Secukinumab produces a quick increase in WNT signalling antagonists in patients with psoriatic arthritis

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ABSTRACT

Objective. *Interleukin-17 (IL-17) is an important cytokine involved in the pathogenesis of bone lesions of psoriatic arthritis (PsA). The aim of our study was to explore the short-term effects (≤6 months) of secukinumab (an anti-IL-17 antibody) on the serum levels of bone turnover markers (BTMs) and on the inhibitors of the WNT signalling pathway.*

Methods. *The study sample consisted of patients with PsA starting treatment with secukinumab 150 mg every month, and healthy controls (HCs). For the PsA group, the DAS28 score was recorded, and serum samples were collected at baseline, and then at Month 1, 3 and 6 of therapy. As for the HCs, a single observation was performed, with the relevant serum collection. Intact N-terminal propeptide of type I collagen (PINP), C-terminal telopeptide of type I collagen (CTX-I-I), Dickkopf-related protein-1 (Dkk-1) and sclerostin were administered.*

Results. *28 patients with PsA and 43 HCs were enrolled. Neither PINP nor CTX-I serum levels showed any significant variation during the observation period. Baseline mean Dkk-1 serum levels for the PsA arm were significantly lower than in the HC ($p<0.05$). Dkk-1 and sclerostin serum levels increased at Month 6 during the treatment with secukinumab ($p<0.05$ vs. baseline). When the PsA arm was compared to the HC, the difference between the serum levels of Dkk-1 lost significance at Month 6.*

Conclusion. *Treatment with secukinumab does not have any significant short-term effect on BTMs, but may influence some fine regulators of the bone cell activity, such as the WNT inhibitors.*

Introduction

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease that affects peripheral joints, connective tissues and the axial skeleton, and is associated with skin and nail psoriasis (1).

Interleukin-17 (IL-17) is an important cytokine involved in the pathogenesis of PsA. Indeed, increased levels of IL-17-producing cells are found in these patients (2), and they have also been correlated with measures of disease activity, structural damage and bone loss. In particular, it has been suggested that chronic skin inflammation could lead to bone loss by IL-17-mediated inhibition of the WNT signalling (3).

Secukinumab is a monoclonal antibody which selectively binds to and neutralises IL-17A and which has shown to be effective in the treatment of psoriasis, ankylosing spondylitis (AS) and PsA (4, 5).

In PsA, various degrees of bone erosions are associated with extensive new bone formation, involving typically the edges of the cartilage joint at the insertion of the entheses (6). The understanding of the "coupling" of these two processes and their derangement may improve the understanding of the pathophysiology of both the systemic and focal bone diseases. The balance between the osteoclast and osteoblast activities mainly depends on the regulation of the WNT pathway, and it is exerted by inhibitors such as Dickkopf-1 (Dkk-1) and sclerostin (7). With the improvement of our knowledge on the canonical WNT pathway, it became clear that the latter plays a key role in the regulation of bone modelling and remodelling, and important insights were obtained concerning the pathophysiology of bone involvement in chronic arthritis (8).

This seems to be the key mechanism through which the structural damage typical of inflammatory arthritis is produced (9,10). Recently, we observed lower Dkk-1 serum levels in PsA patients than in healthy subjects (8), with higher levels in patients with rheumatoid arthritis (8, 11). In our opinion, this observation may contribute to explain the different local bone involvement of the two different diseases: erosive in RA *versus* erosive and productive in PsA.

The effects of the biologic therapy on bone turnover markers (BTMs) and WNT modulators are still inconsistent. Currently, we have few data in patients with RA (12-14) or spondyloarthropathy (13), while data in patients with PsA are lacking.

The aim of our study was to explore the short-term effects of secukinumab on BTMs and the WNT signalling inhibitors, in particular Dkk-1 and sclerostin.

Table I. Baseline values of CTX-I, PINP, Dkk-1 and sclerostin and absolute changes from baseline (B) to Month 1 (M1), 3 (M3) and 6 (M6) of observation of the evaluated markers (mean absolute change ± standard deviation).

	HC baseline values (n=43)	PsA patients (n=28)			
		Baseline values (Mean ± SD)	B M1	B M3	B M6
PINP ng/ml	48.32 ± 12.23	43.5 ± 14.5	-0.31 ± 12.91	-0.81 ± 11.97	0.96 ± 14.87
CTX-I ng/ml	0.31 ± 0.11	0.25 ± 0.16	0.02 ± 0.14	0.04 ± 0.20	0.08 ± 0.27
Dkk-1 pmol/l	25.92 ± 11.26	20.0 ± 13.64[¥]	-1.45 ± 7.89	-1.38 ± 9.49	2.90 ± 7.45*
Sclerostin pmol/l	33.11 ± 16.85	30.9 ± 12.02	-0.76 ± 8.39	3.09 ± 7.54V	3.03 ± 7.77*

*$p<0.05$ *vs*. baseline. [¥]$p<0.05$ *vs*. Dkk-1 of the HC arm at baseline, at Month 1 and Month 3.

Materials and methods

Study design

This is a prospective study, conducted in the PsA clinic in the Rheumatology Division of the Azienda Ospedaliera Universitaria Integrata of Verona. The study sample included patients with PsA classified with the CASPAR criteria (15) consecutively recruited at our centre, and Healthy Controls (HC), matched for age and sex, enrolled among the hospital personnel.

The inclusion criteria for the PsA group were: stable treatment with parenteral methotrexate in the last three months (ranging from 10 to 15 weekly administrations), time from diagnosis ≤3 years. The exclusion criteria for the samples of PsA patients were: previous treatment with biologic drugs, systemic inflammatory diseases, active infections, neoplasms, kidney, liver, endocrine or metabolic bone diseases, pregnancy and current use of biologic treatments, corticosteroids or drugs known to affect bone metabolism. The 28 joints Disease Activity Score (DAS28) was recorded at every time point. The patients of the PsA arm continued the undergoing treatment with methotrexate at stable doses and received treatment with secukinumab 150 mg every month; their serum samples were stored during the treatment at baseline and then at Month 1, 3 and 6 of therapy.

For the HC arm, a single observation was taken, with a relevant serum collection.

All procedures performed in the studies involving human participants complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. The protocol was approved by local Ethics Committee and an informed consent was obtained from all individual participants included in the study.

Biochemical assessment

Aliquots of serum samples were collected and stored at –50°C, and finally assayed for Intact N-Terminal Propeptide of Type I Collagen (PINP), C-terminal Telopeptide of type I Collagen (CTX-I-I), sclerostin and Dkk-1. All samples were processed in the Rheumatology Unit laboratory of the University of Verona at the end of the study.

The bone turnover markers (PINP and CTX-I) were measured with the analyser IDS-ISYS Multi-Discipline Automated System (Immunodiagnostic System, Boldon, UK), based on chemiluminescence technology. The intra-assay Coefficients of variation (CVs) measured in our laboratory were 4% for Intact-PINP (inter-assay CV 6%) and 3% for CTX-I (inter-assay CV 7%). Serum Dkk-1 and sclerostin were measured with ELISA (Biomedica Medizinprodukte, Vienna, Austria), with a sensitivity of 1.7 and 3.2 pmol/L and intra-assay CVs of 7 and 5% (inter-assay CVs 8.2% and 6.9%), respectively.

Statistical analysis

All statistical analyses were performed – as per protocol – with the SPSS software, v. 22 (SPSS, Inc., Chicago, IL, USA). We calculated the absolute and percentage differences from baseline to Month 1, 3 and 6, and all calculated differences were tested for significance by one-sample *t*-test *versus* 0. Then we tested the absolute values of all the markers at any time point *versus* the HC (single observation), with an independent sample *t*-test. Correlations were calculated using linear regression. Two-sided *p*-values of 0.05 or less were considered significant. Data are presented as mean ± SD.

Results

The study sample consisted of 28 patients (10 males and 18 females); mean age was 57 (SD ± 10). The HC arm consisted of 43 subjects (14 males and 29 females), and mean age was 61 (SD ± 5.8). No statistically significant difference in anthropometrics were observed between the two arms.

The mean baseline DAS28 for the PsA arm was 3.88±1.24 (mean ± SD), and showed a statistically significant improvement at Month 3 of treatment (-0.64±0.91), stable at Month 6 (-0.69±1.28).

The baseline values of CTX-I, PINP, Dkk-1 and sclerostin for PsA patients and HCs are shown in Table 1. No statistically significant difference was found for sclerostin, CTX-I or PINP between the HC arm *versus* the PsA patients at baseline, while Dkk-1 mean serum levels of the PsA subjects at baseline were lower than those in the HC arm ($p<0.05$). For the PsA group, neither PINP nor CTX-I showed any statistically significant change over time.

Figure 1 shows the mean values of Dkk-1 induced by the treatment compared with the values observed for the HC arm.

The percentage changes of Dkk-1 and sclerostin in the PsA arm are shown in Figure 2.

Both Dkk-1 and sclerostin demonstrated a significant increase from baseline at Month 6, with an earlier variation for

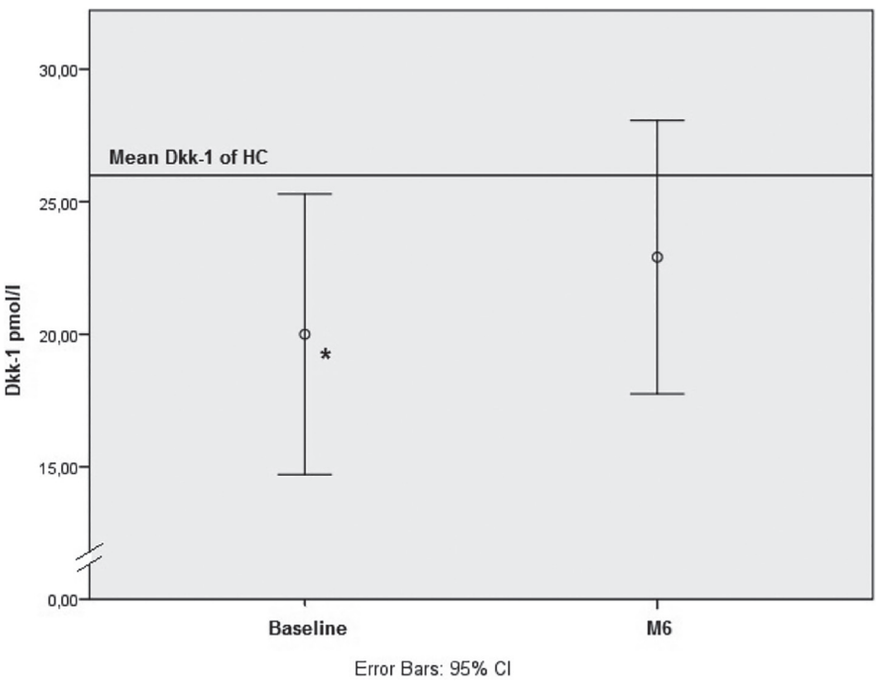

Fig. 1. Comparison between the Dkk-1 values of PsA patients at baseline and at Month 6 *vs*. the HC arm. **p*<0.05 *vs*. HC.

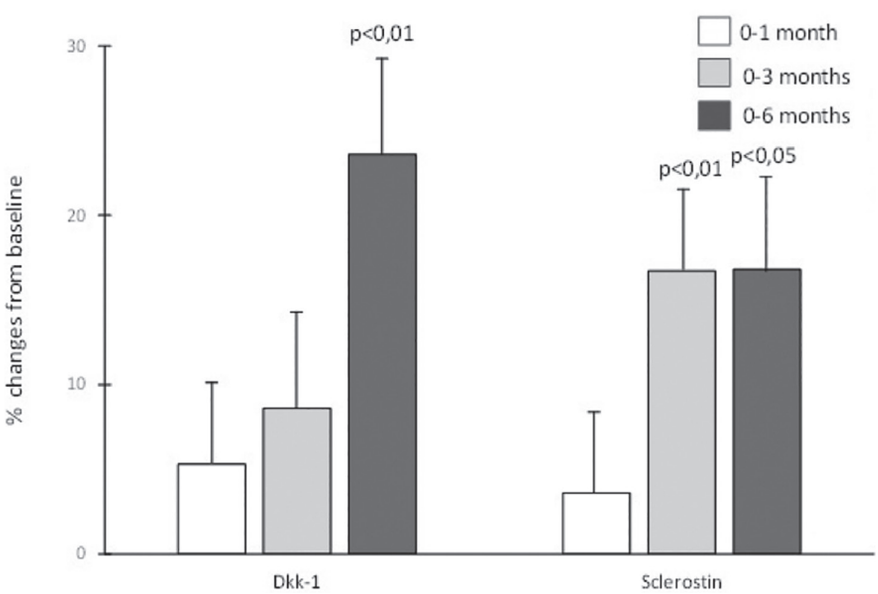

Fig. 2. Percentage changes in Dkk-1 and sclerostin (mean ± SE) at all observation points. **p*<0.05 *vs*. baseline.

sclerostin, which reached significance already at Month 3.

A moderate positive correlation emerged between the percentage changes of Dkk-1 and sclerostin (R^2 = 0.262. *p*=0.000).

Discussion

To the best of our knowledge, this is the first study analysing the changes in the BTMs and the inhibitors of the WNT pathway in patients treated with secukinumab. Our results show that BTMs do not significantly change, at least for the first six month of treatment, while Dkk-1 and sclerostin show a significant increase.

The absence of changes in serum BTMs might be explained by the limited period of observation. Indeed, Dkk-1 increased significantly after only six months. In addition, Dkk-1 and sclerostin might be acting at a local level, at the inflammation sites, without any significant effect on the circulating levels of BTMs.

In previous studies (8,16) we showed that, in patients affected by PsA and AS, Dkk-1 serum levels are significantly lower than in the HCs. Here, this statement is confirmed, and we also observed that the treatment with secukinumab appears to restore normal Dkk-1 serum levels. Previous data showed that the blockade of Dkk-1 was associated with the fusion of the sacroiliac joints in a murine model (17), and that low sclerostin and Dkk-1 levels in AS may be correlated to syndesmophyte formation (18,19). In this study, serum levels of Dkk-1 in the PsA group progressively increased, resulting in the loss of the significant gap vs the HCs after six months of therapy with secukinumab. However, at present it is difficult to recognise whether the increase in Dkk-1 and sclerostin is a direct consequence of the inhibition of the IL-17 pathway, or if it is a counter-regulatory mechanism caused by the decrease in the action of IL-17 on osteoblast and osteocytes, an interesting phenomenon recently demonstrated (3). Based on these premises, a very intriguing area of research might be to investigate whether the drug-induced changes in Dkk-1 could be associated with a reduction in the bone over-proliferation typical of the joint lesions in PsA.

Our study suffers from several limitations. First, the sample size is limited. Second, the time span of the observation is limited to six months. However, these preliminary data may break new ground for further studies about any specific and unexpected effects that secukinumab could have on the bone.

In conclusion, our study showed that the treatment with secukinumab does not have any significant short-term effect on the BTMs, but it does have a significant influence on some fine regulators of the bone cell activity, such as the WNT-inhibitors, suggesting the hypothesis of a drug-induced inhibition of local bone over-proliferation, typical of the bone lesions in PsA.

Further studies on a larger numbers of patients – and with the data on the pos-

sible effects on bone mineral density and structural damage – are warranted, in order to determine whether these preliminary results have any clinical relevance or not.

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