synergistic approach in the combination of fecal microbiota transplantation and F-652 for treatment of GI acute GVHD.[10]

Finally, despite including only patients with GI acute GVHD, a group particularly prone to treatment failure, this study reports an overall response rate of 70% at day 28, comparable to those of 74% and 66% reported respectively with corticosteroid plus itacitinib and corticosteroid plus placebo in the randomized phase 3 GRAVITAS-301 study, which included only 42% of patients with lower GI acute GVHD.[3] This further confirms that F-652 deserves evaluation in a phase 3 randomized clinical trial and that it can likely be a key player in combination with new gut microbiota manipulation approaches, in particular fecal microbiota transplantation, within the next decade.[10]

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Olupot-Olupot et al, page 1402

HU for SCA in Africa: associated malaria benefit

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In this issue of *Blood*, Olupot-Olupot et al[1] report that hydroxyurea (HU) at the maximum tolerated dose (MTD) is associated with lower malaria incidence in an open-label trial among children with sickle cell anemia (SCA) in 4 countries in sub-Saharan Africa (SSA).

Over two-thirds of the estimated 300 000 babies born every year with SCA worldwide live in SSA. Due to limited resources for universal newborn and infant screening and comprehensive care, fewer than half of them live beyond 5 years of age.[2,3] Disease-modifying therapies including HU, chronic blood transfusion, and hematopoietic stem cell transplantation have demonstrated efficacy in reducing SCA-related complications including recurrent vaso-occlusive pain, acute chest syndrome, and stroke. Of these therapies, HU remains the most affordable and feasible option for the vast numbers of patients in SSA. Several clinical trials in SSA have demonstrated the safety and clinical and laboratory benefits of HU therapy, providing compelling evidence for its wider use to reduce the high morbidity and mortality burden.[4-7]

What have we learned from these clinical trials of HU therapy for children with SCA in SSA? The trials have demonstrated safety and clinical benefits consistent with results of studies done in high-income countries. In the first randomized study of its kind, HU dose escalation to MTD among children with SCA in Uganda had superior clinical efficacy to that of fixed-dose HU, with equivalent safety.[7]

An important safety concern in SSA, a region where malaria is endemic, is the clinical effects of HU on malaria infections. The NOHARM trial, a double-blind placebo-controlled trial in Uganda, tested the rate of clinical malaria in children with SCA on HU at a 20-mg/kg fixed dose vs placebo, with ~100 patient-years in each arm. The trial results showed that despite the malaria incidence being ~30% lower in children on HU compared with placebo, this difference was not statistically significant.

The ongoing REACH trial, which provides HU at MTD for over 600 children with SCA in 4 countries in SSA, has produced documented evidence of safety and reduction in sickle-related clinical events. Beyond these positive findings, an intriguing and unexpected ~50% decrease in malaria incidence was observed, most pronounced after achieving MTD and sustained over time course of 6 years. These salutary observations remain largely unexplained. Olupot-Olupot et al therefore performed a longitudinal analysis of all malaria events in the REACH trial to date, focusing on confirmed events, to identify associations between HU treatment and reduced malaria infection rates in this cohort of African children with SCA.

Over a 6-year period, 717 clinical malaria episodes, 346 confirmed by blood smear and/or rapid diagnostic testing, were documented in 336 of 606 study participants over 3300 patient years of HU treatment. Univariate analysis, limited to

4 confirmed infections per child, showed malaria risk was significantly associated with achieving MTD, absolute neutrophil count (ANC), hemoglobin, and splenomegaly. Age, season, MTD does, hemoglobin F, α-thalassemia, and G6PD deficiency had no effect. In multivariate regression analysis of confirmed malaria infections, ANC values < 3.0×10^9/L were associated with lower malaria incidence. Compared with nonpalpable, splenomegaly < 5 cm was associated with higher malaria risk.

Are the observed reductions in malaria infections accurate, and are they truly associated with HU therapy? The authors cannot definitively exclude longitudinal or reporting bias in an open label trial such as REACH. Nevertheless, on the backdrop of the findings of NOHARM, a double-blind, placebo-controlled trial that reported ~30% reduction in malaria infections in children on HU, the observed association with lower malaria incidence in the REACH cohort is likely accurate. NOHARM reported on ~100 patient-years in each arm (HU vs placebo) in a single site with low malaria infection rate. In contrast, REACH reports on over 3300 patient years of HU treatment with high baseline rates of malaria infection.

Univariate and multivariate analysis of confirmed malaria infections identified ANC and splenomegaly as the 2 most important variables affecting malaria risk. How can these be explained? The authors offer 2 possible explanations for the ANC effect. ANC values may have a direct effect on decreased malaria risk through reduced adhesion, inflammation, and endothelial activation; or they simply reflect that higher HU levels have antimalarial benefits. HU inhibits *Plasmodium falciparum* growth and prevents cerebral malaria from *Plasmodium berghei* in mice, at concentrations attainable in vivo with HU treatment in SCA.[8] In patients with untreated SCA, the spleen is packed with sickled erythrocytes, impairing its ability to phagocytose parasitized erythrocytes.[9] HU, by reducing sickling, can, in part, restore this essential antimalarial function of the spleen, thereby reducing clinical malaria infection. This brings us to the association of palpable splenomegaly < 5 cm with increased malaria incidence. The authors' explanation that the spleen could potentially serve as a reservoir for *P falciparum* is not supported by direct evidence. Another consideration is that splenomegaly in SCA is probably a sign of more active hemolysis, and this may predispose to clinical malaria episodes.

Efforts to combat malaria including use of insecticide-treated nets, vector control, chemoprevention, and effective treatment of clinical malaria have reduced malaria mortality rates worldwide from 30 per 100 000 population in 2000 to 13 per 100 000 in 2019.[10] Although the incidence of malaria in SCA is not actually increased, the risk of death from clinical malaria is reported to be higher in children with SCA than other children. It is surprising, therefore, that malaria prevention practice was not consistent across the study sites, a reflection of the lack of consensus among public health authorities in SSA. This needs to be addressed. The emergence of new malaria vaccines will help strengthen malaria prevention efforts in SSA.

The research goal to better understand the clinical significance of the association between HU and lower malaria risk is worthwhile. What is more, this finding together with the proven clinical and laboratory benefits of HU therapy should encourage development of strategies to make HU widely accessible to children with SCA in SSA where the disease burden is heaviest.

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LYMPHOID NEOPLASIA

Comment on Stachelscheid et al, page 1425

TCL1A expression promotes aggressive biology in CLL

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In this issue of *Blood*, Stachelscheid et al[1] report a novel nuclear TCL1A-CDC20 axis that signals DNA damage-prone cell cycle transition and genomic instability, thereby accelerating aggressive chronic lymphocytic leukemia (CLL).

TCL1A is a proto-oncogene first identified in T-cell prolymphocytic leukemia. Upregulation of TCL1A via a gene rearrangement bringing *TCL1* (on chromosome 14q31.2) under the influence of *TCR* (T-cell receptor) enhancer has