Currently, there is no standard approach for patients with chronic GVHD (cGVHD) who do not respond to or who relapse after first-line treatment, and rescue therapy is based on immunosuppressive drugs and glucocorticoids, which are responsible for the development of severe complications. Vitamin D (Vit D) has a potent immunomodulatory effect, as shown in vitro and in animal models, nevertheless there is no information about its use in the cGVHD setting. We evaluated retrospectively the outcome of cGVHD in a series of 12 patients receiving vit D because of proved osteopenia or osteoporosis by bone densitometry after allo-HSCT. These patients also had active cGVHD at the time when vit D treatment was started. We observed a marked improvement in cGVHD for most of these patients, without appreciable secondary effects.

Chronic GVHD was classified as limited versus extensive, and also the National Institutes of Health scoring system was used, based on the data collected from the medical files of the patients. The first-line treatment for cGVHD was CsA or tacrolimus plus prednisone at 1 mg/kg per day, which was switched to alternating days after 4 weeks of treatment. Patient characteristics are summarized in Table 1.

Table 1 - Patient characteristics at transplant.

According to our standard procedures, patients undergoing allo-HSCT have a bone densitometry performed between 6 months and 1 year after transplantation to rule out osteopenia or osteoporosis. In case it is detected, then a dosage of vit D 1000 IU per day (oral) plus calcium carbonate 1250 mg (one pill per os daily) are prescribed for at least 6 months. Chronic GVHD response was assessed according to National Institutes of Health response criteria at 3 and 6 months after the beginning of vit D plus calcium treatment. For skin involvement, a PR was considered to have occurred when at least 50% of the skin involvement appeared to be non-inflammatory or to be fixed, and for complete response, as either the disappearance of all lesions or the presence of fixed and pigmented lesions.

Chronic GVHD was diagnosed at a median day of 147 after transplant (range: 119–491 days). At the time when vit D treatment was started, six patients had received one line of immunosuppressive treatment, three patients had received two lines of treatment, two patients had received three lines and one patient had received four lines of treatment. Seven patients had mild, two patients had moderate and three had severe cGVHD; organ involvement is summarized in Table 2. At 3 months after vit D treatment, three patients obtained complete response, six patients obtained PR and one patient had no response, with six patients displaying mild and one patient showing severe cGVHD.
Finally, at 6 months after treatment, five patients obtained complete response, six patients obtained PR and one patient had no response, with six patients displaying mild and one of them showing moderate cGVHD. No immunosuppressive drugs were added to the treatment during this period. Interestingly, at the beginning of vit D treatment, 10 patients were receiving calcineurin inhibitors, one patient was receiving calcineurin inhibitor plus prednisone and one patient was receiving mofetil mycophenolate plus prednisone. After 6 months of vit D treatment, five patients were not receiving immunosuppressive drugs, whereas seven patients were receiving immunosuppressive treatment based on CsA or tacrolimus (with or without topical treatment in five patients and with other systemic immunosuppressive drug in two patients). We compared patients who received vit D and who had not previously relapsed \((n=6)\) with a cohort of 24 patients, transplanted during the same period of time, who had not received vit D and were on first-line treatment for cGVHD, and had similar characteristics regarding GVHD severity and extension. Interestingly, 50% of the patients receiving vit D were put off on immunosuppression for 6 months after the beginning of treatment as compared with 20% among of those who did not receive vit D \((P=0.1)\).

### Table 2 - Patients outcome before and after vitamin D treatment.

![Table 2](Full table)

Remarkably, six patients had a history of previous relapses of cGVHD before vit D treatment (two of them relapsed after the end of immunosuppression, whereas four relapsed during taper of CsA or tacrolimus). After vit D treatment, only three out of these patients had cGVHD relapse, one of them occurring during the taper of CsA.

Vitamin D is a fat-soluble prohormone, the two major forms being ergocalciferol (vit D\(_2\)) and cholecalciferol (vit D\(_3\)). The most important sources of vit D in humans are sunshine, food and supplementation. The active form of vit D is 1,25-hydroxyvitamin D. Vitamin D is essential for optimal skeletal development, maintenance of bone health and neuromuscular function. It is used in conjunction with calcium in the management and prevention of primary or corticosteroid-induced osteoporosis. Most tissues and cells, including PBMCs possess a vit D receptor, and many have the ability to convert 25-hydroxyvitamin D to 1,25 hydroxyvitamin D. *In vitro* data indicate that vit D inhibits DC-dependent T-cell activation, T-cell proliferation, and decreases the production of type-1 helper cells cytokines IL-2, IFN-γ and TNF-α, thus displaying a very potent immunomodulatory effect.

Previous reports describe the efficacy of a vit D analog MC1288 in preventing acute GVHD in a rat BM transplant model, as well as the relationship between vit D receptor gene polymorphism, and acute and cGVHD. The effects of vit D are mediated by the nuclear vit-D receptor. It is constitutively expressed in monocytes, and in both B- and
T-activated lymphocytes. The effect of vit D on DC and T cells were evaluated by Rosenblatt et al., who demonstrated the inhibitory effect of vit D on T-cell proliferation, or in the production of type-2 helper cells cytokines. In spite of these data, there is a lack of information regarding the use of vit D in the GVHD setting. For this reason, we analyzed those patients who were receiving immunosuppressive treatment and required vit D because of osteoporosis or osteopenia, and compared their outcomes before and after this treatment. No other immunosuppressive drugs were added during the whole period. Interestingly, we found an important improvement in the severity of cGVHD, so that at 6 months after vit D treatment no patients displayed severe cGVHD versus 3 months at the beginning. Moreover, at that time five patients had complete response and were not receiving immunosuppressive treatment. In addition we observed a remarkable reduction of cGVHD relapses or progressions. Accordingly, 9 out of 12 patients had no relapse/progression (Table 2).

In conclusion, treatment with vit D appears to be effective, safe and inexpensive for the management of patients with cGVHD. The current study establishes the basis for further studies with a larger number of patients to better assess the potential immunomodulatory effect of vit D on the cGVHD setting.