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Hematologists Play Vital Role in Advancing COVID-19 Research, Potential Treatments

New studies seek to identify patients most vulnerable to severe COVID-19 illness, develop off-the-shelf treatments to boost immune responses for some patients

(WASHINGTON, Dec. 5, 2020) – There are now millions of cases worldwide of COVID-19 infection, caused by the new virus SARS-CoV-2. As cases continue to soar, researchers around the globe are working urgently to identify risk factors and possible treatments.

People with blood disorders and underlying immune deficiencies are at heightened risk of severe COVID-19 infection. In addition, many chemotherapies, immunotherapies, and stem cell transplants used to treat these diseases further suppress the immune system, and it has been established that COVID-19 infection can trigger clots and other hematologic complications in some individuals. The global hematology community continues to leverage specialized labs, knowledge, and treatments to help predict high-risk groups and improve treatment options, and ASH has remained committed to sharing the latest COVID-19 resources to guide not only hematologists but all those on the front lines of COVID-19 patient care. Included among the resources is the ASH COVID-19 Research Agenda, which includes key questions that experts in hematology and blood research deem of critical importance to researchers, physicians, and patients.

Three studies being presented today during the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition offer glimpses into the complexities of COVID-19 infection, who is at greatest risk of severe illness and complications, and a potential off-the-shelf T-cell-based treatment.

“Taken together, these studies show the multiple approaches that are being pursued to try to understand the risks to these patients and what role genetics may play, as well as applying our knowledge of how T cells work to help create therapies that enable stronger immune responses to COVID-19 infection,” said press briefing moderator **Alisa Wolberg, PhD,** of University of North Carolina at Chapel Hill. “Information to help us predict who will have a severe disease course versus who most likely won’t has huge implications for understanding the basic biology of this disease and to risk stratify patients for treatments.”

The first of the three studies sheds light on which individuals with blood cancers are most vulnerable to severe illness and death based on an ongoing global public reference tool from the ASH Research Collaborative offering real-time data summaries to help guide treatment approaches. A second study detected the presence of several harmful genetic variants in patients hospitalized with COVID-19 that may be associated with increased susceptibility to severe COVID-19 illness. In a third study, researchers were able to build banks of SARS-CoV-2-specific T cells obtained from people who recovered from the virus that are now being studied for potential curative effects in hospitalized patients.

"Our collective knowledge of this virus is rapidly evolving, and it's critically important for us to uncover why some people have such serious illness and complications and others do not," said Dr. Wolberg.

This press briefing will take place on Saturday, December 5, at 8:00 a.m. Pacific time on the ASH annual meeting virtual platform.

Genetic Variants May Explain Why Some People with COVID-19 Have Severe Illness and Others Do Not
376*: Thrombotic Microangiopathy Variants Are Independently Associated with Critical Disease in COVID-19 Patients*

Why some people infected with COVID-19 have few or no symptoms and others become gravely ill continues to puzzle clinicians around the world. One area of inquiry is whether certain genetic mutations might influence the course of COVID-19 for some patients.

Researchers in Greece have, for the first time, found that variants in several complement-regulatory genes and ADAMTS13 that are traditionally associated with an acute, life-threating syndrome called thrombotic microangiopathy (TMA) are also present in a subset of patients who were hospitalized with severe COVID-19, many in the intensive care unit (ICU). In fact, one out of three patients in the study were found to have a combination of these variants or mutations.

Complement is a normal process of our immune systems that helps fight against bacteria, pathogens, and viruses. But for people with certain germline genetic variants – mutations they were born with, but that remain inactive – a triggering event, for example, systemic inflammation or a virus, can spur an overactivation of complement that can trigger TMA. Similar to what clinicians are seeing in some cases of severe COVID-19, TMA is characterized by clots in the small vessels in major organs, most commonly the kidneys. Researchers explain that in COVID-19 infection, the disease targets the lungs. Interestingly, many patients with TMA do not have any underlying conditions, so the genetic variants are thought to play a defining role.

"There are studies confirming complement overactivation in COVID-19, which may be due to the virus itself or to patients' genetic susceptibility, and that is what we studied," said hematologist and principal investigator of this study, **Eleni Gavriilaki, MD, PhD**, of George Papanikolaou General Hospital, Thessaloniki, Greece. "We found that people with TMA-associated mutations may have a genetic susceptibility to severe COVID-19 illness with an increased rate of being hospitalized in the ICU compared to patients who were hospitalized but recovered from a more normal course. Our study also confirms complement is a double-edged sword; it can be good or bad for some people."

This prospective study included 60 consecutive adult patients (34 males and 26 females) hospitalized with confirmed COVID-19 between April and May 2020. Severity of COVID-19 was classified as either moderate to severe or critical disease based on the World Health Organization's (WHO) criteria, and additional information on patients' history and course were recorded up until discharge or death. Researchers obtained patients' DNA from peripheral blood samples and conducted next-generation sequencing, a molecular method that helps read the genome of certain genes, specifically 11 known to be associated with TMAs (complement factor *H/CFH*, CFH-related, *CFI, CFB, CFD, C3, CD55, C5, MCP, thombomodulin/THBD, ADAMTS13*) and then compared it to the normal human genome to see whether the patient had any variants or mutations.

Of the 60 patients hospitalized with COVID-19, 40 (66%) had moderate/severe disease and 20 (34%) had critical disease that required treatment in the ICU. A total of 11 patients (18%) died from COVID-19 disease during the study period.

Researchers identified five complement-related variants that seemed to play a role in more severe COVID-19 illness, including one gene that is related to both complement and coagulation (clotting) that may explain more of the thrombotic profile of COVID-19, which was found in one-third of patients, most of whom were in the ICU. Seven – or 11.7% of patients – carried one harmful or likely harmful variant in one of these genes. The harmful variant *ADAMTS13* (rs2301612, missense) was found in 28 (46%) patients. Researchers also detected two variants, previously detected in complement-related diseases: rs2230199 in *C3* (13 patients); and rs800292 in *CFH* (26 patients). Among them, 22 patients had a combination of these characterized variants. This combination was significantly associated with critical disease that required intensive care, as well as with other markers of disease severity (low lymphocyte counts and high neutrophil-to- lymphocyte ratio). Researchers also identified a protective variant in five patients, none of whom required ICU level care. Interestingly, the data showed men had a higher frequency of variants associated with more severe COVID-19 infection, which upon further research may help explain why men with COVID-19 tend to suffer worse outcomes than women.

Being cared for in the ICU was found to independently predict that a patient would have at least two variants, suggesting that certain variants could be selected for a molecular test to help clinicians identify high-risk patients in clinical practice, said Dr. Gavriilaki. This is important information as researchers look to develop new algorithms or genetic assays to help clinicians determine whether a patient has a mutation that would warrant receiving more close monitoring and aggressive COVID-19 treatment. Ongoing analyses of the data, which will include additional patients, will investigate what variants were associated with death.

The team hopes these findings will bolster studies investigating whether complement inhibitors may be another potential treatment for some patients with COVID-19.

“Inhibitors are a category of medicines that we know are safe and effective, and they could potentially work for some COVID-19 patients by attenuating excessive thrombotic and inflammatory responses,” Dr. Gavriilaki said, adding that there are now clinical trials underway to test their efficacy. G Papanikolaou Hospital is participating in a phase III study of the complement inhibitor AMY-101 in Greece.

“These are important because even when we have the vaccine, people who are immune-compromised are expected to still have serious and critical COVID-19 infection and we need to find ways to help these patients in the long-term,” she said.

Eleni Gavriilaki, MD, PhD of George Papanikolaou General Hospital, Greece, will present this study in an oral presentation on Sunday, December 6, at 12:00 noon Pacific time on the ASH annual meeting virtual platform.

Feasibility Study Paves Way for First U.S. Clinical Trial of Off-the-Shelf T cells Aimed at Boosting COVID-19 Immune Response in High-Risk Patients
612*: Using Allogeneic, Off-the-Shelf, Sars-Cov-2-Specific T Cells to Treat High Risk Patients with COVID-19*

Researchers have successfully built banks of SARS-CoV-2-specific T cells obtained from people who recovered from the virus that are now poised to be used as an experimental treatment in patients hospitalized with COVID-19. This T-cell-based therapy represents a promising step forward in the search

for treatments against COVID-19, especially for patients who are more vulnerable to severe COVID-19 infection and complications because they lack these natural virus-fighting immune cells.

“This approach could be critical in the treatment of COVID-19 given emerging evidence that people who are at the highest risk for needing mechanical ventilation or of dying have underlying T-cell deficiencies,” said lead author **Spyridoula Vasileiou, PhD**, of the Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, and Houston Methodist Hospital, adding that lower T cell counts and dysregulation have been more common in patients with severe versus mild COVID-19 disease.

The team has previously demonstrated the feasibility, safety, and efficacy of administering similar off-the-shelf multivirus-specific T-cell products for BK virus, cytomegalovirus, and three other viruses. They sought to do the same with SARS-CoV-2 by first studying immunity to this virus in people in the community who were exposed to and were able to clear the virus on their own. They identified various parts or proteins of SARS-CoV-2 that their immune systems targeted and used these proteins to grow SARS-CoV-2-specific T cells in the lab at high selectivity and high potency.

“We were able to generate these off-the-shelf T cells at very large numbers, so they are ready and immediately available to patients in need,” said Dr. Vasileiou.

T cells fight viruses in two ways – helper T cells spur B cells and other immune defenders into action and killer T cells seek out and destroy virus-infected cells. These SARS-CoV-2-specific T cells are designed to attack the virus on multiple fronts by targeting a range of SARS-CoV-2 proteins, not just the SARS-CoV-2 spike protein that allows the virus to enter cells. Based on the results of their laboratory tests, the researchers are optimistic that this treatment will boost the immune system in high-risk COVID-19 patients to help them fight the infection.

“By targeting multiple proteins, we are trying to hit the virus hard at multiple different points in its life cycle to be able to very effectively and efficiently eliminate virally infected cells in patients with COVID-19,” said Dr. Vasileiou. “Because these SARS-CoV-2 VSTs are living cells, when we infuse them into patients, the cells will expand in number, migrate to cells infected with the virus, and selectively eliminate them.”

A trial is now underway at Houston Methodist Hospital to determine the safety and optimal (or maximal-tolerated) dose of these SARS-CoV2-specific T cells (SARS-CoVSTs) in hospitalized patients with COVID-19 who are at high risk of requiring mechanical ventilation, including those who have some underlying immune T-cell deficit that is putting them at high risk of severe illness and death. This study will be followed by a randomized pilot trial comparing the administration of this therapy to routine care treatment. If the therapy proves effective, Dr. Vasileiou explained that this treatment may fill an important gap – even after a vaccine becomes available.

“In general, vaccines are preventive agents developed to induce an antibody or B cell response, but these patients who already have the disease have some sort of T-cell deficit where something is going on in the background that renders them unable to marshal a strong immune response,” she said. “So building banks of SARS-CoV-2 specific T cells from healthy individuals who were already able to efficiently fight off the virus should give their immune system a boost.”

She explained that at present – and with no current vaccine – is estimated that about 20% of individuals who get in infected with SARS-CoV-2 require hospitalization due to the virus and could be potentially eligible for this type of therapy. Once vaccines are available, this number is will improve, but therapeutic agents like off-the-shelf T cells will still be needed to treat patients who, despite the vaccine, still develop severe illness from COVID-19.

This study was sponsored by AlloVir.

Spyridoula Vasileiou, PhD, of Baylor College of Medicine, Texas Children's Hospital, will present this study in an oral presentation on Monday, December 7, at 9:00 a.m. Pacific time on the ASH annual meeting virtual platform.

Certain People with Blood Cancers and COVID-19 Infection Vulnerable to Severe Illness, Death
215*: Outcomes of Patients with Hematologic Malignancies and COVID-19 Infection: A Report from the ASH Research Collaborative Data Hub*

A study of 656 people with various types of blood cancers who also had COVID-19 infection found that one out of five had died between April and November, based on an analysis of data from the ASH Research Collaborative COVID-19 Registry for Hematology. For those who needed hospital- or ICU-level care, 33% died. This international registry, which launched in April, is giving near real-time data to hematologists and other clinicians who are caring for patients amid the pandemic and offering important insights into which patients are most vulnerable to severe illness and death.

“We have seen and continue to see that individuals with hematologic malignancies and COVID-19 infection appear to have more severe illness and a higher likelihood of death compared to the general population,” said lead study author, **William A. Wood, MD, MPH**, of the University of North Carolina at Chapel Hill. “This heightened risk of severe infection or death among these patients is concentrated in certain groups of individuals, and data from our global registry has helped to understand this more clearly.”

In particular, people with blood cancers who had the highest likelihood of dying 1) were older, 2) had more severe COVID-19 infection, 3) had opted to forgo more intensive treatment, such as the intensive care unit (ICU), and/or 4) had poorer prognosis before their COVID-19 infection as determined by their treating clinician (less than 12 months at the time of COVID-19 diagnosis). Patients with relapsed/treatment-resistant hematologic disease also appear to be disproportionately more likely to develop moderate to severe COVID-19 infection and death.

“This analysis highlights that patients with hematologic diseases are a medically vulnerable population [when it comes to] COVID-19 infection. It underscores the need for us to continue to encourage our patients to take appropriate precautions to limit exposure to COVID-19, to continue to take precautions in our health care delivery environment to protect these patients, and to prioritize these patients for COVID-19 testing as well as vaccine distribution, once efficacious and safe vaccines are available,” said Dr. Wood. “On the other hand, we also saw that many patients with hematologic malignancies survived COVID-19 infection, including some who had severe disease and received ICU-level care. For this reason, it seems appropriate to pursue maximal care delivery for these patients as long as it aligns with patient preferences.”

The present analysis includes registry data for 656 patients (77% aged 40 and older) with various types of blood cancers collected between April and November from over 100 study sites around the world. Of these, 20% died. The most represented malignancies were leukemia (57%), lymphoma (25%), and plasma cell dyscrasia (18%). Patients, who had a laboratory-confirmed or presumptive diagnosis of SARS-CoV-2 infection, presented with a myriad of symptoms, most frequently fever (65%), cough (56%), dyspnea (39%), and fatigue (31%).

Since its launch, the Registry has quickly accrued data, and researchers have been able to track how therapies to treat COVID-19 have evolved and shifted over time, with many patients with hematologic

malignancies having received azithromycin (143 patients), hydroxychloroquine (137 patients), convalescent plasma (45 patients) or remdesivir (44 patients).

It is expected that as more patient data is accrued over longer periods of time, researchers can track trends that can help guide practice and treatment decisions and ask more specific questions of the data. For example, the registry data could shed light on how patients with leukemia who have received specific therapies within a month of acquiring COVID-19 infection fare overall and whether their disease course is different. The Registry will also allow clinicians to gain insights into potential regional differences in outcomes as well as the effects of other sociodemographic variables including race and ethnicity.

“This is a collaborative, global effort. We were able to launch this resource quickly and with a spirit of volunteerism and collaboration from around the world. Hematologists recognize the value of these data and continue to contribute cases,” Dr. Wood said. “These data have given us a first look into how COVID-19 infection affects patients with blood cancers and will continue to provide actionable information to guide health care delivery during this time.”

Still, the database has some inherent limitations in that it is voluntary, so it does not capture all known cases of patients with blood cancers and COVID-19 infection. Dr. Wood said that this also means some of the rates of adverse clinical outcomes such as COVID-19 severity and mortality may be higher in this registry than in a true population-based dataset.

“We now have information from a resource spanning the continents, showing us that we have a high-risk patient population, but that most patients can recover from this infection,” Dr. Wood said, adding that this is particularly true for individuals with younger age, mild or moderate disease, and more than 12 months pre-COVID prognosis. “That should be reassuring.”

Moreover, the recorded death rate among patients has improved – dropping from 28%, which was seen among the first 250 patients and published concurrently in *Blood Advances*, to 20% with more cases included in the present analysis. Dr. Wood explained that while this may represent true improvements in outcomes over time, this cannot be stated with certainty as the precise dates of diagnosis were not recorded due to the de-identified nature of the registry data.

This analysis is limited to patients with blood cancers; however, information from patients with non-malignant blood disorders is also being collected by the registry. The ASH RC COVID-19 Registry encourages ongoing data contribution to the Registry from hematologists around the world.

William A. Wood, MD, MPH, of North Carolina, Chapel Hill, will present this study in an oral presentation on Saturday, December 5, at 12:00 noon Pacific time on the ASH annual meeting virtual platform.

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Additional press briefings will take place throughout the meeting on health disparities, practice-changing clinical trials, genome editing and cellular therapy, and late-breaking abstracts. For the complete annual meeting program and abstracts, visit www.hematology.org/annual-meeting. Follow ASH and #ASH20 on Twitter, Instagram, LinkedIn, and Facebook for the most up-to-date information about the 2020 ASH Annual Meeting.

The American Society of Hematology (ASH) (www.hematology.org) is the world’s largest professional society of hematologists dedicated to furthering the understanding, diagnosis, treatment, and prevention of disorders affecting the blood. For more than 60 years, the Society has led the development of hematology as a discipline by promoting research, patient care, education, training, and advocacy in

hematology. ASH publishes *Blood* (www.bloodjournal.org), the most cited peer-reviewed publication in the field, and *Blood Advances* (www.bloodadvances.org), an online, peer-reviewed open-access journal.