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RAPID RESEARCH IN COVID-19 PROGRAMME

GETAFIX : Glasgow Early Treatment Arm Favipiravir$^{\chi}$

A randomised controlled study of favipiravir as an early treatment arm in COVID-19 patients

AIMS

Early community treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection may reduce the incidence of severe COVID-19 and the impact of future infection waves. In a randomised phase III trial, called GETAFIX, we evaluated the clinical effectiveness and safety of favipiravir, an oral antiviral medication. We also evaluated the extent to which favipiravir causes genetic mutations in the SARS-CoV-2 virus.

KEY FINDINGS

- Between December 2020 and July 2022, 68,788 adults were invited. 302 (0.4%) were subsequently randomised to receive favipiravir (n=152) or no additional treatment (n=150).
- The average age of patients recruited was 47 years old. 230/302 (76.2%) were vaccinated.
- Severe outcomes were infrequent, with no ICU admissions or deaths.
- We did not observe any clinical effect from taking favipiravir. This was measured by the distribution of disease outcomes up to 15 days after randomisation.
- The was also no difference in the time taken for symptoms to resolve or the time for virus to be cleared from nasal swab samples.
- Favipiravir was well tolerated with no safety concerns. Although we observed evidence of favipiravir-induced SARS-CoV-2 virus mutation, the mutations identified were not of clinical relevance.

WHAT DID THE STUDY INVOLVE?

We performed an open-label, community-based, phase III, randomised trial, recruiting non-hospitalised adults with mild COVID-19 (defined by a WHO ordinal severity score (OSS) ≤3). Positive cases were invited to web-based self-screening within 24h using public health data.

Exclusion criteria included symptoms for >7 days, pregnancy/breastfeeding, severe renal or liver disease, gout, licensed antiviral eligibility. Participants were randomised 1:1 to 10 days favipiravir (Day 1: 3600mg; Days 2-10:1600mg) or no additional treatment.

The primary endpoint, which was used to assess clinical effectiveness, was worst recorded OSS up to and including Day 15. The target total recruitment was 302 cases.

Secondary endpoints included adverse event (AE) rate (a measure of safety) up to Day 60, time-to-viral clearance (a measure of the time it takes for the SARS-CoV-2 swab tests to become clear), time-to-symptom resolution (a measure of how quickly patients feel back to normal), and SARS-CoV-2 sequencing variant rate (≥5% frequency) at Day 15 (a way of assessing whether favipiravir was causing mutations in the SARS-CoV-2 virus).

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Despite initiating therapy promptly, we observed no clinical benefits. The incidence of severe COVID-19 disease was much lower than expected in both arms of our trial, with no ICU admissions, no deaths and only 5 hospitalisations. This probably reflected the fact that most patients were young (mean age 47) and fit (64.9% reported no comorbidity), and the population had a high rate of prior COVID-19 vaccination (76.2%). Favipiravir was well-tolerated and safe.

We observed no difference in time to symptom resolution or time to viral clearance, although our data regarding viral clearance are based on limited numbers of repeat samples. SARS-CoV-2 viral genomic sequencing identified evidence of favipiravir-induced mutagenesis, including an increase in C-to-U variants consistent with the known action of the drug. The mutations identified were not of known clinical relevance but support a cautious approach to use of favipiravir in COVID-19.

WHAT IMPACT COULD THE FINDINGS HAVE?

Prior to the current trial, favipiravir had been associated with potential clinical benefits in early treatment of COVID-19. In Japan it has been used extensively for this purpose. Our findings, which are concordant with results from other recent trials, suggest the drug is not effective.

The current trial was successful in reaching and initiating therapy quickly in community cases. This required development of novel methods for raising trial awareness, case identification and screening. Live public health data was used to maximise study reach, comprising 83,096 positive tests. However, most potentially eligible adults (66,464/68,788, 96.6%) did not respond to email invitations or other means of study advertising, including print, radio and social media. Of those who did respond, 302/2,324 (12.9%) were subsequently randomised following pre-screening +/- formal screening. This attrition reflects the difficulties involved in delivering trials of this nature and suggests more efficient methods are needed for future trials of early intervention for SARS-CoV-2 infection.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Study findings will be disseminated via conference presentations and peer-reviewed publications. The primary manuscript reporting the trial results is currently in submission.

CONCLUSION

We observed no clinical benefits associated with favipiravir administration in mild COVID-19 in a well-vaccinated UK population with limited comorbidity. Favipiravir was well tolerated but was associated with evidence of new mutations in the SARS-CoV-2 virus.

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ADDITIONAL INFORMATION

The last follow-up visit for the final participant was completed in September 2022. SARS-CoV-2 viral genomic sequencing was completed in December 2023. Data cleaning for final statistical analyses was completed in January 2023.
Trial expenditure from grant: **£456,088.90**