CADTH COVID-19 PANDEMIC

COVID-19 CADTH HORIZON SCAN

CADTH Emerging Health Technology for COVID-19: Favipiravir

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Summary

- Favipiravir is an oral antiviral drug that is not approved in Canada. It has emerged as a potential candidate to treat or prevent COVID-19.
- Two published studies have evaluated the efficacy and safety of favipiravir for the treatment of COVID-19. A case series has been reported in critically ill patients with COVID-19 who received a combination of favipiravir and nafamostat mesylate (n = 11); however, this data are limited due to the lack of a control group.
- An open-label, non-randomized, controlled study investigated favipiravir (35 patients) compared to lopinavir-ritonavir (45 patients) for the treatment of COVID-19 in non-severe patients. Favipiravir was more effective than lopinavir-ritonavir in the time to viral clearance — four days (interquartile range [IQR] 2.5 to 9) versus 11 days (IQR 8 to 13), P < 0.001); however, the study lacked a comparison to standard of care alone and was not randomized.
- There are ongoing randomized controlled trials investigating favipiravir monotherapy versus placebo or favipiravir combination therapies for the treatment or prevention of COVID-19. In Canada, researchers received approval from Health Canada to conduct a phase II randomized controlled trial evaluating the chemoprophylaxis of favipiravir compared with placebo in adults living in long-term care homes to prevent COVID-19 outbreaks.

Background

The Technology

Antiviral drugs are being studied against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Favipiravir (Avigan, Fujifilm Holdings Corporation) is an oral antiviral drug that was developed for treating influenza[1] and has emerged as a potential candidate to treat or prevent COVID-19.[2] Favipiravir is a ribonucleic acid (RNA)-dependent RNA polymerase inhibitor that works by interrupting viral RNA replication.[3,4]

Regulatory Status

Favipiravir is not approved in Canada and is not currently accessible outside of clinical trials. An international expert panel issued a weak recommendation for not using favipiravir in patients with non-severe or severe COVID-19 because of low-quality evidence.[5]

Methods

A limited literature search was conducted by an information specialist on key resources including Ovid MEDLINE, Ovid Embase, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were favipiravir and COVID-19. No filters were applied to limit the retrieval by study type.

Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2019 and July 14, 2020.

Clinical trial registries were searched: the U.S. National Institutes of Health's clinicaltrials.gov, COVID-19 studies from the WHO database through clinicaltrials.gov, and Health Canada's Clinical Trials Database.

This horizon scan is not a systematic review and does not involve a critical appraisal or include a detailed summary of study findings.

Summary of the Evidence

Two published, non-randomized studies evaluated the efficacy and safety of favipiravir for the treatment of COVID-19. A summary of the characteristics of the open-label, non-randomized, controlled study (ChiCTR2000029600)[6] and case series[7] are included in Table 1.

Study Design and Patient Population

One open-label, non-randomized, controlled study included patients aged 16- to 75-years-old with a positive nasopharyngeal swab test for COVID-19. Patients were included if they had been ill for less than seven days. Patients were excluded from the study if they exhibited severe COVID-19 symptoms. Of the 56 consecutive patients with a positive laboratory-confirmed COVID-19 test that were screened for eligibility, 35 patients were included in the favipiravir group. There were 45 patients included in the lopinavir-ritonavir group of the 91 laboratory-confirmed COVID-19 patients who were initially screened. The total sample size included 80 patients who were followed up for 14 days following treatment initiation.[6]

One case series was conducted in 11 critically ill patients with confirmed SARS-CoV-2 infection admitted to an intensive care unit (ICU) in a hospital.[6] A clear definition of what constituted a critically ill patient was not provided. The exclusion criteria were not specified. All patients were followed up for at least 33 days.

Intervention and Comparator

The open-label, non-randomized, controlled study investigated favipiravir administered orally at a dose of 1,600 mg on day 1 and 600 mg twice daily on day 2 and thereafter. The comparator group consisted of oral lopinavir-ritonavir, with lopinavir dosed at 400 mg twice daily and ritonavir dosed at 100 mg twice daily. Treatment with favipiravir and lopinavir-ritonavir was administered until viral clearance was confirmed or for 14 days. All patients received treatment with interferon-alpha1b dosed at 60 mcg twice daily via aerosol inhalation.[6]

In the case series, all patients received a combination of treatment with favipiravir and nafamostat mesylate. Nafamostat mesylate was administered intravenously at a dose of 0.2 mg per kg per hour and favipiravir was administered orally at a dose of 3,600 mg on day 1 and 1,600 mg daily on day 2 for up to 14 days.[7] There was no comparator in the case series.

Outcomes

In the open-label, non-randomized, controlled study, the primary end point was time to viral clearance. This outcome was defined based on two consecutive negative results obtained via real-time quantitative polymerase chain reaction over a duration of 24 hours. The other clinical efficacy measure included in the study was the improvement of chest CT scans assessed on days 4, 9, and 14 following treatment initiation. Two medical radiographers who graded and scored CT findings were blinded to the favipiravir and lopinavir-ritonavir groups. A three-point scale was used to grade the CT findings and defined as follows: 1 = normal attenuation, 2 = ground-glass attenuation, and 3 = consolidation. In each patient, each of the six lung zones were assigned a score on a four-point scale of lung parenchyma, as follows: 0 = normal, 1 = 25% abnormality, 2 = 25% to 50% abnormality, 3 = 50% to 75% abnormality and 4 = 75% abnormality. The three-point radiographic score was multiplied by the four-point scale of lung parenchyma and a final total cumulative score was obtained that ranged from 0 to 72. An "improvement" in the chest CT was identified when the total cumulative score was lower than before medication. A ''worsening" in the chest CT occurred when the total cumulative score was higher than before medication and a ''constant" chest CT was defined as no change in the total cumulative score before treatment.[6]

Safety was evaluated according to a standardized questionnaire that assessed adverse events.[6] The type of standardized questionnaire used is not described.

In the case series, the outcomes assessed were not pre-specified. Results were reported for discontinuation from mechanical ventilation, discharge from the ICU, discharge from the hospital, mortality, and safety.

Table 1: Characteristics of Favipiravir Trials

Author, year, country	Study design, sample size (N), study duration	Population	Intervention and comparator	Outcomes
Cai et al. (2020)[6] China	Open-label, non-randomized, controlled study N = 80 Patients were followed up for 14 days of initiation of treatment	**Inclusion criteria:** • Patients aged 16- to 75-years-old with a positive nasopharyngeal swab for COVID-19 • The duration of onset of COVID-19 to enrolment in the study was < 7 days • Take contraception during the study and within 7 days after treatment • Tolerate oral administration of drugs **Exclusion criteria:** • Severe COVID-19 based on any of the following criteria: a resting respiratory rate > 30 per minute, oxygen saturation < 93%, oxygenation index	**Intervention** Favipiravir orally 1,600 mg on day 1 and 600 mg b.i.d. on day 2 for up to 14 days or until viral clearance (n = 35) **Comparator** Lopinavir orally 400 mg b.i.d. and ritonavir orally 100 mg b.i.d., up to 14 days or until viral clearance (n = 45)	• Time to viral clearance • Chest CT improvement at day 4, 9, and 14 • Safety

Author, year, country	Study design, sample size (N), study duration	Population	Intervention and comparator	Outcomes
		< 300 mm Hg, respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment • Chronic liver and kidney disease approaching end stage • Previous exposure to favipiravir or lopinavir-ritonavir and a history of allergic reactions • Concurrent participation in a clinical trial for the treatment of COVID-19 or participated in a clinical trial in the last 28 days		
Doi et al. (2020)[7] Japan	Case series N = 11 Patients were followed up for at least 33 days	**Inclusion criteria:** • Critically ill patients with SARS-CoV-2 infection were admitted to ICU	**Intervention** Nafamostat mesylate 0.2 mg per kg per hour via continuous intravenous infusion for up to 14 days combined with Favipiravir 3,600 mg on day 1 and 1,600 mg daily on day 2 for up to 14 days	• Discontinuation from MV • Discharge from ICU • Discharge from hospital • Mortality • Safety

b.i.d. = twice daily; COVID-19 = coronavirus disease; ICU=intensive care unit; MV=mechanical ventilation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Population Characteristics and Demographics at Baseline

In the open-label, non-randomized, controlled study, the median age of patients in the favipiravir group was 43-years-old (interquartile range [IQR] = 35.5 to 59) compared to 49-years-old (IQR 36 to 61) in the lopinavir-ritonavir group. The proportion of males was slightly higher in the lopinavir-ritonavir group (n = 21, 46.7%) compared to the favipiravir group (n = 14, 40.0%). The median body mass index (BMI) was similar in the favipiravir and lopinavir-ritonavir group (22.7 kg/m^2, IQR 16.2 to 31.6 versus 23.1 kg/m^2, IQR 16.4 to 28.4). Fever was the most common symptom reported among 22 patients (62.9%) and 37 patients (82.2%) in the favipiravir and lopinavir-ritonavir groups, respectively.[6]

In the case series, the median age of patients was 68-years-old (IQR 60 to 69 years). The total number of male patients was 10 (91%). The median body weight was 71 kg (IQR 69 to 82). Fever was the most common symptom reported among nine patients (82%). The most common coexisting disorder among patients was hypertension (n = 4, 26%) followed by diabetes mellitus (n = 4, 36%). The median duration of symptoms before admission was eight days (IQR 7 to 11).[7]

Efficacy

The key efficacy outcome results from the open-label, non-randomized, controlled study are subsequently summarized.

For the primary end point, favipiravir was more effective than lopinavir-ritonavir in the time to viral clearance (4 days [IQR 2.5 to 9] versus 11 days [IQR 8 to 13], P < 0.0001).[6]

At day 14 after initiation of treatment, there were 32 patients (91.4%), one patient (3.2%), and 2 patients (6.5%) considered to have improved, worsened, or had constant chest imaging in the favipiravir group, respectively. This was compared with 28 patients (62.2%) who had an improved chest CT, 9 patients (20.0%) who had a worsened chest CT, and 8 patients (17.8%) who had no change in chest CT in the lopinavir-ritonavir group. The differences between the two groups were considered statistically significant.[6]

The differences in chest CT at days 4 and 9 after initiation of treatment between the two groups were considered not statistically significant.[6]

The main efficacy results from the case series are subsequently summarized.

The median duration of treatment among patients who received nafamostat mesylate and favipiravir was 14 days each (IQR for nafamostat mesylate and favipiravir of 10 to 14 days and 12 to 14 days, respectively).[7]

All 11 patients were followed up for at least 33 days. There were eight patients (73%) who required mechanical ventilation at any point in time. Seven patients had a median duration of mechanical ventilation of 16 days (IQR 10 to 19) and one patient died on day 7 while in ICU on mechanical ventilation. By day 33, nine patients had been discharged from the ICU: seven patients were discharged from the hospital and two patients were sent to the general ward. One patient was still in ICU but without mechanical ventilation.[7]

Safety

In the open-label, non-randomized, controlled study, the total number of adverse events was lower in the favipiravir group (n = 4, 11.4%) compared to the lopinavir-ritonavir group (n = 25, 55.6%). In the favipiravir group, two patients experienced diarrhea, one patient each reported liver injury and poor diet. In the lopinavir-ritonavir group, six patients experienced nausea, five patients each reported vomiting and diarrhea, four patients experienced rash, three patients had liver injury, and two patients experienced chest tightness and palpitations.[6]

In the case series, based on at least 33 days of follow-up, there was one patient who died in ICU on day 7. One patient discontinued treatment due to an adverse event (hyperkalemia on day 9).[7]

Overall, the open-label, non-randomized study lacked a comparison to standard of care alone and the case series did not include a control group. Therefore, the current published evidence is limited to assess the true efficacy and safety of favipiravir for the treatment of COVID-19.

Ongoing Trials

There are ongoing randomized controlled trials (RCTs) investigating favipiravir monotherapy versus placebo or favipiravir combination therapies for the treatment and prevention of COVID-19 outlined in Appendix 1. The RCTs described in this table are based on the information posted on the ClinicalTrials.gov registry.[8] The results were tabulated according to the phase of clinical development and are presented in order of estimated primary trial completion dates (the earliest first).

Of note, there may be reporting errors in the study records posted on ClinicalTrials.gov and not all ongoing trials are posted to this website. Therefore, there may be ongoing clinical trials related to COVID-19 that are missing.

In Canada, researchers received approval from Health Canada to conduct a phase II RCT evaluating the chemoprophylaxis of favipiravir compared with placebo to prevent COVID-19 outbreaks among adults living in long-term care homes.

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Appendix 1: Ongoing Studies

Table 2: Favipiravir — Ongoing Randomized Controlled Trials (Current as of August 4, 2020)

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference
Phase IV					
Favipiravir versus hydroxychloroquine	Efficacy and Safety of Favipiravir Compared to the Base Therapeutic Regiment in Moderate to Severe COVID-19: A Randomized, Controlled, Double-Blind, Clinical Trial	DB, PC Iran N = 40	May 3, 2020	Adult patients with confirmed COVID-19	NCT04359615
Phase III					
Favipiravir versus standard of care (oseltamivir and hydroxychloroquine)	Efficacy and Safety of Favipiravir in Management of COVID-19	OL Egypt N = 100	June 1, 2020	Adult patients with confirmed mild to moderate COVID-19	NCT04349241
Favipiravir versus placebo	A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of Patients With COVID-19-Moderate Type	MC, DB, PC Italy N = 100	July 2020	Adult patients with moderate COVID-19	NCT04336904
Favipiravir versus favipiravir with azithromycin versus. hydroxychloroquine versus hydroxychloroquine with azithromycin	An Open-Label, Multicenter, Parallel-Group, Randomized, Phase III Study to Evaluate the Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-19	MC, OL Turkey N = 1,000	July 30, 2020	Adult patients with possible or confirmed COVID-19	NCT04411433
Favipiravir versus placebo	A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of Adult Patients With COVID-19-Moderate Type	MC, DB, PC Multi-country N = 256	August 2020	Adult patients with moderate COVID-19	NCT04425460

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference
Various antiviral drugs in combination, including favipiravir	A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID-19 AND Lopinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopinavir / Ritonavir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID-19	MC, OL Thailand N = 320	December 31, 2020	Patients ≥ 16- to 1 00-years-old with COVID-19	NCT04303299
Favipiravir versus standard care	A Randomized Controlled Trial of Early Intervention in Patients HospItalised With COVID-19: Favipiravir and StaNdard Care vErsEs Standard CaRe	OL UK N = 450	March 31, 2021	Adult patients with suspected or confirmed COVID-19	NCT04373733
Phase II/IIII					
Favipiravir versus favipiravir with chloroquine versus placebo	Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia	DB, PC China N = 150	April 30, 2020	Adult patients with pneumonia due to COVID-19	NCT04319900
Favipiravir versus standard care	Study on Safety and Efficacy of Favipiravir (Favipira) for COVID-19 Patient in Selected Hospitals of Bangladesh	DB, PC Bangladesh N = 50	July 2020	Adult patients with novel coronavirus	NCT04402203
Favipiravir versus standard care	An Adaptive, Multicenter, Randomized, Open-label, Comparative Clinical Study to Assess Efficacy and Safety of Favipiravir in Hospitalized Patients With COVID-19	Adaptive, MC, OL Russian Federation N = 330	July 2020	Hospitalized adult patients with moderate to severe COVID-19 pneumonia	NCT04434248

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference
Favipiravir versus hydroxychloroquine versus standard care	Treatment of Covid-19 With Favipiravir Versus Hydroxychloroquine: a Randomized Comparator Trial	OL Ireland N = 150	April 14, 2021	Adult patients ≥ 21-years-old with confirmed COVID-19	NCT04387760
Favipiravir versus placebo	A Trial of Favipiravir Therapy in Adults With Mild Coronavirus Disease COVID-19	MC, DB, PC Saudi Arabia N = 576	December 2020	Adults with mild COVID-19	NCT04464408
Favipiravir versus chloroquine versus nitazoxanide versus ivermectin versus niclosamide versus oseltamivir	The Results of COVID 19 Treatment: A Real-life Experience on Patients With COVID 19	SB Egypt N = 120	December 2029	Patients with COVID-19	NCT04345419
Favipiravir versus placebo	Clinical Study Evaluating the Efficacy of Faviprevir in COVID-19 Treatment	OL Egypt N = 40	December 1, 2030	Patients with COVID-19	NCT04351295
Phase II					
Favipiravir and standard of care versus standard of care	Open Label, Randomized, Controlled Phase 2 Proof-of-Concept Study of the Use of Favipiravir v. Standard of Care in Hospitalized Subjects With COVID-19	OL, MC, US N = 50	September 2020	Patients with COVID-19	NCT04358549
Favipiravir versus placebo	An Adaptive Randomized Placebo Controlled Phase II Trial of Antivirals for COVID-19 Infection	Adaptive, DB, PC US N = 190	November 2020	Patients with COVID-19	NCT04445467
Favipiravir versus placebo	Control of COVID-19 Outbreaks in Long Term Care (CONTROL-COVID)	PC Canada N = 760	March 2021	Long-term care homes with an outbreak of COVID-19	NCT04448119
Favipiravir versus standard of care and placebo	A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild or Asymptomatic COVID-19	DB, PC US N = 120	July 2021	Patients with mild or asymptomatic COVID-19	NCT04346628

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference
Phase not reported					
Favipiravir and tocilizumab versus favipiravir versus tocilizumab	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019-A Multicenter, Randomized and Controlled Clinical Trial Study	MC, OL China N = 150	May 2020	Patients with COVID-19	NCT04310228
Favipiravir versus regular treatment other than lopinavir and ritonavir, chloroquine phosphate, hydroxychloroquine sulfate, arbidol, and colomycin	The Mechanism, Clinical Outcome and Therapeutic Intervention of Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	OL China N = 210	June 1, 2020	Patients ≥ 18-years-old to 80-years-old with COVID-19	NCT04333589
Favipiravir and hydroxychloroquine versus versus standard of care	A Trial of Favipiravir and Hydroxychloroquine Combination in Adults Hospitalized With Moderate and Severe Covid-19	OL Saudi Arabia N = 520	November 2021	Patients ≥18 years and older with COVID-19	NCT04392973

DB = double-blind; MC = multi-centre; OL = open-label; PC = placebo-controlled; SB = single-blind;

[a] The date on which data collection is completed for all the primary outcome measures.