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Repurposing of Favipiravir for the Treatment COVID-19: A Meta-analysis

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ABSTRACT

Background: The outbreak of coronavirus disease 2019 (COVID-19) originating from Wuhan, Hubei Province, China at the end of 2019 led to dramatic changes in the healthcare and socioeconomic sectors across the globe. The aim of this meta-analysis was to assess whether favipiravir is a safe and effective option for treatment of COVID-19 patients compared with standard of care (SOC) and/or other applied medicines.

Methods: Data bases were searched up to 31st May 2021 for studies that compare the efficacy and safety of favipiravir and SOC or other relevant therapy in COVID-19 patients. Search results were assessed for relevance on the basis of the following inclusion criteria and relevant results were subjected to a quality estimation using the EPHPP Quality assessment tool.

Results: A total of 10 articles with hospitalized patients and outpatients (n=1016) met our inclusion criteria. Pooled RR 1.24 (95% CI 1.08-1.43, n=5) showed clinical improvement by Day 7 and Day 14 (pooled RR 1.18 (95% CI 1.01-1.37, n=5) and favipiravir was associated with 24% and 18% better outcome compared to other treatment, respectively. Viral clearance by Day 7 and Day 14 with favipiravir was comparable to other treatments (RR 1.1; 95% CI 0.92-1.35, n=5) and (RR 1.07, 95% CI 0.88-1.29, n=5). Safety profile of favipiravir was comparable to that of other treatments (RR 1.21; 95% CI 0.88-1.67) and SEA including death were comparable between treatments (RR 0.64, 95% CI 0.15-2.68, n=4 studies). No correlation between incidence of SEA and treatment option was identified.

Conclusion: There is a significant difference in the clinical improvement detected on Days 7 and 14 in favour of favipiravir. Viral clearance at Days 7 and 14 is comparable between treatments with neither being associated with significantly better outcomes. The safety profiles of favipiravir and SOC regarding SAE show no statistically significant differences.

Key Words: Favipiravir, COVID-19, Meta-analysis, Efficacy, Safety

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) originating from Wuhan, Hubei Province, China at the end of 2019 led to dramatic changes in the healthcare and socioeconomic sectors across the globe. The virus was named by World Health Organization (WHO) as the 2019 novel Coronavirus and was renamed on 11th Feb 2020 as SARS-CoV-2 [1]. According to the Johns Hopkins Coronavirus Resource Center until now over 418,235,000 confirmed Global COVID-19 cases and over 5,850,000 deaths have been reported [2]. SARS-CoV-2 belongs to a family of Coronaviruses [3]. They are single-stranded, positive-sense, RNA containing, and enveloped viruses with a genome size between 27 and 34 kilobases that is comparatively larger than other RNA viruses [3-5]. The investigations showed that SARS-CoV-2 have 75%-80% identical genome sequence as SARS-CoV [6,7].

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There were two global epidemics of atypical pneumonia SARS-CoV and MERS-CoV, respectively in 2002 and 2012 and later MERS-CoV reappearing in South Korea in 2015 [8-10]. Despite the lower mortality rate of SARS-CoV-2 infection compared to MERS-CoV (9.5%) and SARS-CoV (34.4%), the COVID-19 pandemic has raised a significant concern [11].

The observed serious, life-threatening manifestations and complications after infection with the virus were caused by the severe respiratory syndrome, related with diffuse alveolar damage and severe lung injury [12]. It was suggested that different systems might be involved, including respiratory (cough, shortness of breath, rhinorrhea, sore throat, hemoptysis, and chest pain), musculoskeletal (muscle ache), gastrointestinal (Diarrhea, abdominal pain and vomiting), olfactory (hyposmia, anosmia or complete loss of olfactory functions), ophthalmic (conjunctivitis, retinitis), dermatological (erythematous rash, chickenpox-like vesicles), cardiovascular (arrhythmias), rheumatological (arthralgia) and neurologic (headache and confusion) [13-15]. COVID-19 has incubation period between 5-6 days that can be extended up to 14 days [16]. In pediatric patients when compared to adults, the incubation period is a little bit longer up to 14 days [17].

Due to wide prevalence nature of SARS-CoV-2, its mortality rate, and its limited treatment options new therapeutic alternatives need to be provided. One possibility is to repurpose already existing drugs, which would provide beneficial and immediate effects on COVID-19 patients. Globally, the clinical researchers were testing many existing drugs, such as hydroxychloroquine/chloroquine approved to treat Malaria; antiretrovirals lopinavir/ritonavir and darumavir/ritonavir; the serine protease inhibitors camostat mesylate and nafamostat mesylate; anti-parasitic drug ivermectin; drugs that interfere cytokine activities as tocilizumab, sarilumab, and IL-1 receptor antagonist anakinra; anti-inflammatory drugs, including corticosteroids as dexmethazone; anticancer drugs as dasatinib, imatinib and nilotinib; remdesevir originally approved to treat HIV and other nucleoside analogues: Ribavirin, galidesivir and favipiravir ect [18,19].

On February 15, 2020 in China, favipiravir was approved as treatment option for this life threatening infection [20]. Favipiravir, also known as a T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), initially was developed in 2002 at Research Laboratories of Toyama Chemical Co., Ltd, Japan. This is a prodrug of a purine nucleic acid analog, that is phosphoribosylated by cellular enzymes to its active form favipiravir-ribofuranosyl-5'-triphosphate [21]. The mechanism of action include inhibition of RNA dependent RNA polymerase (RdRP), that is needed for RNA viral replication within infected cells, acting as a purine analog and is incorporated instead of guanine and adenine [22].

Favipiravir has a wide range of antiviral effects *in vitro* and *in vivo* and this can be explained by the fact that catalytic domain of RdRP is evolutionary conserved in various RNA viruses. Favipiravir inhibits 53 types of influenza viruses. The range includes influenza A (H1N1, H2N2, H3N2, H4N2, H7N2, H5N1 and other strains), influenza B [23,24] and many other RNA viruses (*Arenaviruses*, Phleboviruses, Hantaviruses, *Flaviviruses*, Enteroviruses; an *alphavirus*, a paramyxovirus, respiratory syncytial virus, and *noroviruses*) [25-27]. However, favipiravir showed weak activity against non-influenza virus RNA viruses and it had no activity to DNA viruses. An *in vitro* study showed that favipiravir has potent inhibitory activity against influenza A, B, and C viruses. The IC50s ranged from 0.013 μg/ml to 0.48 μg/ml for the influenza A viruses, from 0.039 μg/ml to 0.089 μg/ml for the influenza B viruses, and from 0.030 μg/ml to 0.057 μg/ml for the influenza C viruses [28]. Moreover, several studies showed its effectiveness against Ebola virus [29]. Favipiravir suppressed replication of Ebola virus in cell culture by 4 log 10 units with an IC90 of 110 μM [30]. *In vitro* experiments with favipiravir demonstrated that half maximal effective concentration (EC50)-61.88 μM/L of favipiravir, half-maximal cytotoxic concentration (CC50)>400 μmol. L-1, selectivity index (SI)>6.46 effectively inhibits SARS-CoV-2 in Vero E6 cells [31].

Furthermore, in mice lacking type I interferon-alfa/beta receptor (IFNAR-/-) was established that at Day 6 post infection (corresponds to 2-4 days before the time of death in control animals) favipiravir induced rapid virus clearance, reduced viremia, ameliorated clinical and biochemical signs of disease, and prevented a lethal outcome in 100% of the animals [30]. Furuta et al., 2002 observed in mice, which were infected with influenza virus A/PR/8/34, that administration of favipiravir at 100 mg/kg of body weight/day (four times a day) for 5 days was associated with significant reduction in the mean pulmonary virus yields and the rate of mortality.

The results from clinical trials conducted with favipiravir in COVID-19 patients are conflicting and non-conclusive. Therefore, we tried to summarize the existing data to boost the information about efficacy and safety profile of favipiravir in patients with COVID-19. The aim of the present meta-analysis was to establish with an acceptable level of confidence the improvement and tolerability rates in patients with COVID-19 after favipiravir treatment compared to standard of care and/or other drugs.

METHODS

Data Sources and Search Strategy

We searched the following databases from the beginning of 2020 to the end of May 2021, for relevant studies: MEDLINE, SCOPUS, PsyInfo, eLIBRARY.ru, as well as the clinical trial registries for unpublished data (https://www.clinicaltrialsregister.eu/; https://clinicaltrials.gov/; www.chictr.org) and preprint databases MedRxiv and Research Square. The following keywords and various combinations were used in the search: "Coronavirus" OR "COVID-19" OR "SARS-CoV-2" AND "Favipiravir" OR "Avigan" AND "clinical trial" AND "controlled" AND "randomi*" AND "double blind."

Full-text articles and abstracts published in English and Cyrillic were checked for relevance to the topic and were assessed.

Eligibility Criteria and Quality Assessment

Search results were assessed for relevance on the basis of the following inclusion criteria:

- Type of study/trial-epidemiological, controlled and randomized;
- Studies providing information for the investigation of clinical improvement, including assessment of symptoms and radiological results and/or time to negative PCR (information about viral clearance) and/or worsening of clinical symp-

toms or necessity of supplemental oxygen therapy and/or safety of treatments applied;

- Types of subjects representatives of the whole population, specific stratum;
- Patients with proven SARS-CoV-2 infection;
- Access to source data;
- Eligibility for statistical analysis. Studies that correspond to the inclusion criteria were subjected to a quality estimation using the EPHPP Quality assessment tool (**Table S1**). Sources were excluded if they represented trials in which the principle arm reported other outcomes different from changes in clinical condition (improvement or worsening), time to negative PCR test and safety investigation; other conditions apart from COVID-19.

This tool includes assessment of different characteristics like selection bias, study design, blinding, data collection method, confounders, and drop outs in order to help raters form an opinion of quality based upon information contained in the study. Studies that correspond to the aforementioned inclusion criteria are subjected to quality estimation and general ratings are taken into account when results from the study are interpreted.

Data Extraction

All available studies were carefully reviewed and assessed for relevance according to the predefined inclusion criteria. **Figure 1** represents the process of studies selection in order to determine their eligibility for inclusion in the analysis. After removing redundant articles and abstracts then only full-text articles were investigated. Two reviewers independently extracted data. Extracted data includes the following items: Author's name, type of study, year of publication, sample size, target population, type of intervention, dose of intervention, control group, primary and secondary outcomes, follow-up and/or treatment duration (**Table 1**). Outcome variables were extracted and are represented in different tables (**Tables 2 and 3**). The studies with insufficient or incomplete data were not included. Any potential disagreements

Table 1: Summary of characteristics of the included studies

Study: First author (year)	Type of study	Sample Size* Test/ Reference	Target population	Market or INN Name	FVP Dose (daily)	Control group	Primary/secondary endpoints		Follow-up/ treatment duration (days)
							Efficacy	Safety	
Balykova et al. (2020)	open-label, randomized, multicenter comparative study	17/22	Hospitalized with moderate COVID-19 pneumonia	replivir	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-14	SOC	Clinical recovery/Viral clearance	TEAE	14/15
Chen et al. (2020)	prospective, randomized, controlled, open-label multicenter trial	116/120	Inpatients, moderate/severe critical COVID19 pneumonia	FVP	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-10	Umifenovir (Arbidol+SOC	Clinical recovery	TEAE	17-Oct
Cai et al. (2020)	open-label, nonrandomized, controlled study	35/45	Inpatients, moderate COVID19 simptoms	FVP+INFalfa1b	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-14	lopinavir/ ritonavir+INFalfa1b	Clinical improvement/Viral clearance	TEAE	14/14
Dabbous et al. (2020)	randomized-controlled open-label interventional clinical trial	50/50	Inpatients, mild/moderate COVID19 symptoms	FVP+enoxaparin	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-10	Hydroxychloroquine/oseltamivir+enoxaparin	Viral clearance	TEAE	30-Oct
Dabbous et al. (2021)	multicenter randomized controlled study	44/48	Inpatients, mild/moderate COVID19 symptoms	FVP+SOC	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-10	Chloroquine+SOC	Clinical improvement/ Mortality	TEAE	-/10
Ivashchenko et al. (2021)	adaptive, multicenter, open label, randomized, Phase II/III clinical trial	20/20	Inpatients, moderate COVID19 pneumonia	Avifavir	1600 mg b.i.d. day 1/600 mg b.i.d. day 2-14	SOC	Clinical improvement/Viral clearance	TEAE	29/14
		20/20	Inpatients, moderate COVID19 pneumonia	Avifavir	1800 mg b.i.d. day 1/800 mg b.i.d. day 2-14	SOC	Clinical improvement/Viral clearance	TEAE	29/14

Lou et al. (2021)	exploratory single center, open-label, randomized, controlled trial	#####	Inpatients, COVID-19 patients	FVP+SOC	1600 or 2200 mg day 1/600 mg t.i.d. day 2-14	SOC Baloxavir+SOC	Clinical improvement/Viral clearance	TEAE	-/14
Ruzhentsova et al. (2020)	open-labeled, randomized, active-controlled multicenter trial	112/56	Outpatients and in patients with mild to moderate COVID-19	FVP	1800 mg b.i.d. day 1/800 mg b.i.d. day 2-10	SOC	Clinical improvement/Viral clearance	TEAE	28-Oct
Udwadia et al. (2021)	open-label, randomized, parallel-arm, multicenter trial	72/75	Inpatients, mild/moderate COVID-19	FVP+SOC	1800 mg b.i.d. day 1/800 mg b.i.d. day 2-14	SOC	Viral clearance/Clinical cure	TEAE	28/14
Zhao et al. (2021)	multicenter, open-label, randomized controlled trial	36/19	Re-positive outpatients, mild/moderate	FVP+SOC	1600 mg b.i.d. day 1/600 mg b.i.d. day 2 to 7-14	SOC	Viral clearance	TEAE	#####

FVP-Favipiravir; SOC-Standard of care; TEAE-treatment emergent adverse event
*The sample size includes only patients who participated in the comparative analysis (ITT population)

were resolved through discussion among the authors.

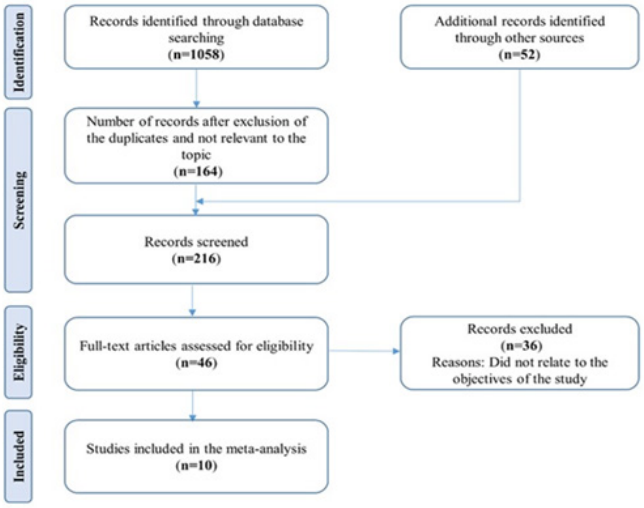

Figure 1: Search process and study flow diagram

Statistical Analysis

The risk ratio (RR) for efficacy and safety variables with 95% confidence intervals (CIs) was obtained from each study. Due to the significant heterogeneity of the individual studies, we chose the random-effects method as the primary analysis and forest plots were constructed. I2 statistics and Cochran test were used to assess the heterogeneity of the included studies where p values of less than 0.10 were used as an indication of the presence of heterogeneity. For all analyses, significance levels were two-tailed, and $p<0.05$ was considered significant. The value of I2 ranges from 0% to 100% and I2 <50% indicated that the heterogeneity of included studies was acceptable.

The sensitivity analyses was carried out by consequently subtracting each study from the analysis set and calculating the pooled prevalence and I2 of the remaining studies, in order to identify studies that may significantly affect the pooled prevalence and heterogeneity, respectively. Funnel plots were used to identify and evaluate publication bias.

All analyses were performed using the module MetaXL (add-ins on Microsoft Excel).

RESULTS

Description of Search

We identified a total of 1058 records after searching the databases and through other sources. The number of screened records was 216 after the removal of duplicates or unrelated to the topic. Only 46 full-text articles were assessed and 36 from them were excluded on the bases of predefined inclusion criteria. Finally, 10 studies were included in our meta-analysis. The complete study selection process is shown in **Figure 1**.

Characteristics of the Included Studies

Ten studies met the inclusion criteria and were subject to analysis. The included studies were published between 2020 and 2021, and were registered in clinical trial registries. Only one study was nonrandomized. Results in Cyrillic were not included. Summarized characteristics of target population are given in **Table 1**. In the present meta-analysis we evaluated incidence of improvement or deterioration among favipiravir group in comparison to SOC or other antivirals at day 4-7 and at day 10-14 (**Table 1**) as well as viral clearance at day 4-7, at day 10-14 and at day 28 (**Table 2**) and adverse events or serious adverse events including death (**Table 3**) identified during use of all treatments.

The minimum follow-up time in all included studies was 14 days, and the maximum was 30 days. The dose of favipiravir in each study was different but generally matches the standard dose for treating influenza infection. All studies included patients with proven COVID-19. The target population was hospitalized patients in [32-38]; one study included outpatients and in patients with mild to moderate COVID-19 [39] and in one study the target population was re-positive outpatients [40].

Outcomes of the Meta-Analysis

Clinical improvement: Five studies assessed clinical improvement at 4-7 days and five studies at 10-14 days (**Figures 2 and 3**) respectively [33-39].

The analysis showed that significant clinical improvement was achieved in the favipiravir group versus the control group at Day 7 (RR=1.24; 95% CI: 1.08-1.43; Q=1; p=0.88; I2=0%) (**Figure 2**). The presented results were homogeneous with symmetrical distribution (Figure S1). Furthermore, in 14 days, the clinical improvement with favipiravir was 18% higher than with other treatments, but this result was not statistically significant (RR=1.18; 95% CI: 1.01-1.37; Q=8.31; p=0.08; I2=52%, with evidence of low heterogeneity and symmetrical distribution (**Figure S2**)

Table 2: Reported outcome measures for clinical improvement and viral clearance.

Study: First author (year)	Outcome measures									
	Clinical improvement				Virus clearance					
	Day 4-7		Day 10-14		Day 4-7		Day 10-14		Day 28	
	FVP N1/N2	Control N1/N2	FVP N1/N2	Control N1/N2	FVP N1/N2	Control N1/N2	FVP N1/N2	Control N1/N2	FVP N1/N2	Control N1/N2
Cai et al. (2020)	8/27	8/37	32/3	28/17						
Chen et al. (2020)	71/45	62/58								
Dabbous et al. (2020)					24/26	28/22	48/2	45/5		
Ivashchenko et al. (2020)			36/4	16/4	25/15	6/14	37/3	16/4		
Lou et al. (2021)	2/7	1/9	5/4	5/5	4/5	5/5	7/2	10/0		
Ruzhentsova et al. (2020)	59/53	20/36	93/19	37/19	91/21	38/18				
Udwadia et al* (2021)	45/8	34/15	48/5	44/5	45/27	44/31	66/6	60/15		
Zhao et al. (2021)									29/7	10/9

N1=cases, N2=non-cases
*Clinical evaluation on days 7 and 14 had 53 patients with FVP and 49 with SOC.

Table 3: Reported AE and SAE including death.

Study: First author (year)	Adverse Events		Serious Adverse Events, including death	
	FVP N1/N2	Control N1/N2	FVP N1/N2	Control N1/N2
Balykova et al. (2020)	11/6	16/6	-	-
Cai et al. (2020)	4/31	25/20	-	-
Chen et al. (2020)	37/79	28/92	-	-
Dabbous et al. (2020)	4/46	21/29	0/50	1/49
Dabbous et al. (2021)	14/30	10/38	1/43	2/46
Lou et al. (2021)	8/1	9/1	-	-
Ruzhentsova et al. (2020)	80/28	33/22	2/106	0/55
Udwadia et al. (2021)	26/47	6/69	0/72	1/74
Zhao et al. (2020)	12/24	7/12	-	-

N1=cases, N2=non-cases

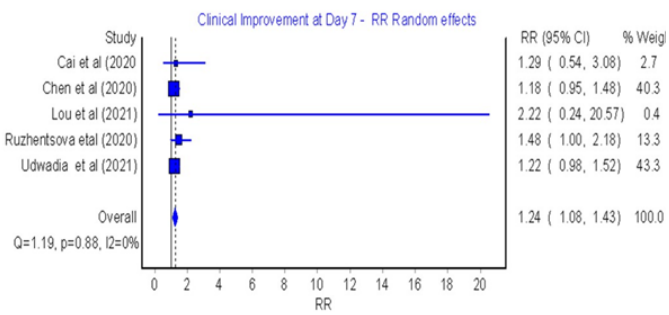

Figure 2: Forest plot: Clinical improvement at Day 7

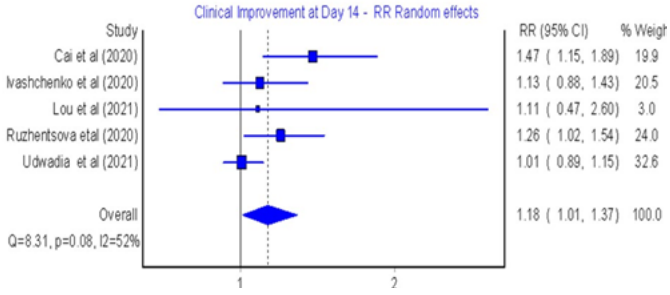

Figure 3: Forest plot: Clinical improvement at day 14 of favipiravir treatment

Viral Clearance

Among the included studies, five studies assessed viral clearance after 4-7 days (**Figure 4**), five after Day 10 of treatment [34,36-40] (**Figure 5**).

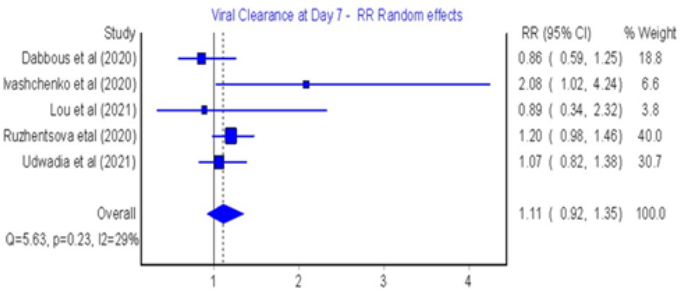

Figure 4: Forest plot: Viral clearance after Days 4-7 of favipiravir treatment.

The meta-analysis of risk ratios (RR) for favipiravir compared with SOC or other antivirals showed that there was no significant

difference at 7 days and 10 days post treatment (RR=1.11; 95% CI: 0.92-1.35; Q=5.63; p=0.23; I2=29% for 4-7 days and RR=1.07; 95% CI: 0.88-1.29; Q=9.49; p=0.05; I2=58% for 10 days post treatment).

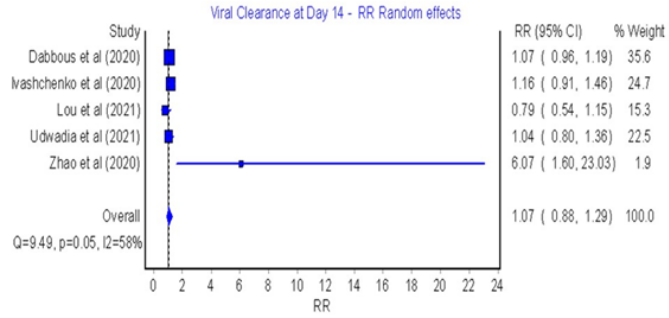

Figure 5: Forest plot: Viral clearance after day 10

(**Figures S3 and S4**) in Supplementary materials shows asymmetric distribution of the results with low insignificant heterogeneity (Q=5.63, p>0.05, I2=29% for 4-7 days; Q=9.49, p=0.05, I2=58% for 10-14 days post treatment).

Adverse Events, Serious Adverse Events including Mortality

All studies included in the meta-analysis reported adverse events and among them only four contained information about serious adverse events including death [34,36,39,41]. Favipiravir treatment did not lead to more adverse outcomes in comparison to control group (RR=1.21; 95% CI=0.88–1.67; Q=35.49; p=0.00; I2=77%), as presented in **Figure 6**, but it was accompanied by a high heterogeneity across the included studies (p<0.05) and low asymmetry in the results (**Figure S5**).

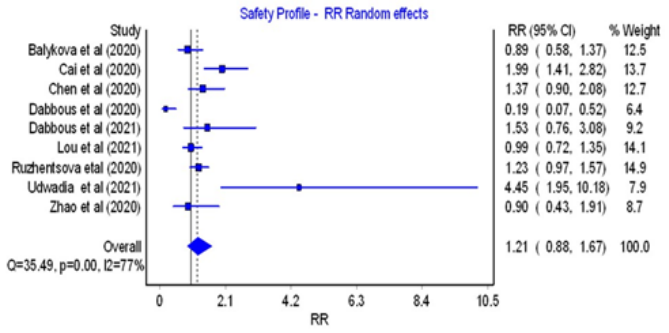

Figure 6: Forest plot: Safety profile

Based on the meta-analysis, the observed serious advese events including death in the favipiravir group was approximately 36% less than the control group, but this finding was not statistically significant (RR=0.64; 95% CI=0.15-2.68; Q=1.14; p=0.77; I2=0%) with no evidence of inter study heterogeneity and low asymmetric distribution of the results (**Figure S6**).

Sensitivity Analysis

The results from sensitivity analysis (**Tables S2-S7**) suggested that the sequential exclusion of individual studies did not lead to large variation in final risk ratios, although there were differences in assessment of weight. The lack of substantial changes in RR suggests consistency in findings and is a tentative confirmation of the possible prevalence for favipiravir compared to the alternatives.

DISCUSSION

Huge amount of efforts would be spent for the development of a new appropriate and effective medicine to treat COVID-19. Meanwhile patients could benefit from a number of approved and already marketed antiviral drugs that need to be repurposed for the current pandemic. A good candidate for that purpose could be is favipiravir. Its first indication is treatment of flu and other viral infections. The drug was firstly used as treatment option for COVID-19 in China, and at the present time favipiravir is approved for use in, Japan, Russia, Ukraine, Uzbekistan, Moldova, Kyrgyzstan, and Saudi Arabia, UAE, Turkey and others. Currently there are more than 30 clinical trials assessing the efficacy of favipiravir against COVID-19 worldwide according to https://clinicaltrials.gov/ [42] (excluding bioequivalence/bioavailability studies).

There is no uniform way to assess clinical efficacy and safety of Favipiravir compared to SOC or other therapies in patients with COVID-19. Our meta-analysis included 10 studies with a total of 1016 patients. Clinical improvement based on the evaluation of symptoms and radiology results, negative RT-PCR and progression/worsening of clinical symptoms or need of mechanical ventilation were used to measure clinical efficacy.

Safety was assessed by comparative analysis of the number of adverse events and/or adverse reactions, as well as measurement of the tolerability of the drug.

In our analysis we investigated the efficacy and safety of favipiravir in the published literature. We have compared favipiravir with standard of care (SOC) control or other antiviral agent/combinations. The obtained results from our study showed 24% higher clinical improvement with favipiravir in 7 days compared to other treatments and vary between 7% and 44%. On the other hand, in 14 days, the clinical improvement with Favipiravir was 18% higher than with other treatments and varies between 1% and 37%. Viral clearance up to 14 days in patients taking favipiravir was comparable to that those receiving other drugs. The difference in viral clearance between favipiravir and reference therapy was between days 4-7 of treatment (**Figure 4**). The tendency was for higher viral clearance by favipiravir, but in order to support that hypothesis, quantitative measurement rather than RT-PCR testing should probably be used. Additionally, the safety profile of favipiravir and that of the reference treatment regarding serious adverse events and reactions did not differ. The overall risk assessment was (RR=1.10, 95% CI=(0.82; 1.48) and it was not statistically significant. It must be noted that the assessment of AEs was based on different methodology in the different studies included and it requires careful interpretation. According to our results, the observed serious adverse events including death in the favipiravir group was approximately 36% less than the control group, but this finding is not statistically significant (RR=0.64; 95% CI=0.15-2.68; Q=1.14; p=0.77; I2=0%) (**Figure 7**). Respectively, no common relationship between SAEs including death and favipiravir treatment could be derived.

Clinical improvement and viral clearence were assessed in the work of Hassanipour et al. There was a significant clinical improvement in the Favipiravir treatment group after seven days of drug intake (RR=1.24, 95% CI: 1.09-1.41; P=0.001, I2=0.0%.

P=0.939). When compared to 14 days of intervention a non-statistically significant clinical improvement was observed (RR=1.10, 95% CI: 0.97-1.25; P=0.108, I2=34.5% and P=0.177). Viral clearance was not statistically significant for days 7-10 and 14, but was more pronounced for the last day of clinical observation. In the analysis it was observed that favipiravir group needed 7% less supplemental oxygen therapy compared to control group but the finding was not-statistically significant (RR=0.93, 95% CI: 0.67–1.28; P=0.664, I2=0.0%, P=0.950). Authors reported only mild to moderate adverse events in both treatment and control group and mortality rate of 30% less for the favipiravir group which did not reach statistical significance. All in all, they concluded that T-705 was administered relatively late and thus its efficacy was low in the clinical setting [42,43].

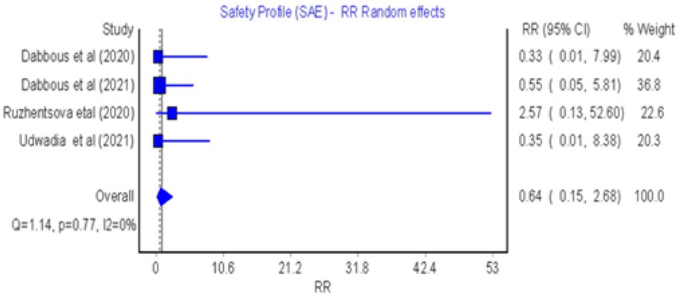

Figure 7: Forest plot: Safety profile SAE including death

Another meta-analysis also examined viral clearance and clinical improvement as the primary outcomes against COVID-19. Patients treated with favipiravir had better viral clearance at day 7 after treatment (OR=2.49, 95% CI=1.19-5.22) compared to comparator group. By day 14 no difference in viral clearance between the two groups was observed (OR=2.19, 95% CI=0.69–6.95). Clinical improvement was significantly higher in the favipiravir group on both day 7 and day 14 compared to comparator group but prevalence was seen at day 14 (OR=3.03, 95% CI=1.17-7.80). Conclusion was made that favipiravir caused viral clearance by day 7 along with clinical improvement within 14 days. Thus, favipiravir proved to be a reliable option for the treatment of mild to moderate COVID-19 disease. The early administration of the drug at the higher end of the dosing range could be an important step for the treatment of mild or asymptomatic COVID-19 [44].

Quite the contrary is described in the work of Özlüşen B et al. They claimed that in some countries (Turkey) favipiravir is administered early in the disease course though with a lack of significant effect. The effect of favipiravir on fatality rate and mechanical ventilation in COVID-19 patients was also studied. A total of 12 studies were included in their analysis. Authors did not identify any superiority of favipiravir over SOC or other antiviral medicines up to 14 days of treatment. In terms of mechanical ventilation significant heterogeneity was observed due to high risk of bias in the included studies. Additionally, it was discussed that viral clearance and viral load were not appropriate measures to follow disease progression [45]. Moreover, clinical improvement was not included in their analysis since clinical improvement differed between studies and could lead to the notion of subjectivity, which is contrary to our results.

Another systematic review suggested the effect of three antiviral drugs, namely remdesivir, favipiravir and lopinavir/ritonavir on COVID-19. When favipiravir was combined with other supportive therapy (tocilizumab) or given as monotherapy it had beneficial role on clinical recovery of patients but no significant effect was noted when compared to control treatment group. Authors believe it was not appropriate to recommend antiviral drugs to be used in clinical setting based on the conflicting results from clinical trials [46].

Efficacy and safety of favipiravir were analysed in the meta-analysis of Shrestha et al. A significant clinical improvement was noted on day 14 of drug administration compared to control (RR 1.29, 1.08-1.54). Viral clearance (day 14: RR 1.06, 95% CI 0.84-1.33) as well as non-invasive ventilation or oxygen requirement (OR 0.76, 95% CI 0.42-1.39), and adverse effects (OR 0.69, 0.13-3.57) did not show statistical significance when the two groups were compared. Lastly, it was stated that statistical significance could be reached for parameters clinical improvement and radiological improvement and juditial use of favipiravir should be supported [47].

Additionally, another meta-analysis evaluated the clinical improvement among COVID-19 patients. Observation was of marginal beneficial effect that was seen in the favipiravir arm in overall clinical improvement comparison to SOC/control, i.e., (4 studies, log OR [95% CI] (−0.19 [−0.51, 0.13]). For days 7-10 and 10-14 treatment with favipiravir was comparable to the SOC/control arm: For day 7-10 (3 studies, OR [95% CI] 1.63 [1.07, 2.48]) and for clinical improvement on day 10-14 (3 studies, OR [95% CI] 1.37 [0.24, 7.82]). Viral negativity after favipiravir treatmrent was associated with the lower odds as compared to the standard of care (SOC)/control treatment group (4 studies, OR [95% CI] 1.91 [0.91, 4.01]) [48].

Major guidelines on the treatment of COVID-19 do not recommend the use of favipiravir because of insufficient and uncertain evidence for its use. Neither Guidelines of NIH nor WHO recommend favipiravir for the treatment of COVID-19. Same applies to Japanese guidelines and Australian guidelines. The Philippine COVID-19 Living Clinical Practice Guidelines recommend for the use of favipiravir only in the context of clinical trials. In Belgium the drug is currently unavailable for treatment outside of clinical trials. Guidelines of the UAE include favipiravir as treatment option for confirmed COVID-19 cases at a dose of 1600 mg PO BID × 2 doses then 600 mg PO BID (total 5 days) among other drugs. In cases with pneumonia favipiravir could be combined with chloroquine/hydroxychloroquine and camostat. It could also be given in combinations with other drugs to critically ill patients for 10 days. Dose might need to be adjusted based on clinical scenario [49-55].

Favipiravir is believed to be a relatively safe drug. Pilkington et al. demonstrated that favipiravir had no serious side effects [56]. In other study the drug was reported to be safe and well-tolerated in short-term use [57]. Chen et al. [35] reported that adverse events are mild and manageable and the most frequently observed adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014). According to Ruzhentsova et al. and Zhao et al., the most common adverse events were asymptomatic hyperuricemia, transient elevation of ALT and AST, and gastrointestinal disorders (diarrhea, nausea, and abdominal pain). Balykova et al. [32] also confirmed these results. Favipiravir treatment in 5 patients (13%) led to mild to moderate side events related to the

elevations in hepatic enzymes, total bilirubin, uric acid and gastrointestinal disorders [58]. Despite its anti-inflamatory activity some ADEs suspected to be caused by favipiravir were reported. They included increased hepatic enzymes, nausea and vomiting, tachycardia, and diarrhea. Severe ADEs included blood and lymphatic disorders, cardiac disorders, hepatobiliary disorders, injury poisoning, and procedural complications. Serious ADEs were more common among male subjects aged 64 and above (48% vs 26%, respectively) [59]. Additionally, cutaneous adverse reactions were reported in patients infected with COVID-19 [60,61].

LIMITATIONS OF THE STUDY

There are some limitations in the present meta-analaysis. First of all, the sample size is low in each study. Second, the dosage and duration of intervention with favipiravir are different. Third, viral clearance is measured by RT-PCR, not quantitative. This approach to determine viral clearance is considered to be quite unreliable and has relatively low resolution. Fourth, the SOC arm included only lopinavir/ritonavir+INFalfa1b, umifenovir (arbidol), baloxavir, chloroquine and hydroxychloroquine/oseltamivir+enoxaparin. Therefore, it is necessary to include more combinations of drugs to evaluate the effectiveness and safety of favipiravir. Additionally, there is no unification of clinical measures of the effect of treatment. This makes comparative analysis somewhat difficult. Moreover, different authors have different approaches when evaluating adverse events, and therefore comparative analysis should be interpreted carefully.

CONCLUSION

No unified approach could be used as standard for measuring the effect of COVID-19 treatment. A wide variety of preparations and approaches exists as reference in the comparative analysis of favipiravir. The regimens of favipiravir administration are approximately the same; difference is noted in the dosage and duration of treatments. There is a significant difference in the clinical improvement detected on Day 7 and day 14 in favour of favipiravir over SOC or other treatments. A slightly higher chance for clinical improvement exhists at Day 7 and Day 14. Viral clearance is expected to be slightly higher by Day 7 of treatment with Favipiravir and comparable to SOC thereafter at Days 7 and 14 is comparable between treatments with neither being associated with significantly better outcomes. The safety profiles of favipiravir and SOC regarding SAE and SAE including death show no statistically significant differences. It should be noted that different authors have different approaches when evaluating adverse events and therefore the comparative analysis should be interpreted carefully.

AUTHOR CONTRIBUTIONS STATEMENT

Y.Z. conceived and designed the analysis; contributed analysis tools; conducted the analysis; drafted the paper and revised the paper. F.C. conceived and designed the analysis; reviewed and revised the paper; and managed the project. G.T. conceived and designed the analysis; collected data; reviewed and revised the paper. L.Y. reviewed and revised the paper; checked compliance. All authors reviewed the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

COMPETING INTERESTS

VP, KU and EF are employees of Tchaikapharma High Quality Medicines Inc. KK and TV have no relevant financial or non-financial interests to disclose.

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AUTHORS' CONTRIBUTION

Conceptualization: [Toni Vekov, Krassimir Kalinov]; Methodology: [Toni Vekov, Krassimir Kalinov]; Formal analysis and investigation; [Velichka Pavlova, Katya Uzunova, Elena Filipova]; Writing-original draft preparation: [Katya Uzunova, Velichka Pavlova]; Writing-review and editing: [Elena Filipova]; Funding acquisition: [Toni Vekov]; Supervision: [Toni Vekov, Krassimir Kalinov].

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