

13 April 2021

## **BRIEF19**

*A daily review of covid-19 research and policy*

### **RESEARCH BRIEFING**

#### **Inhaled steroids may prevent disease progression in mild covid-19.**

An important randomized clinical trial (RCT) recently [published](#) in *The Lancet* assessed the role of inhaled steroids in the treatment of covid-19. Of all of the proposed treatments for covid-19, inhaled steroids have been seen as among the most likely to be successful, since dexamethasone, another steroid taken by mouth or intravenously, was the first treatment to demonstrate improvement in mortality in patients with moderate to severe covid-19. Given that covid-19 pneumonia is a respiratory tract infection, researchers assessed whether inhaled steroids would have a net positive effect. The upshot is that the inhaled steroid that was studied, called budesonide, appears to have had a favorable effect in treating mild covid-19. But the reality is that this trial had some important methodologic issues that make this declaration a somewhat less definitive than we had hoped. So, while this is a moment for optimism—indeed positive randomized trials of old medications being repurposed have been few-and-far-between, it's crucial that we understand the design and limitations of this particular trial.

In this study, 146 patients were randomized to receive either inhaled budesonide (a steroid medication) or no inhaled budesonide. Subjects were included if they sought medical attention within 7 days of the onset of mild covid-19 symptoms. Mild covid-19 symptoms were defined as new onset cough and fever, loss of smell, or both, without the need for supplemental oxygen. The primary outcome of the study was defined as subsequent covid-19-related urgent care visits, emergency department visits, or hospitalizations.

Before we get to the results, a little digression on research methods is necessary. The authors shared the results of two distinct analyses: the per-protocol analysis and the intention-to-treat (ITT) analysis. Per-protocol analysis means that only data from the patients who actually completed the treatment as intended are considered. Conversely, ITT data includes *all* patients who were randomized to receive the treatment, regardless of whether or not they actually received or finished it. [Per-protocol](#) analyses are considered ideal for studying adverse events of medications. But when per-protocol data are used to assess whether a treatment “worked,” potential biases can be introduced that muddy the picture. For example, a test subject who did not finish the treatment that they were assigned to receive is often not a random event. Meanwhile, [ITT](#) is considered the more ideal analysis for assessing the effectiveness of a treatment. That may seem strange; why include data from patients who may not have actually received the treatment in the treatment group? The reason is that doing it this way reduces bias. By keeping the patients in the groups that they were initially assigned to be in, the investigators maintain the comparability between groups that was achieved through the process by which the subjects were randomized to receive either the steroid, or not. In this study, the authors presented *both* analyses.

In the intention-to-treat analysis, 3 percent of participants randomized to receive budesonide needed further medical care compared to 15 percent of patients in the non-budesonide group; the difference was statistically significant. In the per-protocol analysis, however, inhaled budesonide failed to decrease the further need for medical care. Based on these data, the authors determined that the number of patients who would need to be treated in order for one patient to not need further medical care was 8. In medical trials, this is actually quite impressive.

Other (“secondary”) outcomes in this study were maintained mostly through surveying the patients enrolled in the trial. Overall, patients in the inhaled budesonide group recovered on average one day faster, had fewer days with fevers, and were less likely to have symptoms at days 14 and 28 as compared to no inhaled budesonide group. Overall, only 7 percent of the study participants reported self-limited adverse events, suggesting that inhaled budesonide is safe.

As with all trials, there are some imperfections to acknowledge. In this case, the most important of these is that the primary outcome did not directly assess mortality but instead assessed needed for “further medical care.” Another limitation of this study is that the patients enrolled were overall fairly healthy in comparison to the general population, which may limit generalizability of these results. It’s possible the sicker patients—the very ones we are most interested in helping—may have smaller or larger benefits from budesonide.

Nevertheless, the lack of need for further medical care can be considered a surrogate for disease progression, and it appears that inhaled budesonide may prevent progression of covid-19 severity in otherwise fairly healthy patients presenting within the first seven days of mild illness.

—Joshua Niforatos, MD, MTS

## **POLICY BRIEFING**

### **Supreme Court blocks California's restrictions on religious gatherings in private homes.**

Last Friday, in a 5-4 vote, the United States Supreme Court blocked California’s restrictions on religious gatherings in private homes. This decision marks the fifth time that the Supreme Court has sided with religious adherents against California’s covid-19 restrictions. California’s policy limited both religious and non-religious gatherings in homes to no more than three households in an effort to limit transmission of SARS-CoV-2. A pastor and others asked the court to allow them to hold Bible study and prayer meetings in their homes without limits on the number of households that could attend.

A Ninth Circuit Court of Appeals panel had previously ruled that because the state treated secular and non-secular groups alike with respect to restrictions on home gatherings, the state restriction was constitutional. The Supreme Court’s majority challenged the neutrality of these laws, writing that “regulations are not neutral and generally applicable, and therefore trigger strict scrutiny under the Free Exercise Clause (i.e. freedom to practice religion), whenever they treat any comparable secular activity more favorably than religious exercise” and that “[i]t is no answer that a State treats some comparable secular businesses or other activities as poorly as or even less favorably than the religious exercise at issue.”

In her dissent, Justice Kagan (joined by Justices Breyer and Sotomayor) argued that “[i]f the State also limits all secular gatherings in homes to three households, it has complied with the First Amendment. And the State does exactly that...” Kagan noted further that California’s law does not single out religious gatherings but simply treats all at-home gatherings differently than it does commercial spaces. Kagan wrote that the reason for the distinction between at-home gatherings and commercial spaces is that gatherings in private homes are riskier because of the more intimate and prolonged way people gather in them, thus raising the possibility of viral transmission.

Up until early 2021, after the arrival of Justice Amy Coney Barrett, the Supreme Court had generally (by 5-4 votes) deferred to the judgments of health departments and scientists when ruling on covid-19 restrictions. For example, prior to Justice Ruth Bader Ginsburg’s death in fall 2020, the Supreme Court had allowed California and Nevada to restrict religious attendance, with Chief Justice Roberts siding with the then-four liberal justices. That pattern shifted with Barrett’s arrival.

Since then, the Supreme Court has also blocked New York's covid-19-related restrictions on religious services.

Many Conservatives have hailed the New York and California rulings by the Supreme Court ruling as a victory for freedom to worship. However, these wins comes amid an effort to curb viral transmission as the nation continues to expand its vaccination rollout in the midst of increasing concerns about the spread of new coronavirus variants of concern, some of which have the potential to extend this crisis even further.

—*Miranda Yaver, PhD*

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