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Reply

In a careful examination of our recent review of salvage therapies for steroid-refractory acute graft-versus-host disease (aGVHD) [1], Greinix et al. have rightfully identified that the discussion of extracorporeal photopheresis (ECP) did not include all published data. Specifically, our review cited the results of a pilot study conducted by Greinix et al. [2], but did not include a later report that summarized both the results of the pilot study and a prospective phase II trial [3].

In their response to our review, Greinix et al. note that there were important differences in patient characteristics and therapy between the pilot trial and the phase II trial that might have contributed to more encouraging responses. Compared with the pilot trial, the phase II trial showed higher rates of complete remission (CR) of aGVHD in patients with gastrointestinal involvement (73% vs 25%) and grade IV disease (60% vs 12%). This does not appear to be a consistent trend, however; the pilot trial showed higher rates of CR of aGVHD in patients with grade II disease (100% vs 85%), grade III disease (67% vs 43%), and liver involvement (67% vs 55%). Moreover, the ability to draw conclusions about the comparative efficacy of ECP in grade IV aGVHD across the pilot and phase II trials is limited by the small number of subjects (n = 5 in each trial).

Although limited to small, single-center studies, the overall experience reported by Greinix et al. and other published literature suggests that ECP can induce CR of steroid-refractory aGVHD and can facilitate liberation from glucocorticoids. We agree that prospective, well-designed studies on refractory aGVHD are needed to discern the true benefit of salvage therapies.

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Is Complement Alternative Pathway Disregulation Involved in Veno-Occlusive Disease of the Liver?

We were pleased to read the article by Cutler et al. [1] recently published in *BBMT*. Veno-occlusive disease of the liver (VOD) is a serious complication of hematopoietic stem cell transplantation (HSCT), particularly after busulfan (BU)-based conditioning regimens, and it could be very important to identify biomarkers useful to predict its occurrence. We agree with the authors that the pathogenesis of VOD is multifactorial. In this regard we have noticed that some clinical aspects can be commonly observed both in VOD and HELLP (hemolysis, elevated liver enzymes, and low platelet number) syndrome. VOD is thought to be initiated by injury to the area surrounding the central vein; damage is seen in sinusoidal endothelial cells (EC) and in hepatocytes in zone 3 of the liver acinus. Structural damage continues with progressive venular occlusion, culminating in widespread zonal liver disruption. Recently, several cases of HELLP syndrome have been associated with complement disregulation [2], which is frequently observed in aHUS (atypical hemolytic uremic syndrome). In aHUS, microvascular EC injury has been linked to excessive complement activation via the alternative pathway (AP), in that approximately 50% of these patients have AP complement activating missense mutations or functional variants in genes encoding complement regulatory proteins: factor H (CFH), factor I (CFI), membrane cofactor protein (MCP), CFH-related proteins, C4b binding protein, thrombomodulin, C3, and factor B [3-5].

A pilot study was conducted to identify sequence variants of CFH and CFI in 7 patients who had undergone an allogeneic HSCT with BU and cyclophosphamide (CY) conditioning regimen for acute myeloid leukemia (AML). Three patients showed classical signs of VOD according to the Seattle criteria within 35 days from the transplant. The remaining 4 control patients did not exhibit clinical signs of VOD. All samples, for gene sequence evaluation, were obtained before treatment for AML.

No CFI gene sequence variants were detected in either VOD or control groups. Two variants of the CFH gene were detected exclusively in the VOD group. One was a novel intronic variant, IVS 18-86 T>C, whereas the other, p.E936D, had been previously associated with aHUS [5].

Our preliminary study might suggest that disregulation of the complement system may represent the first step of the process. These data could support the conclusions of Cutler et al. [1], suggesting the

development of endothelial damage only in a subset of patients. However, because VOD is a rather rare disease, to confirm our results it is necessary to enrol many more patients in a multicenter study.

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Age and Total-Body Irradiation in Addition to Corticosteroid Dose Are Important Risk Factors for Avascular Necrosis of the Bone

This report by McAvoy et al. [1] highlights important aspects of the risk factors for the development of avascular necrosis (AVN) of the bone after hematopoietic cell transplantation (HCT). They show a clear relationship between steroid exposure and impact of steroid dose on the risk of developing AVN. Our group has recently presented data of a retrospective case-control study [2] and found some important differences compared to McAvoy's findings. We analyzed a variety of known risk factors in a cohort of patients (cases, 50; controls, 156) without a pretransplant diagnosis of AVN undergoing allogeneic HCT (allo-HCT) from a human leukocyte antigen (HLA)-identical related donor (n = 133) or HLA-matched unrelated donor (n = 65) or umbilical cord HCT (n = 6) after either ablative (n = 142) or reduced-intensity (n = 64) preparative regimens. Median time from transplant to AVN diagnosis was 1.2 years (range: 0.12-5.2). Median follow-up was 3.7 years (range: 0.2-8.6) for AVN patients versus 1.9 years (range: 0.3-9.0) for controls ($P < .001$). Patients with AVN were significantly younger than controls at time of transplant (median age 37 versus 48 years, $P < .001$) and were more likely to have a history of tobacco use (68% versus 43%, $P = .012$). In univariate analyses, unrelated donor (48% of AVN patients versus 30% of controls, $P = .043$), use of total-body irradiation (TBI) (irrespective of dose) in preparative regimens (72% versus 46%, $P = .001$), and systemic steroids (SS) to treat graft-versus-host disease (GVHD) (98% versus 84%, $P = .009$) were associated with increased risk of AVN. Mean peak dose of SS was higher in the AVN patients versus controls (1.6 versus 1.4 mg/kg/day prednisone equivalent, $P = .014$). The median duration of SS treatment prior to AVN diagnosis was 228 days (range: 104-400), and 60% of these patients were receiving SS at the time of AVN diagnosis. Median total duration of SS therapy in patients with AVN was 712 days (range: 293-1195) and was significantly longer compared with the control cohort (383 days; range: 38-630) ($P < .001$). Interestingly, this association was seen only in patients age >40 years (AVN versus control; 852 days [range: 591-1616] versus 416 days [range: 15-596], $P < .001$]. The finding of steroid exposure and dose relationship (function of dose and duration) was similar to what was seen in the McAvoy study, although duration of steroid use was not specifically addressed. There were no significant differences in ethnicity, gender, diagnosis, disease status, body mass index (BMI), bone density, incidence or severity of GVHD, or survival between the AVN and control patients. In multivariate analyses, age (<40 years; odds ratio [OR] = 2.55, $P = .008$), TBI (OR = 2.29, $P = .027$), and SS (>1 mg/kg/day; OR = 3.48, $P = 0.052$) were independent predictors of AVN.

Our study identifies the use of TBI in preparative regimens as a risk factor for development of AVN. This factor was not identified in the McAvoy study, but has been previously reported [3]. In our study, age <40 years was associated with a higher risk of AVN, and is an important observation and differs from previous study, where older age has been associated with AVN [4]. The McAvoy study was controlled for age between cases and controls and thus could not address this. Pretransplant smoking was identified as a significant factor in univariate analyses and has