Med Clin (Barc). 2016;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

# Effect of tumour necrosis factor α blockade on bone metabolism in chronic inflammatory joint diseases☆

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ARTICLE INFO

*Article history:*
Received 19 November 2015
Accepted 31 March 2016
Available online xxx

*Keywords:*
Bone mineral density
Bone remodelling markers
Osteoprotegerin
Receptor activator of nuclear kappa-beta
Anti-tumour necrosis factor
Chronic inflammatory joint disease

ABSTRACT

*Background and objective:* To evaluate the effect of anti-TNF treatments on bone mineral density (BMD), bone remodelling markers (BRM) and receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) in patients with chronic inflammatory joint diseases.
*Methods:* A longitudinal prospective study was performed under clinical practice conditions on 31 patients diagnosed of rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis who had received treatment with anti-TNF alpha drugs for one year. BMD, OPG and RANKL soluble form (sRANKL) were studied at the onset and end of the study. During the study (0, 3, 6, 9 and 12 month), disease activity (SDAI, BASDAI and CRP), functional capacity (HAQ, BASFI), BRM and vitamin D were studied.
*Results:* BMD was not modified after one year of treatment. The patients who took corticosteroids had a mean bone mass loss of 3% in the lumbar spine (±1.6, $p = .02$). In regards to the BRM, did not experience significant changes over the course of the study. Disease activity, both SDAI ($p = .002$) and BASDAI ($p = .002$), decreased. OPG was maintained without changes during the year of treatment while both the sRANKL ($0.28 \pm 0.22$, $p = .013$) and sRANKL/OPG ratio significantly decreased ($0.04 \pm 0.03$, $p = .031$).
*Conclusion:* The patients being treated with anti-TNF did not present with a significant loss of DMO during the study (one year), at the same time experiencing an improvement in disease activity. This protection has been clearer in the responding patients.



## Efecto del bloqueo del factor de necrosis tumoral α sobre el metabolismo óseo en las enfermedades inflamatorias articulares crónicas

*Palabras clave:*
Densidad mineral ósea
Marcadores de remodelado óseo
Osteoprotegerina
Ligando del receptor activador del factor nuclear kappa-beta
Anti-factor de necrosis tumoral
Enfermedad inflamatoria articular crónica

RESUMEN

*Fundamento y objetivo:* Evaluar el efecto de los tratamientos anti-TNF sobre la densidad mineral ósea (DMO), los marcadores de remodelado óseo (MRO) y la ratio *receptor activator for nuclear factor κB ligand* (RANKL, «ligando del receptor activador del factor nuclear κB»)/osteoprotegerina (OPG) en los pacientes con enfermedades inflamatorias articulares crónicas.
*Métodos:* Estudio longitudinal prospectivo en condiciones de práctica clínica sobre 31 pacientes diagnosticados de artritis reumatoide, artropatía psoriásica y espondilitis anquilosante que estuvieron durante un año en tratamiento con fármacos anti-TNF alfa. Al inicio y al final del estudio se evaluaron la DMO, la OPG y la forma soluble de RANKL (sRANKL), y durante el estudio (0, 3, 6, 9 y 12 meses), la actividad de la enfermedad (SDAI, BASDAI y PCR), la capacidad funcional (HAQ, BASFI), los MRO y la vitamina D.

☆ Please cite this article as: Aguilar del Rey FJ, García Portales R, Haro Liger M, Rodríguez Andreu J, Casals Sánchez JL, Pérez González R. Efecto del bloqueo del factor de necrosis tumoral α sobre el metabolismo óseo en las enfermedades inflamatorias articulares crónicas. Med Clin (Barc). 2016. http://dx.doi.org/10.1016/j.medcli.2016.03.029

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2387-0206/

*Resultados:* La DMO no se modificó después de un año de tratamiento. Los pacientes que consumieron corticoides tuvieron una pérdida media de masa ósea del 3% en el raquis lumbar (± 1,6, p = 0,02). En cuanto a los MRO, no experimentaron cambios significativos a lo largo del estudio. Disminuyó la actividad de la enfermedad, tanto SDAI (p = 0,002) como BASDAI (p = 0,002). La OPG se mantuvo sin cambios durante el año de tratamiento, mientras que disminuyeron significativamente tanto el sRANKL (0,28 ± 0,22, p = 0,013) como la ratio sRANKL/OPG (0,04 ± 0,03, p = 0,031).
*Conclusión:* Los pacientes en tratamiento con anti-TNF no presentaron una pérdida de DMO significativa durante el seguimiento (un año), a la vez que experimentaron una mejora de la actividad de la enfermedad. Estos resultados han sido más evidentes en los pacientes respondedores.


## Introduction

Chronic inflammatory joint diseases have the development of osteoporosis and the increased risk of fractures in common.[1] And although the inflammatory process differs depending on whether it is rheumatoid arthritis (RA) or spondyloarthropathy (SpA), there is increasing evidence that inflammation itself plays a key role in its development.[2,3] In the case of RA, in addition to generalized osteoporosis, periarticular osteoporosis and erosions occur,[4] whereas what characterizes the SpA is the involvement of the enthesis, with a tendency to develop fibrosis, ossification and formation of new bone, resulting in bone ankylosis.[3] But despite this bone growth, osteoporosis and fractures are common complications in ankylosing spondylitis (AS), even in early stages.[5]

The cause of osteoporosis in these diseases is multifactorial (immobilization, corticosteroids, immunosuppressants, etc.), but it is thought that inflammation plays a key role in its development.[2] The increased production of proinflammatory cytokines, especially *tumour necrosis factor* $\alpha$ (TNF-$\alpha$), by activated T lymphocytes and macrophages, stimulates the formation and activation of osteoclasts, either directly acting on the osteoclast lineage cells or indirectly by the increased expression of *receptor activator for nuclear factor* $\kappa B$ *ligand* (RANKL$\kappa$B) by osteoblasts,[6] favouring osteoclastogenesis.

Significant discoveries at molecular level in recent years have identified the mechanisms involved in the regulation of bone remodelling. The discovery of the osteoprotegerin (OPG) system, RANK and its ligand (RANKL), consisting of several members of the TNF family of receptors and ligands, has contributed to a better understanding of bone pathophysiology and open a new therapeutic avenue in the fight against these diseases.[7]

If we consider that the loss of bone mass is associated with inflammation and disease activity, the most important strategy for prevention would be controlling inflammation.[2] Thus, blocking TNF-$\alpha$ could enhance bone metabolism in these patients. Even this improvement may be independent of disease activity, as observed in various studies.[8]

## Materials and methods

It is a prospective, observational, longitudinal study, conducted for a year in routine clinical practice in one hospital. Patients with RA, psoriatic arthritis (PsA) or active AS that were going to be subject to anti-TNF treatment according to the consensus recommendations of the Spanish Society of Rheumatology 2006[9] and who had previously failed to react to disease modifying drugs (DMARDs), especially methotrexate (MTX), were consecutively included in the study. Patients with densitometric osteoporosis, morphometric vertebral fractures, some endocrine disease with a known effect on bone and mineral metabolism or under treatment with any antiresorptive or bone forming drug were excluded.

Before starting the biological treatment, the patients underwent a baseline examination where demographic data were collected, disease activity was evaluated by the *Simplified Disease Activity Index* (SDAI), questionnaires such as the *Health Assessment Questionnaire* (HAQ), the *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) and *Bath Ankylosing Spondylitis Functional Index* (BASFI) were completed, and blood samples were taken for lab tests (usual blood test, bone remodelling markers [BRM], OPG and RANKL in soluble form (sRANKL). All subjects underwent bone densitometry (BMD) of the lumbar spine and hip (DEXA Lunar of General Electric) and a radiological assessment to evaluate the presence of morphometric vertebral fractures, as their presence was a cause for exclusion.

Whole blood samples were collected for BRM between 8.00 and 10.00 am, at baseline and at 3, 6, 9 and 12 months. The BRM assessed were the *beta C-terminal telopeptide type* I ($\beta$-CTX)$\beta$ as a marker of resorption and the procollagen type I aminoterminal propeptide (P1NP), as a formation marker.

To minimize the analytical and biological variability in bone biomarkers, blood collections were performed on an empty stomach, and due to their instability, they were quickly centrifuged. The serum, part of which was analyzed systematically, was immediately frozen at $-80\,^{\circ}C$ because all determinations of OPG and sRANKL would be analyzed at the end of the study to avoid interassay variation. The *kits* used for both, OPG (Osteoprotegerin model, reference BI-20402) and sRANKL (Ampli-sRANKL model, reference BI-20452) belong to the BIOMEDICA (Austria) brand. The total variation coefficient was 15.4% for OPG and 6.8% for sRANKL.

Follow-up was performed at 3, 6, 9 and 12 months. These visits included blood tests, disease activity assessments and completion of the questionnaires mentioned above. In addition, blood samples were taken at the final visit to assess OPG and sRANKL, besides performing a densitometric study.

We measured the activity with different parameters depending on the disease. We have used C-reactive protein (CRP) in all patients, SDAI for RA and PsA (since all patients only had peripheral involvement) and BASDAI for AS (no patient had peripheral involvement, only axial). We have used the HAQ for patients with RA and PsA and BASFI for AS (for the same reasons argued above). Being a longitudinal study, some losses have been experienced in follow-up, in some analytical determinations which have affected the BRM (P1NP and $\beta$-CTX); for this reason, these markers are analyzed jointly in patients with arthritis (RA and PsA). A good clinical response was defined as an improvement of 16 points in the SDAI,[10] and in AS patients, a BASDAI $\leq 4$.[11] All patients were diagnosed according to the 1987 criteria of the American College of Rheumatology for RA,[12] Kammer criteria in the case of PsA[13] and New York clinical criteria for AS,[14] they all gave their informed consent to