ELSEVIER

Blood 142 (2023) 5355–5356

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

201.GRANULOCYTES, MONOCYTES, AND MACROPHAGES

Intermittent Sargramostim Administration Expands Proliferating Naïve T Cells, Tregs, HLA-DR+ PD-L1+ Monocytes and Myeloid-Derived Suppressor Cells: Results from a Randomized Placebo-Controlled Clinical Trial of GM-CSF in Patients with Peripheral Artery Disease

Alireza Rahbar, MD[1], *Mohammad S. Hossain, PhD*[2], *Cynthia R. Giver, PhD*[3], *Shivang Desai, MD*[1], *Yazan Haroun, MD*[1], *Tanveer Kauser, MD*[1], *Kiran Ejaz, MD*[1], *Arshed A. Quyyumi, MD*[1], *Edmund K. Waller, MD*[4]

[1] School of Medicine, Department of Medicine, Division of Cardiology, Emory University, Atlanta, GA
[2] School of Medicine, Emory University, Atlanta, GA
[3] School of Medicine, Department of Hematology and Medical Oncology, Emory University Winship Cancer Institute, Atlanta, GA
[4] School of Medicine, Department of Hematology and Medical Oncology, Emory University, Winship Cancer Institute, Atlanta, GA

Introduction: Sargramostim (rhuGM-CSF; Leukine ®) is an FDA-approved drug known for mobilizing hematopoietic progenitor cells and expediting hematopoietic reconstitution in patients with acute myeloid leukemia (AML) as well as after autologous and allogeneic bone marrow transplantation. While GM-CSF has been explored as an adjuvant for cancer vaccines due to its ability to promote dendritic cell differentiation and maturation, continuous daily administration of sargramostim has been associated with leukocytosis and adverse side effects. To validate and expand upon our previously published findings that thrice-weekly sargramostim administration in patients with severe peripheral artery disease (PAD) is both well-tolerated and beneficial for claudication symptoms, we conducted a placebo-controlled randomized clinical trial to assess the efficacy of an extended dosing regimen of sargramostim in PAD patients. Data regarding progenitor mobilization kinetics and claudication symptoms will be presented elsewhere. In this analysis, we investigated the impact of intermittent sargramostim dosing on immune cell subsets in the bloodstream, aiming to support the use of this dosing schedule for enhancing adaptive immunity.
Methods: Symptomatic atherosclerotic PAD patients were enrolled and randomly assigned to receive either 500 μg/day of sargramostim or placebo via self-administered subcutaneous injections thrice weekly for 3 weeks, for two separate courses 3 months apart. The study was IRB-approved with adverse events and safety signals monitored by an independent Data Safety Monitoring Board. A total of 61 patients (40 receiving sargramostim and 21 receiving placebo) participated in the immune-monitoring sub-study. Blood mononuclear cells were collected at various time points and cryopreserved. Thawed peripheral blood mononuclear cells (PBMCs) were stained using immune cell-specific antibody cocktails, and analyzed by flow cytometry. Statistical significance was determined using the Student's t-test.
Results: No dose-limiting leukocytosis or drug-related side effects were observed. As expected, the numbers of white blood cells (WBCs) increased by an average of 68% in the blood of sargramostim-treated patients compared to placebo-treated patients, with peak values reached after 3 weeks of intermittent study drug administration, followed by return to baseline before the next treatment course. Absolute counts of CD3+, CD4+, and CD8+ T cells, B cells, and CD14+ monocytes significantly increased one and two weeks after starting intermittent sargramostim treatment compared to the control group. Notably, sargramostim-treated patients exhibited higher levels of proliferating naïve, Ki-67+ CD4+ T cells (106.83/uL ± 70.28) compared to placebo-treated patients (44.94/uL ± 33.84, p=0.001), as well as increased numbers of naïve Ki-67+ CD8+ T cells (33.05/uL ± 25.43 after sargramostim versus 15.77/uL ± 15.73 for placebo, p=0.01) (Fig. 1, A). However, sargramostim treatment did not influence the quantities of central memory CD4+ and CD8+ T cells. Besides the heightened proliferation of naïve T cells, sargramostim treatment also resulted in a significant increase in the numbers of CD3+CD4+CD25+FoxP3+ Tregs (Fig. 1, A), as well as PD-1-expressing CD4+ and CD8+ T cells, compared to the control group. Moreover, sargramostim treatment led to elevated levels of CD14+HLA-DR+ and CD14+PDL-1+ monocytes, as well as myeloid-derived suppressor cells, 2 and 3 weeks after initiation of treatment, when compared to the control group (Fig. 1, B). Conversely, sargramostim treatment had no impact on the levels of gamma-delta T cells, natural killer (NK) cells, plasmacytoid dendritic cells, or classical dendritic cells.

Conclusions: Our findings demonstrate that intermittent dosing with sargramostim is well-tolerated and induces significant but transient increases in the numbers and activation status of T cells in the bloodstream. Sargramostim treatment also increased numbers of proliferating naïve T cells, Tregs, and certain subsets of myelo-monocytic cells with immunosuppressive phenotypes. These results support the use of intermittent sargramostim dosing to avoid excessive leukocytosis and associated adverse effects. Further investigation is warranted to elucidate the clinical implications of these findings in the context of immune modulation.

Disclosures Quyyumi: *Abbott Laboratories:* Research Funding; *Somalogic:* Research Funding. **Waller:** *Allovir:* Consultancy; *CRISPR:* Consultancy; *Novartis:* Consultancy, Research Funding; *CSL Behring:* Consultancy, Research Funding; *ORCA:* Research Funding; *BMS:* Research Funding; *Sanofi:* Research Funding; *NCI R01:* Research Funding; *Secura:* Research Funding; *PartnersTherapeutics:* Research Funding; *Cambium Medical Technologies:* Current equity holder in private company, Other: Founder; *Cambium Oncology:* Current equity holder in private company, Other: Founder; *Verastem:* Consultancy, Research Funding.

OffLabel Disclosure: The data represent additional analyses stemming from the GPAD-3 study, a randomized placebo-controlled clinical trial of GM-CSF to reduce claudication symptoms in patients with peripheral artery disease

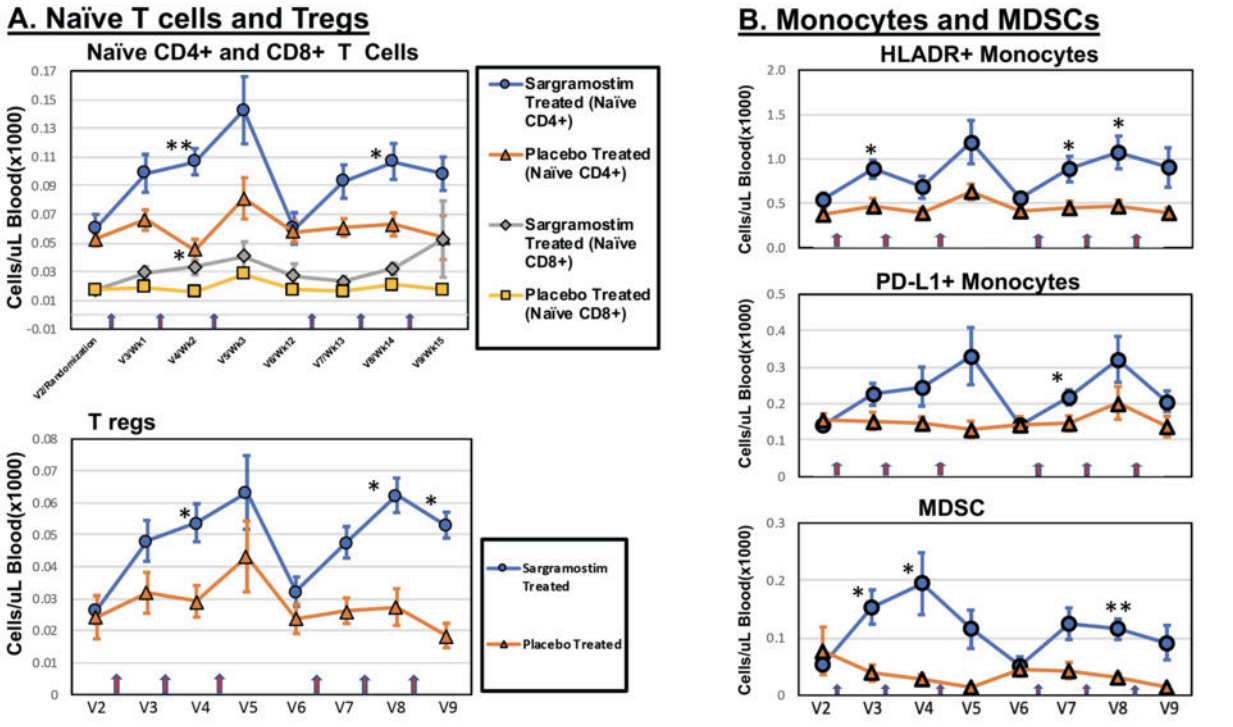

Figure 1. Sargramostim effects on Ki67+ CD45RA+ CD4+ and CD8+ naïve T cells, and CD3+ CD4+ CD25+ Foxp3+ T regs (A), and CD14+HLADR+ monocytes, CD14+PD-L1+ monocytes and CD14+CD33+ CD15+HLADR- MDSCs (B). Multicolor fluorescent conjugated antibody-stained samples were analyzed using a BD Canto Flow cytometer. Asterisks indicate statistical significance by Student's t-Test * p= <0.05 and ** p= <0.005. Red arrows indicate Sargramostim or Placebo injection time points.

Figure 1

https://doi.org/10.1182/blood-2023-186848