Favipiravir: Our Recommendation for Most Effective COVID-19 Treatment Technical Summary

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I. Favipiravir

Favipiravir was tested in patients with COVID and pneumonia. Patients were randomly divided into two groups of 100. One group received Standard of care treatment (control group), the recommended treatment for COVID-19, which could include hydroxychloroquine, chloroquine, or other recommended medication, for 14 days. The other group received 1600 mg of Favipiravir twice a day for 14 days. Outcome variables being studied were clinical improvement status (measured by the WHO ordinal scale) and viral elimination (measured by PCR testing).

1ST VARIABLE – IMPROVEMENT STATUS

We wanted to test if Favipiravir had a significantly higher percentage of patients who showed clinical improvement compared to SOC. To visualize the difference, a bar graph was created (Figure 2). Figure 2 compares the percentage of patients and their improvement status between the treatment (Favipiravir) and control (Standard of care) group. For SOC, 15 of the 100 patients (15%) showed an improvement in clinical status, and 85 (85%) showed no clinical improvement, found in the excel sheet labelled "Favipiravir" in the "Improvement Status Table" under column "SOC". In the treatment group, 27 out of 100 patients displayed clinical improvement (27%), and 73 patients (73%) showed no clinical improvement, found in the excel sheet "Favipiravir" in the "Improvement Status Table" under column "Favipiravir". Percentage of patients was used as the y-axis and the two groups, Favipiravir and SOC, were on the x-axis. Both treatments had two bars, one for "Improvement" and one for "No Improvement", which totaled to 100% (the total percentage of patients for the specific treatment).

To test for a significant difference in the proportions of patients with clinical improvement in treatment and control groups, a chi-square goodness of fit test was run with null hypothesis being that there was no significant difference in improvement status between the two groups. This test was conducted using Standard of Care (control group) as the expected values and Favipiravir (treatment group) as observed value, which is found in excel sheet "Favipiravir" in "Improvement Status Analysis" table. With degrees of freedom = 1, the test statistic was calculated to be 11.19 and p-value equal to 0.00078. Therefore, it can be concluded that the difference in proportions of patients with clinical improvement between the treatment and control group is statistically significant.

2ND VARIABLE – VIRAL ELIMINATION

We wanted to test if Favipiravir had a significantly higher percentage of patients who had viral elimination compared to SOC. To visualize the difference, a bar graph was created (Figure 3). Figure 3 compares the percentage of patients and their viral elimination status between the treatment (Favipiravir) and control (Standard of care) group. For SOC, 79 of the 100 patients

(79%) had viral elimination, and 21 (21%) had no viral elimination, found in the excel sheet labelled “Favipiravir” in the “Viral Elimination Table” under column “SOC”. In the treatment group, 98 out of 100 patients had viral elimination (98%), and 2 patients (2%) showed no viral elimination, found in the excel sheet “Favipiravir” in the “Viral Elimination Table” under column “Favipiravir”. Percentage of patients was used as the y-axis and the two groups, Favipiravir and SOC, were on the x-axis. Both treatments had two bars, one for “Viral Elimination” and one for “No Viral Elimination”, which totaled to 100% (the total percentage of patients for the specific treatment).

To test for a significant difference in the proportions of patients with viral elimination in the treatment and control groups, a chi-square goodness of fit test was run with null hypothesis being that there was no significant difference in viral elimination between the two groups. This test was conducted using Standard of Care (control group) as the expected values and Favipiravir (treatment group) as observed value, which is found in excel sheet “Favipiravir” in “Viral Elimination Analysis” table. With degrees of freedom = 1, the test statistic was calculated to be 21.76 and p-value equal to 3.09E-6. Therefore, it can be concluded that the difference in proportions of patients with viral elimination between the treatment and control group is statistically significant.

II. Ivermectin + Doxycycline

The study was carried out between June 1st to August 30th of 2020 in Dhaka, Bangladesh. The study had a total of 363 patients, with 183 randomly assigned to either the treatment group and 180 randomly assigned to the control group. The treatment group received a combination of Ivermectin and Doxycycline with Standard of Care, while the control group received Standard of Care. The two primary outcomes analyzed include early clinical response to treatment (defined as 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) and viral elimination after 14 days.

IST VARIABLE – EARLY CLINICAL RESPONSE

Figure 4 compares the proportion of patients exhibiting an early clinical response between the treatment and control groups, receiving Ivermectin and Doxycycline + Standard of Care and Standard of Care, respectively. These proportions are displayed through a bar graph, constructed by calculating the percentage of patients with an early clinical response in each group, as seen in the sheet labelled ‘Ivermectin and Doxycycline’ in the “Clinical Trial Data” Excel document. In the treatment group, 111/183 patients (61%) exhibited a clinical response within seven days, compared 80/180 patients (44%) in the control group. These percentages are compared on the x-axis, with the blue bars representing the proportion of patients in either group with no clinical response, and the orange bars representing the proportion of patients with an early clinical response. The percentage of patients is shown on the y-axis, totaling 100%.

To test for a significant difference between the proportions of patients with an early clinical response in the control and treatment groups, a chi-square hypothesis test was run using the control group as the expected frequency and the treatment group (Ivermectin and

Doxycycline + Standard of Care) as the observed frequency. The test statistic was calculated to be 19.48, and with 1 degree of freedom, the p-value was found to be equal to .00001 (see contingency table in 'Clinical Trial Data' under "Ivermectin and Doxycycline"). Therefore, we conclude that the difference in proportions of patients with an early clinical response between the treatment and control groups is statistically significant.

2ND VARIABLE – VIRAL ELIMINATION

Figure 5 compares the proportion of patients in the treatment and control groups with viral elimination, or the proportion of patients receiving a negative PCR test, after 14 days. The proportion of patients for each group is displayed using a bar graph, which was constructed by calculating the percentage of patients in each group with viral elimination after 14 days, shown in the sheet labelled 'Ivermectin and Doxycycline' in the "Clinical Trial Data" Excel document. The treatment group had 169/183 patients (92%) test negative, compared to 114/180 patients (80%) in the control group. On the x-axis, the results of the PCR tests are compared using blue bars to represented viral elimination after 14 days and orange bars to represent no viral elimination. The y-axis displays the percentages of patients in each group with either a positive or negative test, totaling 100%.

A chi-square analysis was also conducted to determine if the difference in proportion of patients with viral elimination after 14 days between the control and treatments groups is statistically significant. Using the proportion of patients with viral elimination in the control group as the expected frequency and the proportion of patients in the treatment group as the observed frequency, the chi-square statistic was calculated to be 17.44, and with 1 degree of freedom, the p-value is equal to .00003 (see contingency table in 'Clinical Trial Data' under "Ivermectin and Doxycycline"). Therefore, we conclude that there is a statistically significant difference between the proportion of patients with viral elimination after 14 days between the control and treatment groups.

III. Remdesivir

Remdesivir was tested in patients with moderate COVID-19. 521 patients were randomly allocated into the Control group and 541 patients were randomly allocated into the Remdesivir group. Patients in the Remdesivir group were administered 200 mg Remdesivir on Day 1 and 100 mg Remdesivir daily until Day 10. Outcome variables we are studying are Time to Recovery and Clinical Status (measured by COVID-19 Ordinal Scale Score). The COVID ordinal scale assesses patient clinical status, with 8 being the highest and indicating death, and 1 being the lowest and no hospitalization/O2 needed. Time to Recovery was when the patients reached Ordinal Scale Scores 1, 2, or 3. Patient clinical status was assessed using the COVID-19 ordinal scale periodically throughout Days 1 to 29, and the percentage of patients reporting each ordinal scale score were recorded. The data is recorded in the sheet titled 'Remdesivir' in the 'Clinical Trial Data' Excel document.

1ST VARIABLE – TIME TO RECOVERY

We want to test if the Remdesivir group had a significantly lower time to recovery than in the Control group, with the null hypothesis that there is no significant difference in the time to recovery between the two groups. Time to Recovery in the Control group was 15 days, while the time to recovery in the Remdesivir group was 10 days.

To visualize the difference, we inserted a bar graph for the table under the subsection 'Primary Outcome – Time to Recovery.' Figure 6 shows the bar graph for the number of days to recovery in the Control and the Remdesivir group. We added error bars for each bar that shows the 95% confidence interval of the Time to Recovery in each group.

We compare the 95% confidence interval to check if there is a significant difference in the time to recovery between the two groups. The 95% confidence interval can be obtained from the clinical trials website cited in the group report. We cannot reproduce the interval ourselves, as the individual data of time to recovery for each patient are not reported by the researchers. The 95% confidence interval does not overlap, so we are 95% confident that the time to recovery is significantly less in the Remdesivir group.

2ND VARIABLE – ORDINAL SCALE

We want to test if the Remdesivir group had a significantly lower COVID Ordinal Scale Score throughout Days 1 to 29. We calculated the average ordinal scale score per group per day by multiplying the proportion of patients with each scale score and the score value, then adding them up. To visualize the difference between the groups, we produced a scatterplot of days on the x-axis and average Ordinal Scale Scores for patients per day for the two groups on the y-axis (Figure 7).

We conduct a chi-square goodness-of-fit test with the null hypothesis that there is no significant difference in the average Ordinal Scale Scores between the two groups. We set the expected values as the scores of the placebo group, and observed values as the scores of the Remdesivir group. The chi-square value obtained is 0.752. At degrees of freedom = 7, the p-value for this chi-square value is 0.998. There is no significant difference between the average COVID Ordinal scale score from days 1 to 29 post enrollment between the placebo and the drug group.

IV. Prophylactic Ivermectin

304 close contacts of family members who tested positive for COVID-19 were divided into the Control group and the Treatment group. 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.

VARIABLE – SYMPTOM DEVELOPMENT

We want to test if there is a significant difference in the patients who develop symptoms in the Control group compared to the Prophylactic Ivermectin group.

In the control group, 58.4% of patients developed symptoms COVID-19 and 41.65 of patients did not develop symptoms of COVID-19. In the prophylactic ivermectin treatment group,

7.4% of patients developed symptoms of COVID-19 and 92.6% of patients did not develop symptoms. Figure 8 visualizes this difference in a double bar graph, with percentage of patients on the y-axis and Control and Prophylactic Ivermectin group on the x-axis. Blue bars represent the percentage of patients who developed symptoms of COVID-19, and orange bars represent the percentage of patients who did not develop symptoms.

Statistical analysis was conducted using chi-square goodness-of-fit test to see whether Prophylactic Ivermectin had significant effect on asymptomatic familial close contacts as a preventative measure of developing symptoms of COVID-19. We conducted the chi-square test using the proportion of control group patients who did or did not develop symptoms as the expected proportion. The expected proportion was applied to the total number of patients in the treatment group to produce the expected values. The values were compared with the observed values of the numbers of patients who did or did not develop symptoms in the patients who were administered Prophylactic Ivermectin. The chi-square test statistic calculated was 217.6. Using the chi-square distribution, we obtained a p-value of 3.04 x 10^-49. We can conclude that the prophylactic Ivermectin is significantly effective in preventing patients from developing symptoms of COVID-19 compared to the control group.