Clinical Cancer Research

Immunomodulatory Effect of Vitamin D after Allogeneic Stem Cell Transplantation: Results of a Prospective Multicenter Clinical Trial

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Abstract

Purpose: We describe the results of a prospective multicenter phase I/II trial evaluating the impact of the use of vitamin D (VitD) from day −5 to +100 on the outcome of patients undergoing allogeneic transplantation (EudraCT: 2010-023279-25; ClinicalTrials.gov: NCT02600988).

Experimental Design: A total of 150 patients were included in three consecutive cohorts of 50 patients each group: control group (CG, not receive VitD); low-dose group (LdD, received 1,000 IU VitD daily); and high-dose group (HdD, 5,000 IU VitD daily). We measured levels of VitD, cytokines, and immune subpopulations after transplantation.

Results: No significant differences were observed in terms of cumulative incidence of overall and grades 2–4 acute GVHD in terms of relapse, nonrelapse mortality, and overall survival. However, a significantly lower cumulative incidence of both overall and moderate plus severe chronic GVHD (cGVHD) at 1 year was observed in LdD (37.5% and 19.5%, respectively) and HdD (42.4% and 27%, respectively) as compared with CG (67.5% and 44.7%, respectively; $P < 0.05$). In multivariable analysis, treatment with VitD significantly decreased the risk of both overall (for LdD: HR = 0.31, $P = 0.002$; for HdD: HR = 0.36, $P = 0.006$) and moderate plus severe cGVHD (for LdD: HR = 0.22, $P = 0.001$; for HdD: HR = 0.33, $P = 0.01$). VitD modified the immune response, decreasing the number of B cells and naïve CD8 T cells, with a lower expression of CD40L.

Conclusions: This is the first prospective trial that analyzes the effect of VitD postransplant. We observed a significantly lower incidence of cGVHD among patients receiving VitD. Interestingly, VitD modified the immune response after allo-SCT. *Clin Cancer Res; 22(23); 5673–81. ©2016 AACR.*

Introduction

Vitamin D (VitD) can be obtained either through the diet or synthesized in the skin after ultraviolet irradiation. Afterward, it undergoes an activation process, becoming into 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). Vitamin D_3 has an important role in calcium homeostasis. However, other important physiologic functions are being described, such as its effect in the immune system (1–4). In this regard, VitD can inhibit the maturation of monocyte-derived dendritic cells, overriding their ability to present antigens to T cells (5, 6). $1,25(OH)_2D_3$ is also a potent inhibitor of T-cell activation and is able to modulate $CD4^+$ T-cell differentiation, favoring the polarization toward a T helper 2 (Th2) phenotype and reducing Th1 (7) and Th17 differentiation (8). Moreover, some authors have described that VitD might enhance regulatory T cells (Treg; refs. 9–11). In this regard, an increase in the proportion of Treg has been reported among patients diagnosed with diabetes after exposure to VitD (12). Finally, a decrease in the number of memory B cells and an inhibition of plasma cell differentiation has been reported upon *in vitro* exposure to $1,25(OH)_2D_3$ (13, 14).

On the basis of these properties, some studies have been described exploiting the immunomodulatory effect of VitD after solid organ transplantation in animal models (14): although a few reports have described the opposite effect, this is an increased immune response upon exposure to VitD. Accordingly, $1,25(OH)_2D_3$ can contribute to enhance the immune response (i.e., against Mycobacterium; ref. 4).

In addition to these effects on the immune system, different studies have described the capability of VitD to induce differentiation of hematopoietic stem cells (15–18). In this regard, the

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Some reports have retrospectively evaluated the impact of vitamin D levels on the outcome of patients undergoing allogeneic stem cell transplantation; however, the current study represents the first prospective multicenter trial designed to evaluate the safety of vitamin D after allogeneic transplantation and the incidence of GVHD. Although a prospective randomized trial should be required to further confirm these data, we observed a very low toxicity profile and a lower incidence of chronic GVHD among patients who received vitamin D without a significant increase in relapses or infections. Considering the benefits and low toxicity profile described in the current study and taking also into account the low costs of the vitamin D, it might be easily incorporated into the standard clinical practice.

potential role of VitD for the treatment of acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) has been evaluated (19–26).

On the basis of these properties, a few reports have retrospectively evaluated the impact of VitD levels on the outcome of patients undergoing allogeneic stem cell transplantation (allo-SCT; refs. 27–29). Although most of these studies describe that low levels of VitD are related to an increased risk of chronic GVHD (cGVHD) and even an increased risk of relapse and nonrelapse mortality, at least one report has described the opposite effect, that is, a higher risk of acute GVHD (aGVHD; ref. 29).

With this background, we designed a phase I/II multicenter trial to evaluate the impact of the use of VitD on the outcome of patients undergoing allo-SCT and its effects on the immune recovery.

Materials and Methods

Patient eligibility criteria

A total of 150 patients older than 18 years from 7 Spanish centers were included in the trial from May 2011 to February 2014. Patients with either a related or unrelated donor with a maximum of 1 HLA allele mismatch of 8 were allowed to be included into the study. Patients gave written informed consent before entering the study in accordance with the Declaration of Helsinki. The following parameters were defined as exclusion criteria: hypercalcemia (calcium level in blood $\geq$10.5 mg/dL), serum creatinine equal or higher than twice the upper normal limit, and use of any *ex vivo* or *in vivo* procedure of T-cell depletion as GVHD prophylaxis. The institutional ethics committees of all participating centers approved the study. The trial was registered at www.clinicaltrialsregister.eu as EudraCT: 2010-023279-25 and at ClinicalTrials.gov as NCT02600988.

Study design

This is a multicenter and prospective phase I/II clinical trial designed to determine the safety and to assess the effect of VitD supplementation on the incidence of GVHD. Three consecutive cohorts with 50 patients in each one were included: in the first group, patients did not receive VitD [control group (CG)]; in the second cohort, low-dose group (LdD), patients received 1,000 IU of VitD per day; and in the last one, high-dose group (HdD), patients received 5,000 IU of VitD per day. VitD was administrated orally from day −5 before transplant until day +100 after transplantation.

Characteristics of patients are summarized in Table 1. No significant differences were observed between the 3 groups, except for an older median age among patients in the LdD. Six of the 150 patients were considered nonevaluable (2 patients from CG, 3 from LdD, and 1 from HdD). Reasons are specified in Table 1.

Ex vivo assays were performed in the first patients included in each cohort from the University Hospital Virgen del Rocío (Seville, Spain; 16 in CG, 10 in LdD, and 14 in the HdD). In addition, 4 healthy controls were also analyzed.

Plasma levels of 25-hydroxivitamin D

Plasma levels of 25-hydroxyvitamin D_3 were measured on days −5, +1, +7, +14, and +21. Concentrations of 25-hydroxyvitamin D were determined by a fully automated immunoassay electrochemiluminescence system (Analytics E711, Roche Diagnostics, GmbH). Normal levels of 25-hydroxyvitamin D_3 were considered from 50 to 250 nmol/L.

Immunophenotypic analysis

Blood samples were collected on heparin on days +21, +56 and, +100 after transplantation. Peripheral blood (100 μL/tube) was stained with the mAbs. After 15 minutes of incubation at room temperature in the dark, samples were washed and acquired.

The following markers were used to identify different subpopulations of dendritic cells (myeloid BDCA1, plasmacytoid, and monocyte-derived dendritic cells): CD16-PB, CD45-V500, HLADR-FITC, BDCA-PE, CD11c-PerCP-Cy5.5, CD86-PE-Cy7, CD123-APC, and CD14-APC-H7. Subpopulations of lymphocytes were calculated using $CD19^+CD8$-FITC, $CD3^+CD56$-PE, CD4-PerCP-Cy5.5, and HLADR-APC. CD45RA-FITC and CCR7-PE were used to distinguish the repertory of naïve/effector/memory T cells. Finally, myeloid-derived suppressor cells (MDSC) were identified on the basis of the pattern $HLADR^-$/low $CD14^+$ cells.

For Treg assessment, after incubation of surface antigens (CD25-FITC, CD127-PE, and CD4-PerCP-Cy5.5), cells were washed in PBS and then fixed and permeabilized with FoxP3 Staining Buffer Set (eBioscience).

Activation assays were performed on 500 μL of peripheral blood stimulated or not with PMA (20 μg/2 mL) and ionomycin (0.91 μg/mL). Brefeldin A (10 μg/mL) was added in both cases. After 4 hours, cells were stained with surface antigens (anti-CD25-FITC and anti-CD3-PerCP-Cy5.5). Staining for cytoplasmatic IFNγ-PE and CD40L-APC was performed using the IntraStain Kit (Dako).

All samples were acquired in a FACSCanto II Flow Cytometer [Becton Dickinson (BD)] using the Diva software (BD), and data analysis was performed using Infinicyt software (Cytognos).

Cytokine assays

Serum levels of Th1/Th2 cytokines (IFNγ, TNFα, IL2, IL6, IL4, and IL10) were determined by flow cytometry using the BD Human Cytokine CBA Kit (BD) according to the manufacturer's instructions. Serum was collected on days +1, +7, +14, +21, +56, and +100 after transplantation. Briefly, samples were acquired in a FACSCanto II and analyzed using FACSArray Software II (BD). The concentration of each cytokine was reported as pg/mL of peripheral blood.

Statistical analysis

Comparisons of quantitative variables among independent groups were performed by Student t test and χ^2 test.

Table 1. Characteristic of the patients

Patients $N = 144$ (%)	**CG 48 (33.3%)**	**LdD 47 (32.6%)**	**HdD 49 (34%)**	***P***
Age, median (range)	47.5 (17–67)	54 (18–70)	43.5 (23–59)	0.01
Sex, male	22 (53.7)	25 (53.2)	25 (51)	0.96
Diagnosis				
AML/MDS	27 (67.5)	28 (59.6)	25 (51)	0.51
ALL	6 (15)	7 (14.9)	12 (24.5)	
NHL/HL	5 (12)	6 (12.8)	9 (18.4)	
Others	2 (5)	6 (12.8)	3 (6.1)	
Unrelated donor	20 (48)	21 (44.7)	20 (40.8)	0.80
Sources (*n*%)				
Peripheral blood	36 (85.7)	44 (93.6)	45 (91.8)	0.41
Bone marrow	6 (14.3)	3 (6.4)	4 (8.2)	
Nonmyeloablative	23 (54.8)	34 (73.9)	27 (56.3)	0.11
Preparative regimen				0.5
Myeloablative				
CY + BU ± ThioTEPA	11 (26.8)	7 (14.9)	8 (16.7)	
CY + TBI ± ThioTEPA	7 (17)	7 (14.9)	8 (16.7)	
Reduced intensity				
Flu + BU ± ThioTEPA	16 (39)	25 (53.2)	28 (58.3)	
Flu/Melphalan–based regimen	7 (17.1)	8 (17)	4 (8.3)	
GVHD prophylaxis				
CsA/MTX	18 (42.9)	13 (27.7)	18 (36.7)	0.28
TKR/MTX	10 (23.8)	9 (19.1)	5 (10.2)	
TKR/SL	14 (33.3)	23 (48.9)	24 (49)	
Others		2 (4.3)	2 (4.1)	
Disease status				0.86
Early	18 (41.8)	20 (42.5)	18 (37.5)	
Advanced	25 (58.1)	27 (57.4)	30 (62.5)	

Abbreviations: ALL, acute lymphoblastic leukemia; BU, busulfan; CsA, cyclosporine A; CY, cyclophosphamide; Flu, fludarabine; HL, Hodgkin lymphoma; MTX, methotrexate; NHL, Non-Hodgkin lymphoma; SL, sirolimus; TBI, total-body irradiation; TKR, tacrolimus. Six patients were considered non-evaluable due to non-compliance of protocol specifications in 5 cases and another patient who did not proceed to transplantation after being registered.

Nonparametric tests, such as U Mann–Whitney, were used for biological comparisons.

Probabilities of overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan–Meier method, and unadjusted comparisons were made using the log-rank test, while relapse, nonrelapse mortality (NRM), and GVHD probabilities were analyzed in a competing risks framework using the cumulative incidence nonparametric estimator and were compared by the Gray test.

NRM was defined as death due to any cause (GHVD related or other), without prior relapse or progression of the underlying disease. The relapse incidence was analyzed from transplant until the time of relapse among patients in remission. DFS was calculated from transplant until disease progression or death, and those patients who did not reach disease response any time after transplant were considered events on day 100. OS was calculated from transplant until death from any cause, and surviving patients were censored at the last follow-up. Patients who engrafted and survived more than 100 days were evaluable for cGVHD.

Adjusted effects on cGVHD were estimated in terms of HRs by Cox models. The effect of those events that took place during the follow-up and after transplant, such as aGVHD, was analyzed by treating their occurrence as a time-dependent covariate in Cox model. cGVHD analysis was performed with and without censoring all patients at the median follow-up of the group with the shortest one (HdD) to rule out the possibility of any bias related to differences in the median follow-up among three subgroups.

The following variables were included in the multivariable analysis for cGVHD: aGVHD, age, disease status, type of donor, source of stem cells, type of conditioning, diagnosis, and GVHD prophylaxis.

Data were analyzed using SPSS.V.15, (OpenEpi v.2.3.1) and the CMPRSK package in R 2.4.1 for the analyses of cumulative incidence curves in the framework of competing risk.

Differences were considered to be statistically significant for two-sided $P < 0.05$. Confidence intervals (CI) refer to 95% boundaries (30).

Results

Safety profile

No serious adverse events, specifically no case of hypercalcemia, were reported. Gastrointestinal disorders according to the criteria by the NCI (Bethesda, MD) were the most relevant treatment-related toxicities (Supplementary Table S1).

Neutrophil count > 0.5×10^9/L and stable platelet count more than 20×10^9/L for all patients were reached at a median of 16 days (range, 10–34 days) and 13.1 days after transplantation (range, 7–32 days), respectively. No significant differences were observed in time to neutrophils and platelet recovery among the three groups: for CG, 16 and 11.5 days; for LdD, 15 and 12 days; and for HdD, 15 and 12 days, $P = 0.125$ and $P = 0.168$, respectively.

We also evaluated the incidence of cytomegalovirus (CMV) reactivation. Remarkably, we observed a trend toward a lower cumulative incidence of CMV reactivation among patients who received VitD: 38% in CG as compared with 27% in LdD and 20% in HdD ($P = 0.06$).

Incidences of acute and cGVHD

No significant differences were observed in terms of cumulative incidence of overall and grades 2–4 aGVHD [for CG group, 57.1% (95% CI, 43.7–74.6) and 43.9% (95% CI, 30.9–62.4); for LdD, 59.6% (95% CI, 46.9–75.7) and 44.7% (95% CI, 32.4–61.7); and for HdD, 57.1% (95% CI, 44.7–73.1) and 51% (95% CI, 38.6–67.4), $P = 0.71$ and $P = 0.98$, respectively; Fig. 1].

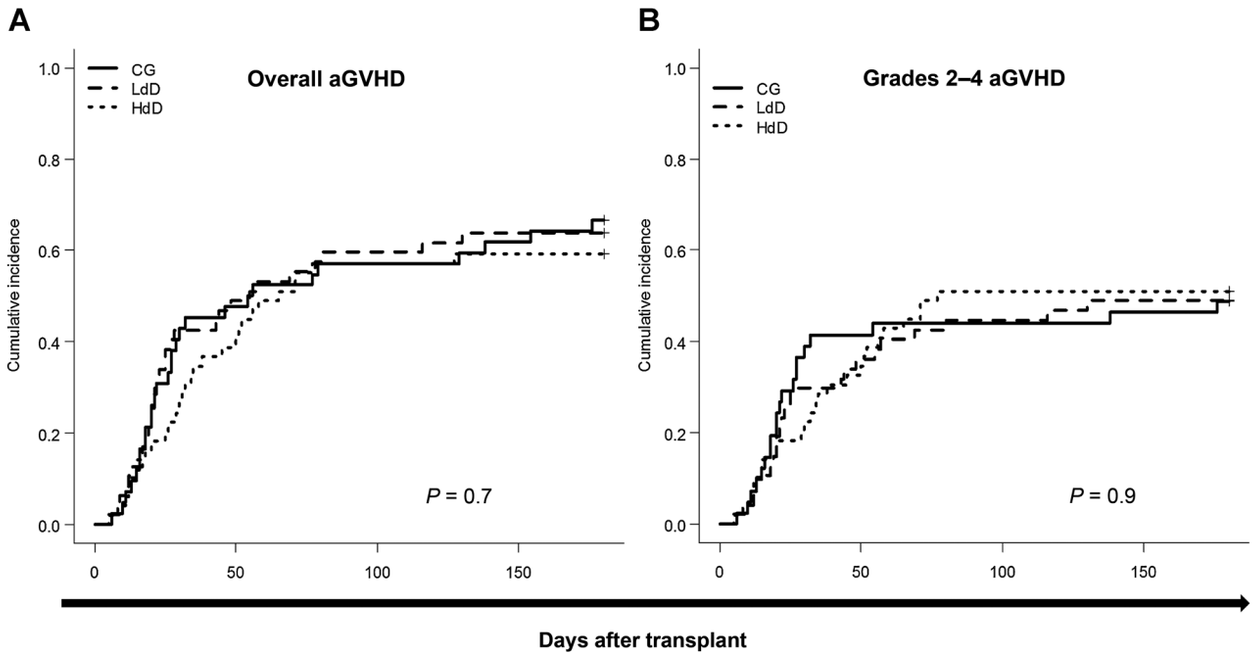

Figure 1.
Cumulative incidence of overall (**A**) and grades 2–4 (**B**) aGVHD. No significant differences were observed among the different cohorts.

In contrast, a significantly lower cumulative incidence of both overall as well as moderate plus severe cGVHD was observed in LdD at 1 year [37.5% (95% CI, 24.9–56.4) and 19.5% (95% CI, 10.4–36.7), respectively] and HdD [42.4% (95% CI, 29.3–61.4) and 27% (95% CI, 16.1–45.2), respectively] as compared with patients who did not receive VitD [67.5% (95% CI, 54.1–84.3) and 44.7% (95% CI, 31.2–64.2), respectively; $P = 0.019$ for overall and $P = 0.026$ for moderate plus severe cGVHD, respectively; Fig. 2]. Almost identical results were observed when we compared the incidence of overall and moderate plus severe

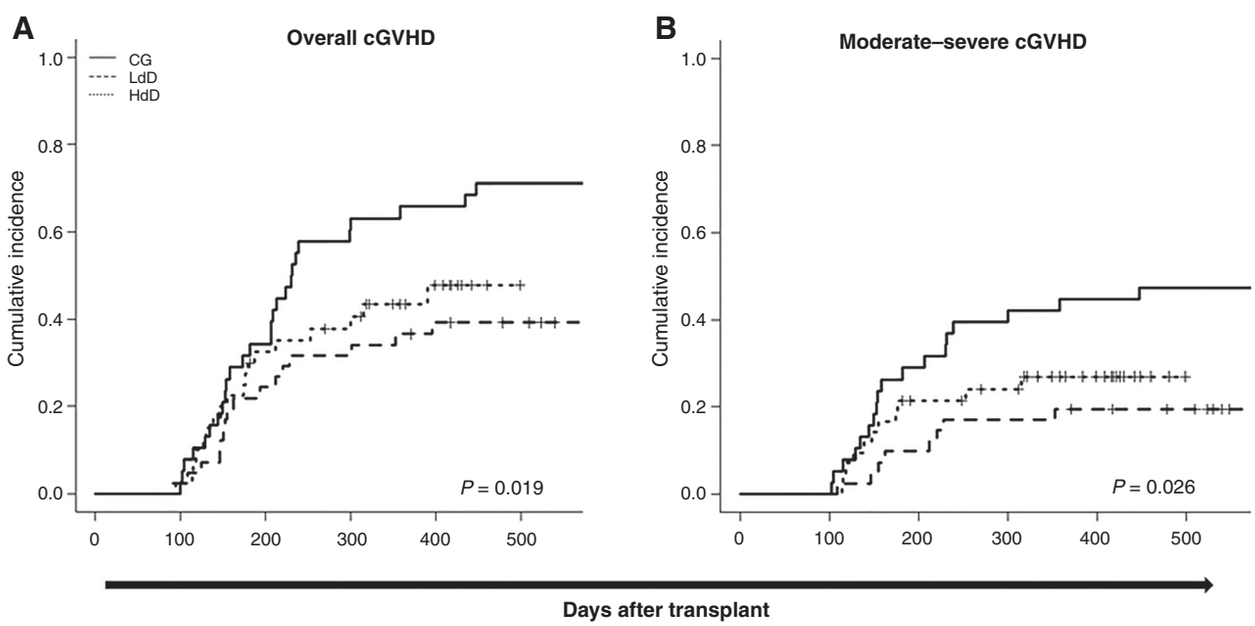

Figure 2.
cGVHD. A significantly higher incidence of both overall (**A**) and moderate plus severe cGVHD (**B**) according to NIH criteria at 1 year was observed between the cohort of patients who did not receive VitD as compared with the other two cohorts of patients (Fine–Gray model).

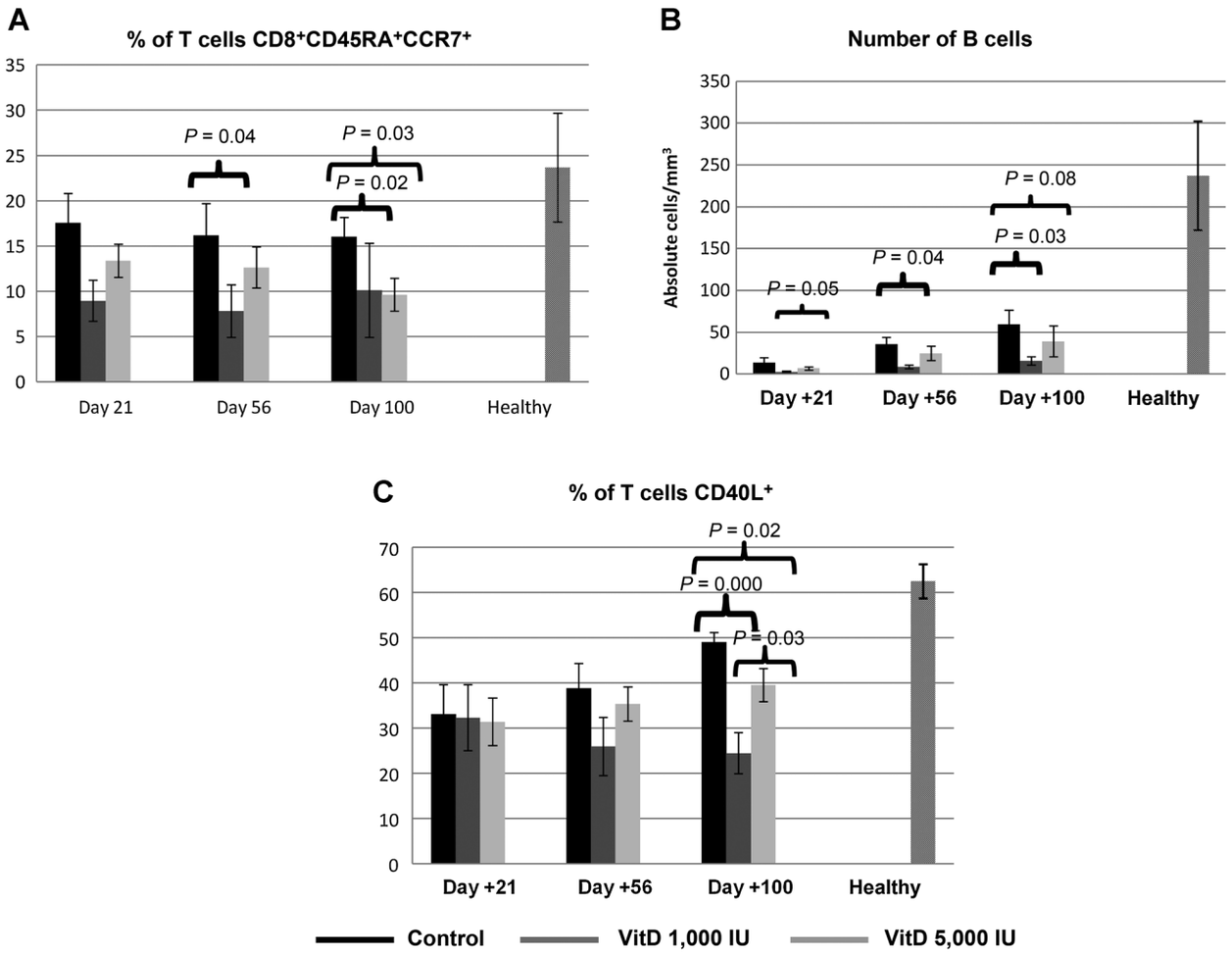

Figure 3.

Subpopulations of lymphocytes after transplantation. **A,** Lower number of circulating naïve $CD8^+$ among patients receiving VitD as compared with those who did not receive it. **B,** Significant decrease in the absolute number of circulating B cells on day 100 for LdD and HdD versus CG. **C,** Lower expression of CD40L as activation marker among patients receiving VitD.

cGVHD censoring all patients at the median follow-up of the HdD group (data not shown).

In multivariable analysis, treatment with VitD significantly decreased the risk of both overall [$P = 0.003$ for LdD (HR = 0.31; 95% CI, 0.14–0.67; $P = 0.002$) and for HdD (HR = 0.36; 95% CI, 0.17–0.75; $P = 0.006$)] and moderate plus severe cGVHD [$P = 0.003$ for LdD (HR = 0.22; 95% CI, 0.08–0.57; $P = 0.001$) and for HdD (HR = 0.33; 95% CI, 0.14–0.79; $P = 0.01$)]. The use of unrelated donors also increased the risk of moderate plus severe cGVHD (HR = 2.74; 95% CI, 1.12–6.67; $P = 0.02$).

Relapse, nonrelapse mortality, and OS

No significant differences were observed in terms of cumulative incidence of relapse at 1 year: for CG, 15.4% (95% CI, 7.3–32.5); for LdD, 31.1% (95% CI, 20.0–48.4); and for HdD, 18.1% (95% CI, 9.5–34.4) $P = 0.1$ (CG vs. LdD, $P = 0.09$). Similarly, no differences were observed in terms of NRM at 1 year: for CG, 17.9% (95% CI, 9.1–35.5); for LdD, 15.6% (95% CI, 7.8–31.0); and for HdD, 19.2% (95% CI, 10.6–34.8) $P = 0.8\%$ (Supplementary Fig. S1).

Finally, no significant differences were observed in DFS and OS: with a median follow-up of 2 years, DFS and OS were 57% (95% CI, 41–70.3) and 71% (95% CI, 55.1–82.7), 42% (95% CI, 27.9–55.9) and 50% (95% CI, 34.4–64.4), and 45% (95% CI, 17.9–69.2) and 55% (95% CI, 20–79.7)for CG, LdD, and HdD, respectively ($P = 0.38$ and $P = 0.24$).

Biological assays

Mean and SEM are summarized in Supplementary Table S2. The most significant differences between the 3 cohorts were a decrease on both the percentage and absolute number of circulating B cells on day 100 for LdD and HdD subgroups as compared with CG, a markedly modified ratio of naïve/memory/effector T cells, with a lower number of circulating naïve $CD8^+$ among patients receiving VitD as compared with those who did not receive it and a significantly lower expression of CD40L as activation marker among patients receiving VitD (Fig. 3).

No differences were observed in leukocytes, total lymphocytes, T cells, $CD4^+$, $CD8^+$, $CD4^+CD8^+$ $CD4^-CD8^-$ NK cells (bright and weak), and subpopulation of dendritic cells or MDSCs.

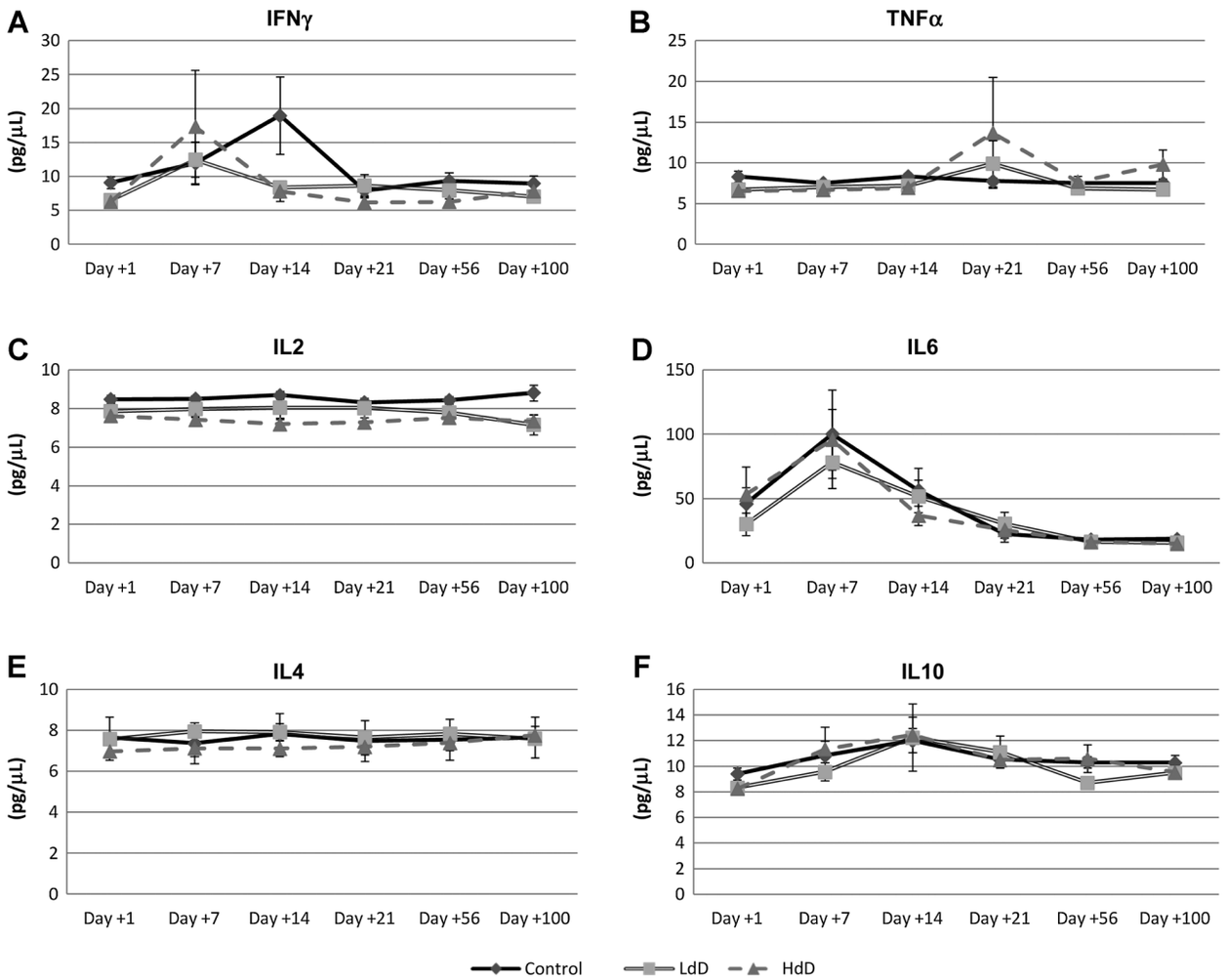

Figure 4.

Serum levels of Th1/Th2 cytokines. IFNγ (**A**), TNFα (**B**), IL2 (**C**), IL6 (**D**), IL4 (**E**), and IL10 (**F**) were measured on patient serum collected on days +1, +7, +14, +21, +56, and +100 after transplantation. Concentration of each cytokine was reported as pg/mL of peripheral blood.

Regarding serum levels of Th1/Th2 cytokines (Fig. 4; Supplementary Table S3), higher levels of IFN were observed in the CG as compared with LdD (on day +1) and with HdD (on day +1 and +14).

Concerning the plasma levels of 25-hydroxyvitamin D_3 (Supplementary Table S4), significantly higher levels were observed among patients receiving high doses of the 1,25-dihydroxyvitamin D_3 as compared with CG beyond day +7, while a trend toward increased levels was observed on day +21 among patients included in the LdD.

Discussion

The current study represents the first prospective multicenter trial evaluating the impact of the use of VitD on the outcome of patients undergoing allo-SCT. Several studies have recently been reported retrospectively evaluating the impact of pretransplant levels of VitD on posttransplant outcomes. Middleton and colleagues observed an association between specific polymorphisms of VDR and the risk of GVHD (31). More recently, von Bahr and colleagues described an association between low levels of VitD and an increased risk of GVHD (28). Similar results have been described by other authors (27), such as Hansson and colleagues (29), who described an increased risk of death, relapse, and cGVHD among those patients with low VitD levels, although, strikingly, grades 2 to 4 aGVHD occurred more frequently among patients with normal levels of VitD.

Considering the lack of information regarding the safety profile of the use of VitD after transplantation, and taking into account that no previous study has been performed to identify the optimal doses to be used after allo-SCT, we designed a phase I/II trial with three different cohorts of patients that subsequently received increasing doses of VitD, ranging from 1,000 to 5,000 IU per day. First, we confirmed that 1,000 to 5,000 IU/day are safe and sufficient to normalize blood levels of VitD in the posttransplant setting. Remarkably, several studies have reported that a significant proportion of patients display low levels of VitD before allo-SCT (27, 28). In this regard, the three cohorts of patients included

in the current trial had a mean level of VitD below the normal range (50–250 nmol/L) on day 5 before transplant, thus confirming previous results described among patients diagnosed with hematologic malignancies in other latitudes (27, 28). Moreover, the proportion of patients displaying low levels of VitD should be even higher after than before allo-SCT as, because of the increased risk of secondary malignancies in skin, patients are instructed to avoid ultraviolet exposure and to use sunscreens and protective clothing after transplantation. In the current study, VitD was administered from day 5 before transplant until 3 months posttransplant, and while the HdD group obtained significantly higher levels of VitD from day +7 as compared with the control group, in the LdD, the levels of VitD increased beyond day +21 posttransplantation.

Remarkably, we observed that the administration of VitD was associated to a significantly lower risk of both overall as well as moderate to severe cGVHD. Considering the limited number of patients required to evaluate safety and efficacy in a phase I/II trial, additional studies with a higher number of patients will be required to further confirm this finding and to more accurately define which patients might obtain a higher benefit from receiving vitamin D, taking into account the effect of the different conditioning regimens as well as the different GVHD prophylaxis on the incidence of cGVHD.

cGVHD remains the main cause of long-term morbidity and mortality after allo-SCT. Unfortunately, the most effective strategies currently available to prevent cGVHD do hamper immune recovery so that the lower GVHD-related mortality does not translate into a better OS due to a higher risk of infections and relapse (32, 33). According to our data, VitD might be able to decrease cGVHD without significantly increasing either the risk of relapse or the risk of infections. Regarding the prior, we did not identify a significantly different risk of relapse between the different cohorts of patients, although some studies have described a potential efficacy of VitD for the treatment of AML and MDS (28, 29). Concerning the latter, we observed a trend toward a lower risk of CMV reactivation among patients receiving VitD, which is in accordance with previous studies describing that VitD can contribute to enhance the immune response (4) and confirms the complex effect of VitD on immune system. In this regard, while VitD decreased the risk of cGVHD, it did not affect the incidence of aGVHD. This differential effect might just be related to the fact that with the schema proposed in the current trial, from days 2 to 4 after allo-SCT, there were no differences in the levels of VitD within the different subgroups, and it is well stablished that the immune response is triggered already in this early posttransplant period (34).

On the other hand, the pathogenesis of cGVHD remains elusive, and contrary to early studies that identified cGVHD simply as an end stage of aGVHD, the current knowledge (35) suggests that cGVHD is a very complex process involving the survival and expansion of donor T and B cells that do not develop immune tolerance against antigens from the recipient (36, 37). In our *ex vivo* assays, we confirmed that patients receiving VitD displayed lower levels of CD40L in T cells and a lower number of B cells. Both findings might be related as T and B cells do interact through CD40L in follicular germinal centers so that the decreased expression of CD40L might in turn hamper T cell–dependent B-cell activation (36). Considering the role of B cells on the development of cGVHD, this finding might play a central role of the effect of VitD on cGVHD incidence. As far as the different subtypes of T cells are concerned, lower naïve $CD8^+CCR7^+CD45RA^+$ cells were observed among patients receiving VitD. In this regard, Coghill and colleagues described that murine T cells lacking CCR7 generate attenuated GVHD responses compared with wild type (38). Other studies have also described that memory T cells display a decreased allo-reactivity (39). In this regard, naïve T cells, and not memory T cells, are capable of inducing severe GVHD (40–45). Recently, Bleakley and colleagues showed a reduced incidence of cGVHD in 35 patients receiving naïve T cell–depleted peripheral blood stem cell transplants (46).

In summary, this is the first prospective trial that analyzes the effect of VitD administration after allo-SCT. Although a prospective randomized trial should be required to further confirm these data, we observed a very low toxicity profile and a lower incidence of cGVHD among patients who received VitD without a significant increase in relapses or infections. Moreover, we also describe the effects of VitD on immune response after transplantation, the most remarkable effects being a significant decrease in T-cell activation as assessed by CD40L expression, a decrease in B-cell counts, and a decreased ratio of naïve/effector T cells.

Disclosure of Potential Conflicts of Interest

D. Valcarcel reports receiving speakers bureau honoraria from Amgen, Astellas, Celgene, GlaxoSmithKline, Novartis, and Pfizer and is a consultant/advisory board member for Celgene, GlaxoSmithKline, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

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