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Hematopoietic Progenitor Cell Mobilization is More Robust in Healthy African American Compared to Caucasian Donors and is not Affected by the Presence of Sickle Cell Trait

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Abstract

Background—G-CSF-stimulated hematopoietic progenitor cells (HPCs) collected by apheresis have become the predominant graft source for HPC transplantation in adults. Among healthy allogeneic donors, demographic characteristics (age, sex, BMI) and baseline hematologic counts affect HPC mobilization, leading to variability in CD34+ apheresis yields. Racial differences in HPC mobilization are less well characterized.

Methods—We retrospectively analyzed data from 1,096 consecutive G-CSF-stimulated leukapheresis procedures in healthy allogeneic African American (AA) or Caucasian donors.

Results—In a multivariate analysis, after adjusting for age, sex, BMI, baseline platelet and MNC counts, and daily G-CSF dose, peak CD34+ cell mobilization was significantly higher among AAs (n=215) than Caucasians (n=881) (123 ± 87 vs 75 ± 47 cells/uL; p<0.0001). A ceiling effect was observed with increasing G-CSF dose (10 vs 16 mcg/kg/day) in AAs (123 ± 88 vs 123 ± 87) but not in Caucasians (74 ± 46 vs 93 ± 53, p<0.001). In AA donors, presence of sickle cell trait (SCT, n=41) did not affect CD34+ mobilization (peak CD34+ 123 ± 91 vs 107 ±72 cells/uL, HbAS vs HbAA, p=0.34). Adverse events were minimal and similar across race.

Conclusions—AAs demonstrated significantly better CD34 mobilization responses to G-CSF than Caucasians. This was independent of other demographic and hematologic parameters. Studying race-associated pharmacogenomics in relation to G-CSF may improve dosing strategies. Adverse event profile and CD34 mobilization were similar in AA donors with and without SCT.

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Our findings suggest that it would be safe to include healthy AA donors with SCT in unrelated donor registries.

Keywords

Apheresis; Race; African American; CD34; Mobilization; Hematopoietic Progenitor Cells; Sickle Cell Trait; Duffy antigen

INTRODUCTION

Hematopoietic progenitor cells (HPCs) collected by apheresis of G-CSF-stimulated donors have surpassed bone marrow as the graft source of choice for hematopoietic stem cell transplantation in adults[1]. Peripheral blood HPC grafts are currently used successfully to treat hematologic and non-hematologic disorders, both benign and malignant[2-4]. Compared to bone marrow aspiration, their relative ease of collection by apheresis and the abundance of CD34+ cell yields make them the preferred source. However, significant variability in HPC yields has been reported even among healthy allogeneic donors. Demographic characteristics such as female sex, advancing donor age, lower body mass index (BMI), lower baseline platelet counts and lower G-CSF dose are known to be negatively correlated with CD34+ cell mobilization[5,6].

Racial differences in G-CSF-mediated HPC mobilization are less well characterized. Physiologically, lower absolute neutrophil counts (ANC) are observed in African Americans (AAs) compared to Caucasians. Benign ethnic neutropenia (BEN) is described in about 5% of healthy AAs and is characterized by a decrease in granulocytes and monocytes with minimal differences in other white blood cell (WBC) subsets[7,8] Postulated mechanisms for this phenomenon include a decreased stem cell reserve or fewer G-CSF receptors per cell among AA subjects. An association with the Duffy blood group antigen null phenotype, seen in 67% of AAs, and a consequent decrease in chemokine-mediated leukocyte recruitment has also been proposed[9-11]. Cord blood units collected from AA donors are reported to have lower total nucleated counts (TNC) and CD34+ cell counts[12]. Further, studies show relatively decreased leukocyte demargination and corticosteroid-mediated leukocyte egress in healthy AA adults[13,14]. Paradoxically, two recent clinical studies noted equivalent or increased G-CSF- stimulated HPC yields among AAs compared to other races[5,15].

Healthy AAs also have lower hemoglobin and MCV compared to their Caucasian counterparts[16]. Low MCV and iron deficiency among healthy donors, which may not affect stem cell mobilization, have been implicated in poor collection efficiencies (due to device-related abnormalities in cell separation mechanics), thus affecting final yields[17].

The effect of sickle cell trait (SCT) among AA HPC donors was evaluated in a small study which showed a trend towards better peripheral blood mobilization but poorer apheresis collection efficiencies in sickle trait versus non-sickle trait AA subjects. This resulted in similar CD34+ cell apheresis yields among the two groups. Additionally, no significant adverse events were reported among AAs with or without SCT during the process of G-

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CSF-stimulation and HPC collection[18]. Despite these data, healthy AA donors who screen positive for SCT are currently excluded from unrelated donor registries.

Our primary objective was to compare G-CSF-stimulated CD34+ cell mobilization and HPC apheresis yields among healthy AA compared with Caucasian donors. Further, we evaluated the role of physiologic interracial differences, including that of sickle cell trait, in HPC mobilization and apheresis collection outcomes.

MATERIALS AND METHODS

Study subjects

We retrospectively analyzed 1,096 consecutive healthy allogeneic related and unrelated first-time HPC apheresis donors who self-characterized their race as African American or Caucasian. Given the possibility of biased results due to significant heterogeneity within the following groups, healthy donors who described their race as Hispanic, Asian, Pacific Islander, mixed and/or other were excluded. All donors were 14 years of age or older and were either healthy siblings enrolled in institutional transplant protocols or unrelated healthy volunteers enrolled in the National Marrow Donor Program (NMDP) or the Department of Transfusion Medicine's research apheresis protocols. Donors underwent G-CSF (filgrastim, Neupogen, Amgen, Thousand Oaks, CA) stimulated HPC collection by apheresis from April 1999 to May 2013. An unstimulated leukapheresis procedure for lymphocyte collection (lymphapheresis) was performed in the 7 days preceding G-CSF administration in 336 subjects. Informed consent was obtained in accordance with the Helsinki Declaration and our Institutional Review Board–approved transplantation and research apheresis protocols. Donor demographic data at the time of HPC collection, including age, sex, weight and height, were obtained by medical record review.

HPC mobilization, collection, and cryopreservation

Subcutaneous injections of G-CSF were administered for 5 consecutive days at a daily dose of 10-16 mcg/kg, with the fifth dose given at least two hours prior to the start of the HPC apheresis procedure. The actual dose administered was obtained from a review of pharmacy and nursing records. Apheresis procedures were performed on the CS-3000 Plus continuous-flow apheresis device (Fenwal Division, Baxter, Deerfield, IL) or a COBE Spectra Apheresis device (Terumo BCT, Lakewood, CO) using prophylactic intravenous calcium infusions as previously described[19]. CD34+ collection efficiencies were similar using the two devices in our center. Volume processed per procedure ranged from 6 to 33 liters (L) for HPC collections (mean ± SD, 19 ± 5 L), depending on the immediate pre-apheresis CD34+ cell count and the targeted cell dose, and from 3 to 25 L (11 ± 3 L) for lymphapheresis procedures. HPC and unstimulated leukapheresis components were cryopreserved in plasma with 5% dimethyl sulfoxide, 6.5% pentastarch, and 4% human albumin per institutional operating procedures. Details of the study design are shown in Figure 1.

Laboratory data

Complete blood count (CBC) including a differential and RBC indices were obtained at baseline, i.e. prior to G-CSF administration or, in patients who underwent lymphapheresis

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collections, prior to lymphapheresis, and were repeated on the day of collection, immediately prior to and following apheresis. Serology records for ABO, Rh and Duffy red cell phenotype were gathered from the Department of Transfusion Medicine database. Donor hemoglobin electrophoresis data were collected from all AA and selected Caucasian subjects at baseline to determine the presence of sickle cell and/or thalassemia traits. CD34+ cell quantitation was performed on peripheral blood immediately pre-apheresis (2 hours after the 5th dose of G-CSF), post-apheresis, and on the apheresis product by flow cytometry as previously described.[20] Flow cytometric techniques did not change significantly during the 14 year period covered in this review.

Statistical analysis

The total mononuclear cell count was calculated as the sum of lymphocyte and monocyte counts reported on the CBC differential. Collection efficiencies were calculated using the formula[21]:

$$\frac{\text{CD34+ cell content in product} \times 100}{(\text{Mean of pre- and post- apheresis CD34+ counts}) \times (\text{Volume processed})}$$

Summary statistics were calculated for all numerical data. Two-tailed unpaired Student t-tests were used to compare groups of two with a presumed normal distribution. Analysis of variance was used to compare more than 2 groups. Categorical variables were compared using a 2-tailed Fisher exact test. Multivariate analyses were performed using stepwise forward logistic regression, based on parameters having significance in univariate analysis, using a commercial statistics program (JMP, Version 7, SAS Institute Inc., Cary, NC). Results are given as the mean ± SD. A p value of <0.01 was considered significant.

RESULTS

Donor demographics

All AA (n=215) and Caucasian (n=881) donors with complete data sets were included. Sex ratio was similar among the two groups (45 vs 52% male; p=0.09). AAs were younger (39 vs 43 years, p=0.001) and had greater weight (86 vs 81 kg, p=0.001) and BMI (30 vs 27; p<0.0001) than Caucasians. The total daily dose of G-CSF was greater in AAs than Caucasians (920 vs 850 mcg, p<0.0001) but the G-CSF dose/kg was similar in the 2 groups (Table 1).

Donor race, CD34+ mobilization, and HPC apheresis cell yields

African Americans mobilized significantly better than Caucasians with mean peak circulating CD34+ counts of 123 vs 75 cells/uL (p<0.0001) (Figure 2). CD34+ apheresis yield was also significantly greater in AAs than Caucasians (51 ± 35 vs 32 ± 21 × 10^6 cells per liter processed, p <0.0001), consistent with higher pre-apheresis counts. Apheresis collection efficiency was similar in the two racial groups (AAs, 64%; Caucasians, 62%; p=0.11). Lymphapheresis within the 7 days prior to starting G-CSF was associated with significantly improved CD34+ cell mobilization; however, the effect did not differ by race (Figure S1).

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In a univariate analysis of factors associated with higher peripheral blood CD34+ counts, three factors were overwhelmingly correlated with better peak CD34 mobilization: higher total G-CSF dose, AA race, and greater BMI, followed by higher baseline platelet and MNC counts, prior lymphapheresis, and male sex. After adjustment for total GCSF dose, AA race was the single parameter most strongly correlated with peak PB-CD34+ mobilization. In multivariate stepwise analysis, after total G-CSF dose and race were included in the model, donor BMI lost much of its contribution. Baseline platelet and MNC counts remained highly correlated, and after they were introduced into the model, prior lymphapheresis, male sex, and younger age remained significantly correlated with peak PB-CD34 counts (Table 2). To ensure that confounding factors were not introducing bias, the analysis was repeated by forcing all other parameters into the multivariate regression model and retaining race until the end; AA race still remained a significant predictor of better CD34 mobilization.

African Americans were significantly less likely than Caucasians to be poor mobilizers and significantly more likely to be super-mobilizers. A pre-apheresis CD34+ cell count of < 20/uL was seen in 1.4% vs 6.1%, and a CD34+ cell count of > 120/uL in 39.1% vs 13.5% of AA versus Caucasian donors, respectively ($p < 0.001$ for both comparisons) (Table 3).

Effect of G-CSF on laboratory parameters

Hemoglobin and mean corpuscular volume were significantly lower among AAs than Caucasians, both at baseline and after G-CSF administration. Platelet counts were similar between the two groups, and showed a similar degree of decline following G-CSF administration. AAs had lower baseline ANC (3.4 vs 4.0×10^3 cells/uL, $p<0.001$) than Caucasians, but demonstrated significantly higher peak WBC and MNC counts after G-CSF administration (Table 4, Figure 3). Among AA donors with BEN, defined as an ANC < 1.5×10^3/uL, G-CSF stimulation resulted in a significantly higher percentage ANC increase compared to donors with pre-G-CSF ANC in the normal range (mean 23-fold increase in ANC among BEN AA donors (n=17) vs 13-fold increase in ANC among other AAs (n=161), $p<0.0001$) (Figure 4). In AA donors with known Duffy phenotype, Duffy antigen expression did not affect CD34 mobilization (peak CD34 counts 114 ± 81 vs 134 ± 85 cells/uL, Fya-b- (n=49) vs Fya+ and/or Fyb+ (n=20), p=0.4). Baseline ANC was similar in AA donors with and without Duffy antigen expression.

G-CSF dose and CD34+ mobilization in African Americans and Caucasians

When stratified by G-CSF dose, at higher doses (16 mcg/kg/d), the difference in mobilization responses between the two groups was less apparent (peak CD34+ counts 123 vs 93 cells/uL, AA (n=33) vs Caucasian (n=73), p=0.07) than at lower doses (10 mcg/kg/d), where peak CD34 counts were 123 vs 74 cells/uL, AA (n=182) vs Caucasian (n=808), $p<0.0001$ (Table S1). Higher G-CSF doses resulted in better CD34+ mobilization in Caucasian but not in AA donors. Mean peak CD34+ counts following G-CSF 16 mcg/kg vs 10 mcg/kg were 123 vs 123 cells/uL (p=0.5) in AAs and 94 vs 74 cells/uL ($p<0.001$) in Caucasians, respectively.

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Effect of sickle cell trait on CD34+ cell mobilization and HPC apheresis yields

African Americans with sickle cell trait (SCT) received significantly higher total G-CSF dose as well as G-CSF dose/kg, by protocol design, related to transplant preparative regimens in those who had siblings with sickle cell disease[3]. Despite this increased dose, in AA donors with known HbS status, the presence of SCT had no effect on CD34+ mobilization (peak CD34+ counts 123 ± 91 vs 107 ± 72 cells/uL, HbAS (n=41) vs HbAA (n=84), p=0.34). Although MCV was lower among AAs with SCT, collection efficiency was similar among AAs with and without SCT (Table S2).

Adverse events

No significant difference in the incidence of severe adverse events (AE ≥ grade 3 by CTCAE criteria[22]) was seen among AA vs Caucasian donors. Among AA donors with SCT, one subject experienced a grade >3 SAE with diffuse body pain on days 4 and 5 of G-CSF administration, requiring hospitalization. This patient had a history of rheumatoid arthritis, requiring opiates at baseline. Among AA donors without SCT, one subject was hospitalized overnight (grade >3 SAE) for bleeding from a central venous catheter site. Accurate assessment of grades 1 and 2 AEs was unavailable due to inconsistent data collection in our retrospective study. NSAID and/or opiate requirement was similar among SCT vs non-SCT AA donors. SCT donors did not demonstrate significant elevations in serum creatinine or transaminases compared to their non-SCT AA counterparts following G-CSF administration. None of 41 HPC components from SCT donors congealed upon thaw.

DISCUSSION

Our study demonstrates that healthy African American donors are characterized by significantly more robust CD34+ mobilization responses to G-CSF than Caucasian donors. This effect was independent of age, gender, BMI, presence of hemoglobin S, and other variables, and occurred despite physiologically lower neutrophil counts among AAs than Caucasians prior to G-CSF stimulation. Other investigators failed to find such robust differences between AA and Caucasian donors, but those studies were smaller and did not take all relevant variables into account in a structured multivariate analysis.[15] A recent study demonstrated findings similar to our study with regard to racial discrepancies in CD34+ cell mobilization. However, collection efficiencies were dependent on donor BMI and sex[22]. In our experience, pre-apheresis CD34+ cell counts were the most important predictors of CD34 yields per liter processed after adjusting for donor demographics, G-CSF dose per kg, laboratory parameters, and procedure related variables.

Benign ethnic neutropenia has been associated with the lack of Duffy antigen expression on red blood cells, which is found in 67% of AAs but is rare in Caucasians. Duffy antigen is a chemokine receptor which can inhibit leukocyte migration[9]. Variability in expression of Duffy antigen thus might be a plausible explanation for the marked difference in HPC mobilization between AA and Caucasian subjects. However, we found no significant differences in HPC mobilization among AA donors with or without Duffy expression on their blood cells. Surprisingly, we found a marked enhancement in neutrophil mobilization

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in response to G-CSF in AA donors with benign ethnic neutropenia vs those with normal baseline ANC counts.

Our analysis was limited by small sample size, and our understanding of the actual mechanisms underlying this racial variation in HPC mobilization is speculative. Genome-wide association studies have identified variants in the c*mpl* gene among AAs[23,24]. MPL is the platelet and megakaryocyte receptor for thrombopoietin (TPO), an essential regulator of megakaryocyte differentiation and platelet production. TPO is also known to regulate the HSC niche[25]. It is possible that MPL variants among AAs may mediate differential responses to G-CSF stimulated stem cell egress from the marrow niche.

A ceiling effect in response to increased doses of G-CSF (>10 mcg/kg) was seen in AAs but not in Caucasians, suggesting that dose titration based on race might be used to optimize HPC yields. From a clinical standpoint, mobilization failures were more common in Caucasians and may result in the need for second day apheresis collections. Preemptive application of knowledge about racial differences in HPC mobilization may help transplant clinicians plan apheresis collection schedules and use resources more effectively, avoiding overcollection in some cases, and averting the need for additional collections in others. The identification of a subgroup of donors more likely to yield robust CD34+ cell collections may also help narrow the choice of donors from unrelated registries. Donors may also be counselled prior to donation on what to expect based on their demographic characteristics.

Lymphapheresis within the 7 days preceding G-CSF administration was found to enhance CD34+ mobilization and increase HPC apheresis yield. Platelet depletion during the prior lymphapheresis procedure may have resulted in a TPO-mediated increase in progenitor cells common to both megakaryocytes and HPCs. The increase was not significant if lymphapheresis was performed greater than 7 days prior to GCSF administration, suggesting a transient HPC stimulation effect. Interestingly, a marginal decrease in platelet counts was observed following G-CSF administration, suggesting a competitive “steal” of common progenitors towards HPC production. The effects of lymphapheresis and the lowering of platelet counts with G-CSF were independent of race.

CD34+ cell collection efficiency was correlated in prior studies with iron deficiency and low MCV and was related to abnormal cell separation mechanics during apheresis[17]. In our cohort, AAs demonstrated significantly lower MCV and hemoglobin levels than Caucasians both at baseline and following G-CSF administration; however, mean CD34+ collection efficiency was similar in both groups. It is likely that the value of the MCV is less important than the cause of a low MCV in terms of impact on apheresis device performance. Iron deficiency is associated with the presence of red cells of highly variable size, as reflected in an elevated red cell distribution width (RDW). We have found that a high RDW in the presence of a low MCV is more likely to be associated with impaired leukapheresis collection efficiency than a low MCV alone. Sickle trait subjects had a normal RDW, thus explaining the lack of impact of the low MCV on CD34+ collection efficiency.

Common adverse events due to G-CSF injections include headaches, bone pain, myalgias, and insomnia. Occasionally, more severe adverse events such as splenic rupture, myocardial

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infarction and arrhythmias have been reported in healthy donors. Adverse events in our donor cohort were generally of mild to moderate severity and were similar to those reported in prior studies[25,26]. In contrast, adverse effects of G-CSF can be significant in patients with sickle cell anemia and include cases of life-threatening sickling crisis[26-29]. One small randomized trial found that G-CSF mobilization and HPC apheresis were as safe in donors with sickle cell trait as they were in AA non-trait donors[18]. Yet donors with sickle cell trait are excluded from participation in the NMDP registry, based largely on a single case of G-CSF-associated multiorgan failure in a patient with compound heterozygous sickle cell/β+ thalassemia, which, unlike SCT, is a form of sickle cell disease.[30] Since sickle cell trait is present in up to 10% of AAs, eliminating these individuals also negatively impacts the unrelated donor pool. Our data include the largest number of consecutive AA donors with sickle cell trait yet reported to undergo G-CSF-assisted HPC collection, and demonstrate no differences in occurrence of severe adverse clinical events, efficacy of CD34 mobilization, efficiency of CD34 collection, or product loss during cryopreservation and thaw, compared with HPC donations from non-trait AA donors.

In conclusion, racial differences in G-CSF-mediated CD34+ cell mobilization are a novel clinical finding and occur in a direction paradoxical to that predicted by known physiologic mechanisms. Further evaluation of race-associated genetic polymorphisms in relation to G-CSF pharmacokinetics may help improve G-CSF dosing strategies. Clinically, identifying donors at risk for either poor or exceptionally good mobilization may help transplant teams plan ahead and allocate resources appropriately. Finally, the absence of significant adverse clinical events or deleterious changes in product quality among donors with sickle cell trait suggests that these individuals may safely be included in unrelated donor registries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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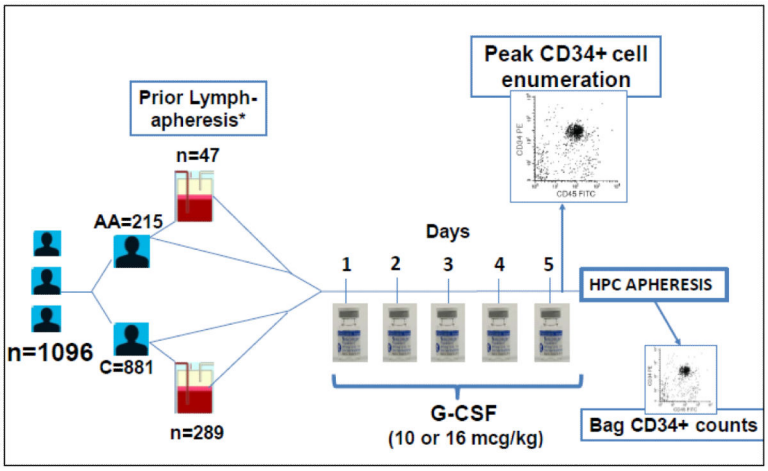

Figure 1. Study design

*Within 7 days before HPC collection. AA=African American, C=Caucasian. Peak CD34+ cell enumeration was performed as a stat pre-apheresis flow cytometry assay with results known within 3 hours of starting the procedure.

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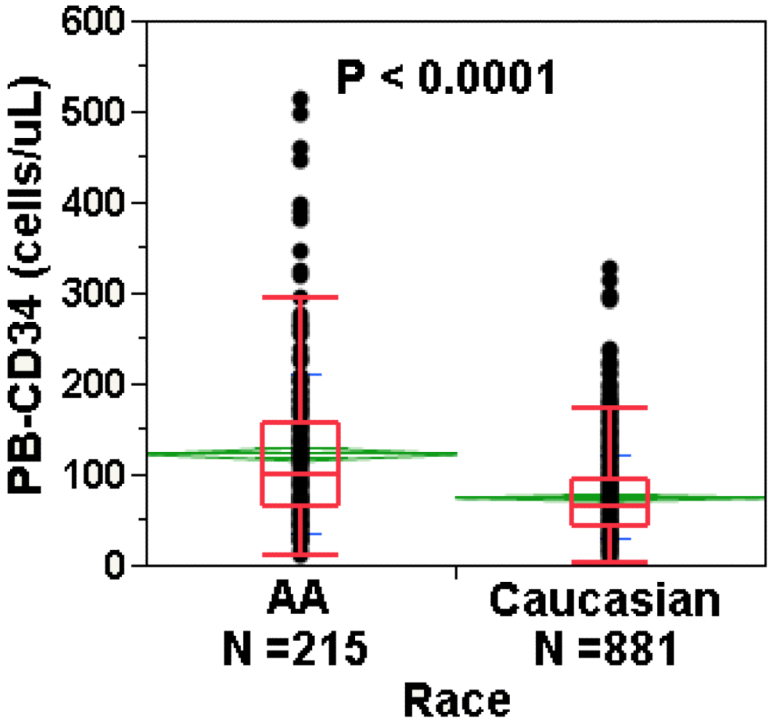

Figure 2. CD34+ cell mobilization responses in African Americans vs Caucasians

G-CSF-assisted HPC mobilization was significantly better in African Americans than Caucasians. PB=peripheral blood. The whisker-plot box contains the middle 25 to 75% of the data, with median shown by the line inside the box, and top and bottom lines outside the box demarcating the lowest 10% and highest 90% of the data. The mean is represented by the line through the center of the diamond, the upper and lower boundaries of the diamond showing the standard deviation.

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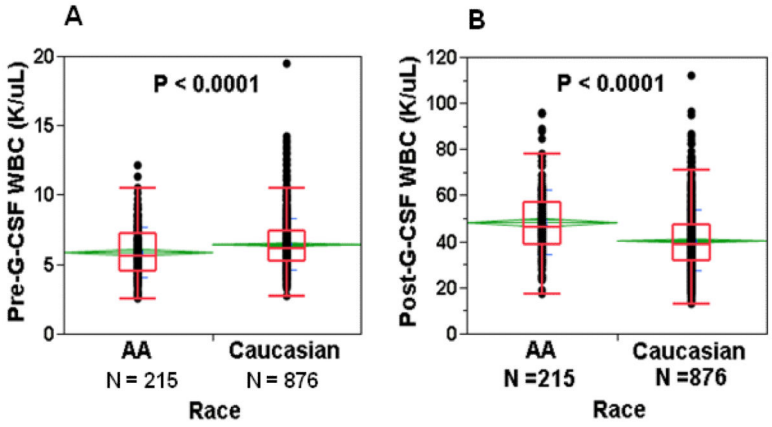

Figure 3. Effect of G-CSF on changes in WBC counts in African Americans vs Caucasians

A. Baseline WBC was significantly lower in African American than Caucasian donors. B. Paradoxically, WBC counts following G-CSF were significantly greater in African Americans than Caucasians. See legend to Figure 2.

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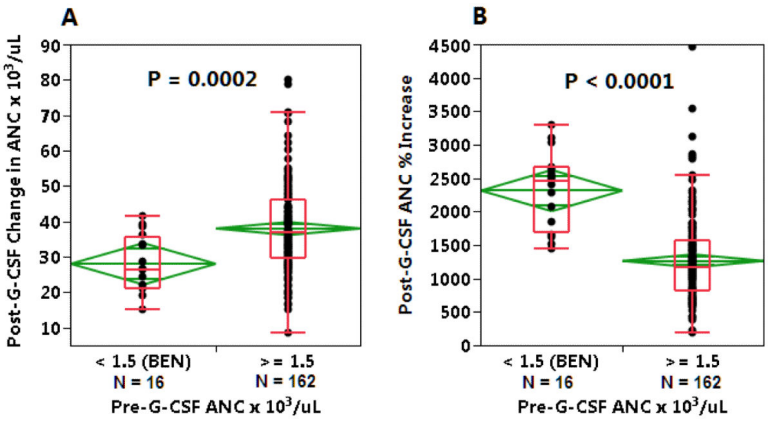

Figure 4. Effect of G-CSF in African Americans with benign ethnic neutropenia

A. ANC increase following G-CSF administration was greater in African American donors without than with benign ethnic neutropenia (BEN, defined as baseline ANC $<1.5 \times 10^3$/uL). B. However, percent ANC increase after G-CSF was significantly greater in AA subjects with BEN. See legend to Figure 2.

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Table 1

Donor demographics

	African Americans	Caucasians	p-value*
N (%)	215 (20)	881 (80)	
Male (%)	97 (45)	458 (52)	0.09
Age (yrs)	39 ± 13	43 ± 14	0.001
Height (cm)	171 ± 11	172 ± 10	0.22
Weight (kg)	86 ± 19	81 ± 19	0.001
BMI	30.4 ± 7.2	26.8 ± 6.1	<0.0001
Total G-CSF dose (mcg/d)	920 ± 196	850 ± 205	<0.0001
G-CSF dose per kg (mcg/kg/d)	10.9 ± 1.7	10.6 ± 1.6	0.03

*P<0.01 considered significant

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Table 2

Regression analysis of factors associated with higher CD34+ cell counts

Univariate Analysis	**p-value**	**Multivariate analysis (after adjusting for total GCSF dose)**	**p-value**
Total G-CSF dose	**$<10^{-24}$**	**African American race**	**$<10^{-19}$**
African American race	**$< 10^{-23}$**	Baseline platelet count	**$<10^{-17}$**
Higher BMI	**$<10^{-23}$**	Baseline MNC count	**$<10^{-9}$**
Higher baseline platelet count	**$<10^{-14}$**	Prior lymphapheresis	**0.0003**
Higher baseline MNC count	**$<10^{-10}$**	Male gender	**0.0003**
Prior lymphapheresis	**0.0004**	Younger age	**<0.001**
Male gender	**0.0009**	Higher BMI	**0.003**
Younger age	**0.08**		

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Table 3

Effect of race on pre-apheresis blood CD34+ cell count

Pre-apheresis blood CD34+ cell count/uL	Caucasian donors		African American donors	
	N	%	N	%
< 20	54	6.1	3	1.4
20-30	74	8.4	5	2.3
31-50	162	18.4	23	10.7
51-80	256	29.1	51	23.7
81-120	216	24.5	49	22.8
>120	119	13.5	84	39.1
Total	**881**	**100**	**215**	**100**

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Table 4

Effect of G-CSF on laboratory parameters

	African Americans	Caucasians	p-value
Baseline platelets (10^3/uL)	260 ± 65	251 ± 58	0.06
Baseline MNC (10^3/uL)	2.46 ± 0.67	2.48 ± 0.69	0.8
Baseline Hb (g/dL)	13.4 ± 1.4	14.2 ± 1.3	<0.0001
Baseline MCV (fL)	85.5 ± 6.3	89.6 ± 4.5	<0.0001
Baseline RDW (%)	13.1 ± 1.7	12.3 ± 1.2	<0.0001
Post-GCSF platelets (10^3/uL)	248 ± 144	231 ± 56	0.09
Post-GCSF MNC (10^3/uL)	6.7 ± 2.1	5.8 ± 1.8	<0.0001
Post-GCSF Hb (g/dL)	12.8 ± 1.5	13.4 ± 1.3	<0.0001
Post-GCSF MCV (fL)	85.8 ± 6.1	90.2 ± 4.6	<0.0001
Post-GCSF RDW (%)	13.0 ± 1.8	12.4 ± 1.3	0.0008