EXTENDED REPORT

Body weight, body composition, and bone turnover changes in patients with spondyloarthropathy receiving anti-tumour necrosis factor α treatment

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Ann Rheum Dis 2005;**64**:1137–1140. doi: 10.1136/ard.2004.028670

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Accepted 2 January 2005
Published Online First 7 January 2005

Objectives: To determine the changes in body weight, body composition, and bone turnover in patients with spondyloarthropathy (SpA) treated with anti-tumour necrosis factor α (TNFα).

Patients and methods: 19 patients with SpA (2 women, 17 men), aged 21–71 years, were studied in a 1 year prospective open study. 17 patients received infliximab: 3 or 5 mg/kg/infusion at weeks 0, 2, 6 and infusions in the case of a relapse (n = 14) or systematically (n = 3); 2 patients received etanercept (25 mg twice a week). Body weight, body composition (lean mass, fat mass), and bone mineral density (BMD; using dual energy *x* ray absorptiometry) were measured at baseline and at months 6 and 12. Serum insulin-like growth factor-I (IGF-I), bone markers (carboxy terminal telopeptide of collagen I (CTX) and procollagen type *I* N terminal propeptide (PINP)) were measured at baseline and months 3, 6, and 12.

Results: In 1 year there was a significant increase in body weight (mean (SD) 2.24 (3.1) kg, p = 0.0004), and in lean mass (1.4 (1.69) kg, p = 0.005), but no changes in fat mass. BMD increased at the spine (5.6%, p = 0.0005) and total femur (2.6%, p = 0.01). CTX decreased from the third month (−50%, p = 0.005) up to 1 year (−30%, p = 0.012), and a trend for an increase in PINP (10%, p = 0.06) and in IGF-I (15%, p = 0.04) was seen at month 3.

Conclusion: These data confirm that treatment with anti-TNFα in SpA is associated with an increase of BMD, which results from a decrease of bone resorption. Increase in body weight and lean mass is observed in parallel with an increase in IGF-1.

Weight loss and decrease in lean mass can occur in patients with chronic advanced diseases,[1 2] and has been described in inflammatory rheumatic disorders, mainly in rheumatoid arthritis (RA).[3–5] Changes are also linked to the disease activity through the effects of cytokines such as interleukin (IL) 1, IL6, and tumour necrosis factor α (TNFα).[6 7] In RA, the hypermetabolism that causes loss of weight and even cachexia[3] has been directly associated with the production of TNFα and IL1.[3] TNFα, a pivotal cytokine in rheumatic disease, can reduce the appetite and lead to a loss of weight by increasing the protein catabolism and probably decreasing anabolic hormones such as insulin-like growth factor-I (IGF-I).[8] TNFα is a powerful regulator of adipose tissue, and increases lipolysis altering fat body mass.[9] However, physical inactivity and corticosteroid treatment contribute to these changes.[3]

In spondyloarthropathy (SpA) no change in body weight and body composition has been described so far.[10 11] However, in our clinical experience an increase in body weight is noticed in patients with SpA treated with anti-TNFα. Body composition, including lean mass, fat mass, and bone mineral density (BMD), can be assessed accurately by dual energy *x* ray absorptiometry (DXA).[12 13]

This prospective study aimed at evaluating changes in body weight and body composition by DXA over 1 year in patients with SpA receiving TNFα blockers. We investigated the predictive factors of these changes, including clinical and biological markers of disease activity. Moreover, we assessed at the same time BMD and biological markers of bone remodelling to extend our previous results.[14] Serum IGF-I was assessed, because its changes could be related to changes in lean mass and BMD.

PATIENTS AND METHODS

Nineteen patients (2 women, 17 men) with SpA according to the European Spondyloarthropathy Study Group criteria were included in this prospective study. They were receiving treatment with TNF blockers because of persistent active disease despite an optimal dose of non-steroidal anti-inflammatory drug and/or treatment with methotrexate or sulfasalazine. Ten patients had SpA without an associated condition; four had psoriatic arthritis, and five inflammatory bowel disease. Their ages ranged between 21 and 71 years (median 40). The mean duration of the disease was 16.5 years (range 5–43). Twelve had received corticosteroid treatment (average cumulative dose 8480 mg), three still received corticosteroids during the study at a mean daily dose of 8 mg. Two were treated with methotrexate during the study at a mean weekly dose of 17.5 mg. Seventeen patients received 3 or 5 mg/kg/infusion of infliximab at weeks 0, 2, 6 and, thereafter, infusions in the case of a relapse (n = 14) or systematically at a 6 or 8 week interval (n = 3). The mean (range) dose of infliximab over 1 year was 1572 mg (800–2850). Two patients received etanercept (25 mg twice a week); the mean dose was 2466 mg yearly.

The clinical activity and severity of the disease were evaluated by a visual analogue scale for global pain, Bath

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMD, bone mineral density; CRP, C reactive protein; CTX, carboxy terminal telopeptide of type I collagen; DXA, dual energy *x* ray absorptiometry; ESR, erythrocyte sedimentation rate; GH, growth hormone; IGF-I, insulin-like growth factor-I; IL, interleukin; PINP, procollagen type I N-terminal propeptide; RA, rheumatoid arthritis; SpA, spondyloarthropathy; TNFα, tumour necrosis factor α

Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI). At baseline, the median (range) scores were respectively 63.3 (23–100), 58.31 (36–84), and 60.75 (14.5–100). At baseline, median (range) erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were respectively 36 mm/1st h (10–80) and 36 mg/l (14–99). Global pain by visual analogue scale, BASDAI, BASFI, ESR, and CRP were assessed at 6 months and at 1 year.

At baseline, mean (SD) height, weight, and body mass index were 170.6 (5.7) cm, 69 (9.5) kg, and 26 (3), respectively. Body composition and BMD were measured by DXA (QDR 2000, Hologic, Bedford, USA). Median (range) lean mass and fat mass were 46.3 (30.8–58.8) kg and 15 (2.6–29.5) kg, respectively. BMD (g/cm^2) was determined at the lumbar spine (second to fourth vertebrae) and at the upper part of the left femur (total femur). At baseline, mean T scores (number of standard deviations (SDs) from the normal mean (SD) obtained from young healthy adults) were −1.30 (1.6) and −1.0 (0.9) at the spine and femur, respectively. BMD and body composition measurements were repeated under identical technical conditions after 1 year's follow up.

Bone remodelling was assessed by measuring the serum levels of carboxy terminal telopeptide of type I collagen (CTX), a marker of bone resorption, and procollagen type I N-terminal propeptide (PINP), a marker of bone formation, using an analyser (Roche Diagnostics, Manheim, Germany). The mean (range) of CTX and PINP levels was 0.367 (0.043–0.889) ng/ml and 70.1 (9.8–99.7) ng/ml, respectively, at baseline. Serum IGF-I was measured by radioimmunoassay (Nichols Institute), and mean baseline (range) levels were 170.4 (119–255) ng/ml. These measurements were made in 15 patients at months 3, 6, and 12.

Statistical analysis

This was a 1 year prospective open study. We described during 3, 6 months and 1 year's follow up, changes in body weight, body composition (lean and fat mass), lumbar spine and femoral BMD, IGF-I, CTX, PINP. Data were compared using Wilcoxon's signed rank sum test. Data were also presented as relative (%) changes. Correlations between the changes during the 1 year study in body weight, body composition (lean mass, fat mass), BMD, and biological variables were tested using Spearman's correlation coefficient.

RESULTS

After 1 year of treatment we observed a significant improvement of the following clinical variables: global pain score (−50%, $p<0.005$), BASDAI (−51%, $p = 0.005$), BASFI (−39%, $p = 0.003$), and the biological measures of inflammation, ESR (−51.1%, $p = 0.001$) and CRP (−58%, $p = 0.001$).

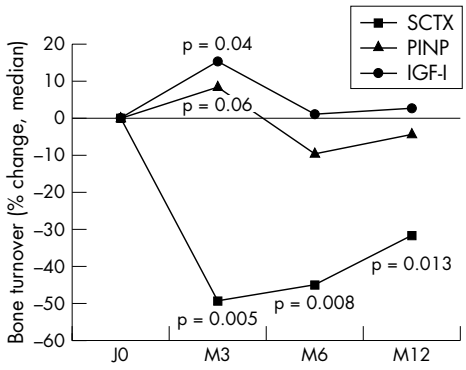

Figure 1 Effect of anti-TNF on bone turnover and IGF-I in 15 patients with SpA.

At 6 months there was a significant increase in body weight (mean (SD) 1.77 (2.4) kg—that is, 2.6 (3.7)% compared with baseline, $p = 0.0012$) and lean mass (0.8 (1.8) kg, 2.1 (4.5)%, $p = 0.03$). At 1 year, compared with baseline, these increases were 2.2 (3.1) kg, (3.4 (4.6)%, $p = 0.001$) and 1.4 (1.7) kg (3.2 (4.2)%, $p = 0.003$) for body weight and lean mass, respectively. The changes between 6 and 12 months were not statistically significant. There was no change in fat mass at any evaluation.

Similar results were obtained for men and women. There was no difference between patients with or without corticosteroids or with or without methotrexate (data not shown). Changes in body mass and composition were not related to baseline body weight or the cumulative dose of anti-TNF received.

Changes in body weight correlated positively with baseline values of CRP ($r_s = 0.52$, $p = 0.007$) and ESR ($r_s = 0.50$, $p = 0.05$). Changes in lean mass correlated only with the baseline BASDAI ($r_s = 0.51$, $p = 0.003$). Neither body weight nor body composition changes correlated with values of CRP, ESR, BASDAI, and BASFI at 6 months and 1 year (data not shown).

At 6 months there was a significant increase in spine and total femur BMD by a mean (SD) of 3.2 (4.0)% ($p = 0.006$) and 1.8 (2.1)% ($p = 0.0002$), respectively. At 1 year the increases reached 5.6 (4.5)% ($p = 0.002$) and 2.6 (3.5)% ($p = 0.01$) at these two sites, respectively, and the 1 year values differed from both the baseline and the 6 month values ($p = 0.0005$ and $p = 0.0032$ for the spine, $p = 0.001$ and $p = 0.0002$ for the total femur from baseline and 6 months, respectively). The changes of BMD did not correlate with body weight or lean mass changes.

At 3 months, there was a large decrease of serum CTX (mean (SD) −50 (42)%, $p = 0.005$), a trend for an increase in PINP (+10 (49)%, $p = 0.06$), and a significant increase in IGF-I (+15 (40)%, $p = 0.04$). A positive correlation between changes of IGF-I and PINP ($r_s = 0.61$, $p = 0.01$) was found. The decrease of CTX was sustained until the end of the study (fig 1); at 1 year, this bone resorption marker was still decreased by 30 (40)% ($p = 0.01$). In contrast, 6 month and 1 year values for PINP and IGF-I did not differ from baseline values.

DISCUSSION

These data show that in patients with SpA receiving anti-TNFα there is a significant gain in body weight and lean mass after 6 months and 1 year of treatment, without changes in fat mass. Such changes of body weight and body composition after initiation of treatment with TNF blockers have never been mentioned in studies of rheumatic disorders, except in juvenile idiopathic arthritis.[15] Moreover, we extend our previous results on positive BMD changes and bone turnover in these patients.[14]

We suggest that these changes are related to the anti-TNF treatment. In RA, weight loss has been attributed to raised TNFα production and energy expenditure.[16] Animal studies have shown that TNFα is implicated in the catabolism of muscle proteins.[17 18] TNFα and other inflammatory cytokines decrease muscle protein synthesis through their effect on the growth hormone (GH)/IGF-I axis,[19] and increase protein degradation. In animal studies, administration of TNFα increased muscle protein catabolism and reduced IGF-I levels in both plasma and skeletal muscle.[19] Studies suggested that catabolic illnesses are associated with the development of a GH resistant state. TNFs have been proposed as potential mediators of hepatic GH resistance during sepsis.[8 20]

Beside this potential direct effect, anti-TNF treatment may have an indirect positive effect on lean mass through the general health improvement of patients, leading to an increase in physical activities. In this hypothesis, any treatment able to improve pain in these patients would have similar effects. However, we are unable to confirm this hypothesis, as we did not assess the level of physical activity of the patients during the study. Moreover, no change in body composition was detected in patients with RA after 12 weeks of high intensive training.[21] We found no change in fat mass, although TNF is a paracrine and autocrine regulator of adipose tissue.

This 1 year prospective open study confirms our previous data on bone improvement in patients with SpA treated with anti-TNF.[14 22] In our opinion, the increase in BMD was not due to confounding factors, like syndesmophytes, which cannot explain the 1 year change, although we did not assess 1 year radiological data. We checked the positioning of patients carefully before each scan, in order to avoid any artefact. We observed an increase in BMD and a large and sustained decrease in bone resorption, assessed by serum CTX.

As far as we know, this is the first study that shows a dissociation between bone formation and bone resorption during anti-TNFα treatment. In our previous study we were unable to detect such an effect on bone resorption, assessed by the urinary excretion of deoxypyridinoline, probably because of lower sensitivity and/or higher variability of this marker compared with serum CTX.[14] The decrease of serum CTX was large and rapid (within 3 months and sustained throughout the study), contrasting with the transient and slight increase of serum PINP, a sensitive index of bone formation, suggesting that the major effect of the anti-TNF is an inhibition of bone resorption. Interestingly, in a small study of patients with active RA, it has been shown that 6 weeks of treatment with infliximab results in a slight decrease of serum ICTP, another type I collagen related bone resorption marker, and a significant increase of the bone formation marker PINP.[23]

The early increase of IGF-I must be emphasised and can explain, at least in part, the gain of BMD and lean mass.[24] IGF-I has an anabolic effect on bone, and stimulates bone turnover as it increases the number and function of osteoblasts. In animal studies, injections of rat GH at the surfaces of tibial diaphyses increase external diaphysial bone dimensions.[25] GH deficiency in adults is associated with abnormalities of body composition, in particular, increased fat mass, especially truncal and reduced lean body mass. GH replacement improves the body composition profile of patients with GH deficiency by increasing lean body mass and reducing fat mass.[26] The overall effect of IGF-I/GH seems beneficial as bone mass is increased together with the lean mass.[27] In our study there was no correlation between the gain of weight, particularly of lean mass and the increase of BMD, but the analysis was difficult because of the small sample size. Indeed previous studies have reported that body weight is significantly related to BMD,[28 29] and that lean mass has a significant role in determining BMD.[30 31]

This study has several limitations. It is an open study and we can only propose the hypothesis that observed changes are related to anti-TNF treatment. A formal study with a control group is necessary to confirm the results.

We confirm the benefit of the treatment by TNF blockers on BMD in patients with SpA over 1 year, with a concomitant decrease in the bone resorption, and transient increase of bone formation and serum IGF-I. This study suggests that the increase in body weight at 6 months and 1 year in patients with SpA is mostly due to a gain of lean mass.

ACKNOWLEDGEMENTS

We thank Fabrice Juillet (Molecular Markers, Synarc, Lyon, France) for expert technical assistance in the measurements of biochemical markers of bone turnover.

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