for COVID-19 received TNR4 while 287 additional patients received other standard of care treatments. After a 14 day follow up period it was found that nearly 85% of the cases in the TNR4 group recovered within 14 days while only 59% of such cases in the comparison group fully recovered. The likelihood of recovery within 14 days was 3.4 times greater than the comparison group. Patients treated with TNR4 had a 75% and 81% lower risk of being hospitalized and death respectively. The U.S. Food and Drug Administration (FDA) does have a black box warning however for use of montelukast in the past—it was associated with some probability of mental disturbances. Overall the study produced impressive reduction in risk and the treatment certainly reduced poor outcomes. But TrialSite shares some observations about this study below.

What follows is a breakdown of this study for the *TrialSite Network*.

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Where is the study published?

The study is published in the *International Journal of Infectious*

Trials based on 'Leaked' Slides from Dr. Andrew Hill

combination therapy called "TNR4" therapy targeting dangerous conditions arising out of infection of SARS-CoV-2, the virus behind COVID-19. Conditions such as attenuated lung and systemic inflammation, endotheliitis, and thrombosis related to the novel coronavirus can lead to longer-term damage and death.

What is the combination therapy TNR4?

This cocktail combination therapy acronym stands for "*New Therapy for Recovery of COVID-19 Infection, 4 medications*" or in Spanish "*Terapia Nueva para la Recuperación en la infección por COVID-19, 4 medicamentos*."

The TNR4 dosages included 1) Ivermectin, 12 mg single dose; 2) Azithromycin 500 mg for 4 days; 3) Montelukast, 60 mg on the first day and then 10 mg between days 2 to 21l and 4) acetylsalicylic acid (aspirin) 100 mg for 30 days.

Are these medications approved by Mexico's regulatory authorities?

Yes. All four of the medications in TNR4 are approved by the Federal Commission for Protection against Health Risks (COFEPRIS or Comisión Federal para la Protección contra Riesgos Sanitarios).

What are the drugs used in this combination therapy known as TNR4?

Ivermectin, Azithromycin, Montelukast and Aspirin.

While the world is certainly now becoming quite aware of the potential of Ivermectin for use targeting COVID-19 and Azithromycin is a well known antibiotic; of course Acetylsalicylic Acid is Aspirin. But what about Montelukast?

Montelukast is apparently used to prevent a number of asthmatic related conditions (wheezing, difficulty breathing, chest tightness and coughing) in children 12 and above. The drug falls under the category of leukotriene receptor antagonists (LTRAs) and works by inhibiting the activity of substances in the human body that are known to trigger the symptoms of asthma and allergic rhinitis. Again the U.S. FDA issued a black box warning in the past and is known as SINGULAIR produced by Merck.

Why did the study team select Ivermectin?

They posited in their report that this promising therapeutic option "can effectively limit infections caused by RNA viruses and is highly capable of reducing viral clearance through protein inhibition." They suggest based on the preclinical and clinical evidence to date that the drug is best used in the non-severe clinical stage of COVID-19. Hence, the use in ambulatory COVID-19 cases in Mexico.

What ethics committee approved this study?

The study protocol and associated procedures were approved by the IRB and EC of the Tlaxcala State Ministry of Health.

How did the study recruit patients?

This substantial study network was employed here to identify prospective enrollees of the study including those that reported respiratory symptoms during 911 emergency calls as well as household contacts, individuals with respiratory symptoms with a positive COVID-19 test seeking attention at a number of primary health care units or at public hospitals of the Ministry of Health, Mexican Institute of Social Security (IMSS); Institute for Social Security and Services for State Workers (ISSSTE) or private healthcare providers.

What was the total patient population targeted?

The patient population of laboratory confirmed COVID-19 cases in the state of Tlaxcala included a total of 6,798 laboratory confirmed cases of COVID-19 from May 11 to September 9, 2020. Of these, 3,399 of the COVID-19 cases were treated at the Tlaxcala Ministry of Health. Of this population, a total of 1,147 cases were considered eligible for ambulatory care, that is patients infected with SARS-CoV-2 presenting mild or moderate symptoms and hence invited to participate in the study.

What were the exclusion criteria for the study?

The authors include in this category those who "refused to participate" (n=251), those individuals under 18 or older than 80 (n=44) and those who initiated treatment on the same day or one day prior to hospitalization or passed away (n=84).

First they completed a questionnaire and then accepted follow up monitor visits either via home visit or phone call for clinical evaluation during the 14 days period. The monitors reviewed sociodemographic characteristics, risk factors and other risk factors such as obesity, smoking and pregnancy.

What was the framework or model of measurement of efficacy?

The study team employed a method known as “next health outcomes.” That is the percentage of patients who completely recovered within the first 14 days after their symptoms commenced. They also factor in the risk of hospitalization and/or death for this endpoint. Another endpoint factored in was undesirable side effects from each of the TNR4 treatments as well as those medications used in the comparison group.

What were the results?

TrialSite summarizes the results, but the full reading can be found here.

Out of a total of 481 participants with COVID on the TNR4 arms of the outpatient, ambulatory study nearly 85% recovered within 14 days versus 59% in the comparison group. The overall likelihood of recovery within 14 days was 3.4 times greater in the TNR4 group than the comparison group. Moreover, patients in the TNR4 group had less severe disease progression as measured by hospitalization or death: that is 75% lower hospitalization rate and 81% lower risk death.

***TrialSite* Comment & Study Limitations**

The study results appear impressive to the comparison group but overall the absolute numbers aren’t great in that only 85% of the COVID-19 positive cases were resolved by day 14. Looked at another way in this relatively young, outpatient group, 15% would be considered high at least by some. The death rate in this cohort, also at 3.1% could be deemed high. Moreover, with a death rate of 18.1% for the comparison group also appears alarmingly high for such an early treatment group.

The study authors didn’t appear to document what the standard of care was in the case where other treatments were used. Moreover, the participants selected were not randomized. Although published, the study results are still pre-proof.

What are the study team recommendations?

They study authors conclude that TNR4 cocktail evidences the improvement of recovery and appears to reduce the risk of more severe disease among this early treatment ambulatory cohort of COVID-19 positive patients. But more research is necessary—that is well designed randomized controlled trials to further investigate the effectiveness of the combination therapy in differing scenarios (e.g. different treatment schemes and healthcare settings).

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