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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ponce et al, page 1389

IL-22, a new beacon in gastrointestinal aGVHD

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In this issue of *Blood*, Ponce et al[1] report the results of a multicenter single-arm, phase 2 study evaluating the safety and efficacy of F-652, a novel recombinant human interleukin-22 (IL-22) dimer used in combination with systemic corticosteroids for treatment of newly diagnosed gastrointestinal (GI) acute graft-versus-host disease (GVHD). There was no dose-limiting toxicity, and the prespecified primary endpoint, response at day 28, was achieved by 19 of 27 patients (70%; 80% confidence interval, 56% to 79%).

Despite improvement in acute GVHD prophylaxis and treatment, GVHD remains the leading cause of early morbidity and mortality, apart from relapse, after allogeneic hematopoietic stem cell transplantation (alloHCT).[2] In particular, lower GI acute GVHD is associated with an increased risk of nonrelapse mortality.[2] Systemic corticosteroids are the standard first-line treatment for acute GVHD, with a low response rate, approximately 50%. Furthermore, although approval of ruxolitinib for steroid-refractory acute GVHD was a significant improvement for patients with this disease, no progress has been made regarding first-line treatment. In fact, several phase 3 randomized studies, which evaluated the adjunction of another immunosuppressive drug to corticosteroids to improve acute GVHD response rate at day 28, were all negative.[3] Therefore, innovative strategies, preferably steroid sparing, are needed to improve response.

During GI acute GVHD, all mature gut epithelial cells, including enterocytes, Paneth, goblet, tuft, and enteroendocrine cells, are targeted. This leads to alteration of the tissue microenvironment, disruption of tissue homeostasis, and amplification of GVHD-induced tissue damage. In addition, during GI acute GVHD, activated T cells also directly target intestinal stem cells in an interferon gamma–dependent manner.[4] In the homeostatic state, intestinal stem cells produce approximatively 10 offspring per hour in each crypt, which then migrate to the villus. Therefore, during GI acute GVHD, depletion of cycling intestinal stem cells in the crypt soon leads to villus atrophy, resulting in refractory colitis.

Importantly, intestinal stem cells and their downstream progenitors express Il-22 receptors, and IL-22 increases proliferation and promotes intestinal stem cell expansion.[5] In the alloHCT setting, the conditioning regimen leads to an increased production of intestinal IL-22 by IL-23–responsive innate lymphoid cells from the transplanted recipient.[6] Nevertheless, during GI acute GVHD, innate lymphoid cell frequency and IL-22 amounts are decreased, leading to increased crypt apoptosis, depletion of intestinal stem cells, and loss of epithelial integrity.[6] Lindemans et al demonstrated in a murine model that treatment with IL-22 in vivo after murine alloHCT enhanced recovery of intestinal stem cells, increased epithelial regeneration, and reduced intestinal pathology and mortality from GVHD.[5]

Based on these preclinical data, Ponce et al evaluated the use of the recombinant human IL-22 dimer, F-652, in GI acute GVHD in a phase 2 prospective study published in this issue of *Blood*. Importantly, F-652 was proven to be safe, xerosis and xerophthalmia being the most common attributable side effects. Of note, IL-22 can have a pathogenic role in chronic inflammatory diseases such as psoriasis.[7] Moreover, we have previously reported that donor T-cell–derived IL-22 can exacerbate the inflammation in the GI tract and contribute to the severity of acute GVHD.[8] Nevertheless, no significant increases in inflammatory cytokine levels were observed after F-652 treatment. Furthermore, the current data suggest that higher concentrations of F-652 translate into improved GVHD response rates.

In addition to its effect on intestinal stem cell proliferation and expansion, IL-22 also induces epithelial production of innate antimicrobial peptides. Therefore, given the relationship between the GI microbiome and acute GVHD outcomes,[9] Ponce et al investigated fecal microbiota composition before and after F-652 treatment. They found that although at baseline all patients exhibited microbiome dysbiosis, after treatment with F-652 and steroids, responders exhibited a distinct fecal microbiota composition associated with an expansion of Lachnospiraceae, including an increase in the genus *Blautia*. Importantly, among a cohort treated with steroids in the absence of F-652 in a retrospective historical control cohort of GI acute GVHD, there was not a similar microbial shift in responding patients. Overall, this suggests that F-652 can contribute to correction of gut microbiota dysbiosis in the setting of GI acute GVHD. These results offer a strong opportunity for development of a

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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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