Repurposed drug baricitinib emerges as major COVID-19 treatment option

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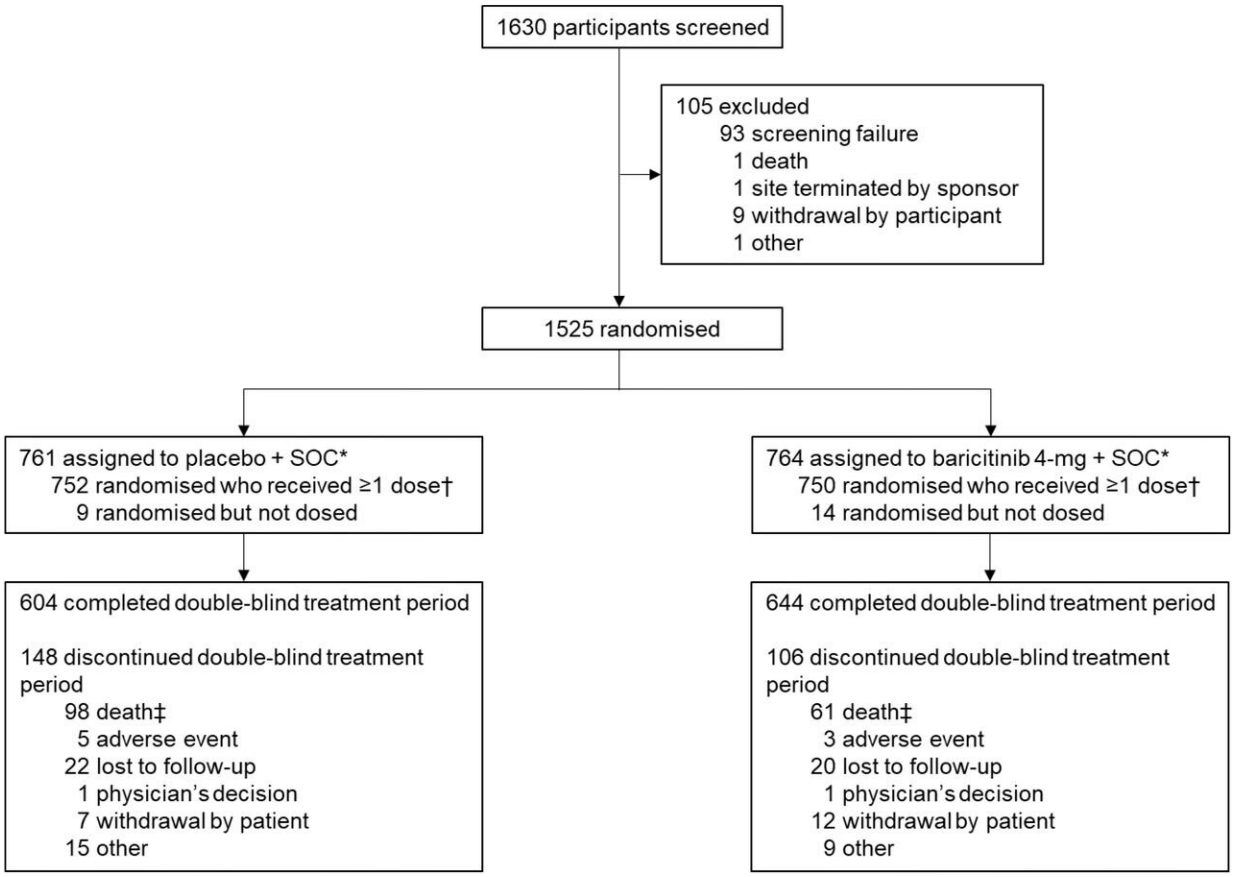

Figure 1: Trial profile. SOC=standard of care. *Included in the intent-to-treat population. †Includes all randomized participants who received ≥1 dose of study drug and who did not discontinue the study for the reason of 'lost to follow-up' at the first post-baseline visit. ‡159 deaths total reported by day 28. There were an additional three deaths that occurred after treatment period disposition but within 28 days. Credit: DOI: 10.1101/2021.04.30.21255934

A repurposed drug that was first used against COVID-19 in the United States by Emory researchers is emerging as a major option for treatment of hospitalized patients needing respiratory support.

The anti-inflammatory drug baricitinib was originally developed for rheumatoid arthritis by Eli Lilly and Company and Incyte. It has now been tested in several clinical trials in people with severe COVID-19, both in combination with and in comparison to other drugs.

Results of the COV-BARRIER study, the most recent to be analyzed, show a substantial reduction in mortality for the critically ill. In a subgroup of 101 patients on mechanical ventilation or ECMO (extracorporeal membrane oxygenation), those who received bariticinib plus standard of care were 46 percent less likely to die by day 28 of treatment, compared to placebo plus standard of care, which includes corticosteroids.

"The reduction of mortality with bariticinib was the largest to be achieved to date for any drug used with corticosteroids in patients having critical disease, which demonstrates that these two anti-inflammatory agents are also safe together," says Vincent Marconi, MD, professor of medicine and global health at Emory University School of Medicine and Rollins School of Public Health.

At the end of July, the Food and Drug Administration issued an amended Emergency Use Authorization for baricitinib to be used alone. Baricitinib was originally approved in combination with the antiviral drug remdesivir, but now can be used without remdesivir for hospitalized patients needing supplemental oxygen, ventilation or life support.

Currently, the National Institutes of Health's COVID-19 Treatment Guidelines recommend baricitinib as a therapeutic option, added to

dexamethasone, for patients who were recently hospitalized with systemic inflammation and rapidly increasing oxygen needs.

From small scale to multi-center trials

Last year, Marconi led initial "compassionate use" testing of baricitinib on critically ill patients with COVID-19 at Atlanta Veterans Affairs Medical Center, which contributed to the drug's inclusion in multi-center clinical trials sponsored by the National Institutes of Health.

One was the international ACTT-2 (Adaptive COVID-19 Treatment Trial), which found that baricitinib treatment resulted in faster recovery and a greater likelihood of clinical improvement, when combined with the antiviral drug remdesivir. More recently, the ACTT-4 study compared dexamethasone head to head with baricitinib. ACTT-4 was halted in April, based on an interim analysis indicating that neither regimen was significantly better. However, this study did not assess the combination of dexamethasone and baricitinib together.

The Lilly-sponsored COV-BARRIER study, with Marconi as co-principal investigator, studied more than 1,500 hospitalized COVID-19 patients treated with baricitinib or placebo. The standard of care included dexamethasone for more than 70 percent of the participants.

The COV-BARRIER study did not show a difference between baricitinib versus placebo for the primary endpoint, the proportion of people progressing to high-flow oxygen, ventilation or death. However, baricitinib treatment reduced mortality by more than 38 percent by day 28, with similar rates of serious adverse events or serious infections.

Groundwork laid with HIV research

Baricitinib is part of a class of drugs called JAK inhibitors (Janus kinase inhibitors). Before the COVID-19 pandemic, Marconi and his colleagues had previous experience at Emory studying a similar drug for HIV, in collaboration with antiviral drug discovery expert Raymond Schinazi, Ph.D.

"Our work with Marconi and colleagues provided a rationale for using JAK inhibitors to treat an inflammatory disease like COVID-19 safely," says Schinazi, who is Frances Winship Walters professor of pediatrics at Emory University School of Medicine. "Baricitinib can now stand alone without an antiviral agent. Prior to this, most physicians were cautious about using the drug alone. The EUA supports further investigation of JAK inhibitors for infectious disease treatments going forward."

Emory and the U.S. Department of Veterans Affairs hold several US and foreign patent rights on the use of baricitinib and other JAK inhibitors to treat coronaviruses, and licensed this technology to Eli Lilly in March 2021. Schinazi and Christina Gavegnano, Ph.D. are listed on the issued patents as sole inventors.

"Our extensive work with Jak inhibitors in the HIV space became a roadmap for tackling COVID-19 in record time," says Gavegnano, who worked with Schinazi as a graduate student and is now an assistant professor in the Department of Pathology and Laboratory Medicine at Emory.

More information: Vincent C. Marconi et al, Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial (2021). DOI: 10.1101/2021.04.30.21255934

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