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Letter to the Editor

Conductor of regulatory cells: Does vitamin D restore the shifted balance of the distinct regulatory cell types in undifferentiated connective tissue disease?

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Conditions characterized by the presence of clinical and serological manifestations suggestive of systemic autoimmune diseases but not fulfilling the classification criteria for defined connective tissue disease (CTD) are common in clinical practice. This phase of disease is defined as undifferentiated connective tissue disease (UCTD) [1]. Our previous studies and data in the literature have shown that 30–40% of patients with UCTD will subsequently develop a defined CTD, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), Sjögren's syndrome (SS), systemic sclerosis (SSc), or polymyositis/dermatomyositis (PM/DM) [2,3]. We can declare that UCTD is a pre-phase of autoimmune diseases. Defects of immune regulation in the various defined CTDs are well-known. Nevertheless, even less is known about cellular deviations of the innate and adaptive immune system in patients with UCTD. Immunoregulatory disturbances of UCTD patients are indicated by certain humoral and cellular abnormalities of the immune system. In our previous works we found an elevated IFN-γ production by T-helper (Th)1 cells, a decreased number of natural regulatory T cells (nTregs) and an increased number of Th17 cells [4,5]. Moreover, UCTD is also characterized by the presence of autoantibodies against nuclear and cytoplasmatic components. In addition, components of innate immunity may also be affected. NK cells are crucial components of the innate immune response. They have the ability both to lyse target cells and to provide immunoregulatory cytokines. Human NK cells amount to ~5–15% of all lymphocytes and are defined by their expression of CD56 and lack of expression of CD3 [6,7]. Lanier et al. identified two distinct NK cell populations based upon their cell-surface density of CD56 [8]. The larger part (~90%) of human NK cells express CD56 at low levels (CD56^{dim}). These cells are the most cytotoxic subset, whereas the other part of NK cells expressing CD56 strongly (CD56^{bright}) has an immunosuppressive/immunoregulatory role [9]. Up to now, however, these subpopulations of NK cells have not been investigated in patients with UCTD.

Cells with immunoregulatory properties may be under the control of vitamin D. Vitamin D directly and indirectly regulates the differentiation and activation of CD4+ T lymphocytes and can prevent the development of autoimmune processes [10–12]. Decreased levels of vitamin D have been reported in different autoimmune disorders such as UCTD, SLE, type 1 diabetes and rheumatoid arthritis [13–16]. Therefore, we re-evaluated some of our previous data from the point of view of NK cell subsets and vitamin D treatment.

Twenty-nine patients with UCTD (all female) were included in this study. Twenty-nine age-matched females formed the control group (mean ± SD; UCTD: 50.4 ± 12.3 years; control: 49.4 ± 11.7 years). Twelve patients were given alfacalcidol tablets (0.5 μg/day) during the 5-week treatment duration. All patients had vitamin D insufficiency (<30 ng/mL) before alfacalcidol treatment. The effect of alfacalcidol treatment on the proportion and absolute number of CD3-CD56+^{dim} and CD3-CD56+^{bright} NK cell subsets was investigated.

We observed a significant increase in the percentage of CD3-CD56+^{bright} NK cells in patients with UCTD compared to healthy controls (medians: 9.7 vs. 6.4%; $p = 0.040$). In addition, the percentage of CD3-CD56+^{dim} cells was significantly decreased in UCTD patients compared to the healthy controls (medians: 89.9% vs. 93.6%; $p = 0.0275$). Interestingly, similar tendencies were found in absolute numbers, but the differences were not statistically significant (CD56+^{bright} medians: 0.014 G/L vs. 0.010 G/L, $p = 0.440$; CD56+^{dim} medians: 0.138 G/L vs. 0.186 G/L, $p = 0.132$). In order to determine the effect of alfacalcidol on NK cell subsets we compared the data before and after treatment of patients with UCTD. Percentages and absolute numbers of CD3-CD56+^{bright} cells were decreased remarkably but not significantly after alfacalcidol treatment (medians: 10.10 vs. 6.18%, $p = 0.106$ and 0.016 G/L vs. 0.013 G/L; $p = 0.355$). A meaningful effect of alfacalcidol was observed on CD3-CD56+^{dim} NK cell subsets, because percentages and absolute numbers of this subset were elevated in patients with UCTD after the treatment; however, these changes were not statistically significant (89.9% vs. 93.2%, $p = 0.326$ and 0.144 G/L vs 0.182 G/L, $p = 0.506$). It seems that a beneficial effect of alfacalcidol treatment could be that it partly restores the abnormalities of NK cell subsets (Fig. 1).

In our previous study alfacalcidol treatment increased the number of natural regulatory T cells (nTregs) and decreased the number of Th17 proinflammatory cells.

On the ground of these and previous results a substantial role of vitamin D is suggested in the control of regulatory cells of the innate and adaptive immune system. Suppressor cells of the innate and adaptive immune system may be regulated (directly or indirectly) in the opposite directions by vitamin D. CD56+^{bright} NK cells and Th17 cells seem to be regulated negatively by vitamin D, whereas this vitamin has a positive homeostatic effect on nTregs. Thus, a lower vitamin D level during an inflammatory response could result in an elevated level of CD56+^{bright} NK cells, Th17 cells, induced regulatory T cells and a decreased level of nTregs. The interaction network of cells with regulatory function is very complex; however, our results suggest that a low level of vitamin D in patients with UCTD could be one of the reasons for abnormalities of regulatory cells. These results and our hypothesis also explain the positive effect of vitamin D treatment in UCTD.

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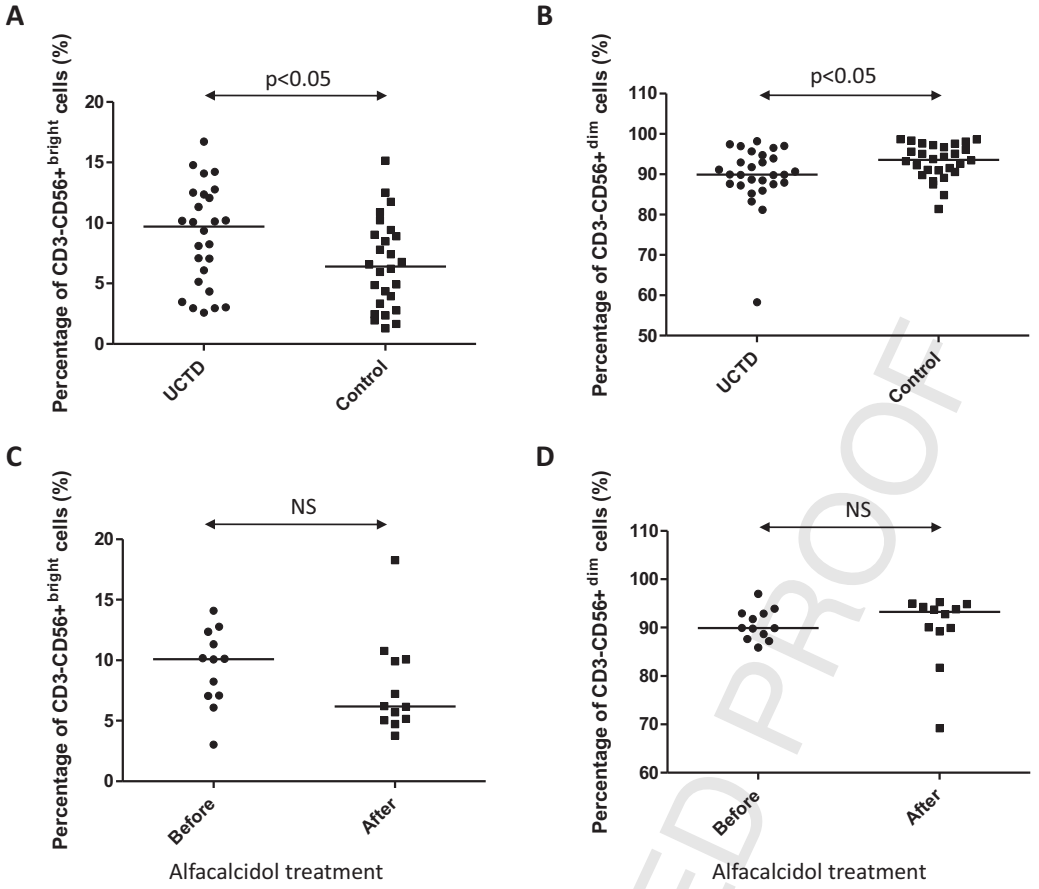

Fig. 1. Proportions of NK cell subsets (CD3-CD56+^{bright} and CD3-CD56+^{dim}) in patients with UCTD (A and B). Percentage of CD3-CD56+^{bright} cells was elevated (C) while percentage of CD3-CD56+^{dim} cells was decreased (D) after treatment with alfacalcidol.

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