Researchers identify a promising drug for treating serious COVID-19 complication in children

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Scientists at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) have identified a promising drug candidate

for the treatment of multi-inflammatory syndrome in children (MIS-C), they report in Clinical Care Explorations. MIS-C is a rare but severe and potentially life-threatening condition that usually develops in children weeks to months after they have experienced a mild or even asymptomatic case of COVID-19.

MIS-C occurs mainly in children and leads to high fevers and a hyperinflammatory response that can affect multiple organs, including the heart, brain and gastrointestinal organs. Symptoms include stomach pain, diarrhea, vomiting, dizziness and rash. Fifty-five of the 6,431 children diagnosed with MIS-C have died since May 2020, according to the Centers for Disease Control and Prevention.

A previous study by researchers from MGH and BWH showed that in cases of MIS-C, the SARS-CoV-2 virus, which causes COVID-19, can remain in the gut for weeks to months after the infection. When SARS-CoV-2 is present in the gut, an impaired mucosal barrier can allow small viral particles, such as the spike protein, to enter the bloodstream, leading to infections such as COVID-19 and in rare cases, the hyperinflammatory response that triggers MIS-C.

"Working collaboratively, we've been able to demonstrate that viral particles that remain in the gut long after COVID-19 infection can instigate MIS-C," says co-senior author David Walt, Ph.D., principal investigator of the Walt Laboratory in the Brigham's Department of Pathology. "Building on this important discovery, we wanted to see if treatment with a drug developed for another condition—celiac disease—could help resolve symptoms in children experiencing MIS-C."

Based on these findings, the team administered the drug larazotide acetate to four extremely ill children ages three to 17 being treated for MIS-C at MGH. Larazotide decreases the release of zonulin, a molecule that can lead to increased gut permeability and an impaired mucosal

barrier. The researchers compared the clinical outcomes of the four children who received larazotide plus steroids and intravenous immune globulin (IVIG) to 22 children who received only steroids and IVIG.

The children who received four daily oral doses of larazotide acetate had a significantly faster resolution of gastrointestinal symptoms and a slightly shorter hospital stay. Serum levels of the highly inflammatory spike protein associated with the SARS-CoV-2 virus dropped much more quickly in children treated with larazotide, clearing from the blood within one day, versus 10 days for children not treated with larazotide.

"These findings suggest that larazotide may provide a safe and beneficial adjuvant therapy for the treatment of MIS-C," state the authors in the new paper. Adds lead author Lael Yonker, MD, pediatric pulmonologist and director of the Cystic Fibrosis Center at MassGeneral Hospital for Children (MGHfC): "Our results demonstrate the urgent need for the development of diagnostic and prognostic tools to advance our understanding and treatment of this devastating disease."

Yonker, with the support of Alessio Fasano, MD, director of the Mucosal Immunology and Biology Research Center and chief of the Division of Pediatric Gastroenterology and Nutrition at MGHfC, first applied to the FDA for emergency compassionate use of larazotide in the treatment of MIS-C in February 2021. With the approval of parents, the clinicians successfully administered larazotide to several severely ill children who were not responding to the prescribed therapies. Yonker and Fasano, along with colleagues from MGH, the Walt Laboratory at BWH and other institutions, published their results in July 2021 about earlier clinical successes with larazotide.

An expert in celiac disease and autoimmune disorders, Fasano developed larazotide acetate in the early 2000s as an adjunctive treatment for celiac disease. Larazotide is currently in Phase 3 human clinical trials for this

purpose. Given its outstanding safety profile and early success in treating gastrointestinal complications of MIS-C, Yonker and Fasano initiated a clinical "proof of concept" randomized, double-blind, placebo-controlled study in August 2021 to evaluate the efficacy of larazotide acetate for children hospitalized with MIS-C at MGH.

The latest research is the cumulative result of "a strong team effort," notes Fasano. "We connected the dots to capitalize on the ongoing research related to the activation of the zonulin pathway in a variety of inflammatory conditions." Recent research includes findings that demonstrate how closely MIS-C resembles Kawasaki disease, another inflammatory condition in children.

"Kawasaki disease is caused by a zonulin-dependent mechanism that has a similar effect upon important organs, including the heart and gastrointestinal system," says Fasano. "This led us to the conclusion that a similar mechanism can also be at play in MIS-C. It was only logical to propose the compassionate use of larazotide in kids affected by MIS-C," he says, adding that clinical results with a small number of children have been "so promising that the FDA gave us the green light last August to start a clinical trial in children admitted to MGH who are affected by MIS-C."

"What makes our approach unique is that we have been able to identify the zonulin-dependent leak of the spike protein from the gut lumen into the circulatory system. This provides us not only with a diagnostic tool by searching for the spike protein in blood but also with a therapeutic target of blocking zonulin-dependent increased gut permeability to treat this serious complication of COVID-19 infection," says Fasano.

The research was published in *Critical Care Explorations*.

More information: Lael M. Yonker et al, Zonulin Antagonist,

Larazotide (AT1001), As an Adjuvant Treatment for Multisystem Inflammatory Syndrome in Children: A Case Series, *Critical Care Explorations* (2022). DOI: 10.1097/CCE.0000000000000641