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INVESTIGATIVE REPORT

Immunological and Clinical Effects of Alphacalcidol in Patients with Psoriatic Arthropathy: Results of an Open, Follow-up Pilot Study

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The aim of this study was to describe the effect of systemic alphacalcidol (1αOH vitamin D_3) treatment on clinical and immunological parameters in patients with psoriatic arthropathy. Among the 19 patients investigated, 10 were treated with 0.25 μg oral alphacalcidol twice daily for 6 months, while 9 other patients served as controls. In the peripheral blood of the treated group but not in the controls, a statistically significant decrease was observed in the percentage of CD3/CD69-positive activated and CD8-positive interferon-γ-producing T cells and in the serum level of interferon-γ during the first 3 months and also in the clinical activity of the disease during the whole 6-month follow-up period. Our results show that systemic alphacalcidol treatment has an immunomodulatory effect on patients with psoriatic arthropathy. This effect is manifested by a short-term temporary decrease in type 1 immune responses and a continuous decrease in disease activity. ***Key words: alphacalcidol treatment; psoriatic arthropathy; immunomodulatory effect.***

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Beyond the calcaemic effect of vitamin D_3 this vitamin also has important immunomodulatory effects. It exerts various effects on the monocyte-macrophage system, on T and B lymphocytes and on dendritic and natural killer (NK) cells. Regarding the monocyte-macrophage system it increases the phagocytotic activity of monocytes, the antibody-dependent cellular cytotoxicity (ADCC) reaction and the differentiation of myeloid progenitor cells towards macrophage development (2–4). In addition, lack of vitamin D_3 results in an increased risk of infections and an inverse relationship between the concentrations of the activated form of vitamin D_3 calcitriol ($1,25(OH)_2D_3$) and mortality has been observed in human immunodeficiency virus (HIV)-infected adults (5, 6).

Vitamin D_3 decreases: (*i*) the proliferation of all T-helper (Th) cells; (*ii*) the development and function of Th1 cells; (*iii*) the production of interferon-γ (IFN-γ), interleukin (IL)-1, IL-2, IL-5, IL-6, IL-12, tumour necrosis factor (TNF) α and β; (*iv*) the immunoglobulin secretion of the B lymphocytes; and (*v*) the integrin-mediated T-lymphocyte homing (1, 7–11).

Concerning the dendritic cells (DC), vitamin D_3 and its active metabolites inhibit their differentiation and maturation leading to a down-regulated expression of MHC-II, co-stimulatory molecules and IL-12 production, and also a decrease in a dose-dependent manner in the proliferation and antigen-presenting function of the skin Langerhans' cells (12, 13). Moreover, calcitriol enhances IL-10 production and promotes DC apoptosis (3). Together, these effects of activated vitamin D_3 inhibit DC-dependent T-cell activation (12).

There is much evidence that topical vitamin D_3 compounds are beneficial in dermatology. Among these are the local immunomodulatory effects of tacalcitol, calcipotriol and maxacalcitol, which suppress keratinocyte proliferation and induce terminal differentiation and can be used successfully in the treatment of dermatological diseases, including psoriasis (14–16). In addition, in patients with psoriasis the systemically used calcitriol exerted a favourable effect on skin symptoms (17). On the other hand, reviewing the literature, only one study was found on the clinical effects of systemic vitamin D_3 analogues calcitriol and alphacalcidol (1αOH vitamin D_3) in patients with psoriatic arthritis (PA), and no study has dealt with their immunomodulatory effects in these patients (18).

The aim of the present study was to evaluate changes in the function of the immune system during systemic alphacalcidol treatment in patients with PA using various laboratory examinations, and to describe its effect on clinical parameters in these patients.

METHODS

Study population

The study population consisted of patients with rheumatoid arthritis (RA)-like PA, who received regular follow-up care at the Department of Rheumatology, Kenézy Gyula Hospital, and at the Department of Dermatology, University Medical School of Debrecen. The study was approved by the local ethics committee and informed consent was obtained from all subjects before the study was started.

The diagnosis of PA was established according to the original diagnostic criteria of Moll & Wright (19). The diagnosis was made in the presence of an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) and psoriasis and in the absence of serological tests for rheumatoid factor and anti-CCP (cyclic citrullinated peptide) antibodies. Overall, 19 patients were included in the study, 10 of whom were enrolled into the alphacalcidol-treated group, with the remaining 9 in the control group. There were 6 women and 4 men in the treatment group with a mean age of 60 ± 8 years; the disease course of psoriasis was 15 ± 11 years, while the presence of arthritis was 8 ± 6 years. The control group comprised 4 women and 5 men with a mean age of 53 ± 13 years; the presence of psoriasis was 21 ± 8 years, while arthritis has been apparent for 8 ± 1 years.

Study protocol

The follow-up period was 6 months. The inclusion criteria were the established diagnosis of PA with polyarticular (RA-like) joint involvement. Patients with nephrolithiasis and other inflammatory arthropathies were excluded. There were three visits during the course of the follow-up: the first visit at the start of follow-up, and additional visits 3 and 6 months later. The study window period was ± 14 days during each visit. At the time of each visit several clinical parameters were analysed: the psoriasis area and severity index (PASI), patients' global assessment using a 100-mm visual analogue scale (VAS), the activity of articular involvement by the three variable disease activity score (DAS28), and other routine laboratory data, such as erythrocyte sedimentation rate, serum calcium, phosphorous, urea, creatinine and liver enzymes, urine calcium/creatinine ratio, and immunological parameters, including the percentages of CD3, CD4, CD8-positive T cells, CD56-positive NK cells and CD19-positive B cells (20). T-cell activation was evaluated by HLA DR and CD69 cell surface expression and the ratios of Th1/Th2 and T-cytotoxic (Tc)1/Tc2 cells were measured by evaluating intracellular IFN-γ and IL-4 levels. The monocyte-macrophage population was estimated by investigating CD14-positive/CD16-positive and CD14-positive/CD16-negative cells, and regulatory T cells were measured by CD4/CD25 simultaneous staining. Serum levels of IFN-γ, IL-10 and IL-4 were also examined.

In addition, bone densitometry (Lunar DPX Pro, Lunar Corporation, Madison, WI 53717, USA) and X-ray of the hands and feet were performed at the first visit. The bone densitometry measurements were performed at the lumbar spine (L1–L4) and proximal femur area.

Therapeutic protocol

Each of the 19 patients was treated with methotrexate (MTX) 10 mg weekly combined with non-steroidal anti-inflammatory drugs (NSAIDs) started at least 3 months before being enrolled into the study. If the patient was over 65 years of age or had a history of upper gastrointestinal (GI) complications (ulcer, bleeding, perforation) or complaints, nimesulide was administered 100 mg twice daily. If the patient was below 65 years of age and was free of GI symptoms, diclofenac 75 mg twice daily was given.

The selection of patients into the alphacalcidol-treated group and the control group was made on the basis of having osteopenia or not. In 10 patients with osteopenia (<–1 T-score by the neck of femur or lumbar spine bone densitometry), oral alphacalcidol treatment 0.25 μg twice daily was initiated (this group served as the treated arm) and continued throughout the whole study period. We chose to treat only the osteopenic subgroup because in Hungary alphacalcidol is not a registered drug for the treatment of PA, but rather for the treatment of osteopenia. The remaining 9 patients with normal bone density served as the control arm.

Topically, all patients used creams with no active ingredients.

Study end-points

The primary end-points were measurements of the alterations in the function of the immune system evaluated by immunological laboratory tests and of changes in the clinical parameters (VAS, DAS28, PASI scores) in the alphacalcidol-treated and control groups. The secondary end-points were the detection of the changes in the serum calcium level and in the urine calcium/creatinine ratio.

Determination of lymphocyte and monocyte subsets

Immunofluorescent staining for flow cytometric analysis was performed by incubating 100 μl of whole blood with the corresponding monoclonal antibodies for 30 min. Red blood cells were lysed according to the Q-Prep protocol (Beckman-Coulter, Fullerton, CA, USA). Samples were subsequently washed in phosphate-buffered saline (PBS) containing bovine serum albumin (BSA) (1%) and resuspended in 1% paraformaldehyde. Lymphocyte and monocyte subsets were identified by the three-colour flow cytometry with antibodies to CD3, CD4, CD8, CD19, CD56, CD25, CD14 and CD16 (BD Biosciences, San Diego, CA, USA, Immunotech, Marseille, France and Sigma-Aldrich Co., St Louis, MO, USA). The expression of T-lymphocyte activation markers, namely, HLA-DR and CD69 was also determined on CD3-positive cells with corresponding monoclonal antibodies (BD Biosciences). Events were recorded by Coulter EPICS XL flow cytometer (Beckman Coulter Inc., Miami, FL, USA). At least 5000 events were counted and evaluated for the expression of CD3, CD3/CD4, CD3/CD8, CD19, CD3/CD56, CD3/CD69, CD3/HLADR, CD4/CD25^{bright} and CD14/CD16.

Evaluation of soluble and intracellular cytokines

Serum levels of IL-10, IL-4 and IFN-γ were measured using BD OptEIA ELISA kits (BD Biosciences), according to the manufacturer's instructions. Intracellular flow cytometry was utilized to determine the percentage of IFN-γ- and IL-4-producing lymphocytes within the CD4- and CD8-positive subsets. Briefly, heparinized whole blood was diluted 1:1 with RPMI medium (Sigma-Aldrich Co.), and cells were stimulated for 4 h at 37°C, in 5% CO_2 atmosphere with 0.5 mg/ml ionomycine (Sigma-Aldrich) and 1 μg/ml phorbol myristate acetate (PMA; Sigma-Aldrich) in the presence of 5 mg/ml Brefeldin A (Sigma-Aldrich) to induce cytokine production. Lymphocytes were then stained with either anti-human CD4-Quantum Red or anti-human CD8-Quantum Red (Sigma-Aldrich). Red blood cells were subsequently lysed with FACS Lysing Solution (BD Biosciences), and lymphocytes were permeabilized with FACS Permeabilizing Solution (BD Biosciences). To detect intracellular cytokines, cells were labelled with either anti-human IFN-γ-FITC/IL-4-PE (BD Biosciences) or with anti-human IL-10 (Caltag Laboratories, Burlingame, CA, USA), washed, and fixed with 1% paraformaldehyde. Events were counted by Coulter EPICS XL flow cytometer (Beckman Coulter Inc.). A gate was set on CD4- or CD8-positive lymphocytes and at least 5000 cells were counted and evaluated for the expression of IFN-γ and IL-4.

Statistical analysis

Statistical analysis of the results was performed using an SPSS 11.0 software. Statistical differences between measured va-

lues were analysed using a paired *t*-test. *p*-values <0.05 were considered statistically significant. All values are shown as mean ± standard deviation.

RESULTS

Clinical data

Nineteen patients with PA were investigated. The mean age of the alphacalcidol treated (osteopaenic) group was higher (60 ± 8 years) than that of the control group (53 ± 13 years). This difference can be explained by the increased prevalence of decreased bone density with age. Therefore, the older patients had a higher probability of having osteopaenia and getting into the treated arm. In our opinion this difference in age did not influence the immunological status of the groups. The disease course of psoriasis in the treated arm was shorter (15 ± 11 vs. 21 ± 8 years), while the presence of arthritis was almost the same in the two groups (7.7 ± 6 vs. 8.4 ± 1.4 years).

Before alphacalcidol treatment the clinical and laboratory parameters were not significantly different between the treated and the control groups. The VAS scores were 57 ± 17 vs. 60 ± 21 mm, the DAS scores were 45 ± 11 vs. 49 ± 21 mm, and the PASI scores were 12.8 ± 4.3 vs. 11.9 ± 4.4, respectively, on the average. In order to monitor the potential side-effects we looked at serum calcium levels and the urine calcium/creatinine ratio. At the start, the serum calcium levels were 2.34 ± 0.1 mmol/l vs. 2.29 ± 0.06 mmol/l, while the urine calcium/creatinine ratios were 0.33 ± 0.19 vs. 0.25 ± 0.29 in the treated and in control groups, respectively (data not shown).

The only significant change in clinical parameters was observed in the DAS28. In the alphacalcidol-treated group, but not in controls, a continuous decrease in DAS28 during the 6 months of follow-up was detected reaching 29 ± 10 mm ($p=0.048$). The PASI and VAS scores also were decreased in the treated group, but the difference was not significant. No further significant changes in the main clinical parameters were detected.

Immunological laboratory parameters

At the start of the study there were no significant differences between the two groups with regard to their immunological laboratory parameters.

In the treated group a significant decrease in the percentage of CD69-positive activated T cells was observed (1.54 ± 1.15% vs. 0.56 ± 0.33%, $p=0.04$) (Fig. 1.). There was also a significant decrease in the percentage of IFN-γ-producing CD8-positive T lymphocytes (7.6 ± 3.4% vs. 4.3 ± 3.0%, $p=0.04$) (Fig. 2.), as well as in the serum IFN-γ levels (34.3 ± 25.1 pg/ml vs. 5.5 ± 4.0 pg/ml, $p=0.03$), after 3 months of treatment

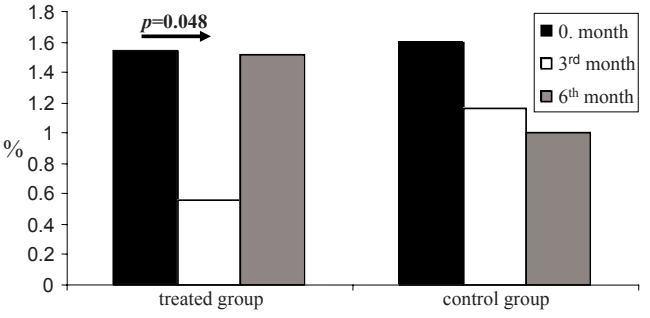

Fig. 1. Percentage of CD3/CD69-positive activated T cells. There was a significant decrease in the percentage of CD3/CD69-positive T cells in the treated group 3 months after introducing the alphacalcidol therapy.

with alphacalcidol (Fig. 3.). These alterations reflect a down-regulation in the activation of T cells and a decreased cytokine production of cytotoxic T lymphocytes in the alphacalcidol-treated group. There were no statistically significant changes in the percentages of other T-cell populations (CD3/CD4-positive, CD3/CD8-positive, CD4/IFN-γ-positive, CD4/IL-4-positive, CD8/IL-4-positive), neither were there significant changes in the ratio of regulatory T cells, B cells, NK cells and activated monocytes during the first 3 months of follow-up. However, a non-significant decrease in the ratio of CD56-positive NK cells was observed after 6 months of alphacalcidol treatment (19.0 ± 6.0% vs. 16.4 ± 6.7% ns). In the control group no significant changes in the immunological laboratory parameters were observed (data not shown).

DISCUSSION

Several animal studies have shown beneficial immunomodulatory effects of vitamin D_3 and its active metabolites in experimental autoimmune encephalomyelitis (21), in diabetes (22) and also in allograft transplanta-

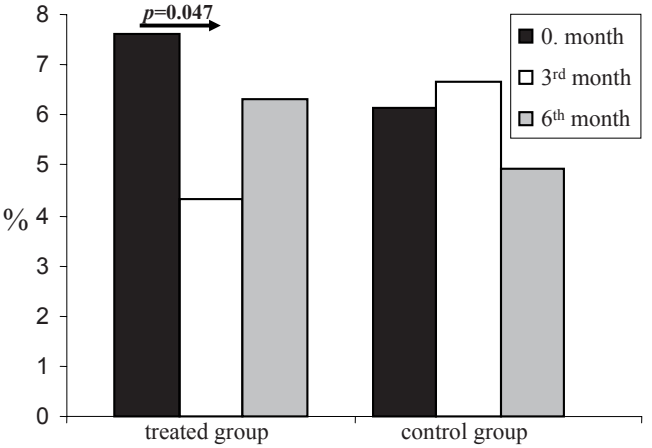

Fig. 2. Percentage of IFN-γ-producing CD8-positive T cells. A significant decrease in the percentage of IFN-γ producing CD8-positive T lymphocytes was detected 3 months after introducing the alphacalcidol therapy.

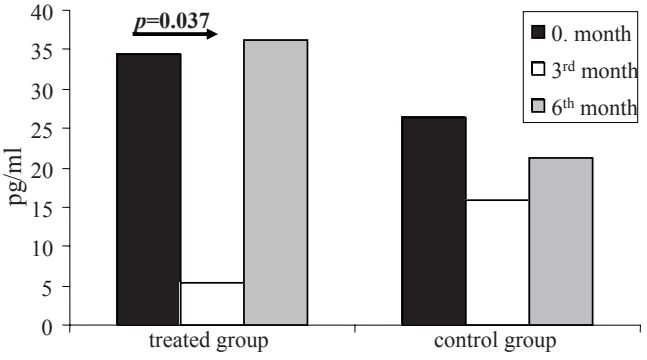

Fig. 3. Serum level of IFN-γ. A significant decrease was found in the serum IFN-γ level in the treated group 3 months after introducing the alphacalcidol therapy.

tion models (23, 24). In experimental arthritis models treatment with activated forms of vitamin D_3 suppressed the incidence and activity of arthritis (25, 26).

There were only a few human studies on the clinical effects of vitamin D_3 metabolites in various arthritic conditions. Some authors observed a slight, but not significant improvement in the clinical and laboratory parameters of RA patients after systemic alphacalcidol treatment (27, 28)

There is evidence on the clinical effectiveness of oral treatment with activated forms of vitamin D_3 on skin symptoms of psoriatic patients. Perez and co-workers (17) applied calcitriol in a 2.4 μg daily dose, with calcium restriction, on patients with plaque-type psoriasis with a success rate of 88% without major side-effects. In our study a slight but statistically non-significant improvement in skin symptoms (e.g. PASI score) was observed, though we used much lower doses than the other investigators. On the other hand, the clinical effects of systemic alphacalcidol treatment on PA were examined in only one pilot study. Huckins and co-workers (18) conducted a 6-month open-label trial in which 10 patients with active PA received 2 μg of oral alphacalcidol once daily. They noted statistically significant improvements in the tender joint count and physician global impression, but immunological laboratory data were not recorded (18).

In our present study we found a significant immunomodulatory effect during systemic alphacalcidol treatment in patients with polyarticular PA. This effect resulted in a continuous decline in the disease activity score (DAS28) after 6 months and significant changes in different immunological parameters. The percentage of CD69-positive activated T cells, the ratio of IFN-γ-producing CD8-positive T lymphocytes and the serum IFN-γ level were significantly decreased after 3 months of treatment. Our results clearly indicate that the effect of systemic alphacalcidol treatment results in a short-term temporary decrease in the activation of type 1 immune responses and in a continuous decrease in disease activity. Theoretically, the decrease in pain arising from the periarticular bone can adulterate the results of the DAS28 score. Our belief, however, is that the decrease in DAS28 score is really a consequence of the immunomodulatory effect of alphacalcidol. For once the articular pain is not a part of the clinical picture of osteopaenia, since the osteopaenia is a basically a silent disease. Beside this, the components of DAS28 (joint swelling and tenderness, erythrocyte sedimentation rate) are quite reliable markers of the arthritis activity. Finally, the follow-up period (6 months) is too short for a substantial increase in bone density following alphacalcidol treatment. The temporary decrease in the parameters at 3 months was associated with a decrease in clinical disease activity at 6 months, although there was no clear causative relationship between these data. Yet, we believe that these findings point towards the fact that the administration of this drug has a beneficial immunological effect in these patients.

There is evidence that psoriasis and PA are T-cell driven type 1 immune-mediated diseases. CD8-positive T lymphocytes play a crucial role in the pathogenesis of PA. In the synovial fluid and in the synovium there is a dominant CD8-positive T-cell population and these cells may be the driving force behind the immune response in the PA joint (29). Cytokines secreted from immunocompetent cells induce proliferation and activation of the synovial and epidermal fibroblasts leading to clinical manifestations of arthritis in patients. Moreover, serum levels of different cytokines can be a marker of disease activity in patients with PA (30).

IFN-γ plays an important role in the pathogenesis of PA. It increases the expression of MHC-II antigens and intercellular adhesion molecule-1 (ICAM-1) on the surfaces of synovial membranes and keratinocytes, and facilitates the production of pro-inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-8) (31). IFN-γ also shifts the immune response towards a type 1 direction, and decreases suppressor T-cell activity (32, 33).

Our results support the idea that the observed decline in disease activity can be explained by the alphacalcidol-mediated decrease in type 1 immune response. We believe that the administration of alphacalcidol to patients with PA improves the laboratory parameters and the clinical disease course and will become a valuable alternative in the future.

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The authors declare no conflicts of interest.

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