iron restriction helps to restore gut epithelial integrity, improve microbiome composition, and prevent the systemic translocation of deleterious microbial metabolites and antigens, and it may contribute to the reduction of disease severity. However, more work is needed to definitively demonstrate the impact of the intestine and microbiota in SCD. Gut microbial communities have been shown to be significantly affected by dietary iron.

Probiotics, such as *Lactobacillus* species, are highly enriched following low-iron treatment.[9] Indeed, *Lactobacillus* species have been shown to enhance barrier integrity.[10] Further work in characterizing gut microbial communities, microbial metabolites, and germ-free or antibiotic experiments is needed to better define the impact of dietary iron on alterations on intestinal function and microbial changes in SCD.

Beneficial effects of iron restriction in anemia seem paradoxical, but it is well established that iron restriction strategies alleviate major SCD morbidities. This study provides new evidence that VOEs, tissue injury, and organ damage improve following dietary iron restriction (see figure). Moreover, a novel connection was identified, implicating the beneficial outcomes to changes in the host/microbiota interactions. This study shows that SCD affects gut microbial dysregulation, and it is linked with systemic iron levels, which can be successfully restored by dietary iron restriction (see figure). This study opens the possibilities of identifying novel microbial compounds with therapeutic potential for SCD management.

There are still many open questions that need to be addressed: How does iron restriction improve anemia in SCD? Is this dependent on decreasing the levels of HbS or does iron-induced oxidative stress in RBCs play a role? Are intestinal changes in SCD the mediator of local and systemic inflammatory and immune changes? What are the factors in the intestine, both host and microbial, that determine the extent of local and systemic tissue damage? Can we design studies in humans using information in mouse models to understand the efficacy of iron-restricted diets in patients with SCD?

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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https://doi.org/10.1182/blood.2022018791

LYMPHOID NEOPLASIA

Comment on Davis et al, page 200

COVID-19 prophylaxis: half-full or half-empty glass?

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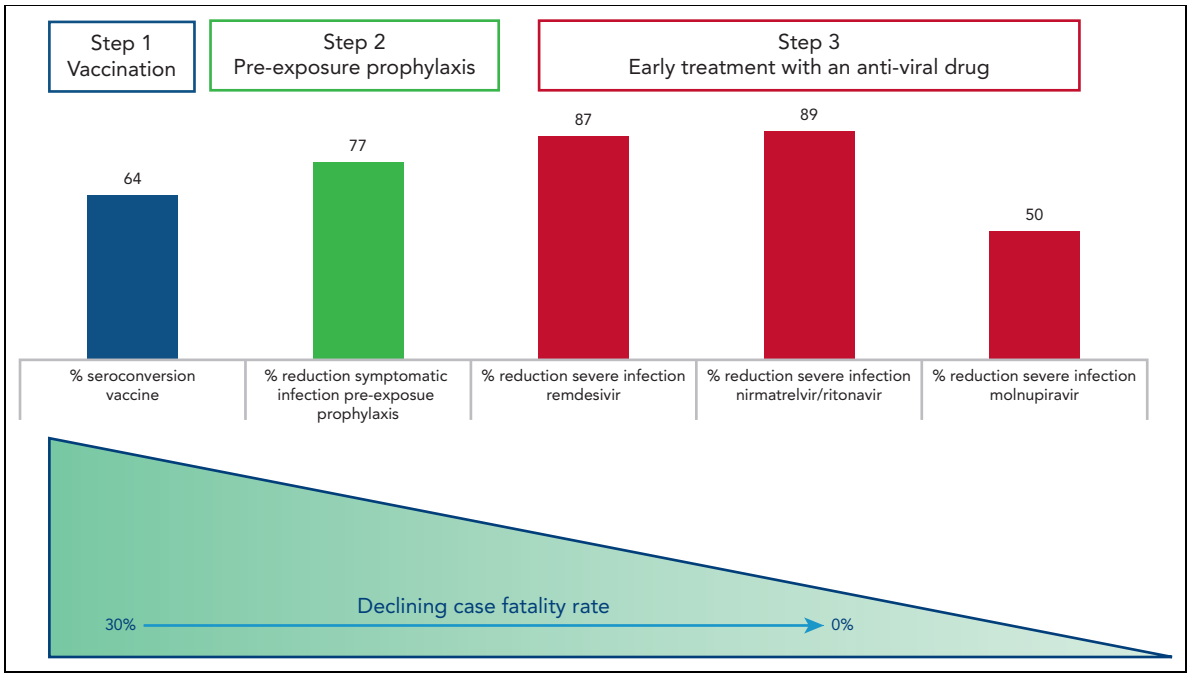
In this issue of *Blood*, Davis et al[1] report their experience with tixagevimab–cilgavimab preexposure prophylaxis in a cohort of 251 patients with chronic lymphocytic leukemia (CLL), B-cell lymphomas, multiple myeloma, or B-cell acute lymphoblastic leukemia.

With a case-fatality rate up to 34% in hospitalized patients in the prevaccine era[2] and a significantly reduced response to vaccination, COVID-19 represents a major issue for patients with tumors of the hematopoietic and lymphoid tissues. Searching for additional strategies to better protect patients with hematological malignancies, the use of preexposure prophylaxis seemed a smart and feasible approach. In patients whose immune system function is compromised, passive immunization relying on effective neutralizing antibodies administered once to achieve protective antibody levels regardless of the B-cell function should mean long-term protection and reduced risk. Indeed, the PROVENT study showed a symptomatic infection rate of only 0.2% in a study population chosen because of a low probability of responding to vaccination or higher risk of exposure in those treated with tixagevimab–cilgavimab. There was a 77% reduction in the risk of symptomatic COVID-19 compared with placebo.[3] That said, only 383 of 5197 (7.4%) subjects in the study were considered at high risk of infection because of a cancer diagnosis and only 24 (0.5%) because of an immunosuppressive disease.

The report of Davis et al provides relevant information on the complex area of SARS-CoV-2 infection prevention and management in the most difficult to protect category of patients with hematological malignancies, that is, those with B-cell lymphoproliferative disorders.



Sequence of interventions to prevent and successfully treat COVID-19 infection in patients with B-cell malignancies. Vaccinations are able to elicit seroconversion in up to two-thirds of patients with B-cell malignancies.[6] Tixagevimab and cilgavimab reduced the probability of developing a symptomatic infection before the BA.4 BA.5 Omicron variants became predominant,[4] and early administration of antiviral agents within 3 to 7 days from the onset of symptoms offered an effective protection against severe disease in the majority of patients.

Even though recent reports suggest a reduced incidence of severe SARS-CoV-2 infections with fewer patients in need of hospitalization and a lower case fatality rate, this group of patients, in particular those with active disease or those requiring treatment, remains more vulnerable to adverse clinical outcomes including severe infections and deaths.[4] This vulnerability is potentially driven, at least in part, by the impaired response to SARS-CoV-2 vaccines with a seroconversion rate and T-cell response definitely lower than healthy subjects or people with solid tumors. The lowest rates were detected in patients with CLL, with seroconversion ranging from 23% to 66%[5] and T-cell responses being present in 30% to 40%.[6]

At a median follow-up of 3 months from preexposure prophylaxis, Davis et al identified 27 (11%) subjects with confirmed COVID-19 breakthrough infection, with 22 (9%) at least 30 days after tixagevimab–cilgavimab administration. Interestingly, 63% of infected patients had received at least 3 doses of SARS-CoV-2 vaccine, the vast majority of the breakthrough infections occurred in patients who had recently received B-cell-depleting agents, were on active treatment, or were within 6 months of hematopoietic stem cell transplantation. Only 4 (15%) patients required hospitalization, and no COVID-19-related death was reported. It is important to note that 63% of the patients were treated with antiviral drugs, that is, nirmatrelvir–ritonavir, molnupiravir, or remdesivir, in a timely manner. Though no specific testing for the variants was done in this retrospective study, most infections occurred between June and August 2022 when Omicron variant BA.5 was dominant. These findings support the preclinical data showing reduced efficacy of tixagevimab–cilgavimab against Omicron BA.5 compared with BA.2[7] and support the administration of a 300-mg + 300-mg dosage of tixagevimab–cilgavimab (as per Food and Drug Administration label) to try to offset the potentially reduced neutralization activity against Omicron BA.4/5 also in patients.

In patients with hematological malignancies, at least 2 studies on tixagevimab–cilgavimab prophylaxis with less than 3 months of follow-up showed the occurrence of symptomatic COVID-19 in about 4% of patients.[8,9] Reassuringly, 0 of 52 patients in one series[8] and 2 of 1112 (0.2%) in the other[9] died because of COVID-19, well below the 34% mortality rate in hospitalized patients that was observed in the initial wave of COVID-19.[2] Furthermore, a very low hospitalization rate (5.9%) with no COVID-related death was recently described in a preprint publication that included a large series of immunocompromised patients, 45% of whom had a hematologic disease, after preexposure prophylaxis and administration of antiviral agents.[10]

In conclusion, though the effectiveness of tixagevimab and cilgavimab in the Omicron era remains difficult to assess, the data by Davis and coworkers on patients with B-cell malignancies add to a growing body of evidence that clearly point to a dramatic improvement of the outcome of COVID-19 infection in fragile patients thanks to vaccination, preexposure prophylaxis, and early treatment with antiviral agents (see figure). We have won some battles against COVID-19 but not (yet) the war, as SARS-CoV-2 variants are rapidly changing over time. Thus, it is crucial to remain on the alert and continue to (1) inform and educate our patients on the infection risks and the importance of a timely diagnosis for administering the appropriate treatment and (2) investigate and test prophylactic and therapeutic

strategies tailored in particular to protect the most vulnerable subgroups of patients, including those with impaired immune function and at higher risk of dismal outcome upon infection.

Conflict-of-interest disclosure: L.S. received honoraria from AbbVie, AstraZeneca, BeiGene, and Janssen; speaker bureau for Octapharma. A.C. received honoraria from AbbVie, AstraZeneca, Gilead, Janssen. ■

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https://doi.org/10.1182/blood.2022018858

RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Cherukury et al, page 203

Is CBD ready for prime time in sickle cell disease?

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In this issue of *Blood*, Cherukury et al demonstrate that cannabidiol (CBD), a nonpsychoactive phytocannabinoid, can decrease hyperalgesia and markers of systemic inflammation in murine models (HbSS-BERK) of sickle cell disease (SCD).[1] The effects of CBD on pain and markers of inflammation were both dose and sex dependent. This promising study suggests that CBD may be effective for the treatment of chronic pain in SCD and/or could be disease modifying owing to its anti-inflammatory properties.

Although the sale and consumption of most cannabis products remain illegal on a federal level in the United States, an ever-increasing number of states is passing laws permitting the sale of medicinal cannabis for a wide range of conditions, including SCD and chronic pain from any source. Chronic pain in SCD is one of the greatest contributors to poor quality of life, yet there is a paucity of evidence-based interventions to mitigate this complication. Existing disease-modifying medications may only attenuate chronic pain modestly.[2] Owing to the dearth of effective treatment strategies and the increasing reluctance of medical providers to prescribe opiates for chronic pain, many patients have resorted to recreational marijuana in an attempt to alleviate their pain and other disease-related symptoms. Retrospective studies have shown that 31% to 51% of people living with SCD self-report using cannabis, and the majority endorse using it for pain relief.[3] One retrospective study showed that medical cannabis use was associated with a decrease in hospital admissions.[4] In contrast, the only randomized controlled study of inhaled cannabis in SCD failed to show a significant decrease in pain ratings; this small study, however, showed a promising improvement in mood with cannabis.[5] Thus, there remains a critical need for rigorous studies evaluating whether cannabis products could be effective for the treatment of chronic pain in SCD.

Cannabinoids act primarily on 2 endogenous receptors, cannabinoid receptor 1 (CBR1), which is mainly localized in the nervous system and associated with transmission of pain as well as anxiety, sleep, and appetite, and is responsible for the psychoactive effects of cannabis, and cannabinoid receptor 2 (CBR2), which is mostly localized on immune cells.[6] Many studies aimed at treating chronic pain with cannabinoids have tested the effects of tetrahydrocannabinol, the primary active ingredient in cannabis, which may relieve pain via its agonist activity on CBR1. However, CBR1 activity can also trigger undesirable psychoactive side effects. In contrast, CBD has no direct activity on CBR1 and instead acts as an agonist on CBR2, as well as receptors for neurotransmitters (eg, serotonin).[6] Controlled studies examining the effectiveness of CBD alone as a treatment for seizure disorders, anxiety, and addiction cravings have been ranging from outright positive to encouraging, although studies investigating its effects on chronic pain have yielded mixed results.[6] Despite these considerations, we can hypothesize the anti-inflammatory activity of CBD could be particularly beneficial for the chronic pain of SCD. In SCD sterile inflammation owing to circulating free heme and ischemia–reperfusion injury from vaso-occlusion can induce neuroinflammation, which in turn can lead to hyperalgesia through central and peripheral sensitization.[7] Mediators of inflammation such as the cytokines interleukin-1β and tumor necrosis factor α, and histamines can also activate