Studies Demonstrate Use of Gentian Calprotectin Test to Triage COVID-19 Patients

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NEW YORK – Based on studies demonstrating the utility of calprotectin as a tool to predict which COVID-19 patients may need intensive care, Norwegian *in vitro* diagnostic firm Gentian plans to position its test as an alternative to conventional enzyme-linked immunosorbent assays, or ELISAs.

Two recent studies, which relied on Gentian's calprotectin immunoassay, have showcased the use of assaying the biomarker calprotectin to determine which COVID-19 patients will likely progress to severe disease and require intensive care. Based on the studies, Moss, Norway-based Gentian – whose test runs on standard chemical analyzers on the market and has a turnaround time of about 10 minutes – believes its test can be used in place of ELISAs, which are conventionally used to measure the marker in blood but can take hours to deliver a result.

"There is a lack of capacity for ICU beds and ventilators," said Aleksandra Mandic Havelka, director of clinical affairs for Gentian Diagnostics AB, the company's Stockholm, Sweden-based subsidiary which sells and supports the test. "In this difficult time, it is helpful to have a biomarker that can predict who will develop severe COVID-19 with hyperinflammatory host response," she said. "We see a huge value in the biomarker in the management of COVID-19 patients."

Calprotectin has been used as a marker for inflammation since the 1980s, but it has not been widely adopted in the clinic as it has a sluggish turnaround time and is run manually using ELISAs. Gentian launched its test for the marker in 2017, relying on an internally developed particle-enhanced, turbidimetric approach, which allows it to deploy the test on chemical analyzers in the market, such as Roche's Cobas c501/502, Mindray's BS-200E, or Abbott's Architect.

While the assay is used to predict inflammatory response in a host of conditions, such as sepsis, when the COVID-19 pandemic began, Gentian saw an opportunity to use the assay to gauge severity in patients with SARS-CoV-2, and several studies involving Gentian's test commenced.

Mandic Havelka, who is also an investigator at Karolinska Institute, is an author on one of these new studies, which was presented last month at the annual meeting of the American Association for Clinical Chemistry, broadcast online.

For the study, which also involved researchers from Uppsala University in Sweden, the investigators monitored calprotectin levels using Gentian's assay in 121 patients with COVID-19 infections admitted to Uppsala University Hospital, as well as 10 controls, non-infected cancer patients in the same ICU. They also monitored levels of the antigen e-selectin using an ELISA sold by R&D Systems of Minneapolis used to determine endothelial cell damage.

They found that the COVID-19 patients had higher levels of calprotectin in their blood compared to case controls and there was a positive correlation between calprotectin and e-selectin. The researchers concluded that as calprotectin is released very rapidly in response to infections, it could serve as an early marker in COVID-19 infections, as well as a predictor of endothelial cell damage and organ failure.

"Calprotection was able to distinguish between COVID-19 and non-COVID-19 severely ill patients with great sensitivity and specificity," said Mandic Havelka of the study.

Meantime in Cartagena

Additionally, researchers from Hospital Universitario Santa Lucia in Cartagena, Spain, also used Gentian's GCAL calprotectin assay to measure levels of the biomarker in patients suffering from COVID-19. The work, which included contributions for researchers at Hospital Universitari Son Espases in Palma de Mallorca, Spain, as well as the Karolinska, was also discussed at AACC.

In the study, the researchers assessed calprotectin levels and their correlation with in-hospital mortality and the need for mechanical ventilation in COVID-19 patients. As part of the study, they also looked at C-reactive protein levels in patients, as well as levels of D-dimer, another biomarker associated with inflammation. The Spanish researchers ran the Gentian assay on Roche's Cobas c 502 instrument. Altogether, 66 COVID-19 patients were assessed. The mortality rate was 12 percent, while 14 percent of the patients required mechanical ventilation. Calprotectin, CRP, and D-dimer levels were all higher in patients who died, as well as those who required ventilation.

The investigators included that calprotectin might have a potential role in the assessment of prognosis in COVID-19 patients. "As one of the earliest biomarkers for neutrophil activation, calprotectin is of special interest for the early identification of patients at risk for development of severe events and mortality," they said, while urging additional investigations of the findings.

Luis García de Guadiana-Romualdo, an investigator at the Hospital Universitario Santa Lucía in Cartagena, said the study demonstrated the clinical applicability of Gentian's calprotectin assay.

"There are ELISA methodologies to measure calprotectin, but the problem with this type of assay is its lack of practicality for an emergency laboratory, where calprotectin, as a marker of inflammation and infection, can be useful," said García de Guadiana-Romualdo.

ELISA "is a poorly automated methodology that requires long times for sample processing and is less precise," he said. "The availability of tests such as Gentian's, based on turbidimetry, would allow their incorporation into emergency laboratories with an adequate turnaround time."

Before that happens though, more studies are needed to confirm these preliminary findings, García de Guadiana-Romualdo stressed. "More studies are necessary to validate the initial results in infectious pathology, as well as to assess the usefulness of this marker for the monitoring of antibiotic therapy," he said.

Mandic Havelka noted that the Spanish study was significant as it also assessed CRP levels in patients. She noted that calprotectin is a "much faster biomarker" for inflammation and infection, as it presents earlier in patients, making it "better suited for making urgent decisions" in caring for COVID-19 patients.

She added that research into the application of the Gentian assay in COVID-19 continues. "We will continue to do more research, to do additional studies, and to do studies in North America," said Mandic Havelka, declining to name US partners at this time. The GCAL assay has obtained a CE-IVD mark in Europe, but is available in the US for research use only.

Gentian has also been collaborating with investigators at Charité – Universitätsmedizin Berlin, who are using the calprotectin assay to predict disease prognosis in COVID-19 patients. The investigators detailed the work in a letter to the editor in the *Journal of Infection* in November.

As part of the work, they measured calprotectin levels in 66 patients admitted to the hospital with suspected COVID-19, 19 of whom turned out to be positive for the disease. Of multiple markers assessed, calprotectin proved to be the best predictor of multiple organ failure, they reported.

"Our data strongly argue for calprotectin representing a valuable biomarker for risk stratification, in particular with regard to subsequent" multiple organ failure, the investigators wrote in the letter, noting that measuring calprotectin in blood is "easily applicable in routine laboratories."

Mandic Havelka said Gentian hopes the visibility gained via these new studies will "open the doors for routine use in COVID-19" in the future. She said the company is open to exploring new collaborations.