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.

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Cherukury et al, page 203

Is CBD ready for prime time in sickle cell disease?

Susanna A. Curtis[1] **and Enrico M. Novelli**[2] | [1]Mount Sinai Hospital and [2]University of Pittsburgh

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

pain fibers directly.[7] Further, sterile inflammation itself contributes to the development of vaso-occlusion in an amplification cycle, and so it is a potential target to decrease disease severity.[8] To investigate the potential anti-inflammatory and analgesic effects of CBD, Cherukury et al administered synthetic, pure CBD at either 20 or 50 mg/kg/d intraperitoneally to humanized transgenic sickle mice (HbSS-BERK) that, like humans with SCD, experience hyperalgesia. They demonstrated not only an improvement in mechanical and cold stimulated hyperalgesia but also a decrease in the markers of systemic inflammation (eg, tumor necrosis factor α) and of neurogenic inflammation (eg, substance P), suggesting that CBD may also have disease-modifying properties.

So, should people living with SCD self-treat with CBD? Hemp-derived CBD, unlike tetrahydrocannabinol, became federally legal after passage of the 2018 Farm Bill, and the market has since taken off with a reported $4.6 billion in sales in the United States in 2020. However, quality and consistency in the products sold is poor; an analysis of 20 CBD products found that only 3 of them contained what was marked on the label, and some had elevated levels of dangerous solvents and gases.[9] One form of oral CBD that is approved by the US Food and Drug Administration (FDA) exists, but is currently only approved for the treatment of seizure disorders.[6] In the study by Cherukury et al, doses of 20 mg/kg/d were associated with a decrease in inflammatory markers in female mice, whereas doses of 50 mg/kg/d only decrease inflammatory cytokines in males, demonstrating that the response is sex and dose specific. Thus, people with SCD should only use CBD after rigorous studies have examined the optimal dose and route of intake for humans, and when FDA-regulated products are available. One potential path forward for CBD in SCD may parallel that of L-glutamine, which existed for years as a nutraceutical supplement purported to have many benefits; carefully controlled studies demonstrated that pharmacologic doses of L-glutamine in people with SCD decreased rates of pain episodes, which led to the FDA approval of L-glutamine for the treatment of SCD in 2017.[10] The groundbreaking work by Cherukury et al demonstrates that CBD could potentially act as a treatment for chronic pain in SCD, an area of critical need, and as a disease-modifying agent, highlighting the need for further studies of CBD and other cannabis compounds in SCD. However, amid the current Wild West of cannabis regulation or lack thereof in the United States, these studies will need to be conducted rigorously. Thus, it behooves the SCD community to lobby the US Drug Enforcement Administration to change the classification of cannabis products in the Controlled Substances Act, where they currently share the same classification (schedule 1) with heroin and hallucinogenic recreational drugs, which creates significant barriers to clinical studies. This step will pave the way for large scale, FDA-led testing of cannabis compounds. In the meantime, although CBD seems to be promising, we urge caution when recommending or using cannabis products outside of clinical trials.

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