Pharmacological Reports
https://doi.org/10.1007/s43440-020-00175-2

SHORT COMMUNICATION

Favipiravir use for SARS CoV-2 infection

Alberto Boretti[1]

Received: 14 September 2020 / Revised: 8 October 2020 / Accepted: 14 October 2020
© Maj Institute of Pharmacology Polish Academy of Sciences 2020

Abstract

Introduction The pandemic of SARS CoV-2 has required urgent medical treatments for numerous patients. As no specific antiviral agents were available, different off-the-shelf alternatives have been explored.

Objective Here, we review the rationale behind the use of Favipiravir, and report of the specific studies supporting this treatment being conducted.

Methods Here we analyze the relevant literature to conclude about the present opportunities offered by this therapeutic agent.

Results This antiviral drug approved influenza in Japan since 2014, has a demonstrated in vitro activity against SARS CoV-2 and is being investigated in several trials for SARS CoV-2. Signals of benefit were shown in a small trial for SARS CoV-2. However, in another small study, there was no advantage.

Conclusions Further studies, statistically more significant, are urgently needed to understand the best opportunities offered by this treatment.

Keywords SARS CoV-2 · Favipiravir · Human trials · Animal studies · Laboratory experiments

Introduction

Initial estimations of the SARS CoV-2 mortality rate were extremely large, at about 1% of the infected in the simulations of [1]. Then [2], that first investigated the number of those with SARS CoV-2 antibodies in the supposed to be unaffected population, demonstrated the existence of a significant amount of people asymptomatic or mild. Thus, the revised SARS CoV-2 mortality rate is about 0.12–0.20%. The daily peak fatality rates for the United Kingdom, predicted by [1] were 210. The measured peak fatality rate for the United Kingdom (7-days rolling averages) has been less than 14. Countries that enforced less severe restrictions such as Sweden or the Netherlands did better at below 10 than countries such as the United Kingdom that had 14 or Belgium that had 30 [3]. For Saudi Arabia, the fatality rate (percentage of deaths in closed cases) is 0.83% (549 over 66,339, as per the data updated June 3) [4]. The above 0.83% is not the infection fatality rate, which is the number of deaths from the SARS CoV-2 disease divided by the total number of cases of SARS CoV-2, but only the fatality rate in medium-to-severe cases requiring medical attention. According to the World Health Organization (WHO), their data to early March were already suggesting that 80% of the infections were mild or asymptomatic, 15% were severe infection, requiring oxygen and 5% were critical infections, requiring ventilation [5]. By taking 20% of the 0.83% fatality rate in closed cases between the medium-to-severe SARS CoV-2 cases, the fatality rate of Saudi Arabia is, therefore, 0.166% [4], within the range indicated by [2]. As a reference, the death rate for influenza and pneumonia for Saudi Arabia [6] is 49.64 per 100,000 or 0.050%. Thus, the fatality rate of SARS CoV-2 is more than the flu. In addition, the fatality is mostly limited to the vulnerable [7–9]. In a healthy population, a strong immune system resulting from exercise, good nutrition, and regular supplements of vitamins and minerals is a guarantee of safety against SARS CoV-2. The Charles de Gaulle aircraft carrier case is a proof. Of almost 2000 people supposed to be healthy and with a strong immune system likely all uniformly challenged by the virus, only 1081 were infected, and of the 1081, only 24 ended up in the hospital, with only 1 of them in need of intensive care [9]. After less than 2 weeks, there were only two Marines still

✉ Alberto Boretti
deanshipofresearch@pmu.edu.sa

[1] Prince Mohammad Bin Fahd University, PO Box 1664, Al Khobar 31952, Kingdom of Saudi Arabia

Published online: 27 October 2020

in the hospital, and one of them still in need of intensive care [9]. After 3 weeks, only the one previously in intensive care was still hospitalized but out of the intensive care [9]. Thus, the fatality rate in this sample of the total Charles de Gaulle aircraft carrier population was thus zero.

It is within this context, of therapies mostly needed in patients with an immune system compromised for age or comorbidities, where contraindications may exist for the use of the more toxic drugs, that SARS CoV-2 therapies must be applied. Within this context, it is necessary to carefully consider the safety-to-efficacy profile of the drugs used for SARS CoV-2 therapy.

In people with a weak immune system, for ages or comorbidities, drug toxicity may constitute a serious threat to the survival of the patients, producing in some cases more damage than benefit. The last controversy about chloroquine and hydroxychloroquine is focused on the safety-to-efficacy profile [10–12]. Thus, it is extremely relevant to evaluate therapies with minimal side effects and contraindications.

Favipiravir use for SARS CoV-2 infection

An emerging drug now becoming popular in Japan and Russia is Favipiravir.

Figure 1a is the molecule of Favipiravir (from https://molview.org/?cid=492405).

Favipiravir (Avigan) is a known antiviral for influenza [13]. It is indicated for novel influenza strains that cause more severe disease rather than seasonal influenza [13]. Favipiravir triphosphate is a purine nucleoside analog. Favipiravir is a member of pyrazines and a primary carboxamide.

Figure 1b is the molecule of Oseltamivir, as Favipiravir and Oseltamivir are often combined. Oseltamivir is a cyclohexenecarboxylate ester. It is an antiviral prodrug being hydrolyzed to the active free carboxylic acid in the liver. Oseltamivir is used to slow the spread of influenza. It has a role as a prodrug, an EC 3.2.1.18 (exo-alpha-sialidase) inhibitor, an antiviral drug, an environmental contaminant, and a xenobiotic.

The mechanism of action is likely the selective inhibition of viral RNA-dependent RNA polymerase [14, 15]. In vitro

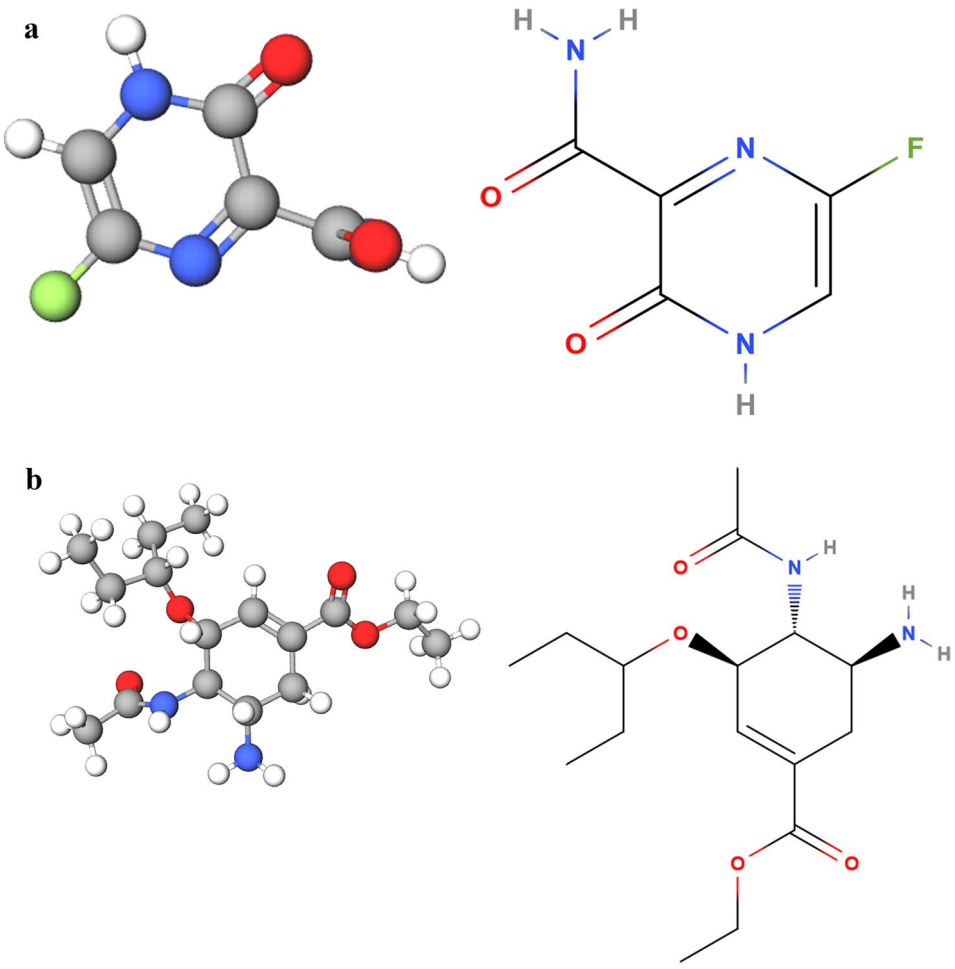

Fig. 1 **a** Favipiravir molecule from molview.org/?cid=492405. The formula is $C_5H_4FN_3O_2$. The molecular weight is 157.1 µg, hydrogen bond donors 2, hydrogen bond acceptors 4. Percent composition is C 12.0107 µg×5 38.226%; H 1.00794 µg×4, 2.5663%; F 18.998404 µg×1, 12.093%; N 14.0067 µg×3, 26.747%; and O 15.9994 µg×2, 20.368%. Systematic name is 5-fluoro-2-oxo-1*H*-pyrazine-3-carboxamide. **b** Oseltamivir molecule from molview.org/?cid=65028. The formula is $C_{16}H_{28}N_2O_4$. The molecular weight is 312.4 µg, hydrogen bond donors 2, hydrogen bond acceptors 5. Percent composition is C 12.0107 µg×16, 61.514%, H 1.00794 µg×28, 9.0339%, N 14.0067 µg×2, 8.9670%, and O 15.9994 µg×4, 20.485%

studies on influenza A H1N1 viruses suggesting induced lethal RNA transversion mutations through the production of nonviable viral phenotype [16, 17] suggest that Favipiravir works as a chain terminator at the site of incorporation of the viral RNA thus reducing the viral load. Shiraki and Daikoku [17] advocate the use of Favipiravir against novel influenza strains. Favipiravir does not inhibit RNA or DNA synthesis in mammalian cells and it is not toxic to mammalian cells [18]. However, Favipiravir also seems not effective in primary human airway cells [19]. This may cast doubts about the efficacy in the use for SARS CoV-2 infection.

Favipiravir works against a broad range of influenza viruses [20]. These include A(H1N1) pdm09, A(H5N1) and A(H7N9) avian virus [20]. Favipiravir also inhibits influenza strains resistant to current antiviral drugs, and produce a synergistic effect in combination with Oseltamivir [20]. A small trial of 168 patients severely ill from influenza were treated with Favipiravir plus Oseltamivir (40) and Oseltamivir alone (128) [21]. A combination of Favipiravir and Oseltamivir accelerates clinical recovery [21].

For the specific use against SARS CoV-2, [22] evaluated the in vitro efficacy of different drugs, from Remdesivir to Chloroquine, also including Favipiravir. With Favipiravir, half-maximal effective concentration $EC_{50} = 61.88$ μM, $CC_{50} > 400$ μM, $SI > 6.46$ were required to reduce the viral infection. Wang, Cao, Zhang, Yang, Liu, and Xu et al. [22] recommended further in vivo studies as efficacy against the Ebola virus challenge in mice was large despite an EC_{50} value in Vero E6 cells as high as 67 μM.

Li and De Clercq [23] include Favipiravir together with Remdesivir, Galidesivir, and Ribavirin in between the existing antiviral agents' RNA-dependent RNA polymerase inhibitors to repurpose to treat SARS CoV-2 infection. Dong et al. [24] also include Favipiravir, together with Chloroquine, Arbidol, and Remdesivir, all under clinical studies in China to test their efficacy and safety for SARS CoV-2 infection. Costanzo et al. [25] declare Favipiravir as one of the most promising drugs for SARS CoV-2, however, mentioning only the small study [26] discussed hereafter as supporting evidence. These are, however, experts' opinions not supported by proper trials.

Favipiravir safety evidence in the treatment of other pathologies is reviewed in Ref. [27]. Study follow-up was between 5 and 21 days. The proportions of grade 1–4 adverse events (AE) on Favipiravir was 28.2% vs 28.4% in the comparison arms with Oseltamivir, Umifenovir, and Lopinavir/Ritonavir. The proportion of discontinuations due to AE on Favipiravir was 1.1% vs 1.2% in the comparison arms. Serious AEs were 0.4% in both arms. While Favipiravir demonstrates a favorable safety profile, safety concerns remain for hyperuricemia, teratogenicity, and QTc prolongation [28].

Regarding SARS CoV-2 application, according to [29], for analogies with the treatment with the same drug of the Ebola virus, while the drug EC_{50} against SARS CoV-2 is 9.4 μg/m they suggest a higher value of EC_{50}, in the range of 40–80 μg/mL, about same of the Ebola dosage. Cardiac and hepatic monitoring during treatment is suggested, the same as monitoring of Favipiravir concentration [29]. In addition to the in vitro study [22] indicating that Favipiravir (T-705) inhibited SARS CoV-2 replication in Vero E6 cells with EC_{50} values of 61.88 μM (9.4 μg/mL), the independent study [30] indicated EC_{50} values > 100 μM (15. 7 μg/mL). As Favipiravir is a prodrug requiring metabolic activation in the host cells to form its triphosphate form, this may contribute to the differences between the two studies [28].

Up to date, there is not enough information from specific trials to infer any conclusion on the use of Favipiravir for SARS CoV-2 infection. An open-label non-randomized trial of only 80 patients performed in China [26] was reported in the literature. This work was published in one engineering rather than a medical journal. This small study found a reduced viral clearance time, improved CT scan, and fewer side effects in comparison to Lopinavir/Ritonavir [26].

Recently, in a small trial of 240 SARS CoV-2 patients, 120 were treated with Favipiravir and 120 with Arbidol [31]. Among patients with SARS CoV-2, in comparison, Favipiravir did not significantly improve the clinical recovery rate on Day 7 but improved the latency to relief for pyrexia and cough. Favipiravir had mild and manageable adverse effects.

There are a few ongoing trials. clinicaltrials.gov [32] reports as per June 6, 2020, 1416 SARS CoV-2 Studies from the World Health Organization Database. A search for Favipiravir returns 20 trials. The total number of Favipiravir trials for SARS CoV-2 and other applications is 73 (Table 1) (from [33]). Those with results are a small percentage of the total.

Discussion and conclusion

Given the demonstrated in vitro of activity of Favipiravir against SARS CoV-2 and signals of benefit in early clinical experience for SARS CoV-2, but also the existence of contraindications that limit the window of cases where the safety-to-efficacy profile is promising, further studies are urgently needed.

The literature works that reviewed specific Favipiravir use for SARS CoV-2 are mostly comments, letters to the editors, or replies, and not research works reporting gold standard trials passed through a proper peer review. Results of trials have not yet been reported in the literature, with the only exception of one very small study and not all the parameters needed under control.

General for SARS CoV-2, the trials performed, under particularly challenging circumstances, without proper control of the relevant parameters, and based on a statistically

Table 1 Current trials of Favipiravir (from [33])

#	Title	Status	Study results	Conditions	Interventions
1	Bioequivalence study of Favipiravir 200 mg film tablet (ATABAY, Turkey) under fasting conditions	Completed	Has results	Bioequivalence	Drug: Favicovir 200-mg film tablet | Drug: Avigan 200-mg film tablets
2	Bioequivalence study of Favipiravir 200 mg film tablet (Novelfarma, Turkey) under fasting conditions	Completed	Has results	Bioequivalence	Drug: Favira 200-mg film tablet | Drug: Avigan 200-mg film tablets
3	Bioequivalence study of Favipiravir 200 mg film tablet (World Medicine, Turkey) under fasting conditions	Completed	No results available	Bioequivalence	Drug: test: Favipiravir 200 mg (LOQULAR) | Drug: reference: Favipiravir 200 mg (Avigan)
4	Tolerance and activity evaluation of high doses of Favipiravir against Ebola virus in the semen	Terminated	No results available	Ebola virus survivor	Drug: Favipiravir
5	A pharmacokinetics study of favipiravir in patients with severe influenza	Completed	No results available	Influenza, human | Critical illness | Influenza	Drug: Favipiravir | Drug: Oseltamivir 75-mg capsule
6	The effectivity and safety of favipiravir compared to Oseltamivir as adjuvant therapy for COVID-19	Recruiting	No results available	Covid19	Drug: Favipiravir | Drug: Oseltamivir 75 mg
7	Efficacy of Favipiravir against Ebola (JIKI)	Completed	No results available	Ebola Virus Disease	Drug: Favipiravir
8	Study on safety and efficacy of Favipiravir (Favipira) for COVID-19 patient in selected hospitals of Bangladesh	Recruiting	No results available	COVID-19 | Favipiravir (Favipira)	Drug: Favipiravir | Drug: only standard treatment
9	Efficacy and safety of Favipiravir in the treatment of COVID-19 patients over 15 years of age	Recruiting	No results available	COVID-19	Drug: Favipiravir
10	Favipiravir and hydroxychloroquine combination therapy	Recruiting	No results available	COVID19	Combination product: Favipiravir and Hydroxychloroquine
11	Study of the use of favipiravir in hospitalized subjects with COVID-19	Active, not recruiting	No results available	COVID-19	Drug: Favipiravir + standard of care | Drug: standard of care
12	Clinical trial evaluating the efficacy and safety of Favipiravir in moderate to severe COVID-19 patients	Recruiting	No results available	Covid19	Drug: Avigan | Drug: placebo comparator
13	A multi-center, randomized, double-blind, placebo-controlled, phase 3 study evaluating Favipiravir in treatment of COVID19	Not yet recruiting	No results available	COVID-19	Drug: Favipiravir | Other: placebo
14	Bioequivalence study of Favir 200 mg film tablet Kocak under fasting conditions	Completed	No results available	Bioequivalence	Drug: Favir 200-mg FT|Drug: Avigan 200-mg FT
15	Favipiravir therapy in adults with mild COVID-19	Recruiting	No results available	COVID-19	Drug: Favipiravir | Drug: placebo
16	Early intervention in COVID-19: Favipiravir verses standard care	Recruiting	No results available	Coronavirus Infection	Drug: Favipiravir | Other: standard of care management

Table 1 (continued)

#	Title	Status	Study results	Conditions	Interventions
17	Favipiravir vs hydroxychloroquine in COVID-19	Recruiting	No results available	SARS-CoV 2 | COVID-19	Drug: Hydroxychloroquine | Drug: Favipiravir | Other: routine care for COVID-19 patients
18	Efficacy of Faviprevir in COVID-19 treatment	Recruiting	No results available	COVID	Drug: Favipiravir | Drug: placebos
19	Favipiravir combined with tocilizumab in the treatment of corona virus disease 2019	Recruiting	No results available	COVID-19	Drug: Favipiravir combined WITH Tocilizumab | Drug: Favipiravir | Drug: Tocilizumab
20	Bioequivalence study of Favipiravir from Flupirava 200 mg tablet (European Egyptian Pharmaceutical Industries, Egypt) versus Avigan 200 mg tablets (Man. by Toyama Chemical Co., Ltd Japan)	Completed	No results available	Healthy	Drug: Flupirava | Drug: Avigan
21	Efficacy and safety of Favipiravir in management of COVID-19	Completed	No results available	Coronavirus Disease (COVID-19)	Drug: Favipiravir | Drug: standard of care therapy
22	Oral Favipiravir compared to placebo in subjects with mild COVID-19	Enrolling by invitation	No results available	Sars-CoV2 | COVID-19	Drug: Favipiravir | Drug: placebo | Other: standard of care treatment
23	Clinical study to evaluate the performance and safety of Favipiravir in COVID-19	Active, not recruiting	No results available	COVID-19	Drug: Favipiravir | Other: placebo
24	Clinical trial of Favipiravir tablets combine with chloroquine phosphate in the treatment of novel coronavirus pneumonia	Recruiting	No results available	Novel coronavirus pnuemonia	Drug: Favipiravir tablets + chloroquine phosphatetablets tablets | Drug: Favipiravir tablets | Drug: placebo
25	FLARE: Favipiravir ± Lopinavir: a RCT of early antivirals	Recruiting	No results available	COVID-19	Drug: Favipiravir | Drug: Lopinavir/Ritonavir | Other: Favipiravir placebo | Other: Lopinavir/Ritonavir placebo
26	Favipiravir in hospitalized COVID-19 patients	Not yet recruiting	No results available	COVID-19	Drug: Favipiravir | Drug: Hydroxychloroquine
27	Phase 3 efficacy and safety study of Favipiravir for treatment of uncomplicated influenza in adults—T705US316	Completed	No results available	Influenza	Drug: favipiravir | Drug: placebo
28	Pharmacokinetics of Favipiravir in volunteers with hepatic impairment	Completed	No results available	Healthy | Hepatic impairment	Drug: Favipiravir
29	Dose-finding study of Favipiravir in the treatment of uncomplicated influenza	Completed	Has results	Influenza	Drug: Favipiravir | Drug: placebo comparator
30	Phase 3 efficacy and safety study of Favipiravir for treatment of uncomplicated influenza in adults	Completed	No results available	Influenza	Drug: favipiravir | Drug: placebo
31	Efficacy of Favipiravir against severe Ebola virus disease	Completed	No results available	Ebola virus disease	Other: WHO-recommended therapies | Drug: Favipiravir

Table 1 (continued)

#	Title	Status	Study results	Conditions	Interventions
32	Safety and efficacy of Maraviroc and/or Favipiravir vs currently used therapy in severe COVID-19 adults	Not yet recruiting	No results available	COVID-19	Drug: Maraviroc + currently used therapy | Procedure: currently used therapy for COVID-19 non-critical patients | Drug: Favipiravir + currently used therapy | Drug: Maraviroc + Favipiravir + CT
33	Favipiravir plus hydroxychloroquine and Lopinavir/Ritonavir plus hydroxychloroquine in COVID-19	Completed	No results available	COVID-19 | Favipiravir | Kaletra | Hydroxychloroquine | Lopinavir/Ritonavir	Drug: Favipiravir | Drug: Hydroxychloroquine | Drug: Lopinavir/Ritonavir
34	Control of COVID-19 outbreaks in long term care	Recruiting	No results available	COVID-19 | SARS-CoV-2	Drug: Favipiravir | Drug: Favipiravir placebo
35	An adaptive study of Favipiravir compared to standard of care in hospitalized patients with COVID-19	Active, not recruiting	No results available	COVID-19	Drug: Favipiravir | Drug: standard of care
36	Study of Favipiravir compared to standard of care in hospitalized patients with COVID-19	Completed	No results available	COVID-19	Drug: Favipiravir | Drug: standard of care
37	Efficacy and safety of hydroxychloroquine and Favipiravir in the treatment of mild to moderate COVID-19	Recruiting	No results available	Sars-CoV2 | COVID-19	Drug: Favipiravir (3200 mg + 1200 mg) | Drug: Favipiravir (3600 mg + 1600 mg) | Drug: Favipiravir (3200 mg + 1200 mg) combined with Hydroxychloroquine | Drug: Favipiravir (3200 mg + 1200 mg) combined with Azithromycin|Drug: Hydroxychloroquine | Drug: Hydroxychloroquine combined with Azithromycin
38	An adaptive clinical trial of antivirals for COVID-19 infection	Recruiting	No results available	COVID	Drug: Favipiravir
39	Corona virus disease 2019 patients whose nucleic acids changed from negative to positive	Recruiting	No results available	COVID-19	Drug: Favipiravir
40	T-705a multicenter study in adults subjects with uncomplicated influenza	Completed	No results available	Influenza	Drug: placebo | Drug: Favipiravir
41	Favipiravir, protease inhibitors, Oseltamivir -Gpo, hydroxychloroquine for treatment of COVID-19	Recruiting	No results available	SARS-COV-2 infections | COVID-19	Drug: oral
42	Study of efficacy and safety of TL-FVP-t vs. SOC in patients with mild to moderate COVID-19	Active, not recruiting	No results available	COVID-19	Drug: Favipiravir|Drug: standard of care (SOC) | Drug: standard concomitant therapy
43	An open non-comparative study of the efficacy and safety of Aprotinin in patients hospitalized with COVID-19	Active, not recruiting	No results available	COVID-19	Drug: Aprotinin
44	Convalescent plasma therapy in severe COVID-19 infection	Recruiting	No results available	Covid19 | Convalescence	Biological: convalescent plasma

Table 1 (continued)

#	Title	Status	Study results	Conditions	Interventions
45	COVID-19 treatment in South Africa	Recruiting	No results available	COVID-19	Other: standard of care (Paracetamol)|Drug: Artesunate-amodiaquine | Drug: Pyronaridine-artesunate | Drug: Favipiravir plus Nitazoxanide|Drug: Sofosbuvir/daclatasvir
46	Assessment of safety and efficacy of CCP	Active, not recruiting	No results available	Covid19	Biological: COVID convalescent plasma
47	Use of hydroxychloroquine alone or associated for inpatients with SARS-CoV2 virus (COVID-19)	Withdrawn	No results available	Coronavirus infections|SARS-CoV 2 | SARS (Severe Acute Respiratory Syndrome) | Pulmonary disease	Drug: Hydroxychloroquine sulfate | Drug: Hydroxychloroquine sulfate + Azythromycin
48	The use of dendritic cell/tumor hybridomas as a novel tumor vaccine in patients with advance melanoma	Completed	No results available	Metastatic melanoma	Biological: DC/tumor fusion vaccine
49	A phase I/II study to assess the safety and efficacy of vaccinations with allogeneic dendritic cells: autologous tumor-derived cells subjected to electrofusions in patients with AJCC stage IV renal cell carcinoma	Completed	No results available	Renal cell carcinoma	Biological: electrofusion DC vaccine
50	A phase I/II trial of the MUC1 inhibitor, GO-203-2C in patients with relapsed or refractory acute myeloid leukemia	Active, not recruiting	No results available	Acute myeloid leukemia, in relapse | Recurrent adult acute myeloid leukemia	Drug: GO-203-2c | Drug: GO-203-2c + Decitabine
51	Convalescent plasma of Covid-19 to treat SARS-COV-2 a randomized double blind 2 center trial	Recruiting	No results available	SARS pneumonia	Biological: Convalescent Plasma of patients with COVID-19 | Other: placebo (hartmann plus albumine)
52	PD-1 alone or with dendritic cell/renal cell carcinoma fusion cell vaccine	Terminated	Has results	Renal cell carcinoma	Drug: CT-011 | Biological: DC/RCC fusion vaccine
53	Blockade of PD-1 in conjunction with the dendritic cell/myeloma vaccines following stem cell transplantation	Active, not recruiting	No results available	Multiple myeloma	Drug: CT-011|Biological: dendritic cell fusion vaccine
54	Primary tumor harvest for the purpose of possible use in a future clinical trial in patients with ovarian, fallopian tube or primary peritoneal cancer	Completed	No results available	Ovarian cancer|Peritoneal cancer|Fallopian tube cancer	Procedure: tumor collection
55	Vaccination of patients with ovarian cancer with dendritic cell/tumor fusions with granulocyte macrophage colony-stimulating factor (GM-CSF) and imiquimod	Active, not recruiting	No results available	Ovarian cancer | Primary peritoneal cancer | Fallopian tube cancer	Drug: GM-CSF | Biological: dendritic cell/tumor fusion vaccine | Drug: imiquimod
56	Vaccination of patients with breast cancer with dendritic cell/tumor fusions and IL-12	Terminated	Has results	Breast cancer	Biological: dendritic cell/tumor fusion vaccine | Drug: interleukin-12
57	Vaccination with dendritic cell/tumor fusions with autologous stem cell transplants in patients with multiple myeloma	Completed	No results available	Multiple myeloma	Biological: dendritic cell tumor fusion

Table 1 (continued)

#	Title	Status	Study results	Conditions	Interventions
58	Vaccination of patients with renal cell cancer with dendritic cell tumor fusions and GM-CSF	Active, not recruiting	Has results	Renal cancer	Biological: dendritic cell tumor fusion vaccine | Drug: granulocyte macrophage colony-stimulating factor (GM-CSF)
59	Arsenic trioxide and tyrosine kinase inhibitors for chronic myelogenous leukemia (CML)	Terminated	No results available	Chronic myelogenous leukemia	Drug: arsenic trioxide
60	Chemotherapy and peripheral stem cell transplantation followed by Trastuzumab in treating women with metastatic breast cancer	Withdrawn	No results available	Breast cancer	Biological: trastuzumab | Drug: carboplatin|Drug: carmustine | Drug: cisplatin | Drug: cyclophosphamide | Drug: thiotepa | Procedure: peripheral blood stem cell transplantation
61	Reduced intensity conditioning with clofarabine, antithymocyte globulin (ATG), total lymphoid irradiation (TLI) followed by allogeneic stem cell transplant	Active, not recruiting	No results available	Acute myeloid leukemia | Myelodysplastic syndrome | Acute lymphocytic leukemia | Relapsed/refractory chronic lymphocytic leukemia | Relapsed/refractory non-Hodgkin's lymphoma | Hodgkins disease | Relapsed refractory multiple myeloma	Drug: antithymocyte globulin | Drug: Clofarabine
62	The use of dendritic cell/tumor fusions as a novel tumor vaccine in patients with multiple myeloma	Completed	No results available	Multiple myeloma	Biological: dendritic cell tumor fusion vaccine
63	Interleukin-12 in treating women with metastatic breast cancer who have received high-dose chemotherapy and peripheral stem cell transplantation	Unknown status	No results available	Breast cancer	Biological: recombinant interleukin-12
64	Vaccine therapy in treating patients with stage III or stage IV melanoma	Unknown status	No results available	Melanoma (skin)	Biological: autologous dendritic cell tumor fusion vaccine | Biological: gp100 antigen | Biological: therapeutic autologous dendritic cells
65	Nonmyeloablative allo SCT for the treatment of hematologic disorders	Completed	No results available	AML | ALL | CML chronic phase, accelerated phase, or blast crisis | CLL | MDS | Relapsed non-Hodgkin's or Hodgkin's lymphoma | Aplastic anemia | Multiple myeloma | Myeloproliferative disorder (P Vera, CMML, ET)	Drug: Cyclophosphamide | Drug: fludarabine | Drug: cyclosporine | Drug: methotrexate | Biological: G-CSF
66	Nonmyeloablative allogeneic stem cell transplantation from HLA-matched unrelated donor for the treatment of hematologic disorders	Completed	No results available	AML | ALL | CLL | Myelodysplastic syndrome | Non-Hodgkin's lymphoma | Hodgkin's lymphoma | Multiple myeloma | Aplastic anemia | Myeloproliferative disorder	Drug: cyclophosphamide; fludarabine; cyclosporine; CAMPATH-1H (Alemtuzumab); GM-CSF
67	Phase I study of sequential cord blood transplants	Completed	No results available	Lymphoma | Leukemia | Multiple myeloma | Myelodysplastic syndrome	Procedure: sequential cord blood transplantation

Table 1 (continued)

#	Title	Status	Study results	Conditions	Interventions
68	Study of parathyroid hormone following sequential cord blood transplantation from an unrelated donor	Terminated	Has results	Leukemia, myeloid, chronic | Anemia, aplastic | Myelofibrosis | Lymphoma | Hodgkin disease | Leukemia, lymphocytic, chronic | Leukemia, myelocytic, acute | Leukemia, lymphocytic, acute	Drug: Parathyroid Hormone (teriparatide)
69	A study of PVX-410, a cancer vaccine, and Citarinostat ± Lenalidomide for smoldering MM	Recruiting	No results available	Smoldering multiple myeloma	Drug: Hiltonol | Drug: Citarinostat | Drug: Lenalidomide | Biological: PVX-410
70	Immuno-oncology drugs elotuzumab, anti-LAG-3 and anti-TIGIT	Recruiting	No results available	Multiple myeloma | Relapsed refractory multiple myeloma	Drug: Elotuzumab, pomalidomide, dexamethasone | Drug: Anti-LAG-3 | Drug: Anti-LAG-3 + Pomalidimide + Dexamethasone | Drug: Anti-TIGIT | Drug: Anti-TIGIT + Pomalidimide + Dexamethasone
71	Safety study of unlicensed, investigational cord blood units manufactured by the NCBP for unrelated transplantation	Recruiting	No results available	Infusion reactions	Biological: unlicensed CBU
72	A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs)	Recruiting	No results available	Hematologic malignancies | Inherited disorders of metabolism | Inherited abnormalities of platelets | Histiocytic disorders | Acute myelogenous leukemia (AML or ANLL) | Acute lymphoblastic leukemia (ALL) | Other acute leukemia | Chronic myelogenous leukemia (CML) | Myelodysplastic (MDS)/myeloproliferative (MPN) diseases | Other leukemia | Hodgkin lymphoma | Non-Hodgkin lymphoma | Multiple myeloma/Plasma cell disorder (PCD) | Inherited abnormalities of erythrocyte differentiation or function | Disorders of the immune system | Automimmune diseases | Severe aplastic anemia	Drug: A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs)
73	Expanded access protocol for GBM patients with already manufactured DCVaxÂ®-L who have screen-failed protocol 020221	Available	No results available	GBM | Glioblastoma multiforme	Biological: DCVax-L

irrelevant population, are not certainly the gold standard in medical research. These experiences have left more doubts than certainties, also because of the conflict of interest affecting the health sector [27], the rush for publishing in SARS CoV-2, and mostly the interference by the Mainstream Media.

Large, randomized, placebo-controlled studies of hospitalized SARS CoV-2 patients conducted without preconceived agenda and properly monitoring all the relevant parameters are urgently needed to understand if Favipiravir, as well as other products, are beneficial, and in which specific cases may be used to treat SARS CoV-2 infection with a positive safety-to-efficacy profile.

Author contributions This is a single author paper.

Compliance with ethical standards

Conflict of interest The author received no funding and has no conflict of interest to declare.

References

1. Ferguson N, Laydon D, Nedjati Gilani G, Imai N, Ainslie K, Baguelin M, Bhatia S, Boonyasiri A, Cucunuba Perez ZU, Cuomo-Dannenburg G, Dighe A. Report 9: impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. https://doi.org/10.25561/77482.
2. Bendavid E, Mulaney B, Sood N, Shah S, Ling E, Bromley-Dulfano R, Lai C, Weissberg Z, Saavedra R, Tedrow J, Tversky D. COVID-19 antibody seroprevalence in Santa Clara County, California. MedRxiv. 2020. https://doi.org/10.1101/2020.04.14.20062463v1.full.pdf.
3. Boretti A. After less than 2 months, the simulations that drove the world to strict lockdown appear to be wrong, the same of the policies they generated. Health Serv Res Manag Epidemiol. 2020a;16(7):2333392820932324. https://doi.org/10.1177/2333392820932324.
4. Boretti A. COVID-19 fatality rate for Saudi Arabia, updated 3 June 2020. J Glob Antimicrob Resist. 2020b;1(22):845–6. https://doi.org/10.1016/j.jgar.2020.07.014.
5. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4#:~:text=For%20COVID%2D19%2C,infections%2C%20requiring%20ventilation. Accessed 3 June 2020.
6. https://www.worldlifeexpectancy.com/cause-of-death/influenza-pneumonia/by-country/. Accessed 3 June 2020.
7. Boretti A. Sustainable post Covid19 lockdown strategy through evidence-based policy: analysis of Covid19 fatalities across Europe. Integr J Med Sci. 2020c;7:172. https://doi.org/10.15342/ijms.7.172.
8. Boretti A. Analysis of the Charles De Gaulle aircraft carrier Covid19 epidemic: infectivity and fatality in the young, healthy, active population: lesson from the Charles de Gaulle aircraft carrier Covid19 experience. Integr J Med Sci. 2020d;7:174. https://doi.org/10.15342/ijms.7.174.
9. Boretti A. Some doubt the Covid19 containment measures on the generally healthy population made any difference for Italy: Covid19 fatalities much larger in Europe, United States and Canada than elsewhere. Integr J Med Sci. 2020e;7:179. https://doi.org/10.15342/ijms.7.179.
10. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31180-6.
11. Mehra MR, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31324-6.
12. Piller C, Servick K. Two elite medical journals retract coronavirus papers over data integrity questions. Science. 2020 (10.1126). https://www.sciencemag.org/news/2020/06/two-elite-medical-journals-retract-coronavirus-papers-over-data-integrity-questions. Accessed 5 June 2020
13. Du YX, Chen XP. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020a. https://doi.org/10.1002/cpt.1844.
14. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5′-triphosphate towards influenza A virus polymerase. PLoS ONE. 2013;8(7):e68347.
15. Coomes EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother. 2020. https://doi.org/10.1093/jac/dkaa171.
16. Baranovich T, Wong SS, Armstrong J, Marjuki H, Webby RJ, Webster RG, Govorkova EA. T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. J Virol. 2013;87(7):3741–51.
17. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;22:107512.
18. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, Gowen BB, Julander JG, Morrey JD. T-705 (favipiravir) and related compounds: novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95–102.
19. Yoon JJ, Toots M, Lee S, Lee ME, Ludeke B, Luczo JM, Ganti K, Cox RM, Sticher ZM, Edpuganti V, Mitchell DG. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. Antimicrob Agents Chemother. 2018;62(8):e00766–18.
20. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivir Res. 2013;100(2):446–54.
21. Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, Pan J, Zheng J, Lu B, Guo L, Wang C. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. J Infect Dis. 2020;221(10):1688–98.
22. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
23. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020. https://doi.org/10.1038/d41573-020-00016-0.
24. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58–60.
25. Costanzo M, De Giglio MA, Roviello GN. SARS-CoV-2: recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. Curr Med Chem. 2020. https://doi.org/10.2174/0929867327666200416131117.

26. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020. https://doi.org/10.1016/j.eng.2020.03.007.
27. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir—a potential treatment in the COVID-19 pandemic? J Virus Erad. 2020;6(2):45.
28. Du YX, Chen XP. Response to "Dose rationale for favipiravir use in patients infected with SARS-CoV-2." Clin Pharmacol Ther. 2020b. https://doi.org/10.1002/cpt.1878.
29. Eloy P, Solas C, Touret F, Mentré F, Malvy D, de Lamballerie X, Guedj J. Dose rationale for favipiravir use in patients infected with SARS-CoV-2. Clin Pharmacol Ther. 2020. https://doi.org/10.1002/cpt.1877.
30. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KP, Chu DK, Chan MC, Cheung PP, Huang X, Peiris M. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antivir Res. 2020;3:104786.
31. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Zhang J, Yin P. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020. https://doi.org/10.1101/2020.03.17.2003743.
32. https://clinicaltrials.gov/ct2/who_table. Accessed 3 Oct 2020.
33. https://clinicaltrials.gov/ct2/results?cond=&term=Favipiravir&cntry=&state=&city=&dist=. Accessed 3 Oct 2020.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.