

## 1. Abstract

### Title

Evaluation of the role of adalimumab on extraarticular manifestation - bone metabolism and bone mineral density in patients with active rheumatoid arthritis.

### Keywords

Bone mineral density, bone turnover markers, rheumatoid arthritis, osteoporosis.

### Rationale and Background

Osteoporosis with an increased risk of osteoporotic fractures is a well-known complication of rheumatoid arthritis (RA). It is mostly attributable to a combination of disease severity and use of oral glucocorticoids. Thirty-four percent of patients with RA suffer from low-trauma fracture within five years from the diagnosis. However, increased risk of fractures is apparent also in patients who do not take oral glucocorticoids. Based on this, it is evident that intensive bone resorption including signs of periarticular osteopenia, bone erosions, and generalized osteoporosis can be induced by the process of local and systemic inflammation in RA. Circulating hormones and pro-inflammatory cytokines represent major regulatory molecules involved in the development of local bone damage and generalized osteoporosis. There is evidence of uncoupling between bone formation and bone resorption in RA, leading to increased osteoclast formation and subsequent joint destruction in the context of inflammation. It has been demonstrated that small molecules involved in the process of bone resorption are particularly regulated by pro-inflammatory cytokines such as tumor necrosis factor (TNF- $\alpha$ ).

This was a non-interventional, prospective, multicenter and multicountry observational study, in which adalimumab was prescribed in the usual manner in accordance with the terms of the local market authorization with regards to dose, population and indication as well as local guidelines. The decision to prescribe or not to prescribe an anti-TNF was taken prior to entry of a subject in the study.

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## Research questions and objectives

- To determine whether TNF blocking therapy with adalimumab can modulate bone turnover markers as well as bone mineral density in a cohort of Czech, Slovak and Romanian patients with active RA. The end point was an evidence of prevention of generalized bone loss in patients with active RA treated with adalimumab in pragmatic prescribing situations.
- Clinical outcomes were assessed by analyzing changes in Bone Mineral Density (BMD) of spine and hip by bone densitometry (DEXA) before the start of treatment (M0), after 12 month (M12) and 24 month (M24). Changes in bone turnover markers reflecting both synthesis – osteocalcin (OC) and C-terminal type I procollagen peptide (CICP), and degradation - C-telopeptide of type I collagen (CTX-I) were determined at baseline (M0), at month 3 (M3) and 12 (M12).

## Study Design

This was a prospective, single-arm, multi-country and multicenter study. Adalimumab was prescribed to patients with RA in the usual manner in accordance with the terms of the local market authorization with regards to dose, population and indication as well as local guidelines. The decision to prescribe or not to prescribe an anti-TNF was taken prior to entry of a subject in the study.

Four visits were planned per patient. Screening/Inclusion Visit was performed when the decision to start anti TNF- $\alpha$  therapy was made. Inclusion of patient succeeded at day 0 (S/I Visit). The Second Visit followed 3 months after the Screening/Inclusion Visit.

The Third and Fourth Visit took place at the month 12 and the month 24 of the patient treatment.

The study was completed between March, 2009 (First Patient First Visit was on 2009-03-19) and May, 2014 (Last Patient Last Visit was on 2014-05-12).

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## Setting

The study took place in biologic centers in Czech Republic, Slovakia and Romania specialized for rheumatology and prescribing biological treatments. There were 27 active sites in Czech Republic, 4 sites in Slovakia and 3 sites in Romania. Rheumatologists observed their subjects during standard treatment regimen for a period of 104 weeks.

## Subjects and Study Size, Including Dropouts

The total number of patients involved in the study was 131. Most of the patients are from the Czech Republic (98 subjects (74.8%)), while there were 27 and 6 patients from Slovakia and Romania, respectively.

The full Analysis set (FAS) includes all subjects. The Per-protocol Population (PP) includes 87 subjects. 44 subjects were excluded from PP due to premature discontinuation.

## Variables and Data Sources

All diagnostic procedures in the study were performed in the frames of routine clinical practice. The data obtained from the assessments were recorded in the patient's source documentation and CRF. The assessments used in the study were standard for this indication and patient population.

## Results

### Primary endpoints

a) **L1-L4.** The mean values of L1-L4 BMD (g/cm<sup>2</sup>) at Baseline, Month 12 and Month 24 were 1.060, 1.072 and 1.062, respectively. The mean values of L1-L4 T-Score at Baseline, Month 12 and Month 24 were -0.568, -0.420 and -0.398, respectively. The mean values of L1-L4 Z-Score at Baseline, Month 12 and Month 24 were -0.024, 0.145 and 0.213, respectively. The median differences of the DEXA L1-L4 parameters between Baseline and Month 12/24 were not significant.

b) **Proximal Femur.** The mean values of Proximal Femur BMD (g/cm<sup>2</sup>) at Baseline, Month 12 and Month 24 were 0.882, 0.908 and 0.896, respectively. The mean values of Proximal Femur T-Score at Baseline, Month 12 and Month 24 were -0.699, -0.599 and -0.678,

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respectively. The mean values of Proximal Femur Z-Score at Baseline, Month 12 and Month 24 were -0.183, -0.096 and -0.144, respectively. The median differences of the DEXA Proximal Femur parameters between Baseline and Month 12/24 were not significant.

**2. Bone turnover markers.** (Very few (5-14) subjects.)

a) **Osteocalcin (OC).** The mean values of Osteocalcin (OC) ( $\mu\text{g/L}$ ) at Baseline, Month 3, Month 12 and Month 24 were 23.237, 24.138, 21.022 and 25.703, respectively. The median difference between Baseline and Month 3/12/24 is not significant.

b) **C-terminal type I procollagen peptide (CICP).** The mean values of C-terminal type I procollagen peptide (CICP) ( $\text{ng/ml}$ ) at Baseline, Month 3, Month 12 and Month 24 were 22.810, 36.404, 20.943 and 36.418, respectively. The median difference between Baseline and Month 3/12/24 is not significant.

c) **C-telopeptide type I collagen (CTX-I).** The mean values of C-telopeptide type I collagen (CTX-I) ( $\mu\text{g/L}$ ) at Baseline, Month 3, Month 12 and Month 24 were 0.419, 0.425, 0.462 and 0.453, respectively. The median difference between Baseline and Follow-ups is not significant, except for BL-Month 24 ( $p=0.0156$  with 7 subjects).

**3. Morning stiffness.** The rate of subjects with morning stiffness at Baseline, Month 3, Month 12 and Month 24 were 97.7%, 71.3%, 60.9% and 60.9%, respectively. The decrease between Baseline and Follow-Up (Month 3/12/24) values is significant ( $p < 0.0001$ ). The mean values of the duration of morning stiffness (min) at Baseline, Month 3, Month 12 and Month 24 were 95.0, 37.5, 27.7 and 25.8, respectively. The median differences of the duration of morning stiffness between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

**4. Tender Joint Count.** The mean values of the number of tender joints at Baseline, Month 3, Month 12 and Month 24 were 14.3, 3.1, 1.9 and 1.7, respectively. The median differences of the tender joint counts between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

## Secondary endpoints

**1. Swollen Joint Count.** The mean values of the number of swollen joints at Baseline, Month 3, Month 12 and Month 24 were 9.5, 2.3, 1.0 and 1.0, respectively. The median

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differences of the swollen joint counts between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

2. **DAS 28 (Assessment of Disease Activity).** The mean values of DAS 28 at Baseline, Month 3, Month 12 and Month 24 were 6.237, 3.547, 2.855 and 2.829, respectively. The median differences of DAS 28 values between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

3. **VAS (Visual Analogue Scale).**

a) **Physician's Global Assessment of Disease Activity.** The mean values of Physician's Global Assessment of Disease Activity at Baseline, Month 3, Month 12 and Month 24 were 68.0, 29.7, 23.0 and 21.5, respectively. The median differences of the VAS values between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

b) **Subject's Global Assessment of Disease Activity.** The mean values of Subject's Global Assessment of Disease Activity at Baseline, Month 3, Month 12 and Month 24 were 71.1, 31.4, 24.7 and 24.0, respectively. The median differences of the VAS values between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

c) **Subject's Assessment of Pain.** The mean values of Subject's Assessment of Pain at Baseline, Month 3, Month 12 and Month 24 were 71.3, 29.4, 25.8 and 24.2, respectively. The median differences of the VAS values between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

4. **ESR.** The mean values of ESR (mm / 1 hr) at Baseline, Month 3, Month 12 and Month 24 were 37.769, 17.969, 17.154 and 17.667, respectively. The median differences of ESR (mm / 1 hr) values between Baseline and Month 3/12/24 are significant ( $p < 0.0001$ ).

## Discussion

No significant change was detected in the primary end-point (mean change of L1-L4 and proximal femur). No clear trend was detected in any variable: L1-L4 showed a non-significant increase between baseline and Month 12, but practically did not show any difference between baseline and Month 24. A similar profile was detected for proximal femur.

Regarding the bone turnover markers only few complete set of observations could be used in the analysis (due to lack of missing data, which was a consequence of observational nature of the study). Only one parameter of the examined 3, C-telopeptide

type I collagen showed a statistically significance increase between baseline and Month 24 (p = 0.0156).

Independently from the laboratory data the study resulted in very positive achievements in subjective, patient-reported outcomes. Morning stiffness, tender joint count, swollen joint count, DAS28 and VAS all showed a statistically significant improvement (p < 0.0001) at any time point compared to the baseline.

Similar statement can be postulated regarding physician's global assessment of disease activity, subject's global assessment of disease activity and subject assessment of pain.

Consequently prevention of generalised bone loss in patients with active RA treated with adalimumab can only be partly supported with the help of this observational study. The design of the study did not make possible the comparison of adalimumab treated and non-treated patients (no control group was observed) and the bone turnover markers - which otherwise showed required trends - could only be obtained for a minority of the enrolled subjects (131 enrolled subjects, 7 subjects with complete set of CTX-I).

Regarding the safety profile the observed 12 adverse events (from 12 subjects) is a reasonable rate considering the nature of the disease, the demographic data and medical history. The four adverse events classified as probably or possibly related to adalimumab treatment can also be considered as normal risk of the treatment.

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