To the editor:

The impact of HMG-CoA reductase inhibition on the incidence and severity of graft-versus-host disease in patients with acute leukemia undergoing allogeneic transplantation

Acute graft-versus-host disease (GVHD) is the major cause of morbidity and mortality after allogeneic stem-cell transplantation (SCT).[1] In the December 15, 2007, issue of *Blood*, Zeiser and colleagues[2] reported protective effects of atorvastatin against acute GVHD in a major histocompatibility complex (MHC) mismatched mouse model, while preserving graft-versus-leukemia (GVL) activity and donor engraftment. Through a series of elegant experiments the authors were able to delineate different effects of atorvastatin in donor T cells (Th-2 polarization) and recipient antigen presenting cells (downregulation of costimulatory molecules and MHC-II expression) leading to reduction in acute GVHD. Statins have shown promise in Th-1–mediated autoimmune diseases by promoting a Th-2 bias.[3,4] Hori et al reported activity of statins in patients with refractory chronic GVHD by promoting Th-2 polarization.[5] The effects of statins on acute GVHD after human allogeneic stem cell transplantation have not been previously reported.

We therefore asked whether statin use at the time of allogeneic SCT would result in reduced acute GVHD while sparing GVL activity. Sixty-seven consecutive patients with acute leukemia underwent T cell–replete allogeneic SCT between June 2002 and October 2006 at our institution. Patients taking statins (defined as any 3-hydroxy-3-methylglutaryl-coenzyme-A [HMG-CoA] reductase inhibitor) at 40 mg/day or more for at least 1 month before and 3 months after allogeneic SCT (n = 10) were compared with those without a history of statin use (n = 57). The median age was 43 years (range, 20-73 yrs). Diagnosis included acute myeloid leukemia (AML; n = 49) and acute lymphoblastic leukemia (ALL; n = 18). The 2 groups had similar baseline characteristics including age, diagnosis, stem cell source, donor type, degree of HLA-compatibility, GVHD prophylaxis, conditioning regimen, and disease risk category (standard-risk defined as patients with acute leukemia receiving a transplant in first complete remission; Table 1). Acute GVHD was scored according to modified Glucksberg criteria.[6] The rate of grade 2-IV acute GVHD was 10% (n = 1) in the statin group compared with 40% (n = 23) in the no-statin group (P = .08). Fifty-six patients were evaluable for chronic GVHD. No difference in the incidence of chronic GVHD was seen in patients using statins (55%) compared with those in the no-statin group (57%; P = .9). No patient in either group experienced primary or secondary engraftment failure. On subgroup analysis of patients with AML only (n = 49), a significantly reduced incidence of grade 2-IV acute GVHD was seen in the statin group (0%) compared with 43% (n = 18) in the no-statin group (P = .02). Rates of chronic GVHD were 43% and 58% in similar order (P = .68). We further tested to determine whether statin use, while reducing acute GVHD, mitigated the GVL effect in patients with AML. Kaplan-Meier estimates of progression-free survival (PFS) at 3years in AML patients with or without statin use were 54% and 28%, respectively (P = .17; Figure 1). This nonsignificant trend of improved PFS indicates that the GVL is preserved in patients using statins at the time of allografting.

In summary, our findings suggest that the recent observations made by Zeiser and colleagues in a murine model may have clinical relevance and hints at the potential of statins in reducing acute

Table 1. Baseline characteristics of patients in the statin and no-statin groups

	Statin group, n (%) (n = 10)	No-statin group, n (%) (n = 57)	*P*
Median age, y (range)	50 (27-62)	42 (20-73)	.72
Sex			.29
Male	4 (40)	35 (61)	—
Female	6 (60)	22 (39)	—
Stem-cell source			.58
PBSC	10 (100)	51 (89)	—
BM	0	6 (11)	—
Donor source			.14
HLA-matched sibling	9 (90)	36 (63)	—
HLA-matched unrelated	1 (10)	16 (28)	—
HLA-mismatched unrelated	—	5 (9)	—
Diagnosis			.71
AML	8 (80)	41 (72)	—
ALL	2 (20)	16 (28)	—
Disease risk			.49
Standard-risk	6 (60)	25 (44)	—
High-risk	4 (40)	32 (56)	—
Myeloablative conditioning			.09
Yes	7 (70)	52 (91)	—
No	3 (30)	5 (9)	—
GVHD prophylaxis			.39
CSA/MTX	5 (50)	47 (82)	—
FK/MTX	3 (30)	10 (18)	—
CSA	2 (20)	—	—
Median $CD34^+$ cell dose (10^6 cells/kg recipient weight)	5.44	4.82	.73
Median $CD3^+$ cell dose (10^6 cells/kg recipient weight)	2.76	2.66	.81
Conditioning regimen			.20
TBI/Cy	2 (20)	8 (14)	—
Bu/Cy	6 (60)	33 (58)	—
Flu/Bu	2 (20)	5 (9)	—
Others	—	11 (19)	—

BM indicates bone marrow; Bu/Cy, busulfan and cyclophosphamide; CSA, cyclosporine; FK, tacrolimus; Flu/Bu, fludarabine and busulfan; MTX, methotrexate; PBSC, peripheral blood stem cells; TBI/Cy, total body irradiation and cyclophosphamide; and —, not applicable.

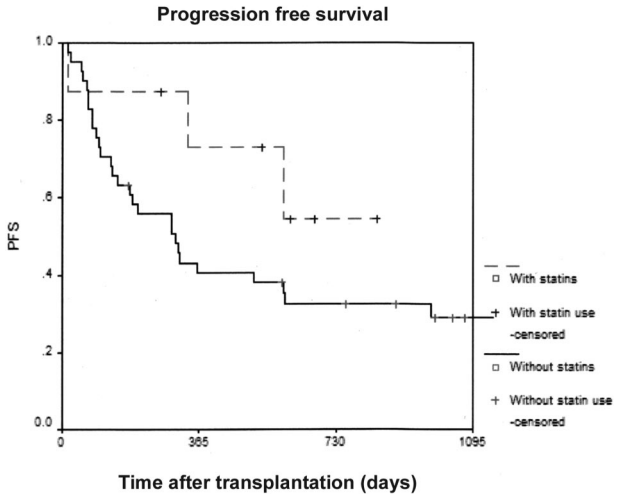

Figure 1. Kaplan-Meier estimates of progression-free survival after allogeneic stem cell transplantation in patients with acute myeloid leukemia.

GVHD while preserving donor engraftment and GVL effect, at least in AML. Our results should be interpreted with caution given the limited and retrospective nature of this analysis. The optimal dose and timing of statin use to prevent GVHD is unknown. Whether priming healthy donors with statins before stem cell mobilization would provide added protection against acute GVHD compared with statin use in transplantation patients warrants further investigation.

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Contribution: M.H. designed and performed the study, analyzed and interpreted the data, and wrote the manuscript; F.T.A. provided assistance with the statistical design and analysis of the study; S.M.D. designed and performed the study, analyzed and interpreted the data, and wrote and approved the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

Elucidating the role of monocyte-derived hepcidin

Anemia of chronic disease is an important cause of morbidity in patients suffering from chronic inflammatory states and has been rechristened anemia of inflammation with the onset of molecular insights into the pathogenesis of this disease in recent years.[1]

Theurl and colleagues have shown that hepcidin, the key regulator of systemic iron homeostasis produced chiefly in the hepatocytes and to a lesser extent in circulating monocytes, can cause iron retention within these cells when expressed in higher amounts as during inflammation.[2] This corroborates the findings of work done earlier in mice addressing the importance of toll-like receptor 4 (TLR4)–stimulated production of hepcidin in myeloid cells.[3]

However, to truly observe the role of monocyte-derived hepcidin under in vivo conditions, it would require hepatocyte-specific and time-dependent conditional knockout of hepcidin production to note whether interleukin 6 (IL-6) is still able to induce the production of hypoferremia at least locally if not systemically. This is because IL-6 appears to induce hepcidin production both in the monocytes and in the hepatocytes. This for obvious reasons is practical only in a murine model as opposed to humans, but nevertheless important in firmly establishing the concept put forward by the authors.[2]

Theurl et al have shown a strong correlation between the levels of serum IL-6 and monocyte hepcidin mRNA levels, but go on to state in their discussion that the sequestration of hepcidin produced by monocytes locally may be of specific importance at inflammatory sites with poor perfusion, such as the interstitium. An important question to consider is the contribution made by production of cytokines by the cells at such sites rather than a systemic correlation to support the statement.

Finally, Theurl et al have not commented on why serum ferritin levels do not correlate with the monocyte hepcidin mRNA levels, though hepcidin causes iron retention within these cells. The above issues need to be addressed to firmly establish the role of monocyte-derived hepcidin in the regulation of iron homeostasis in anemia of chronic disease.

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Conflict-of-interest disclosure: The author declares no competing financial interests.

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Response:

Monocyte hepcidin and the anemia of chronic disease

We appreciate the comments of our colleagues and agree with them that conditional knockouts of hepatocytes would be a pivotal tool to provide us with new information on the true role of monocyte-derived hepcidin for the control of body iron homeostasis under inflammatory conditions. An alternative approach would be to study this issue by functional knockout of monocytes using clodronate liposomes.

However, it has to be kept in mind that the amount of hepcidin produced by monocytes/macrophages is a magnitude lower than that reported for hepatocytes.[1] Thus, due to its low concentration, systemic effects on iron absorption as observed in transgenic or hepcidin knockout mice are unlikely to be exerted by monocyte-derived hepcidin.[2,3] Accordingly, the presumed function of monocyte hepcidin is to readily control