Favipiravir: Our Recommendation for Most Effective COVID-19 Treatment

Nathan Chiappone, Lauren Fowler, Jordan Jontz, Hyun Song

I. URGENT NEED FOR COVID-19 DRUGS AND FOUR DRUG SUGGESTIONS

Our goal is to find drugs and therapies that are safe and effective to implement as a treatment for Sars-CoV-2 at the pharmaceutical company run by Dr. Howard Prinz.

Since January 2020, the COVID-19 pandemic has caused over 2.8 million deaths worldwide, including over 550,000 in the United States. [1] Patients with the most severe form of COVID often develop pneumonia, which accounts for a majority of the mortality associated with COVID-19. [10] There is an urgent need for effective drugs for patients who are affected by COVID-19, especially for patients affected with the most severe form of COVID-19 related pneumonia. [10]

We have conducted extensive research through the NIH official clinical trial database, studying drugs that have completed the Phase 3 or Phase 4 of clinical trial. [2] We focused on the drugs' effect on **clinical improvement status**, measured in the COVID-19 Ordinal Scale, and **viral clearance**. [3][4] *In this report, we present three drugs we believe are effective options to improve either the clinical improvement status or viral clearance in patients infected with SARS-CoV-2, and one drug that we believe will be an effective option in preventing the development of SARS-CoV-2 in exposed patients: Ivermectin with Doxycycline, Favipiravir, Remdesivir, and Prophylactic Ivermectin (Table 1) (Figure 1). Out of these four drugs, we most highly recommend Favipiravir due to its ability to effectively treat patients with severe COVID-19 and COVID-related pneumonia.*

Table 1. Summary of the four drugs' effects on clinical improvement status, viral clearance, & prevention. Ivermectin with Doxycycline and Favipiravir significantly improve symptoms and viral clearance. Remdesivir significantly improves time to recovery and somewhat improves clinical status of patients. Prophylactic Ivermectin significantly decreases the risk of developing symptoms post-exposure.
++: Improvement in drug group compared to placebo, significant ($p < 0.05$)
+: Improvement in drug compared to placebo, but not significant
N/A: Study did not test for particular outcome measure variable

	Favipiravir	Ivermectin & Doxycycline	Remdesivir	Prophylactic Ivermectin
Clinical Improvement	++	++	++ (Time to Recovery) + (Ordinal Scale Score)	N/A
Viral Clearance	++	++	N/A	N/A
Preventative – Symptom Development	N/A	N/A	N/A	++

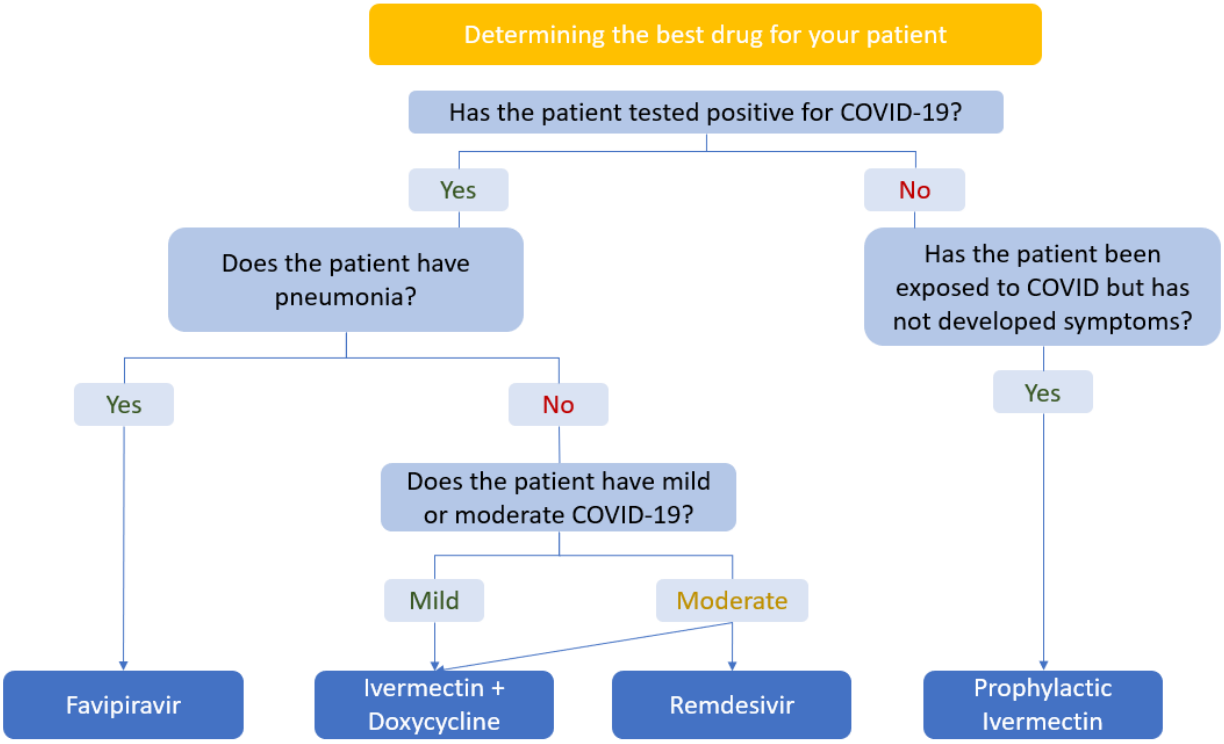

Figure 1. Flowchart comparing which drugs will be useful for different scenarios and symptoms.

Favipiravir was tested in 200 patients, with one treatment group receiving Favipiravir and the control group receiving Standard of Care. The objective of the study was to test the efficacy and safety of Favipiravir in treating COVID patients with pneumonia, by measuring clinical improvement (by the WHO categorical ordinal scale of clinical improvement) and viral elimination. [3] Favipiravir is a broad-spectrum inhibitor of viral RNA polymerase (RdRp) that reduces viral replication and thereby reducing COVID-19 symptoms. [5]

Ivermectin with Doxycycline was tested in 363 subjects, with one treatment group receiving a combination of Ivermectin and Doxycycline with Standard of Care, and the control group receiving Standard of Care. The objective of the study was to test the efficacy of Ivermectin with Doxycycline in treating patients with mild to moderate severity of COVID-19, measured by early clinical response and viral clearance time. Ivermectin is a drug commonly used for treatment of parasitic infections, and has antiviral activity against viruses such as Zika virus, Influenza A virus, and Dengue virus. [6] When used with doxycycline, an antibiotic, Ivermectin has been proposed to reduce viral replication and thus improve symptoms in patients with COVID.

Remdesivir was tested in 1062 patients, where the patients received the drug intravenously for 10 days. The number of days to recovery was significantly lower in patients who received Remdesivir. The average COVID Ordinal Scale Score of clinical improvement showed the Remdesivir group had better clinical outcome, but this was not significant. Remdesivir is the only FDA-approved drug for the treatment of COVID-19. Remdesivir inhibits RNA replicase (RdRp) of the

coronavirus, reducing viral replication and thereby stopping the virus from spreading throughout the body. [7]

Prophylactic Ivermectin was tested in 340 patients who were asymptomatic, familial close contacts; this study was both unmasked and randomized with a treatment and control group. For treatment, two doses of Ivermectin 72 hours apart with doses ranging from 15mg to 24mg depending on the body weight of the patient. Whether the patients developed symptoms were measured in both groups.

II. DRUGS FOR PATIENTS WHO HAVE PNEUMONIA

Favipiravir Improves Clinical Status and Viral Elimination in COVID Patients with Pneumonia

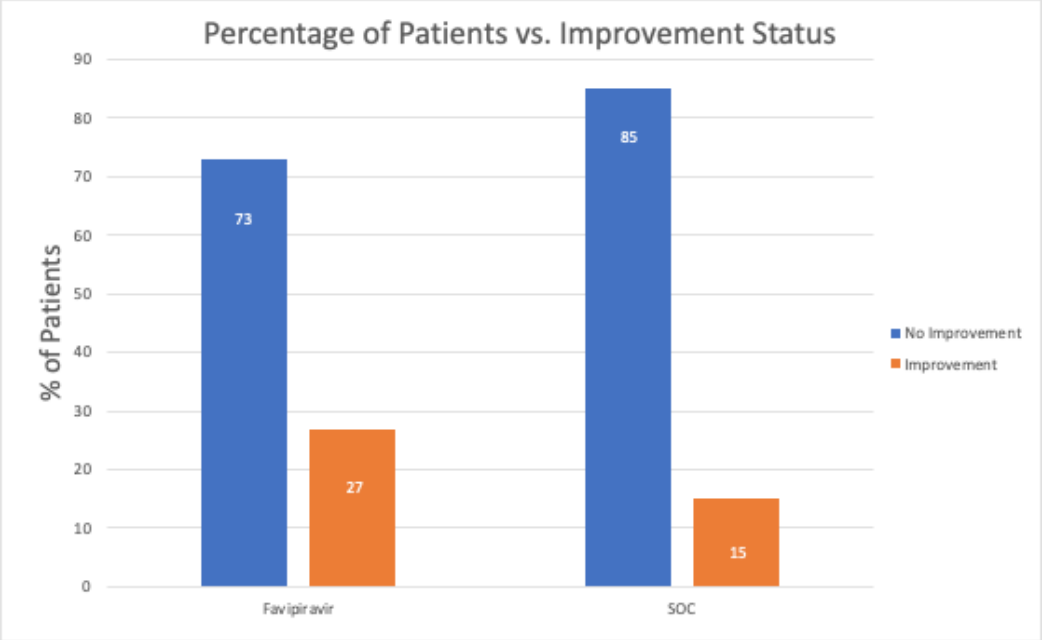

Figure 2. Patients who took Favipiravir Showed Greater Improvement Status Compared to Those Treated with Standard of Care. The percentage of patients demonstrating improvement (orange) or no improvement (blue) based on the WHO categorical ordinal scale is being compared between the control (SOC) group and the treatment (Favipiravir) group. The WHO categorical ordinal scale is 0 = uninfected to 8 = dead.[3] Patients were considered to have improved if they increased by two or more categories on the ordinal scale by day 10 of being diagnosed. Patients in the Favipiravir group were given the treatment of Favipiravir twice a day for 14 days. Patients in the SOC group received the recommended treatment for COVID-19, which could include hydroxychloroquine, chloroquine, or other recommended medication. [8] 27% of the patients given Favipiravir showed improvement, and 15% of the patients given SOC showed improvement.

Patients who took Favipiravir showed greater clinical improvement compared to patients treated with Standard of care (Figure 2). A proportions test was run on the data using the proportion of patients who improved with Favipiravir (27%) and the proportion of patients who improved while being treated with SOC (15%) (Figure 2). The difference in proportions was found to be significant (p-value = 0.0008). Therefore, we can conclude that the percentage of patients with COVID and pneumonia who took Favipiravir and saw clinical improvement was significantly greater than patients with COVID and pneumonia who were treated with SOC.

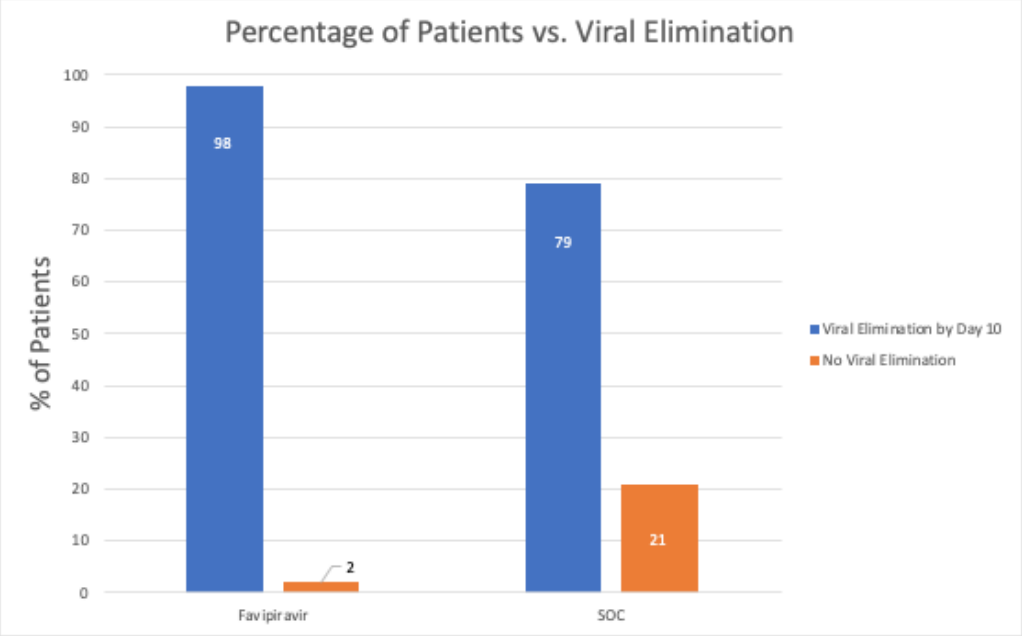

Figure 3. Patients who took Favipiravir Showed More Viral Elimination Compared to Those Treated with Standard of Care. The percentage of patients demonstrating viral elimination (orange) or no viral elimination (blue) is being compared between the control (SOC) group and the treatment (Favipiravir) group. Viral elimination was determined by how many patients received a negative PCR test by day ten of being diagnosed. [9] Patients in the Favipiravir group were given the treatment of Favipiravir twice a day for 14 days. Patients in the SOC group received the recommended treatment for COVID-19, which could include hydroxychloroquine, chloroquine, or other recommended medication. [8] 98% of patients given Favipiravir showed viral elimination, and 79% of patients given SOC showed viral elimination.

The percentage of patients who took Favipiravir showed more viral elimination compared to the percentage of patients treated with Standard of Care (Figure 3). A proportions test was run on the data using the proportion of patients who showed viral elimination with Favipiravir (98%) and the proportion of patients who showed viral elimination while being treated with SOC (79%) (Figure 3). The difference in proportions was found to be significant (p-value = 3.09 x 10-6). Therefore, we can conclude that the percentage of patients with COVID and pneumonia who took Favipiravir and had viral elimination was significantly greater than patients with COVID and pneumonia who were treated with SOC.

III. DRUGS FOR PATIENTS WHO HAVE MILD TO MODERATE COVID

Ivermectin + Doxycycline: Significant Improvement in Early Clinical Response and Reduction in Viral Elimination Time

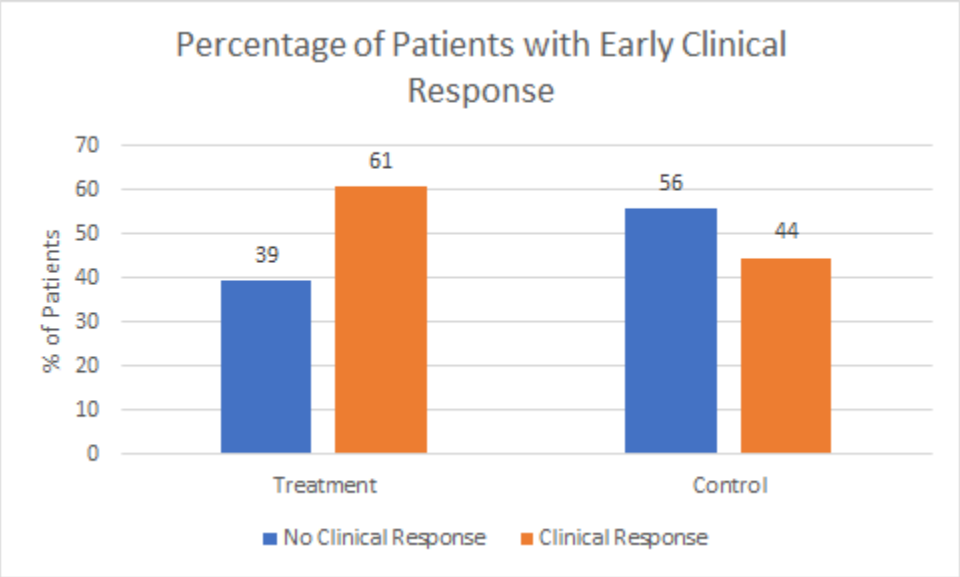

Figure 4. Ivermectin + Doxycycline increases frequency of early clinical improvement compared to Standard of Care. This figure displays the percentage of patients in both the control and treatment groups demonstrating a clinical response to their treatment within seven days, which is defined as patients with a normal body temperature persisting for at least three days, improvement in respiratory symptoms and lung lesions, an $SpO_2 >$ 93% without assistance, and a lack of complications requiring hospitalization. The treatment group (183 patients) received a combination of Ivermectin and Doxycycline with Standard of Care, while the control group (180 patients) received Standard of Care alone. 80/180 patients in the control group demonstrated an early clinical response, compared to 111/183 patients in the treatment group.

The primary outcome of this study was to determine if Ivermectin + Doxycycline increases the percentage of patients with a clinical response to treatment within seven days. A greater percentage of patients in the treatment group exhibited an early clinical response to their treatment than the control group, with 61% of patients in the treatment group meeting the criteria of a clinical response as opposed to 44% in the control group (Figure 4). The proportions of patients with an early clinical response between the two groups were compared, and the difference was found to be significant (p-value = 1.0×10^{-5}). Therefore, we conclude that the combination of Ivermectin + Doxycycline with Standard of Care is effective at increasing frequency of early clinical improvement.

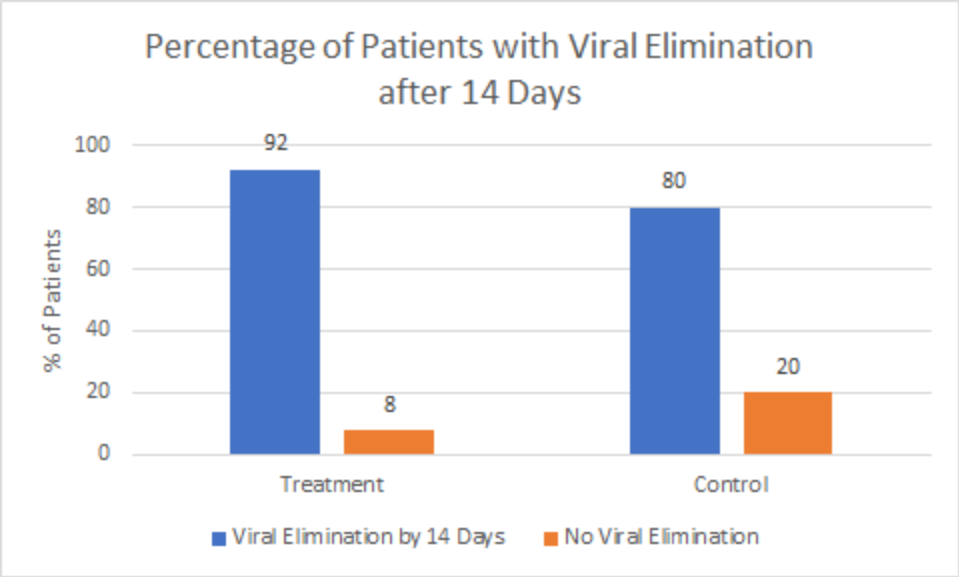

Figure 5. Ivermectin + Doxycycline effective at reducing time needed for viral elimination. This graph displays the rate of viral clearance after two weeks between the treatment and control groups. Viral clearance is defined as a negative COVID-19 test analyzed using PCR (polymerase chain reaction) test, which replicates and detects the viral genetic material unique to SARS-CoV-2. [9] After two weeks, 114 of 180 patients in the control group tested negative for COVID-19 (80.0%), compared to 169 of 183 patients in the treatment group (92.3%).

To determine if Ivermectin + Doxycycline has a significant reduction on viral clearance time, the proportions of patients testing negative for COVID-19 with a PCR test were compared between the treatment and control groups. The treatment group had a greater percentage of patients with viral clearance after the period of two weeks than the control group, and the difference was found to be significant (p-value = 3.0×10^{-5}) (Figure 5). Therefore, we conclude that this treatment of Ivermectin and Doxycycline + Standard of Care significantly reduces the time needed for viral elimination.

Remdesivir: Significant Reduction in Time to Recovery

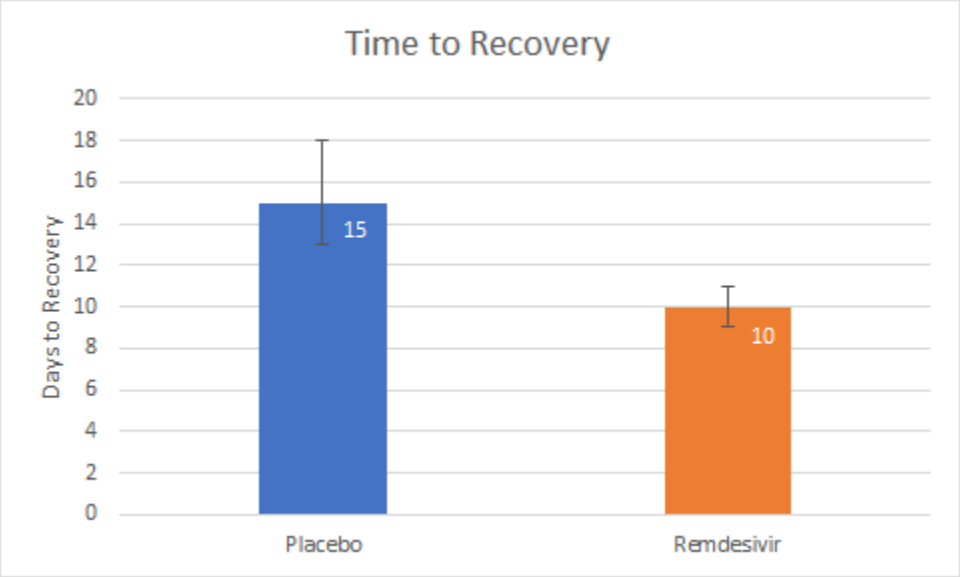

Figure 6. Time to recovery for patients was significantly reduced with administration of Remdesivir. 521 patients were randomly allocated to the Placebo group, and 541 patients were administered Remdesivir for 10 days. Number of days it took for patients to recover from moderate COVID-19 was significantly lower when patients were treated with Remdesivir than patients in the placebo group.

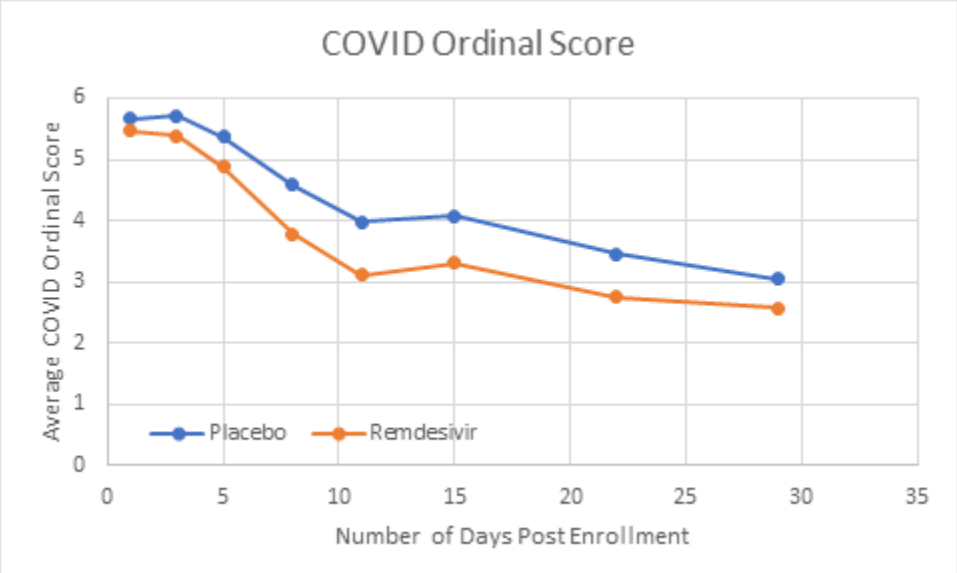

Figure 7. Remdesivir is Somewhat Effective in Improving Clinical Status of Patients. Clinical status of patients was measured in the COVID Ordinal Scale Score. [3] Highest COVID Ordinal Scale Score is 8, indicating death, and lowest score is 1, indicating discharged and not requiring additional treatment. COVID Ordinal Scale was assessed in the same patients studied in Figure 6. Average COVID Ordinal Scale Scores between days 1 to 29 for patients in Placebo group were higher than Scores of patients in the Remdesivir group, indicating a better clinical status in the Remdesivir group.

When looking at the data for primary outcome measure, time to recovery, we can find that patients who took the Remdesivir drug had a significantly shorter recovery period than patients who did not take the drug. (Figure 6). When looking at the data for secondary outcome measure and the clinical status of the patients, there was no significant difference in the average COVID Ordinal scale scores from day 1 to 29. However, the ordinal score was consistently lower in the drug trial group, especially on day 11 post enrollment (Figure 7). We can conclude that the drug Remdesivir has a significant effect on time to recovery, and can somewhat lower need for oxygen and hospitalization.

IV. DRUGS TO PREVENT COVID SYMPTOM DEVELOPMENT

Prophylactic Ivermectin: Results

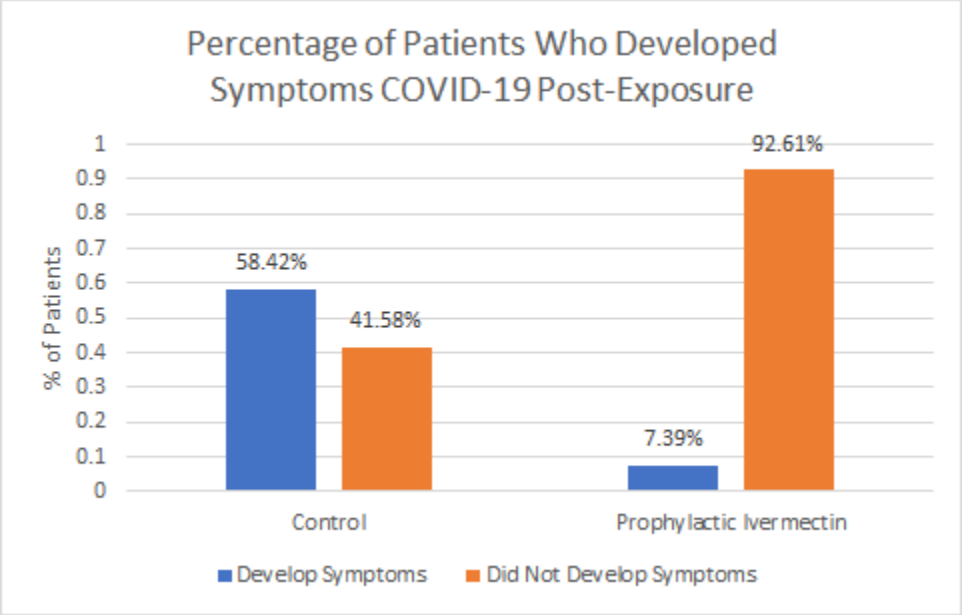

Figure 8. Ivermectin is significantly effective in preventing patients from developing symptoms post-exposure. Primary outcome of this study was to determine if patients who were exposed to COVID-19 would develop symptoms if they were treated with Prophylactic Ivermectin. 304 close contacts of family members who tested positive for COVID-19 were divided into the Control group and the Treatment group. Patients who were treated with Prophylactic Ivermectin are much less likely to develop symptoms than patients in the control group. In the control group, it is more likely for patients to develop symptoms than not develop symptoms.

There is a significant difference between the percentage of patients who developed symptoms when treated with prophylactic Ivermectin compared to the control group (Figure 8). We recommend two total doses of Ivermectin for patients who have been exposed to COVID-19 as a method to prevent the patients from later developing symptoms.

V. CONCLUSION

Our team of researchers recommends the drug Favipiravir for effective treatment of COVID-19-related pneumonia. According to a study by Northwestern Medicine, COVID-related pneumonia accounts for the most deaths caused by COVID-19 [10]. Because of this, we recommend Favipiravir due to its ability to significantly increase clinical improvement and reduce viral elimination time in patients with COVID-related pneumonia.

Along with Favipiravir, our team also recommends the following three drugs: Ivermectin with Doxycycline, Remdesivir, and Prophylactic Ivermectin. Ivermectin with Doxycycline is significantly effective in improving clinical status and viral clearance, and Remdesivir is significantly effective for reducing time to recovery and somewhat effective in improving clinical status. Prophylactic Ivermectin is also significantly effective in preventing patients who were exposed to the virus from developing symptoms.

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