FAVIPIRAVIR

RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19, unless in the context of a clinical trial. *(Very low quality of evidence)*

Consensus Issues

Given that there are on-going clinical trials on favipiravir, the recommendation explicitly stated that there was no recommendation on the use of favipiravir unless it will be used for clinical trials. In addition, there may be some implications with regard to possible reimbursements and will encourage patients to join the clinical trial.

EVIDENCE SUMMARY

Should favipiravir be used as treatment for COVID-19?

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Key Findings

Six (6) randomized controlled trials were found on the use of favipiravir among patients with COVID-19. All 6 studies had some concerns in terms of risk of bias, but none of them had high risk of bias in any of the appraisal criteria. [1-6] The overall quality of evidence was downgraded due to inconsistencies in combining the studies in some of the outcomes, limited sample size, and risk of bias.

Pooled results of three studies monitoring clinical improvement on day 7 showed a modest effect favoring favipiravir compared to standard care, however, clinical improvement on day 28 showed no clinical significance. Incidence of viral negative conversion was not significantly different between favipiravir and standard of care on day 3 as well as on day 7. However, time to negative conversion showed a minimal advantage towards favipiravir compared to standard care. Pooled results on the incidence of adverse events (i.e., hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain) showed no significant difference between favipiravir and standard care.

Introduction

Favipiravir is an anti-viral drug used to treat influenza because of its activity against influenza viruses and potential effect against the SARS-CoV-2[1]. Because of its anti-viral properties as well as recent clinical experience on its use for patients with COVID-19, several studies have been done to assess its clinical efficacy against coronavirus infections.

Review Methods

An updated search was done through MEDLINE and Cochrane Central last 31 March 2021 (from date of initial search which was Dec. 31, 2020) using a combined MeSH and free text search on the terms coronavirus infections OR covid-19 OR SARS-Cov-2 and favipiravir. The term randomized controlled trial was also added as method filter. Only randomized controlled trials among patients with COVID-19 of varying severity that compared favipiravir with placebo or the defined standard care (using national guidelines at the time the study was conducted) were included. Systematic reviews were also looked into as secondary sources. The COVID-NMA Initiative was also reviewed and was the primary source for most of the RCTs included in this evidence summary as well as the pooled analysis. We excluded studies that specifically compared Favipiravir with other active treatments or as part of a combination treatment.

Results

We found no new RCTs on favipiravir compared to placebo or standard care published from January 2021 to March 2021. We have updated the citations to include all recently published papers that were initially included here as pre-prints [3,6].

All patients included in the RCTs were adults with RT-PCR confirmed COVID-19 infection ranging from mild to severe. Favipiravir was used in different dosing strategies either alone or in combination with standard or supportive care, then compared to either the standard care defined by local guidelines which also includes other antiviral treatment, at the time the studies were conducted. The characteristics of the included studies are summarized in Appendix 1.

Results varied among the studies with two (2) of them not showing a significant difference on any of the outcomes monitored [1,3] while the others reported some effects favoring favipiravir in terms of viral clearance observed from days 3-10, [4,5] clinical improvement [5] or time to clinical cure, oral shedding of the virus and supportive oxygen therapy [6].

Pooled results of three studies [1,4,5] monitoring clinical improvement on day 7 (Figure 1) showed a modest effect favoring favipiravir compared to standard care with a relative risk (RR) of 1.58 (95% CI 1.15, 2.16). However, clinical improvement on day 28 based on five studies [1,2,4-6] (Figure 2) showed no clinical significance at an RR of 1.02 (95% CI 0.95, 1.09). [7] Time to clinical improvement favored favipiravir in the pooled results of 3 studies [4-6] with an HR of 1.74 (95% CI 1.33, 2.27) [7] (Figure 3). WHO progression score level 6 or above at day 7 was only reported in one (1) study [RR 3.0, (95% CI 0.37, 24.17)] [1], while the studies that were supposed to measure this outcome including the outcome of WHO progression score level 7 or above, did not observe an event even at days 14-28. [7] All-cause mortality data by day 7 were monitored in three (3) studies where the trial by Dabbous reported one (1) death in the standard care group [RR 0.33 (95% CI 0.01, 7.99)]. [3,4,7] On day 28, all-cause mortality was monitored by four (4)

studies. In addition to the Dabbous study, only the study by Udwadia reported another death in the standard care group [RR 0.33 (95% CI 0.04, 3.16)]. [1,3,4,6,7]] There were just not enough events observed for clinically relevant outcomes such as death, respiratory distress or failure, and mechanical ventilation to make a strong conclusion for or against the use of favipiravir.

Incidence of viral negative conversion (Figures 4 and 5) was not significantly different between favipiravir and standard of care on day 3 (RR = 1.22; 95% CI 0.99,1.50) based on pooled results from 3 studies [1,5,6] as well as on day 7 (RR=1.10; 95% CI 0.96, 1.27) based on pooled results from all 6 studies. However, time to negative conversion showed a minimal advantage towards favipiravir compared to standard care with a pooled HR of 1.32 (95% CI 1.03, 1.69)7 based on 2 studies (Figure 6). [5-6]

Pooled results on the incidence of adverse events showed no significant difference between favipiravir and standard care (RR 1.54, 95% CI 0.87-2.75) (Figure 7). [7] Adverse events from the studies ranged from hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain. [1-6] In one study [5], liver transaminases seemed considerably high in the favipiravir group. [5] Although patients in the favipiravir group had higher AST (31.5% vs 20%) and ALT (21.3% vs 10.9%) levels, these findings did not reach clinical significance. However, a significant blood uric acid elevation was observed in 41.7% of patients in the favipiravir group compared to 3.6% in the standard care group ($p<0.0001$) in the same study. This was also noted in the Udwadia study where 16.4% had hyperuricemia in the favipiravir group and none in the standard care group. [6]

Serious adverse events such as acute respiratory distress syndrome, death from heart failure, bone fracture, increasing oxygen desaturation were also reported in the studies and pooled results showed an overall RR of 1.20 (95% CI 0.48, 3.00) (Figure 8). [7]

All 6 studies had some concerns in terms of risk of bias, but none of them had high risk of bias in any of the appraisal criteria. [1-6] The risk of bias ratings for each study per outcome are presented in the forest plots (Figures 1-8). The overall quality of evidence was downgraded due to inconsistencies in combining the studies in some of the outcomes, limited sample size, and risk of bias. Details on the reasons for the risk of bias, the downgrading of evidence, along with the relative and absolute effects of favipiravir compared to standard care is shown in the GRADE Evidence Profile.

Recommendations from Other Groups

Major guidelines on COVID-19 have not issued a recommendation for the use of favipiravir in their set of management options as there is still insufficient and uncertain evidence for its use. These guidelines include the NIH COVID-19 Treatment Guidelines, [8] Surviving Sepsis Campaign Guidelines on the Management of Critically Ill Adults with COVID-19, [9] and the Infectious Disease Society of America Guidelines Covid-19 Guidelines. [10] The Australian Guidelines for Clinical Care of People with COVID-19 [11] recommends against using favipiravir unless in the context of a randomized controlled trial.

Research Gaps

There are 22 ongoing studies on favipiravir compared to placebo or standard care listed in the NIH – U.S. National Library of Medicine's *ClinicalTrials.gov* [12] and one (1) in the Chinese Clinical Trail Registry *ChiCTR.* [13]

References

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[10] Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

[11] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v32.1 2020 Dec 24.

[12] NIH – U.S. National Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cond=Covid19+OR+coronavirus&term=favipiravir&cntry=&state=&city=&dist=

[13] Chinese Clinical Trials Registry, ChiCTR, http://www.chictr.org.cn/searchprojen.aspx?title=&officialname=&subjectid=&secondaryid=&applier=&studyleader=&ethicalcommitteesanction=&sponsor=&studyailment=&studyailmentcode=&studytype=0&studystage=0&studydesign=0&minstudyexecutetime=&maxstudyexecutetime=&recruitmentstatus=0&gender=0&agreetosign=&secsponsor=&regno=&regstatus=0&country=&province=&city=&institution=&institutionlevel=&measure=favipiravir&intercode=&sourceofspends=&createyear=0&isuploadrf=&whetherpublic=&btngo=btn&verifycode=&page=1

Appendix 1: Characteristics of Included Studies

Study & Setting	Treatment Intervention	Comparator	Design & Risk of Bias	Participants & Sample Size	Outcomes
Lou 2020[1] (China)	Favipiravir (1600 or 2200mg initial, then 600mg tid) up to 14 days + existing antiviral treatment	Baloxavir marboxil group: baloxavir marboxil (80 mg od) on day 1 and day 4; for patients who are still positive in virological test, they can be given again on day 7 + existing antiviral treatment Existing antiviral treatment or standard care: Lopinavir/ritonavir (400mg/100 mg bid or darunavir/cobicistat 800 mg/150 mg, qd and arbidol 200 mg tid)	RCT Some concerns in the risk of bias	30 hospitalized adults (ages 18-85) with COVID-19 infection of unclear severity	Primary Viral negative on day 14; Time from randomization to clinical improvement by 2 points on NEWS2 or live discharge (whichever came first) Secondary Viral negative on day 7; Incidence of mechanical ventilation on day 14; ICU Admission on Day 14; All-cause mortality on day 14.
Ivashchenko 2020[2] (Russia)	Favipiravir 1800/800mg (1800mg day 1; 800mg days 2-14) Favipiravir 1600/600mg (1600mg day 1; 600mg days 2-14)	Standard care according to Russian guidelines that included hydroxychloroquine or chloroquine; or lopinavir/ritonavir	RCT Some concerns in the risk of bias	60 hospitalized adults (ages 18 and above) with moderate PCR-confirmed COVID-19 on screening	Primary Elimination of SARS-CoV-2 at day 10 (by 2 negative PCR tests) Secondary Rate of viral clearance by day 5; Time to normalization of clinical symptoms; changes on CT scan by day 15; incidence and severity of adverse events
Dabbous 2020[3] (Egypt)	Favipiravir (600mg up to 10 days)	Standard care defined as Oseltamivir (75 mg 12 hourly for 10 days) and hydroxychloroquine (400 mg 12 hourly on day-one followed by 200 mg 12 hourly daily on day 2 to 10 days) conforming to the national standard of care therapy.	RCT Some concerns in the risk of bias	100 hospitalized adults (ages 18-80) with PCR-confirmed COVID-19 and mild to moderate symptoms according to the national protocol classification	Primary Viral clearance on days 3, 7 and 14 (2 successive negative PCRs 48hrs apart); Normalization of body temperature for 48 hrs; Improvement of radiological abnormalities at day 14 and discharge rate. Secondary Normalization of C-reactive protein and serum ferritin levels
Balykova 2020[4] (Russia)	Favipiravir (1200mg day 1 then 600mg for 14 days)	Standard care in accordance to the Temporary Guidelines of the Ministry of	RCT Some concerns in	200 hospitalized adults (ages 18-80) with	Clinical improvement according to the WHO Categorical Scale of Clinical

		Health of Russia that included hydroxychloroquine + azithromycin; hydroxychloroquine, lopinavir + ritonavir	the risk of bias	PCR-confirmed COVID-19 of moderate severity	Improvement; Clinical and laboratory data; Improvement of CT scan of the chest organs and the clearance of the SARS-CoV-2 virus; The frequency and nature of the occurrence of adverse events; The need for invasive and non-invasive oxygen support; Mortality
Ruzhentsova 2020[5] (Russia)	Favipiravir (1800mg bid on day 1, followed by a maintenance dose 800mg bid on days 2-10)	Standard care that included either umifenovir (200 mg 4 qid) + intranasal interferon alpha-2b (10000 IU/ml – 3 drops in each nasal channel 5 times a day), or hydroxychloroquine (400mg bid on day 1 followed by 200mg bid or 200mg bid on day 1 followed by 100mg bid) during the period up to 10 days, depending on the severity of the condition of the patient	RCT Some concerns in the risk of bias	168 hospitalized and outpatient adults (ages 18-60) with mild to moderate PCR-confirmed COVID-19 w/out respiratory failure	<u>Primary</u> Time to clinical improvement (based on a reduction of patient clinical status on at least 1 score according to WHO 8-Category Ordinal Scale for Clinical Improvement compared to screening; Time to viral clearance at day 28 (in 2 negative PCR results) <u>Secondary</u> Rate of clinical improvement at day 7; Viral clearance at day 5; Rate of clinical improvement at day 14; Rate of viral clearance at separate days; Time to body temperature normalization; Rate of resolution of resolution of lung changes on CT at day 14; Time to resolution of main disease symptoms; The rate of artificial lung ventilation; rate of transfer to ICU; Death rate during the 28 days
Udwadia 2020[6] (India)	Favipiravir (1800mg bid on day 1, 800mg bid) + standard supportive care for up to 14 days	Standard care that included antipyretics, cough suppressants, antibiotics, and vitamins (drugs with potential antiviral activity against SARS-CoV-2 and HCQ were prohibited)	RCT Some concerns on the risk of bias	150 hospitalized adults (ages 18-75) with PCR-confirmed COVID-19 and mild to moderate symptoms	<u>Primary</u> Viral clearance on negative RT-PCR result for 2 consecutive times (28 days maximum) and at hospital discharge <u>Secondary</u> Time to clinical cure based on clinician assessment; Time to first use of high flow supplemental oxygen/ ventilation/ECMO; Time to hospital discharge (RT-

					PCR negativity on 2 consecutive tests); Adverse events

Appendix 2: GRADE Evidence Profile

Author(s): K. Probyn, N. Henschke, G. Villanueva, Y. Sguassero, C. Bollig, C. Schmucker, J. Meerpohl
Question: Favipiravir compared to Standard care for Mild/Moderate/Unclear COVID-19 [a]
Setting: Worldwide
Bibliography: https://covid-nma.com

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard care	Relative (95% CI)	Absolute (95% CI)		
Viral negative conversion D7												
6 [b]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	290/386 (75.1%)	207/310 (66.8%)	**RR 1.10** (0.96 to 1.27)	**67 more per 1,000** (from 27 fewer to 180 more)	⨁⨁◯◯ LOW	
Clinical improvement D28												
5 [e]	randomised trials	serious [f]	not serious	not serious	serious [g]	none	209/327 (63.9%)	139/252 (55.2%)	**RR 1.02** (0.95 to 1.09)	**11 more per 1,000** (from 28 fewer to 50 more)	⨁⨁◯◯ LOW	
Clinical improvement D60 or more - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
WHO progression score (level 7 or above) D28												
3 [h]	randomised trials	serious [i]	not serious	not serious	very serious [j]	none	0/185 (0.0%)	0/185 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
WHO progression score (level 7 or above) D60 or more - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
All-cause mortality D28												
4 [k]	randomised trials	serious [l]	not serious	not serious	very serious [l]	none	0/235 (0.0%)	2/235 (0.9%)	**RR 0.33** (0.04 to 3.16)	**6 fewer per 1,000** (from 8 fewer to 18 more)	⨁◯◯◯ VERY LOW	
All-cause mortality D60 or more - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events												
4 [m]	randomised trials	serious [n]	serious [o]	not serious	serious [p]	none	149/327 (45.6%)	72/251 (28.7%)	**RR 1.54** (0.87 to 2.75)	**155 more per 1,000** (from 37 fewer to 502 more)	⨁◯◯◯ VERY LOW	
Serious adverse events												
4 [q]	randomised trials	serious [n]	not serious	not serious	very serious [l]	none	9/297 (3.0%)	5/241 (2.1%)	**RR 1.20** (0.48 to 3.00)	**4 more per 1,000** (from 11 fewer to 41 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR**: Risk ratio

Explanations

a. Last update: March 2, 2021
b. Balykova L, 2020; Dabbous HM, 2020; Ivashchenko AA, 2020; Lou Y, 2020; Ruzhentsova T, 2020; Udwadia Z, 2020
c. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results
d. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect
e. Ivashchenko AA, 2020; Lou Y, 2020; Ruzhentsova TA, 2020; Udwadia Z, 2020, Balykova L, 2020
f. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, outcome measurement and selection of reported results
g. Imprecision downgraded by 1 level: due to low number of events and/or participants
h. Balykova L, 2020; Lou Y, 2020, Udwadia Z, 2020
i. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviation from intended intervention
j. Imprecision downgraded by 2 levels: no events in both groups and low number of participants
k. Balykova L, 2020; Lou Y, 2020; Dabbous HM, 2020; Udwadia Z, 2020
l. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
m. Balykova L, 2020; Ivashchenko AA, 2020; Ruzhentsova T, 2020; Udwadia Z, 2020
n. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended intervention and outcome measurement
o. Inconsistency downgraded by 1 level: I^2=79.6%
p. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for no effect and the possibility for harm
q. Balykova L, 2020; Lou Y, 2020; Ruzhentsova T, 2020; Udwadia Z, 2020

Appendix 3: Forest Plots

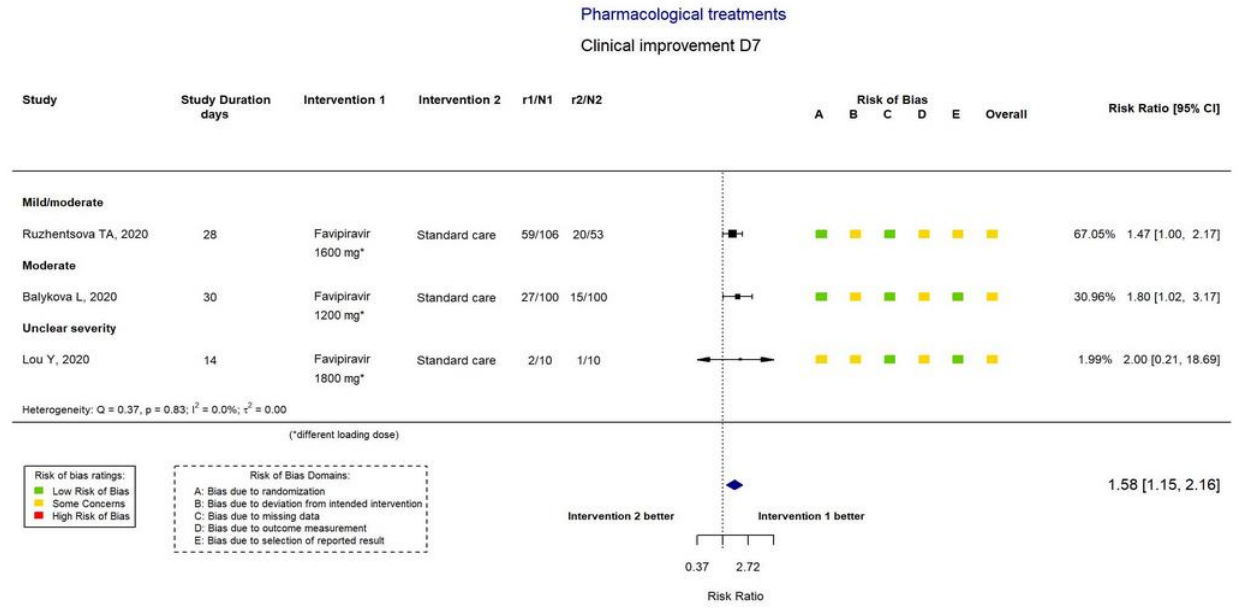

Figure 1. Clinical Improvement Day 7 (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

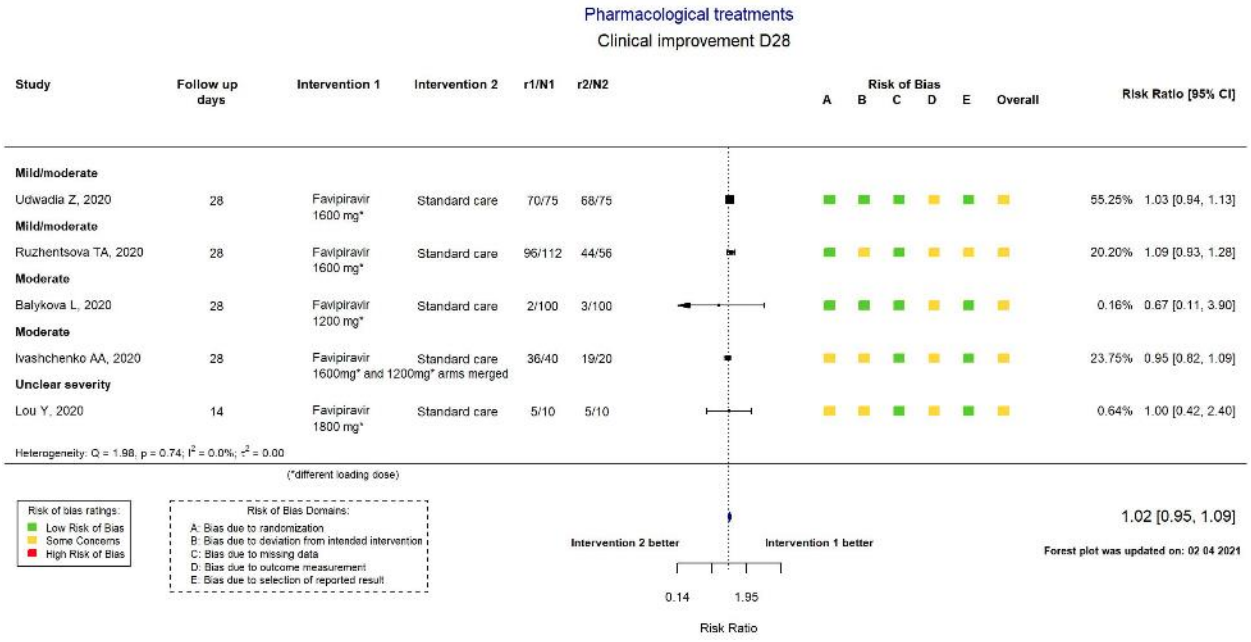

Figure 2. Clinical Improvement Day 28 (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

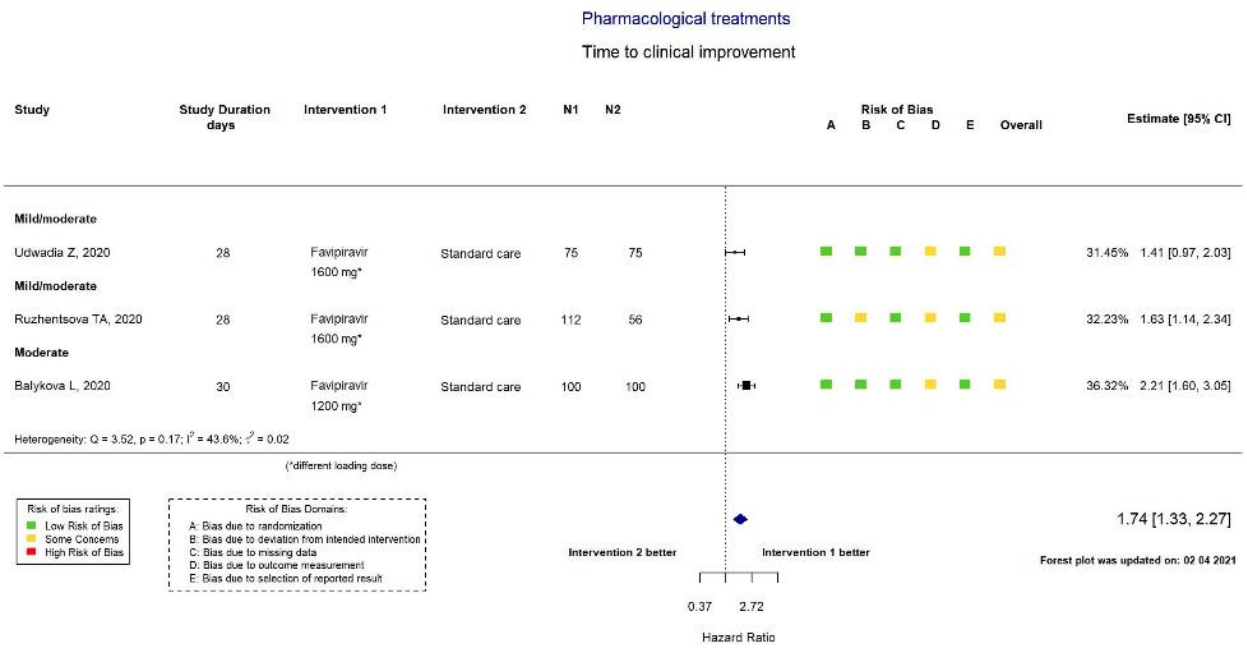

Figure 3. Time to Clinical Improvement (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

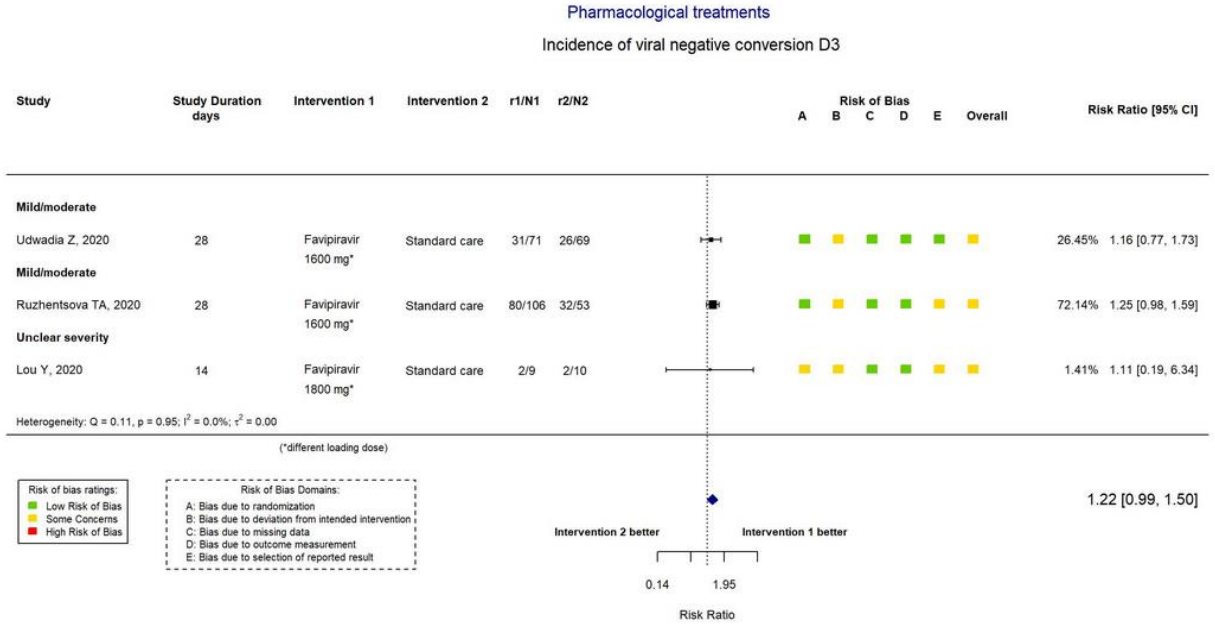

Figure 4. Incidence of Viral Negative Conversion Day 3 (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

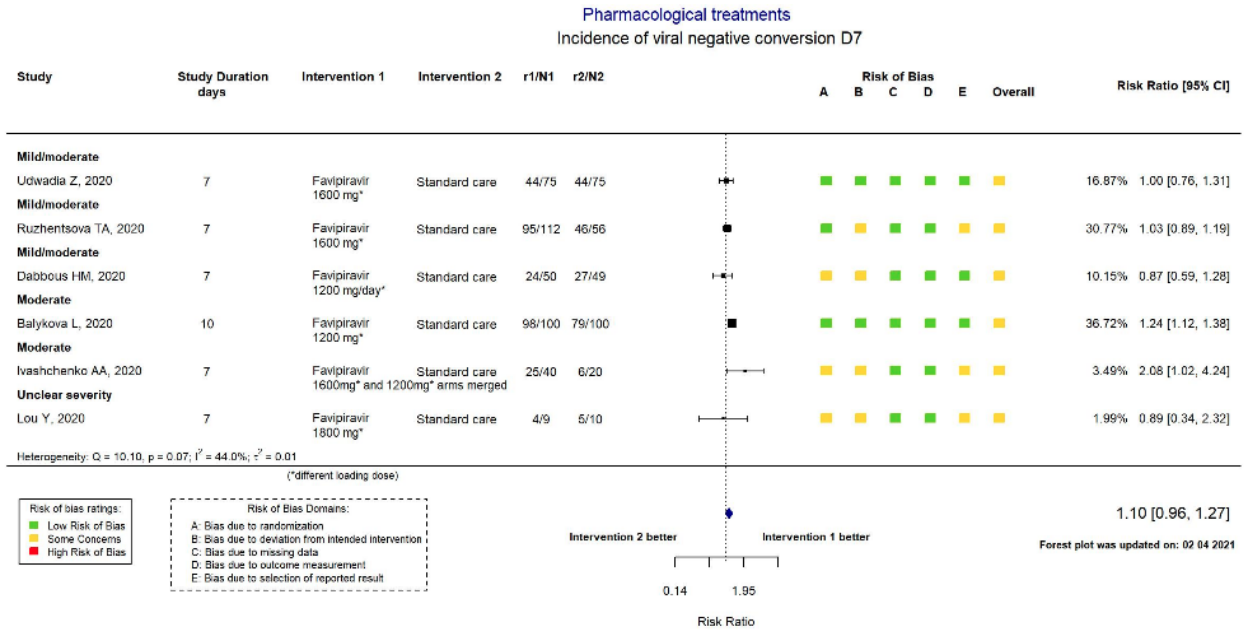

Figure 5. Incidence of Viral Negative Conversion Day 7 (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

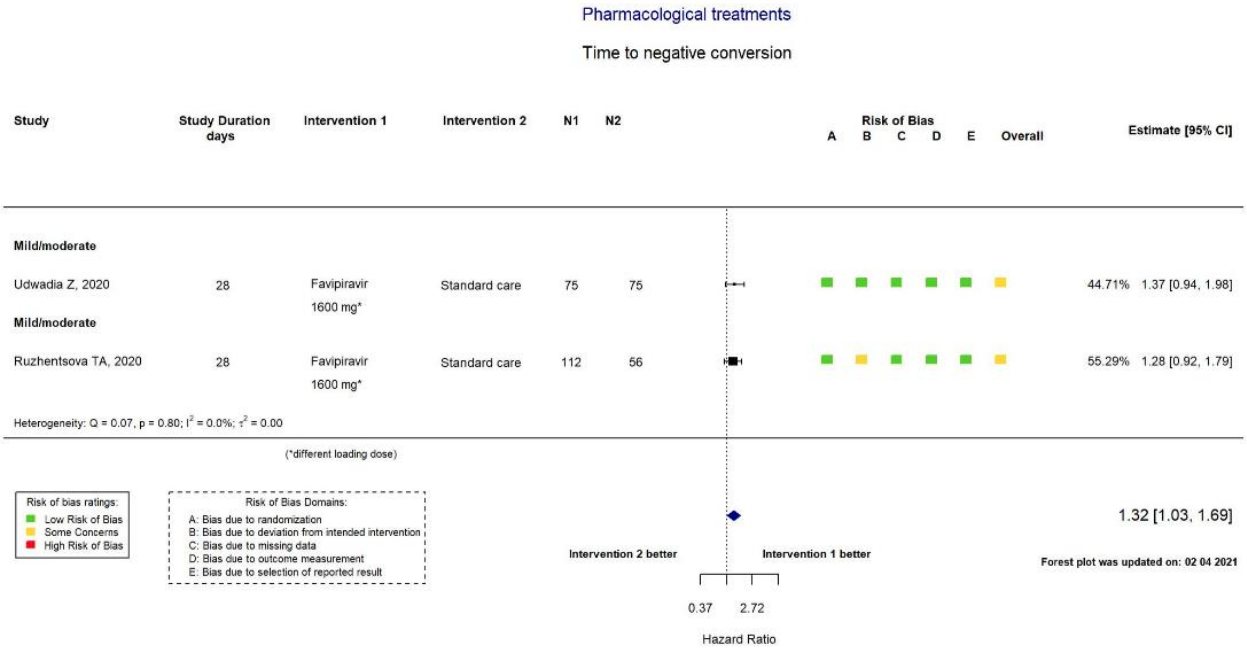

Figure 6. Time to Negative Conversion (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

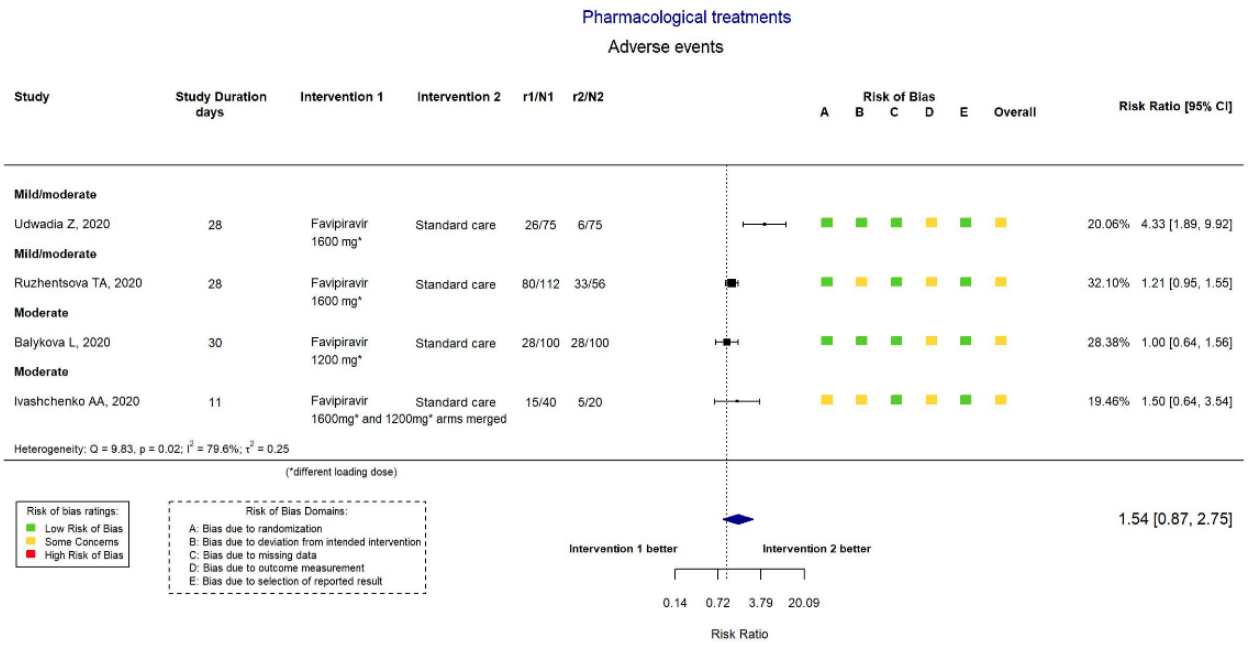

Figure 7. Adverse Events(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

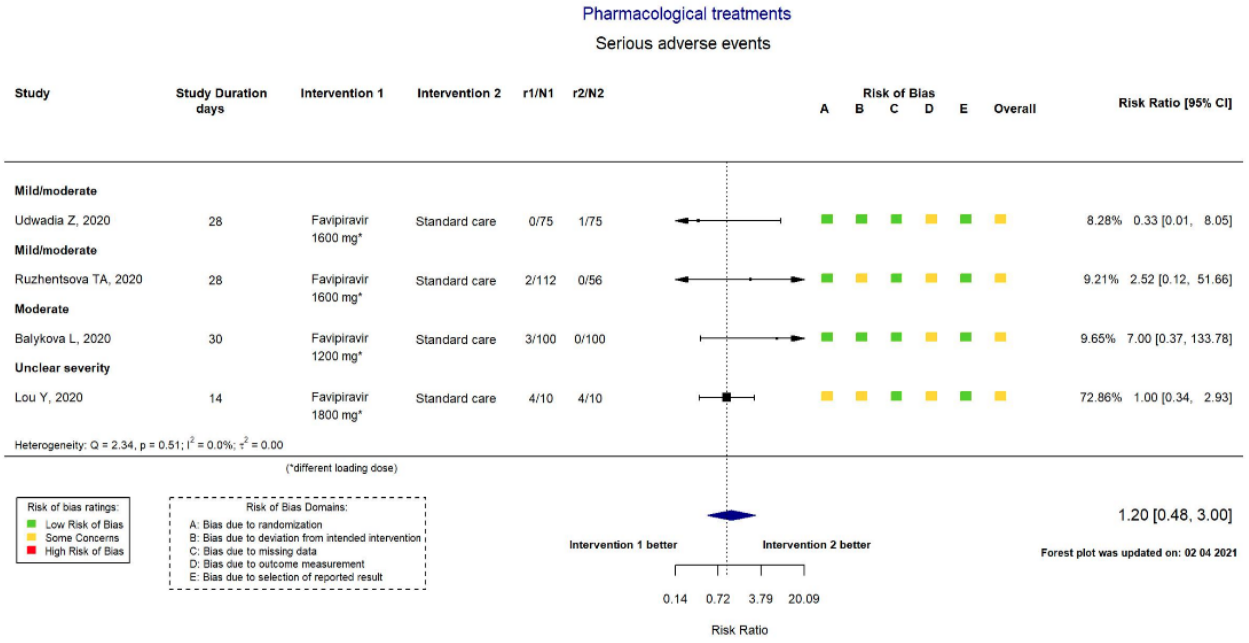

Figure 8. Serious Adverse Events (from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

Appendix 4: Characteristics of Ongoing Studies

Title	Study Results	Conditions	Interventions	Characteristics
Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal	No Results Available	• Covid19	• Drug: Favipiravir • Drug: Placebo • Drug: Remdesivir	Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Clinical Trial of Favipiravir Treatment of Patients With COVID-19	No Results Available	• SARS-CoV-2 Infection	• Drug: Favipiravir	Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
The Prevent Severe COVID-19 (PRESECO) Study	No Results Available	• Covid19	• Drug: Favipiravir • Drug: Placebo	Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Triple (Participant, Care Provider, Investigator) • Primary Purpose: Treatment

Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19	Has Results	• COVID-19	• Drug: Favipiravir • Drug: Standard of care	Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients	No Results Available	• Covid19	• Drug: AVIGAN • Drug: Placebo Comparator	Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Treatment