Should favipiravir be used for COVID-19?

This write-up summarises a rapid evidence review of favipiravir for treating COVID-19. The information may be revised as new evidence emerges.

Background

A news article titled “Japanese flu drug 'clearly effective' in treating coronavirus, say China” was published in the Guardian on 18 Mar 2020.1 Favipiravir (brand name Avigan), an antiviral drug, is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor which can block the replication of RNA viruses and may have antiviral action against SARS-CoV-2.2

It was approved in Japan in 2014 for the treatment of novel or re-emerging pandemic influenza virus infections. Use is limited to cases in which other influenza antiviral drugs are not sufficiently effective because favipiravir was only investigated in non-clinical studies in avian influenza A (H5N1 and H7N9), and efficacy against seasonal influenza A or B has not been sufficiently demonstrated.3

Clinical evidence

There are two published trials for favipiravir for the treatment of COVID-19:

- An open-label, non-randomised trial in Shenzhen (N=80)4 examined the efficacy of favipiravir (n=35) versus lopinavir/ritonavir (n=45) for treating COVID-19. Significantly shorter viral clearance time (primary endpoint) was found for favipiravir versus lopinavir/ritonavir (median 4 days versus 11 days; p<0.001). Patients receiving favipiravir also showed significant improvement in chest imaging compared with those receiving lopinavir/ritonavir, with an improvement rate of 91.43% versus 62.22% (p = 0.004). Fewer adverse reactions were reported for favipiravir (11.43%) compared to lopinavir/ritonavir (55.56%) (p<0.01).

- An open-label, randomised trial in Wuhan (N=240)5 examined the efficacy of favipiravir (n=120) versus arbidol (n=120) for treating COVID-19. There was no difference in the 7-day clinical recovery rate (primary endpoint) for favipiravir versus arbidol in the overall population (61.21% versus 51.67%; p=0.14). However, for a sub-population of non-critical patients without hypertension or diabetes, the 7-day clinical recovery rate was significantly better with favipiravir (71.43%; 70/98) versus arbidol (55.86%; 62/111) (p = 0.02).

According to other media reports:

- A Japanese health ministry source suggested that favipiravir was not as effective in patients with more severe symptoms, from their clinical studies of 70 to 80 participants.1
- One medical centre in South Korea started administration of favipiravir on 22 February and, while the drug has not been approved for treating COVID-19, the Ministry of Food and Drug Safety (MFDS) in South Korea is considering a fast-track approval to import favipiravir.6

Two large international trials were completed on favipiravir for the treatment of uncomplicated influenza (NCT02008344; NCT02026349); however, no results have been published in scientific journals. Favipiravir was also trialed for treating Ebola virus, although there was no evidence that favipiravir monotherapy was effective.9

Planned or ongoing clinical trials of favipiravir for the treatment of COVID-19 are summarised in Table 1.
Table 1: Ongoing or planned studies for favipiravir in patients with COVID-19

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Study Design (Location)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Date of primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04303299^16</td>
<td>OL, R (Thailand)</td>
<td>Lopinavir/darunavir + ritonavir + favipiravir +/- chloroquine</td>
<td>Placebo</td>
<td>October 2020</td>
</tr>
<tr>
<td>NCT04310228^11, ChiCTR2000030894^12</td>
<td>OL, R, MC (China)</td>
<td>Favipiravir +/- tocilizumab</td>
<td>Tocilizumab</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04319900^13, ChiCTR2000030987^14</td>
<td>R, DB (China)</td>
<td>Favipiravir +/- chloroquine</td>
<td>Placebo</td>
<td>April 2020</td>
</tr>
<tr>
<td>NCT04333589^15</td>
<td>R, OL, MC (China)</td>
<td>Favipiravir</td>
<td>Standard treatment (treatment other than chloroquine, hydroxychloroquine, arbidol and colomycin)</td>
<td>June 2020</td>
</tr>
<tr>
<td>Fujifilm Tomoya Chemical Co. Ltd. ^16</td>
<td>phill (Japan)</td>
<td>Favipiravir</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>ChiCTR2000030113^17</td>
<td>R (China)</td>
<td>Favipiravir</td>
<td>Lopinavir + ritonavir</td>
<td>May 2020^*</td>
</tr>
<tr>
<td>ChiCTR2000029600^18</td>
<td>NR (China)</td>
<td>Favipiravir +/- lopinavir + ritonavir</td>
<td>Interferon alpha atomization +/- lopinavir + ritonavir</td>
<td>April 2020^*</td>
</tr>
<tr>
<td>ChiCTR2000029548^19</td>
<td>OL, R (China)</td>
<td>Favipiravir:</td>
<td>Baloxavir marboxil or lopinavir + ritonavir</td>
<td>June 2020^*</td>
</tr>
<tr>
<td>NCT04346628^20</td>
<td>OL, R (US)</td>
<td>Favipiravir</td>
<td>Standard treatment</td>
<td>April 2021</td>
</tr>
<tr>
<td>ChiCTR2000029544^21</td>
<td>R (China)</td>
<td>Favipiravir</td>
<td>Baloxavir marboxil</td>
<td>May 2020</td>
</tr>
<tr>
<td>ChiCTR2000029996^22</td>
<td>R, OL (China)</td>
<td>Favipiravir (high, middle and low dosage)</td>
<td>-</td>
<td>April 2020</td>
</tr>
<tr>
<td>NCT04345419^23</td>
<td>R, SB (Egypt)</td>
<td>Favipiravir</td>
<td>Chloroquine or nitazoxanide or ivermectin or nicosamide</td>
<td>December 2029</td>
</tr>
<tr>
<td>NCT04349241^24</td>
<td>R, OL (Egypt)</td>
<td>Favipiravir</td>
<td>Standard treatment</td>
<td>October 2020</td>
</tr>
<tr>
<td>NCT04351295^25</td>
<td>R, OL (Egypt)</td>
<td>Favipiravir</td>
<td>Placebo</td>
<td>December 2030</td>
</tr>
<tr>
<td>NCT04356496^26</td>
<td>R (France)</td>
<td>Favipiravir</td>
<td>Hydroxychloroquine or imatinib or telmisartan</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT04336904^27</td>
<td>R, DB (Italy)</td>
<td>Favipiravir</td>
<td>Placebo</td>
<td>July 2020</td>
</tr>
</tbody>
</table>

Abbreviations: MC, multicentre; OL, open label; R, randomised; DB, double blind; phill, phase III; NR, non-randomised; SB, single blind; ^study completion date

Recommendations from professional bodies

No FDA-approved drugs have demonstrated safety and efficacy in randomised controlled trials for patients with COVID-19.28, 29 World Health Organization (WHO), UK National Health Service (NHS) and Australian health authorities have not provided any advice on the use of favipiravir. It is also not included in the 7th edition of Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia for tentative treatment of COVID-19.2, 30

In Singapore, the National Centre for Infectious Diseases (NCID) notes there are no proven or licensed therapies for any coronavirus infection. In interim treatment guidelines for COVID-19, NCID does not recommend favipiravir for routine treatment of COVID-19 due to the absence of good quality peer-reviewed data supporting its use.31 The Pharmaceutical Society of Singapore (PSS)32 notes that several interventions (including favipiravir) are undergoing clinical trials.

Conclusion

Given that the published evidence for favipiravir is limited, further investigation is needed to conclude its efficacy and safety for treating patients with COVID-19. Nine clinical trials are planned and are likely to report results in the months ahead. These findings will determine whether favipiravir should be used more widely in this setting. Currently, no international professional bodies recommend the use of favipiravir for the treatment of COVID-19.
References


26. Register ECT. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19) - a multiarm, multi-stage (NAMMS) randomized trial to assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial) [Access Date 27 April 2020. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-001435-27].


