Favipiravir use for SARS CoV-2 infection

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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...
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 cyclohexene carboxylate 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
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 \mu M, CC_{50} > 400 \mu M, 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 \mu M.

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 \mu g/mL they suggest a higher value of EC_{50} in the range of 40–80 \mu g/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 \mu M (9.4 \mu g/mL), the independent study [30] indicated EC_{50} values > 100 \mu M (15. 7 \mu g/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 (Favipina) | 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                                             |
| #  | Title                                                                 | Status                        | Study results                  | Conditions                  | Interventions                                                                 |
|----|----------------------------------------------------------------------|-------------------------------|--------------------------------|-----------------------------|-------------------------------------------------------------------------------|
| 17 | Favipiravir vs hydroxychloroquine in COVID-19                       | Recruiting                    | No results available           | SARS-CoV2 | COVID-19                     | Drug: hydroxychloroquine | Drug: Favipiravir | Other: routine care for COVID-19 patients |
| 18 | Efficacy of Favipiravir in COVID-19 treatment                       | Recruiting                    | No results available           | COVID                     | Drug: Favipiravir | Drug: placebos               |
| 19 | Favipiravir combined with tocilizumab in the treatment of coronavirus 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 pneumonia | Drug: Favipiravir tablets + chloroquine phosphate 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 |
| #  | 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 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 |
| # | 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: Pyrona-
|    |                                                                      |                                 |                              |                                                 | dinedartesunate Drug: Favipiravir plus Nitzoxanide Drug: Sofosbuvir/daclatasvir |
| 46 | Assessment of safety and efficacy of CCP                           | Active, not recruiting          | No results available         | Covid-19                                        | 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 (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 | Convalvescent 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 (harmann 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                                           |
| # | 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 | Hodgkin’s 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                  |                                                                                      |                                                                                                                                                                           |
| 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, CML, 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 | Aplastic anemia | Multiple myeloma | 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 |                                                                                                                                                                           |
| #  | 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-TIGIT | Drug: Anti-TIGIT + Pomalidomide + 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 abnormalities 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 | Autoimmune 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.

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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-Dulcevic K, 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.
3. 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.
4. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4#:%7E:text=For%20COVID%2019%2C%20infections%20requiring%20ventilation. Accessed 3 June 2020.
5. https://www.worldlifeexpectancy.com/cause-of-death/influenza-pneumonia-by-country/. Accessed 3 June 2020.
6. 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/jims.7.172.
7. 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/jims.7.174.
8. 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/jims.7.179.
9. 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.
10. 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.
11. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug of interest to declare. Integr J Med Sci. 2020d;7:172. https://doi.org/10.15342/jims.7.174.
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/whointable. Accessed 3 Oct 2020.

33. https://clinicaltrials.gov/ct2/results?cond=&term=Favipiravir&cntry=&state=&city=&dist=, Accessed 3 Oct 2020.

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