Hyperlipidemia and Statin Use after Allogeneic Hematopoietic Stem Cell Transplantation

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An increased incidence of cardiovascular complications has been documented in recipients of allogeneic hematopoietic stem cell transplantation (HSCT). Despite this, little is known about the risk factors for hyperlipidemia or the role of lipid-lowering therapy early after transplantation. We performed a retrospective analysis of all patients who underwent allogeneic HSCT at the Dana-Farber Cancer Institute from 1998 to 2008 and who survived more than 100 days. The incidence of hypercholesterolemia and hypertriglyceridemia in the first 2 years after transplantation was 73.4% and 72.5%, respectively. In multivariable analysis, the development of acute graft-versus-host disease was independently associated with both hypercholesterolemia (odds ratio [OR] = 1.62) and hypertriglyceridemia (OR = 1.54) after transplantation. Statin use was instituted in 29% of patients and was associated with a significant net reduction in total cholesterol (65 mg/dL, \( P < .0001 \)), triglyceride (118 mg/dL \( P < .0001 \)), and LDL levels (59 mg/dL \( P < .0001 \)) without any significant adverse effects. These data suggest that hyperlipidemia is common in the first 2 years after allogeneic transplantation when most patients remain under the care of the transplantation physician and lipid-lowering therapy may be underutilized. Given the cardiovascular risk associated with hyperlipidemia and the tolerability of statins, further prospective evaluation of lipid abnormalities and their treatment seems well warranted.


KEY WORDS: Hyperlipidemia, Hypercholesterolemia, Hypertriglyceridemia, Statin, GVHD, Lipid

INTRODUCTION

There is a growing appreciation that coronary artery disease and myocardial infarction are relatively common late complications of allogeneic hematopoietic stem cell transplantation (HSCT) [1-3]. Hyperlipidemia is a well-known risk factor for atherosclerotic heart disease [4]; several reports have documented the incidence of hyperlipidemia and cardiovascular events late after HSCT [1,3,5-8]. However, little is known about the incidence of hyperlipidemia within the first 2 years. If there is a characteristic pattern of changes in lipid profiles early after transplantation, more aggressive lipid modification therapy at that time may help ameliorate late cardiovascular complications.

HMG-CoA reductase inhibitors (statins) are the mainstay of treatment for hyperlipidemia, have salutary effects on low-density lipoprotein (LDL), and are widely used in the general population [9]. However, because of the concern of potential liver toxicity, drug interactions, and monitoring for liver graft-versus-host disease (GVHD), they are often discontinued at the time of HSCT and may not be started after transplantation. The reported rate of statin use in HSCT patients ranges from 5% to 15% in previously reported series, although it is unclear whether their use is safe and/or effective in this setting [10-12].

We performed a retrospective chart review on all patients who underwent allogeneic HSCT at the Dana-Farber Cancer Institute/Brigham and Women’s Hospital from 1998 to 2008, survived more than 100 days posttransplantation, and had lipid measurements after transplantation. We describe the incidence and time course of hyperlipidemia after allogeneic HSCT, identify risk factors for hyperlipidemia, and examine the use and effect of statin therapy for hyperlipidemia.
METHODS

Patient Population

The subjects of this retrospective study were 1493 consecutive patients who underwent allogeneic HSCT at the Dana-Farber Cancer Institute from 1998 to 2008 and who survived more than 100 days following transplantation. A total of 732 subjects had no total cholesterol measurements from day 30 to 2 years after transplantation and were excluded from the analysis. Patients were treated according to investigational protocol, if applicable, or institutional standard of care. Myeloablative conditioning regimens included cyclophosphamide (1800 mg/m² × 2 days) plus total body irradiation (14 Gy total in 7 fractions over 4 days) or busulfan (16 mg/kg orally or 12.8 mg/kg intravenously total) in 16 divided doses. Reduced-intensity conditioning regimens consisted of fludarabine (30 mg/m² intravenously) and busulfan (0.8 or 1.6 mg/kg intravenously) for 4 days. GVHD prophylaxis consisted predominantly of a calcineurin inhibitor and methotrexate, tacrolimus plus sirolimus with or without low dose methotrexate, or ex vivo T cell depletion with or without additional immune suppression. Lipid profiles were analyzed by standard methods either at the discretion of the primary transplantation physician or according to protocol. Routine practice was for lipid profiles to be drawn after a minimum 9-hour fast. This retrospective analysis was approved by the Office for the Protection of Research Subjects at the Dana-Farber Cancer Institute.

Data Extraction

Patient and donor characteristics, stem cell source, conditioning and prophylactic regimens, and incidence and severity of acute and chronic GVHD (aGVHD, cGVHD) were retrieved from the bone marrow transplant data repository at the Dana-Farber Cancer Institute. Lipid values and outpatient medication history were accessed via an electronic medical record system covering more than 10 hospitals and associated clinics in the greater Boston area. Hyperlipidemia was defined as any outpatient total cholesterol value ≥200 mg/dL or triglyceride value ≥200 mg/dL. These cutoffs were derived from current treatment guidelines [4]. Lipid values obtained within 30 days of transplantation were excluded from the statistical analysis. Patients with any 30-day prescription for a statin listed among their current or discontinued medications were considered to have been treated with statins. Only prescriptions starting from day 0 to 2 years after transplantation were considered.

Statistical Analysis

Patient baseline characteristics were reported descriptively and the chi-square test or the Wilcoxon rank sum test was used for group comparison. Differences in lipid levels between pre- and posttransplantation measurements were tested using the Wilcoxon signed rank test. Whether the status of hyperlipidemia was in agreement before and after transplantation was tested using McNemar’s test. Cumulative incidence of aGVHD and cGVHD was calculated reflecting time to relapse or death without developing GVHD as a competing risk. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method. Potential prognostic factors for hyperlipidemia after HSCT were examined in the univariable and multivariable logistic regression analysis. The functional form of year of transplantation was examined using restricted cubic spline function [13]. All tests were 2 sided. All calculations were performed using SAS 9.2 (SAS Institute, Cary, NC) and R 2.10.1 (The CRAN project).

RESULTS

Patient Characteristics

The characteristics of the patients included in the study are detailed in Table 1. Among the 761 patients included in the study, median age at transplantation was 49 years (range: 17-73), 60% had myeloid neoplasms, 42% received grafts from matched related donors, 46% from matched unrelated donors, and 55% received myeloablative conditioning. Greater than 95% of patients received tacrolimus-based GVHD prophylaxis. Sirolimus was included as GVHD prophylaxis for 50%. The cumulative incidence of grade II to IV aGVHD was 26% at 200 days after transplantation; the cumulative incidence of cGVHD at 2 years after transplantation was 60% (Table 2). Also listed in Tables 1 and 2 are the baseline characteristics and cumulative incidence of GVHD for 732 excluded patients who underwent HSCT within the same time period, were alive at day 100, but did not have lipid values checked within 2 years after transplantation. The patients who had lipid values checked were older (P = .001), more likely to be male (P = .016), more likely to have received peripheral blood stem cell grafts (P < .001), more likely to have received sirolimus-based GVHD prophylaxis (P < .001), more likely to have received reduced-intensity conditioning regimens (P = .047), and were more likely to be overweight (P = .02) compared with patients who did not have their lipid values checked (Table 1). Lipid values were checked more frequently in the year 2002 and later than before 2002 (P < .001) (Table 1). There was no difference in the cumulative incidence of aGVHD at 200 days after transplantation in either group, although cGVHD was more common in those who had their lipids checked (P < .001) (Table 2).
Of the 761 patients included in the study, 556 (73.4%) had at least 1 posttransplantation total cholesterol value $\geq 200 \text{ mg/dL}$ and were considered hypercholesterolemic according to the ATP-III treatment guidelines (Table 3). Five hundred sixty patients also had at least 1 total cholesterol value recorded in the 90 days before transplantation. Of these, 179 (32.0%) were hypercholesterolemic before transplantation (Table 3). Among the 560 patients with both pre- and posttransplantation values, the median peak total cholesterol levels before and after transplantation were 178 and 241 mg/dL, respectively (pre–post change: 62 mg/dL, $P < .0001$ (Figure 1A). Posttransplantation hypertriglyceridemia (defined as any triglyceride measurement $\geq 200 \text{ mg/dL}$) was present in 531 patients (72.5%) (Table 3). Five hundred seventy-three patients had pretransplantation triglyceride levels measured. Of these, 225 (39.3%) were hypertriglyceridemic (Table 3). The number of patients with both pre- and posttransplantation triglyceride values was 554; among these, the median peak triglyceride levels before and after transplantation were 171 and 275 mg/dL, respectively (pre–post change: 109 mg/dL, $P < .0001$) (Figure 1B). Compiled total cholesterol and triglyceride values for the first 2 years after transplantation are presented in Figure 1C and 1D.

Comparison of Hyperlipidemia before and after Transplantation

To clarify the changes in lipid levels occurring with transplantation, we identified patients who had preexisting hyperlipidemia and those who had de novo hyperlipidemia after transplantation. Among 179 patients with preexisting hypercholesterolemia, 164 patients (92%) remained hypercholesterolemic after transplantation. Of the 381 patients with pretransplant total cholesterol $\geq 200 \text{ mg/dL}$, 249 patients (65%) became newly hypercholesterolemic after transplantation. Among patients who experienced a change in their status (hypercholesterolemic or not) before and after transplantation, 94% developed de novo hypercholesterolemia ($P < .001$; McNemar’s test). For patients with preexisting hypercholesterolemia, total cholesterol was higher after transplantation compared with those who had de novo hypercholesterolemia after transplantation (275 mg/dL versus 259 mg/dL, $P = .004$).

Among 216 patients with preexisting hypertriglyceridemia, 193 patients (89%) remained hypertriglyceridemic after transplantation. Of the 338 patients with pretransplantation triglyceride $< 200 \text{ mg/dL}$, 215 patients (64%) became newly hypertriglyceridemic after transplantation. Among patients who experienced a change in their status (hypertriglyceridemic or not)
before and after transplantation, 90% developed de novo hypertriglyceridemia ($P < .001$; McNemar’s test). For patients with preexisting hypertriglyceridemia, triglyceride values were higher after transplantation compared with those who had de novo hypertriglyceridemia after transplantation (398 mg/dL versus 305 mg/dL, $P < .001$).

To confirm that pretransplantation lipid levels were drawn on a random subset of patients, the rate of posttransplantation hypercholesterolemia and hypertriglyceridemia for those with and without pretransplantation values were compared. There was no difference in the rate of posttransplantation hypercholesterolemia for patients with and without pretransplantation values (74% versus 73%, $P = .75$). Similarly, there was no difference in the rate of posttransplantation hypertriglyceridemia for patients with and without pretransplantation values (74% versus 69%, $P = .24$).

**Risk Factors for Hyperlipidemia**

To identify risk factors for posttransplantation hyperlipidemia, patients with at least 1 total cholesterol $\geq 200$ mg/dL or triglyceride $\geq 200$ mg/dL from day 30 to 2 years after transplantation were identified. Logistic regression analysis was performed using baseline patient characteristics (age $\geq 50$, male gender, type of malignancy, overweight [body mass index $\geq 25$]), transplantation variables (unrelated or mismatched donor, stem cell source, conditioning regimen intensity, sirolimus-based GVHD prophylaxis), and posttransplantation variables (presence of grade II-IV aGVHD). In univariable analysis, being overweight at the time of transplantation and the development of grade II to IV aGVHD were associated with both posttransplantation hypercholesterolemia and hypertriglyceridemia (data not shown). Male gender and sirolimus use were associated only with posttransplantation hypertriglyceridemia (data not shown).

Multivariable logistic regression analysis was also performed using similar variables in the model (Figure 2A-B). There was a strong inverse correlation between sirolimus use and the presence of acute GVHD, so sirolimus use was not included in the model. The development of grade II to IV aGVHD was an independent risk factor for both posttransplantation hypercholesterolemia and hypertriglyceridemia (odds ratio [OR] = 1.62, $P = .02$ and OR = 1.54, $P = .036$, respectively) as was being overweight at the time of transplantation (OR = 1.64, $P = .0063$ and OR = 2.12, $P < .0001$, respectively). Male recipients (OR = 0.67, $P = .03$) and those receiving bone marrow allografts (OR = 0.57, $P = .02$) were less likely to have posttransplantation hypercholesterolemia compared with female recipients or those receiving peripheral blood stem cell allografts.

**Hyperlipidemia in Patients with aGVHD**

Among the patients with grade 0 to I aGVHD, the frequency of posttransplantation hypercholesterolemia was 71%, whereas among patients with grade II
to IV aGVHD, the frequency was 81% (P = .007). In patients with grade 0 to I aGVHD, the frequency of posttransplantation hypertriglyceridemia was 70%, whereas among patients with grade II to IV aGVHD the frequency was 79% (P = .01). The median peak total cholesterol level was 235 mg/dL for patients with grade 0 to I aGVHD and 262 mg/dL for patients with grade II to IV aGVHD (P < .001). The median peak triglyceride level was 264 mg/dL for patients with grade 0 to I aGVHD and 300 mg/dL for patients with grade II to IV aGVHD (P = .002).

Corticosteroid therapy is known to elevate serum lipids. Of the hypercholesterolemic patients with grade II to IV aGVHD, 81% were being treated with steroids at the time of their peak total cholesterol measurement. Of the hypertriglyceridemic patients with grade II to IV aGVHD, 73% were being treated with steroids at the time of their peak triglyceride measurement.

**Statin Usage after Transplantation**

Outpatient prescription records of the 761 patients in the study were searched for the presence of any statin medication. Sixty-two patients (8%) had been prescribed any statin medication before transplantation. Among these, statin therapy was resumed in 53 patients after transplantation (85%). Overall, 220 patients (29%) were prescribed statin therapy within the first 2 years after transplantation. Atorvastatin was the most frequently prescribed statin (54%), followed by simvastatin (29%), pravastatin (8%), rosuvastatin (7%), lovastatin (2%), and fluvastatin (<1%).

The median day of initiation of statin therapy was 400 days after transplantation (range: 1-723 days). Changes in lipid values were calculated for patients who had values recorded in the 90 days before initiation of statin therapy and who had values recorded from 180 to 270 days following initiation of statin therapy. Median values obtained immediately before and after statin initiation are plotted in Figure 3 (total cholesterol before statin: 255 mg/dL, after statin: 190 mg/dL, N = 94, P < .0001; triglyceride before statin: 318 mg/dL, after statin: 200 mg/dL, N = 91, P < .0001; HDL before statin: 45 mg/dL, after statin: 52 mg/dL, N = 76, P = .51; LDL before statin 158 mg/dL, after statin 99 mg/dL, N = 49, P < .0001).

The medical records of the 220 statin-treated patients were reviewed for the presence of adverse drug reactions leading to discontinuation of the statins. In 76 patients (35%), statin therapy had been discontinued. The reasons for discontinuation included reaching target LDL (N = 11, 5% of all statin treated patients), relapse of disease with reinduction chemotherapy or second transplantation (N = 13, 6%), and evidence of possible statin toxicity (N = 7, 3%).
Of the 7 patients with possible statin toxicity, 2 had biopsy-proven aGVHD of the liver, 1 had suspected aGVHD of the liver, and 1 had veno-occlusive disease of the liver documented within the same time period as the discontinuation of statin therapy. Only 1 patient had elevation of liver enzymes attributed to statin therapy, although the measurements did not meet accepted criteria for statin toxicity [14]. One patient had muscle cramps without an elevation in creatine phosphokinase and 1 patient had rhabdomyolysis with creatine phosphokinase = 3186 U/L. Four patients (2%) discontinued statin therapy because of personal preference. In 41 patients (19% of all statin treated patients, 54% of all discontinuations), the reason for discontinuation of statin therapy was not documented in the medical record. There was no clear evidence of statin liver toxicity or rhabdomyolysis in any of these 41 cases.

**DISCUSSION**

Hyperlipidemia and atherosclerotic heart disease are increasingly recognized as late complications of allogeneic HSCT [8,15]. Several small studies have reported the incidence of posttransplantation hyperlipidemia to range from 11% to 58% [1,5-7,16,17]. The incidence of adverse cardiovascular events including myocardial infarction and stroke may also be more common in allogeneic HSCT recipients, particularly in those with aGVHD, when compared with siblings or recipients of autologous HSCT [1,3,18]. The present study examines the early posttransplantation changes in serum lipids in a large cohort of allogeneic HSCT recipients. We have described a pattern of elevated total cholesterol and triglyceride levels in the patients who had their lipids measured within the
first 2 years after transplantation. In the largest series of patients reported to date, we have demonstrated that aGVHD is an independent risk factor for both posttransplantation hypercholesterolemia and hypertriglyceridemia. Statins appeared to be effective in improving the lipid profiles in those in whom they were used and the incidence of toxicity appeared to be low. Whether early initiation of statin therapy after allogeneic HSCT would be effective in lowering the risk of cardiovascular events attributable to transplantation is currently unknown.

As a retrospective study, our analysis has several inherent limitations. Because lipid panels were collected at the discretion of outpatient providers, our results may not accurately estimate the true incidence of hyperlipidemia in all HSCT recipients. In particular, the group of patients who had their lipids checked was older, more likely to be overweight, and more likely to be male than the group of patients who did not have their lipids checked. Total cholesterol and triglyceride levels were chosen for the primary analyses because these data were available in the majority of patients, whereas LDL levels were not. Although total cholesterol and triglyceride levels are a part of the recommended cardiovascular risk assessment, therapeutic goals are based on LDL levels [4]. Further, the medical record did not allow verification that lipid panels were drawn in the fasting state, although our routine practice has been for these labs to be drawn after a 9- to 12-hour fast. Because our institution draws from a large referral base, some patients living farther away from our center may have had their lipids checked and managed locally. Their lipid measurements, prescription history, and potential adverse reactions to statins may not have been available for this study. In addition, because >95% of our patient population received tacrolimus for GVHD prophylaxis, we were unable to assess the contribution of this or cyclosporine to hyperlipidemia. Finally, the association of aGVHD with hyperlipidemia may be confounded by concomitant steroid use in many cases.

In addition to their beneficial lipid-lowering effects, statins are known to possess anti-inflammatory properties that likely contribute to their clinical benefit. A large randomized, placebo-controlled trial of rosvastatin in patients with normal lipid profiles showed a reduction in C-reactive protein levels and improved survival [19]. Several randomized studies of cardiac transplantation recipients have demonstrated a mortality benefit for statin use, and 2 have shown a decrease in major cardiac allograft rejection by statins [20-24]. Similar findings have been made in lung and renal allograft recipients, although not all studies have shown benefit in the latter [25-28]. Further, a number of trials in patients with rheumatoid arthritis and multiple sclerosis have demonstrated improved outcomes in patients treated with statins [29-33]. Thus, statins have a proven clinical benefit in multiple settings as adjunctive immune suppressive therapy.

Recent reports have begun to investigate the effect of immunomodulation with statins in allogeneic HSCT. A study in 2008 reported decreased incidence of grade II to IV aGVHD in recipients who had been on statins 1 month before transplantation and who continued on them for 3 months after transplantation [10]. A subsequent larger study showed decreased incidence of aGVHD in recipients of grafts from statin-treated donors [11]. Acute GVHD was not prevented when statin treatment was limited to the recipient alone. Recipient treatment was associated with decreased rates of cGVHD and an increased rate of relapse or disease progression [12]. Interpretation of these studies is confounded by the low rate of statin use in recipients and the potential biased use of statin therapy in patients free from complications of transplantation for other reasons. The mechanism underlying these observations is unknown, but in vitro and animal studies suggest Th2 polarization of the donor T cell pool may play a role [34,35].

With the growing body of evidence that statins may be important as adjuvant immune suppressive therapy and for controlling hyperlipidemia after transplantation, it is necessary to consider the frequency and efficacy of their use after HSCT. The frequency of statin use in our population of patients was higher when compared with prior studies (29% versus 15% in Hamadani et al. [10] and 5% in Rotta et al. [11]). The National Health and Nutrition Examination Survey study data shows a steady rise in statin use in the general population from 6.5% of all U.S. adults in 1999 to 2000 to 11.7% in 2003 to 2004, the latest available published data [9]. Because we required only 1 month of statin use to qualify, our study may overestimate the rate of statin use compared with these other works. Despite this, the efficacy of statin use in our study does not appear to be inferior to that seen in the general population. According to National Health and Nutrition Examination Survey data from 2003 to 2004, the average LDL of hyperlipidemic U.S. adults in the absence or presence of statin therapy was 158.4 mg/dL and 100.7 mg/dL, respectively, which is consistent with our findings in Figure 3 [9].

There are a number of obvious barriers to statin use after HSCT including interaction with other hepatotoxic or heparically metabolized medications, the potential for confounding the diagnosis of or worsening aGVHD or veno-occlusive disease of the liver, and the risk of inhibiting graft-versus-leukemia effects [12,36,37]. Statins are routinely used in cardiac transplantation, suggesting that their coadministration with calcineurin inhibitors is safe, although the use of azoles in such patients is much less common than in the allogeneic HSCT population [21-23]. Further,
multiple studies in patients with chronic hepatitis C and primary biliary cirrhosis have shown that statin therapy is well tolerated in patients with chronic liver disease [38-42]. Our data suggest that significant adverse reactions to statin therapy are relatively infrequent in the posttransplantation setting. Clearly, close monitoring should accompany the use of these medications in allogeneic HSCT patients.

These data provide the first detailed look at the patterns of hyperlipidemia that occur early after HSCT. They provide the strongest evidence to date that aGVHD is an independent risk factor for hyperlipidemia. Current guidelines recommend screening for hyperlipidemia in HSCT recipients at the same frequency as in the general population [43]. These guidelines were published before the cardiovascular risks of HSCT were well appreciated and they do not account for the rising age of the population undergoing HSCT [1,3,8,44,45]. Our data lend further support to the proposal of Griffith et al. [15] that lipid profiles be assessed 4 weeks after transplantation and then every 3 months while on immune suppressive therapy. Clinicians should be particularly attuned to lipid abnormalities in patients receiving sirolimus or in those who develop GVHD. Nevertheless, the risks and benefits of aggressive lipid-lowering therapy have not yet been established in this population. Several important questions remain: Is it safe to treat to established LDL goals? What are the risks of statin therapy? What role do statins play as adjuvant immune suppression? How can non-LDL lipid goals be safely achieved? Answering such questions will require a prospective trial of the use of statins in allogeneic HSCT.

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