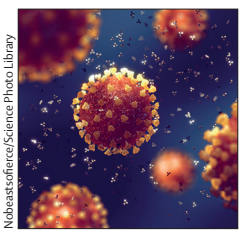
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

PIONEER trial: favipiravir to treat moderate COVID-19



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As the COVID-19 pandemic claimed lives across the globe, several randomised clinical trials were conducted to evaluate the safety and efficacy of investigational and repurposed therapeutics for the treatment of COVID-19. As a result, a number of new antivirals are now licensed to treat COVID-19, such as nirmatrelvir–ritonavir (Paxlovid), molnupiravir, and remdesivir.[1–3] Favipiravir is an RNA-dependant RNA polymerase inhibitor with activity against a range of RNA viruses. The agent is licensed in Japan to treat influenza virus and has been studied and subsequently used to treat SARS-CoV-2 infection in several Asian countries.[4] This approval was driven by small studies that suggested a reduction of time to clinical improvement or cure in COVID-19 compared with standard of care in mostly mild or moderate cases of COVID-19 not requiring supplemental oxygen.[5] Treatment initiation with favipiravir within 10 days from symptoms onset in moderate cases was allowed in one of the studies. However, those with moderate COVID-19 comprised 40% of the cohort, whereas the majority were mild cases and, therefore, it is difficult to draw conclusions on the basis of the small number of patients with moderate COVID-19.[6]

In *The Lancet Respiratory Medicine*, Pallav L Shah and colleagues[7] report results of a multicentre, open-label, phase 3, randomised controlled trial of oral favipiravir for 10 days in patients newly hospitalised with COVID-19 in five centres in the UK (n=2), Brazil (n=2), and Mexico (n=1). 499 patients were randomly assigned to favipiravir and standard care (n=251) or standard care alone (n=248); an additional three patients had also been randomly assigned to hydroxychloroquine, azithromycin, and zinc before the withdrawal of the study group after instruction from the UK Medicines and Healthcare products Regulatory Agency, due to concerns regarding hydroxychloroquine and cardiac toxicity. Recruitment started in May, 2020, and concluded in May, 2021. During the initial phase of enrolment, uncertainty regarding effective therapies for COVID-19 dominated medical communities and the currently licensed antivirals with activity against SARS-CoV-2 were also being studied. Standard of care, including use of dexamethasone, remdesivir, and tocilizumab as recommended, after their authorisation for use to treat COVID-19, was allowed and was similar in both groups. The prespecified primary outcome was time to recovery, defined as improvement by two or more points on a seven-category ordinal scale from randomisation to day 28. Mortality and survival without ventilation at 28 days were secondary outcomes. SARS-CoV-2 infection was confirmed in 446 (89%) of 499 study participants by RT-PCR, whereas the diagnosis was only presumed on the basis of compatible clinical and radiological presentation, and absence of alternate diagnosis in the remaining 53 (11%) of 499 participants in the cohort. Notably, underlying malignancy at baseline was reported in only 17 (3%) of 502 patients and there were no immunocompromising conditions reported otherwise. Difference in time to recovery and survival without ventilation was similar between the two groups, except in a post-hoc analysis, in which there was a faster rate of recovery in patients younger than 60 years who received favipiravir and standard care compared with those who had standard care alone (HR 1·35 [95% CI 1·06–1·72]; p=0·01). Notably, there was no significant difference in mortality between the favipiravir and standard care group and the group that received standard care alone. A sensitivity analysis that only included RT-PCR-confirmed cases of COVID-19 yielded similar findings. Median time from symptoms onset to randomisation was 8·9 days (IQR 6·2–11·1), which is notably longer than the duration used for nirmatrelvir–ritonavir or molnupiravir.[1,2] 415 (83%) of 502 participants in the cohort required oxygen supplementation at baseline and, thus, the majority of the included cohort had moderate or severe COVID-19.

Adding favipiravir to standard care when managing COVID-19 that requires hospitalisation did not meet the primary endpoint in patients aged 60 years and older, a group at high risk of poor outcomes. Although the median duration of 8·9 days from symptoms onset to treatment initiation could be a factor in absence of benefit, several other studies explored early initiation of favipiravir within 7 days from symptoms onset in mild cases and reported no notable difference in time to clinical improvement or duration of viral shedding with favipiravir compared with standard care or other investigational therapies that were later proven ineffective in treating COVID-19.[8–10]

In a multicentre, open-label, randomised clinical trial,[11] early initiation of favipiravir to treat mild COVID-19 did not substantially reduce progression or requirement of supplemental oxygen when compared with standard care.

The authors stipulate that the dose used to treat SARS-CoV-2 is based on the approved dose to treat influenza virus, despite in-vitro evidence suggesting a higher dose might be required to effectively treat SARS-CoV-2 given a high half maximal effective concentration.[12] These findings call for further work to explore the appropriate dosage to treat SARS-CoV-2, based on pharmacodynamic–pharmacokinetic studies and in-vitro testing.

The evidence provided by Shah and colleagues, which supports findings in smaller cohorts, should motivate health authorities in countries where favipiravir is used to revise recommendations for its' use to treat patients who are hospitalised with COVID-19.

SS is a site investigator for the NOVATION-1 study to evaluate the safety and efficacy of aerosolized novaferon and standard of care versus placebo and standard of care in hospitalised adult patients with moderate to severe COVID-19.

Sarah Shalhoub
sarah.shalhoub@lhsc.on.ca

Schulich School of Medicine and Dentistry, Western University, London, ON N6A 5C1, Canada.

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Is tezepelumab the ubiquitous biologic for severe asthma?

Biologic therapies have transformed severe asthma management.[1] The use of these treatments has been based on the identification of specific phenotypic characteristics, which predict patient response to specific monoclonal antibody therapies. Measurements of total serum immunoglobulin (Ig)-E, blood eosinophil counts, and fractional concentration of exhaled nitric oxide (FeNO), enable the identification of specific type 2-high phenotypes responsive to specific biologic therapies. However, in clinical practice the paucity of biologics effective for both type 2-high and type 2-low asthma phenotypes is an important limitation of this therapeutic approach.

This major therapeutic gap has been filled by tezepelumab, a human monoclonal antibody that targets thymic stromal lymphopoietin (TSLP), which has a key role in the initiation and persistence of airway inflammation in asthma, through regulation of multiple downstream inflammatory pathways.[2] Two landmark, 52-week, randomised, double-blind, placebo-controlled trials reported that in patients with severe asthma, tezepelumab reduced the risk of severe exacerbations by more than 50%.[3,4] One of these, the PATHWAY study, found that the severe exacerbation rate was lower irrespective of the baseline blood eosinophil count, FeNO level, or type 2-status (defined by a composite measure of total serum IgE level and blood eosinophil counts), indicating that the inhibition of TSLP has broader physiological effects beyond type 2 cytokine inhibition.[3] The other trial, NAVIGATOR, found that tezepelumab therapy resulted in fewer exacerbations and better lung function, asthma control, and health-related quality of life than placebo.[4] Risk reduction was less in patients with a low blood eosinophil


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