Doherty Institute | The University of Melbourne | The Royal Melbourne Hospital | ASCOT AustralaSian COVID-19 Trial

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

ASCOT Trial Manuscript Results Summary: Antiviral Domain

The ASCOT Study is looking to find the most effective treatments for **COVID-19**. The study is made up of 'domains' for testing different treatment types.

We have recently published the results from the Antiviral Domain.

This domain was designed to test whether administration of an antiviral treatment, known as Nafamostat, was better than not receiving Nafamostat for patients in hospital with COVID-19.

Nafamostat for COVID-19 was tested because:

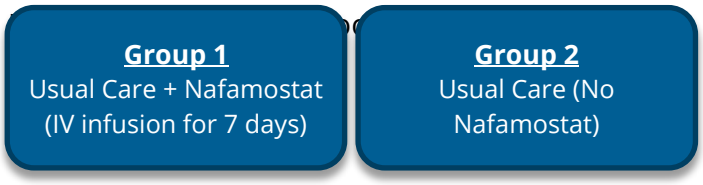
- Nafamostat is a medicine that might stop the virus from multiplying by blocking the virus from entering human cells
- Laboratory studies had shown that Nafamostat had higher activity against the virus than other medicines.
- Laboratory studies also showed that Nafamostat could have blood thinning properties, which may help treat blood clots that have been associated with COVID-19 disease.

Nafamostat has been safely used in humans for other conditions, such as pancreatitis, but has not yet been approved for use in COVID-19.

Methods

The methods section of a paper describes how the study was done and explains how the results were analysed.

Patients who agreed to participate in the Antiviral Domain were randomly allocated (like the toss of a coin) to either receive Nafamostat for up to 7 days by intravenous (IV) infusion, or to not receive Nafamostat.



Data Analysis

The data were analysed using a type of statistics called *Bayesian Statistics.*

Posterior Probability

Posterior probability is a Bayesian term to describe the probability an event will happen based on the evidence we have (in this case, the data from the Antiviral Domain).

Before the trial started, we made a *statistical decision* that if there was a 99% posterior probability that receiving Nafamostat reduced the likelihood of the *primary outcome* occurring (when compared to not receiving Nafamostat) we would be highly confident it was a better treatment.

Primary Outcome

The *primary outcome* of a study is the most important measure of whether a treatment is better than another. In the ASCOT study, we wanted to know if after 28 days, the participant:

- Had died
- Needed any breathing support (such as a *ventilation mask* or a *ventilator*)
- Needed any powerful medication (called *vasopressors and inotropes*) to maintain an adequate blood pressure

If a participant meets any of the 3 points above, they are considered to have *met the primary outcome*.

Secondary Outcomes

Secondary outcomes are other measures that are important to document during the study. Because this kind of medication may have side effects, the following *safety events of interest* were also monitored:

Hyperkalaemia

Elevated potassium levels (too much potassium in your blood)

Receiving Nafamostat may increase potassium levels, so it was important that this was monitored for possible harm.

Bleeding Events

Events that can occur as a result of the blood thinning properties of a mediction

Receiving Nafamostat may make you more likely to have bleeds, so it was important that this was monitored for harm.

If a participant meets any of the 2 points above, they are considered to have *met a secondary outcome*.

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Results

The section of the paper that summarises what was found when the study data was analysed by statisticians.

We analysed data from 160 patients who participated in this part of the ASCOT study.

Primary Outcome

The following percentage of participants in each group were recorded as having *met the primary outcome* (which is a bad outcome):

Usual Care + Nafamostat
5% met primary outcome
4 out of 82 participants

Usual Care (No Nafamostat)
11% met primary outcome
8 out of 73 participants

Secondary Outcomes

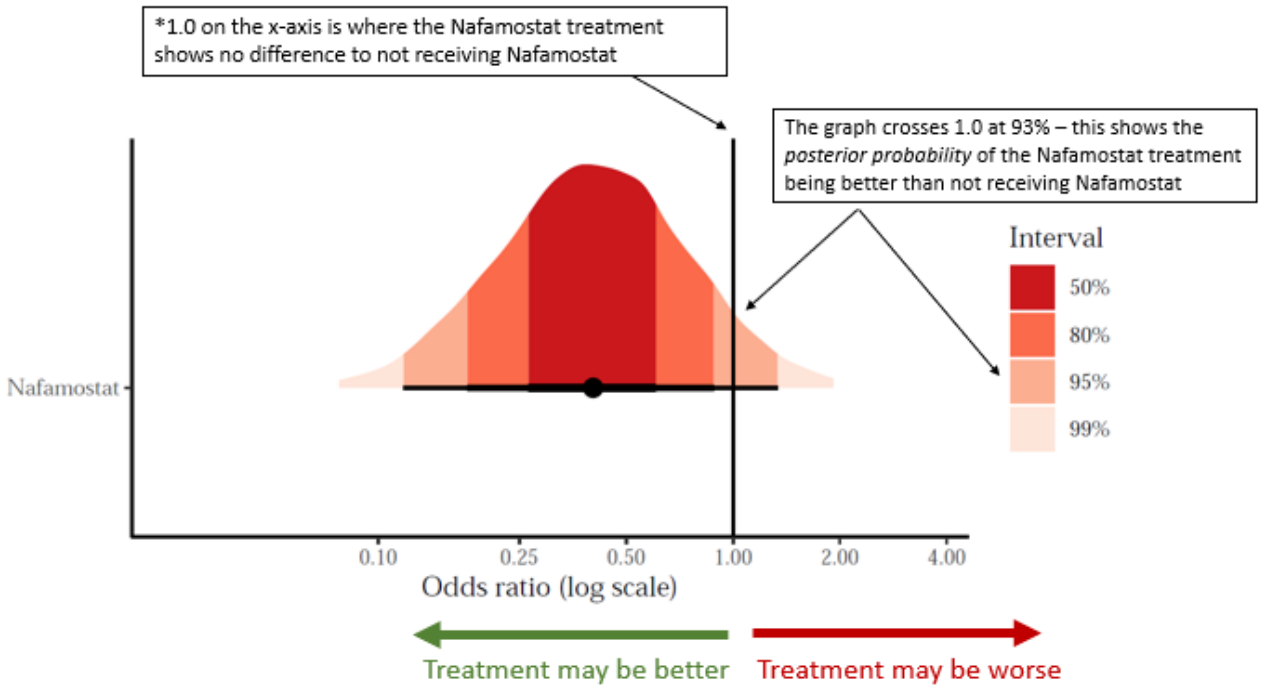
The following percentage of participants in each group were recorded as having *met a secondary outcome of experiencing a safety event (side effect) of interest:*

Usual Care + Nafamostat
9% experienced hyperkalaemia
8% experienced a bleeding event

Usual Care (No Nafamostat)
1% experienced hyperkalaemia
1% experienced a bleeding event

Posterior Probability

There was an 93% *posterior probability* that Nafamostat was effective at reducing the odds of the primary outcome occurring, compared to not receiving Nafamostat. The odds ratio graph (*below*) shows the likelihood of nafamostat being either better or worse than not receiving Nafamostat.



Discussion

The discussion describes what the results of the study mean, how accurate the results are, if there were any limitations of the study, and if any other things were found out that may be important.

In summary, the fewer participants that reach the *primary outcome*, the better the treatment is. Only 5% of participants who received Nafamostat *met the primary (bad) outcome*, compared to 11% who did not receive Nafamostat. This could mean that Nafamostat may be better.

However, although fewer participants who received Nafamostat met the primary (bad) outcome, more of those participants met the *secondary outcome of experiencing a safety event (side effect) of interest.*

- *Hyperkalaemia*: 9% of participants who received Nafamostat experienced this side effect. It did not result in any harm and was resolved by stopping the Nafamostat.
- *Bleeding events:* 8% of participants who received Nafamostat experienced this side effect. It is important to note that all these participants were also receiving anticoagulation (blood-thinning) medication as well, which may have contributed.

We usually look for at least a 95% (and often 99%) *posterior probability* before we make a strong recommendation for a treatment. Because there was a *93% posterior probability,* these results show moderate evidence that Nafamostat may be better.

Importantly, these results were based on data from only a small number of participants (160 total) because the study had to be stopped when Covid-19 became a milder illness, and fewer patients were coming to hospital with Covid-19. More participants would provide more data which in turn, may have provided more certainty about the results.

Given the small numbers of study participants and higher rates of side effects, stronger evidence of its effectiveness is needed before we can recommend Nafamostat as a treatment for patients with COVID-19. It might work, but we can't be sure.

Publication

Morpeth, Susan C., et al. "Nafmostat for COVID-19: a randomised clinical trial." *NEJM Evidence* (2023): DOI: 10.1056/EVIDoa2300132

More information

For more information on the ASCOT study and the results from the Antiviral Domain, please refer to the study website: https://www.ascot-trial.edu.au/

Glossary

There are a few other statistics terms that may help you make sense of the manuscript:

- *Odds ratio* – An odds ratio (OR) calculates the relationship between a variable and the likelihood of an event occurring. A common interpretation for odds ratios is identifying risk factors by assessing the relationship between exposure to a risk factor and a medical outcome.
- *Adjusted odds ratio* – an odds ratio that controls for other variables and is used to control for bias. In real life, it's rare to have a very clear relationship between a variable and an outcome.