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[7]; NCT02026349[8]); 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.

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Table 1: Ongoing or planned studies for favipiravir in patients with COVID-19

Study identifier	Study Design (Location)	Intervention	Comparator	Date of primary completion
NCT04303299[10]	OL, R (Thailand)	Lopinavir/darunavir + ritonavir + favipiravir +/- chloroquine	Placebo	October 2020
NCT04310228[11], ChiCTR2000030894[12]	OL, R, MC (China)	Favipiravir +/- tocilizumab	Tocilizumab	May 2020
NCT04319900[13], ChiCTR2000030987[14]	R, DB (China)	Favipiravir +/- chloroquine	Placebo	April 2020
NCT04333589[15]	R, OL, MC (China)	Favipiravir	Standard treatment (treatment other than chloroquine, hydroxychloroquine, arbidol and colomycin)	June 2020
Fujifilm Tomoya Chemical Co. Ltd.[16]	phIII (Japan)	Favipiravir	Not reported	Not reported
ChiCTR2000030113[17]	R (China)	Favipiravir	Lopinavir + ritonavir	May 2020^
ChiCTR2000029600[18]	NR (China)	Favipiravir +/- lopinavir + ritonavir	Interferon alpha atomization +/- lopinavir + ritonavir	April 2020^
ChiCTR2000029548[19]	OL, R (China)	Favipiravir:	Baloxavir marboxil or lopinavir + ritonavir	June 2020^
NCT04346628[20]	OL, R (US)	Favipiravir	Standard treatment	April 2021
ChiCTR2000029544[21]	R (China)	Favipiravir	Baloxavir marboxil	May 2020
ChiCTR2000029996[22]	R, OL (China)	Favipiravir (high, middle and low dosage)	-	April 2020
NCT04345419[23]	R, SB (Egypt)	Favipiravir	Chloroquine or nitazoxanide or ivermectin or niclosamide	December 2029
NCT04349241[24]	R, OL (Egypt)	Favipiravir	Standard treatment	October 2020
NCT04351295[25]	R, OL (Egypt)	Favipiravir	Placebo	December 2030
NCT04356495[26]	R (France)	Favipiravir	Hydroxychloroquine or imatinib or telmisartan	July 2020
NCT04336904[27]	R, DB (Italy)	Favipiravir	Placebo	July 2020

Abbreviations: MC, multicentre; OL, open label; R, randomised; DB, double blind; phIII, 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

1. The Guardian. Japanese flu drug 'clearly effective' in treating coronavirus, says China. 18 March 2020 [Access Date 20 March 2020. Available from: https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china].
2. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug discoveries & therapeutics. 2020;14(1):58-60.
3. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau Ministry of Health, Labour and Welfare, Japan. Report on the Deliberation Results: Avigan Tablet 200 mg 4 March 2014 [Available from: https://www.pmda.go.jp/files/000210319.pdf].
4. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020.
5. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.
6. Clarivate Analytics. BioWorld Article: Fujifilm stock rises as Japan considers Avigan for COVID-19 treatment 25 February 2020 [Access Date 23 March 2020. Available from: [https://www.bioworld.com/articles/433290-fujifilm-stock-rises-as-japan-considers-avigan-for-covid-19-treatment]].
7. ClinicalTrials.gov. Phase 3 Efficacy and Safety Study of Favipiravir for Treatment of Uncomplicated Influenza in Adults [Access Date 6 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02008344?term=Favipiravir&draw=1&rank=6].
8. ClinicalTrials.gov. Phase 3 Efficacy and Safety Study of Favipiravir for Treatment of Uncomplicated Influenza in Adults - T705US316 [Access Date 6 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02026349?term=Favipiravir&draw=1&rank=4].
9. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS medicine. 2016;13(3):e1001967.
10. ClinicalTrials.gov. Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquin for Treatment of COVID19 : A Randomized Control Trial (THDMS-COVID19) [Access Date 23 March 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04303299?term=Favipiravir&draw=2&rank=11].
11. ClinicalTrials.gov. Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019 [Access Date 23 March 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04310228?term=Favipiravir&draw=2&rank=7].
12. Chinese Clinical Trial Registry. Favipiravir Combined With Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial [7 April 2020]. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=51126].
13. ClinicalTrials.gov. Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia [Access Date 6 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04319900?term=favipiravir&draw=2&rank=9].
14. Chinese Clinical Trial Registry. A Randomized Controlled Trial for Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (COVID-19) [Access Date 7 April 2020. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=51329].
15. ClinicalTrials.gov. A Prospective Study on Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive [Access Date 6 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04333589?term=favipiravir&draw=3&rank=12].
16. FUJIFILM Holdings Corporation. Fujifilm announces the start of a phase III clinical trial of influenza antiviral drug "Avigan Tablet" on COVID-19 and commits to increasing production 31 March 2020 [Access Date 6 April 2020. Available from: https://www.fujifilm.com/jp/en/news/hq/3211].
17. Chinese Clinical Trial Registry. Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir [Access Date 6 April 2020. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49988].
18. Chinese Clinical Trial Registry. Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) [Access Date 6 April 2020. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49042].
19. Chinese Clinical Trial Registry. Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients [Access Date 6 April 2020. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49015].
20. ClinicalTrials.gov. Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild COVID-19 [Access Date 27 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04346628].
21. Registry CCT. A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients who are still positive on virus detection under the current antiviral therapy [Access Date 27 April 2020. Available from: http://www.chictr.org.cn/hvshowproject.aspx?id=22227].
22. Registry CCT. A randomized, open-label, controlled trial for the efficacy and safety of Farpiravir Tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19) [Access Date 27 April 2020. Available from: http://www.chictr.org.cn/hvshowproject.aspx?id=22594].
23. ClinicalTrials.gov. A Real-life Experience on Treatment of Patients With COVID 19 [Access Date 27 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04345419].
24. ClinicalTrials.gov. Efficacy and Safety of Favipiravir in Management of COVID-19 (FAV-001) [Access Date 27 April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04349241].
25. ClinicalTrials.gov. Efficacy of Faviprevir in COVID-19 Treatment [Available from: https://clinicaltrials.gov/ct2/show/NCT04351295].
26. Register ECT. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19) : a multiarm, multi-stage (MAMS) 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].
27. ClinicalTrials.gov. Clinical Study To Evaluate The Performance And Safety Of Favipiravir in COVID-19 [Access date 27 April 2020. Available from https://clinicaltrials.gov/ct2/show/NCT04336904].
28. Centers for Disease Control and Prevention. Information for Clinicians on Therapeutic Options for COVID-19 Patients [Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html].
29. US Food & Drug Administration. Coronavirus Disease 2019 (COVID-19) [Available from: https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19].
30. National Health Commission (NHC) of the People's Republic of China. Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia [Access Date 23 March 2020. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/11/22/chinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment].
31. National Centre for Infectious Diseases (NCID). Interim Treatment Guidelines for COVID-19. [Access date 26 April 2020 at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx].
32. Pharmaceutical Society of Singapore. COVID-19 Advice for the General Public [Access Date 7 April 2020. Available from: https://www.pss.org.sg/know-your-medicines/covid-19-advice-general-public].