EXTENDED REPORT

Bone anabolic changes progress in psoriatic arthritis patients despite treatment with methotrexate or tumour necrosis factor inhibitors

Stephanie Finzel,¹ Sebastian Kraus,¹ Sarah Schmidt,¹ Axel Hueber,¹ Juergen Rech,¹ Klaus Engelke,² Matthias Englbrecht,¹ Georg Schett¹

¹Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany

²Institute of Medical Physics, University of Erlangen-Nuremberg, Erlangen, Germany

Correspondence to

Professor Georg Schett, Department of Internal Medicine 3, Rheumatology and Immunology, University of Erlangen-Nuremberg, Krankenhausstrasse 12, Erlangen D-91054, Germany; georg.schett@uk-erlangen.de

Received 23 February 2012

Accepted 19 July 2012

Published Online First

21 August 2012

ABSTRACT

Objectives To investigate whether methotrexate or tumour necrosis factor inhibitors (TNFi) affect osteophyte formation in patients with psoriatic arthritis (PsA).

Methods 41 patients with PsA were examined for the presence of osteophytes and erosions at the metacarpophalangeal joints by high-resolution micro-CT imaging. The size of each individual lesion was quantified at baseline and 1-year follow-up in PsA patients treated with TNFi (N=28) or methotrexate (N=13). Groups were comparable for age, sex, disease duration and activity and baseline burden of osteophytes.

Results In total, 415 osteophytes (TNFi N=284, methotrexate N=131) were detected. Osteophyte size increased significantly from baseline to follow-up in the TNFi group (mean±SEM change +0.23±0.02 mm; $p<0.0001$) and the methotrexate group (+0.27±0.03 mm, $p<0.0001$). In both treatment groups, the majority of osteophytes showed progression (TNFi 54.3%, methotrexate 61.1%), whereas regression of lesions was rare (less than 10%). In contrast to osteophytes, clinical disease activity decreased in both groups of PsA patients and erosions showed an arrest of progression in both groups.

Conclusions Osteophytes progress in PsA patients treated with either methotrexate or TNFi. These data provide the first evidence that pathological bone formation in the appendicular skeleton of patients with PsA is not affected by current antirheumatic treatment strategies.

evidence from clinical trials with TNFi in patients with AS suggest that new bone formation, ie, syndesmophyte formation, is not affected by TNFi, indicating that TNFi, albeit inhibiting the inflammatory disease process in AS, do not achieve structure-modifying effects.^{6–8} The reasons for this lack of effect of TNFi on new bone formation are not fully understood but may be based on the fact that TNF itself blocks bone formation.^{9–10} In consequence, neutralisation of TNF may facilitate new bone formation and support the generation of bony spurs. Another explanation could be that specific features of the axial disease in AS, such as the lack of a synovial membrane along the intervertebral spaces, could create a certain microenvironment that promotes bone formation independently from inflammation and TNF.¹¹ Following this latter concept, the effects of TNFi on bone formation along peripheral joints may be substantially different.

To test this hypothesis we took into consideration that PsA is associated with profound bone formation along the peripheral joints. Although PsA shares similarities with RA with respect to bone erosion, there are fundamental differences in pathological bone formation.^{12–13} RA virtually lacks anabolic bone responses, whereas such changes are a key feature of spondyloarthropathies including PsA. Interestingly, despite well-documented effects of TNFi on bone erosion of PsA patients,^{14–15} the role of TNFi on osteophyte formation in PsA is unclear.

INTRODUCTION

Inhibition of tumour necrosis factor (TNF) has revealed significant bone-sparing effects in the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Both diseases are characterised by bone erosions, which are based on osteoclast-mediated bone resorption.¹ TNF is of seminal importance for the differentiation and function of the bone resorbing cell^{2–4} and it has thus not been surprising that tumour necrosis factor inhibitors (TNFi) are highly effective in blocking the progression of bone erosion in patients with RA and PsA.⁵

The effect of TNFi on pathological bone formation in inflammatory arthritis is less established. So far data are confined to syndesmophyte formation in ankylosing spondylitis (AS), which is characterised by new bone formation and ankylosis of the intervertebral spaces and axial joints. Current

METHODS

Patients

A total number of 41 PsA patients was included in this study. All patients fulfilled the CASPAR criteria for the classification of PsA.¹⁶ Patients were recruited at the rheumatology outpatient clinic of the university clinic of Erlangen and were included in the study if they: (1) showed involvement of the metacarpophalangeal joints either due to asymmetric oligoarticular disease or symmetrical polyarthritis; (2) were on stable therapy with either methotrexate or TNFi; and (3) agreed to undergo micro-CT investigation of the hand. Only two patients refused to undergo the examination. Thirteen patients were on methotrexate monotherapy (mean dose 16.6 mg/week), the other 28 patients were on TNFi monotherapy. Five of them

were treated with etanercept (50 mg/week), 11 were on infliximab (3 mg/kg every 6 weeks) and 12 patients were on adalimumab (40 mg every 2 weeks). All TNFi were used according to the dosages approved for the treatment of PsA. Treatment with methotrexate or TNFi was stable for at least 3 months before the baseline micro-CT examination.

The mean duration of treatment before study entry was not significantly different between methotrexate (45.7 months) and TNFi (37.8 months). Furthermore, patients receiving methotrexate and TNFi were comparable for age (mean $\pm$ SEM: methotrexate 56.2 $\pm$ 13.2 years; TNFi 50.4 $\pm$ 8.5 years; $p=0.11$), sex (methotrexate 4/13 men; TNFi 10/28 men; $p=0.70$), disease duration (methotrexate 55.2 $\pm$ 3.1 years; TNFi 50.1 $\pm$ 2.5 years; $p=0.19$) and baseline disease activity (methotrexate: disease activity score in 28 joints (DAS28) 3.7 $\pm$ 1.3; TNFi: DAS28 4.0 $\pm$ 1.5; $p=0.24$). Also, the distribution between asymmetric oligoarticular disease and symmetrical polyarthritis was similar among the two groups (methotrexate group 38/62%; TNFi group 42/58%). Disease activity dropped in both groups after 1 year (methotrexate: DAS28 2.8 $\pm$ 1.2; TNFi: DAS28 3.2 $\pm$ 1.7; $p=0.47$) with no difference among groups after 1 year.

For comparative purposes, a group of 43 patients with RA (25 treated with TNFi and 18 treated with methotrexate) with low disease activity (mean $\pm$ SEM DAS28 3.0 $\pm$ 1.1) was also analysed for baseline size of osteophytes and their progression after 1-year follow-up. The study was performed in accordance with the Declaration of Helsinki. Approval from the local ethics committee and national radiation safety agency (Bundesamt für Strahlenschutz) and written informed consent was obtained for the study.

Micro-CT and evaluation of images

All patients received a micro-CT scan at a resolution of 82 $\times$ 82 $\times$ 82 μ m voxel size of the metacarpophalangeal joints 2, 3 and 4 of the right hand using an XtremeCT scanner (SCANCO Medical AG, Brüttisellen, Switzerland). The scan was performed within a region of 80 slices distal and 242 slices proximal of top of the metacarpal head 3. Scan time was 8 min per patient and scan. The scans were done at baseline and after 1 year. For exact positioning the hand was positioned in a stretched posture and padded.¹⁷ All scans were performed by a single investigator (SF) trained in the technique. The metacarpophalangeal joints 2–4 were evaluated for the presence of osteophytes in both the coronal and axial plain. An osteophyte was defined as a bony protrusion emerging from the juxta-articular cortical shell.¹⁷ The maximal height of each osteophyte was documented by assessing the maximal distance between the surface of the osteophyte and the original cortical bone surface by using the measuring function of the open source dicom viewer Osirix. Measurement of osteophyte size was done by two readers (KE and SK), who were unaware of the identity, clinical data and treatment modalities of the patients and also blinded to the sequence of the scans. Interobserver reproducibility (KE and SK) was very high ($p<0.001$, $r=0.9692$). For interobserver reproducibility all measures were taken at one session, whereas for intra-observer reproducibility measures were taken at two different sessions. Intra-observer reliability (SK) was also very high ($p<0.001$, $r=0.9722$).

Statistics

The height of osteophytes at baseline measurement and follow-up measurement after 1 year was compared by unpaired Student's *t* test as the Gaussian distribution was found. Group

comparisons were also performed by unpaired Student's *t* test. Calculations were done using SPSS program V.18.0. A *p* value of less than 0.05 was regarded as statistically significant.

RESULTS

Baseline characteristics

At total number of 415 osteophytes was found in this group of PsA patients, 284 of them in the TNFi-treated group (9.43 osteophytes/patient, 3.14 osteophytes/joint) and 131 of them in the methotrexate-treated group (10.08 osteophytes/patient, 3.36 osteophytes/joint). The mean $\pm$ SEM size of osteophytes at baseline was 0.81 $\pm$ 0.03 mm in the TNFi and 0.77 $\pm$ 0.03 mm in the methotrexate group.

Changes in osteophyte size in the TNFi-treated group

There was consistent and highly significant progression of osteophyte size between baseline assessment and follow-up after 1 year (mean $\pm$ SEM change +0.23 $\pm$ 0.02 mm; $p<0.0001$). Probability plots showed a clear shift to progression of osteophyte size in the majority of patients (>0.1 mm increase in size $N=143/54.3\%$) (figure 1A). The mean $\pm$ SEM progression of osteophyte size in this subgroup was +0.46 $\pm$ 0.03 mm. No progression was found in 102 lesions (38.6%) and only a few lesions showed evidence of regression (>0.1 mm decrease in size $N=19/7.2\%$). The mean $\pm$ SEM improvement in this subgroup was -0.36 ± 0.05 mm.

Figure 1 Progression of osteophyte size in patients with psoriatic arthritis (PsA) treated with tumour necrosis factor inhibitors (TNFi) or methotrexate (MTX). Probability plots of osteophytes in PsA patients treated with TNFi (A) or methotrexate (B). Each dot represents one osteophyte. The x-axis indicates numbers, y-axis the mm change of osteophyte size between baseline investigation and follow-up after 1 year. Negative values (blue) indicate reduction in the size of the osteophyte, positive values (red dots) indicate increase of osteophyte size. This figure is only reproduced in colour in the online version. This figure is only reproduced in colour in the online version.

Clinical and epidemiological research

Changes in osteophyte size in the methotrexate-treated group

Similar to the TNFi group, we found a consistent and highly significant progression of osteophyte size between baseline assessments and follow-up after 1 year (mean±SEM change +0.27±0.03 mm; $p<0.0001$). Again, probability plots showed a clear shift to progression of osteophyte size in the majority of patients (>0.1 mm increase in size N=80/61.1%) (figure 1B). The mean±SEM progression in this subgroup was +0.45±0.03 mm. No progression was found in 40 lesions (30.5%) and only a few lesions showed evidence of regression (>0.1 mm decrease in size N=11/8.4%). The mean±SEM improvement in this subgroup was -0.21±0.02 mm. Overall, there was no sign of improvement in osteophytes in PsA following treatment with TNFi or methotrexate. Examples of micro-CT images of osteophytes in TNFi and methotrexate-treated PsA patients are shown in figure 2.

Comparative analyses with erosion progression in PsA and osteophyte progression in RA

To exclude the possibility that erosions also progress in these two groups of PsA patients we assessed the longitudinal changes of erosion width and depth during methotrexate and

TNFi therapy. In contrast to osteophytes, the width of erosions (N=88) did not progress in the methotrexate (mean±SEM -0.03±0.09; median -0.0, 95% CI -0.20 to 0.14) or TNFi (0.073±0.018; median 0.0, 95% CI 0.04 to 0.10) treated PsA patients (figure 3A). The depth of erosions even decreased slightly in TNFi-treated patients after 1 year (-0.12±0.06; median -0.02, 95% CI -0.24 to -0.01), suggesting that the dynamics of erosions and osteophytes in PsA are different. To test if the absence of an effect of methotrexate and TNFi on peripheral osteophyte formation is specific for PsA, we also assessed a group of RA patients for the progression of osteophytes. Although RA patients show many fewer osteophytes than PsA patients and these lesions are significantly smaller in size in RA compared to PsA,¹² osteophytes (N=111), if present, significantly increased in size in RA after 1 year of treatment with methotrexate (mean±SD: width -0.02±0.08; depth -0.02±0.07) or TNFi (mean±SD: width 0.03±0.05; depth -0.12±0.06) (figure 3B).

Baseline osteophyte size and progression of osteophytes

When comparing the three patterns of osteophytes dynamics (progression, arrest or regression) in TNFi-treated PsA patients,

Figure 2 Examples of osteophytes in psoriatic arthritis (PsA) patients treated with tumour necrosis factor inhibitors (TNFi) or methotrexate. Osteophytes at the metacarpal heads of PsA patients treated with TNFi (A) or methotrexate (B). Left images are at baseline, right images are taken at 1-year follow-up. This figure is only reproduced in colour in the online version. This figure is only reproduced in colour in the online version.

Figure 3 Comparative analyses with osteophyte progression in rheumatoid arthritis (RA) and changes of erosions in psoriatic arthritis (PsA). (A) Changes in osteophyte size in patients with RA and PsA at the metacarpal heads treated with either tumour necrosis factor inhibitors (TNFi) or methotrexate (MTX) between baseline and 1 year. (B) Changes in depth and width of bone erosions in patients with PsA at the metacarpal heads treated with either TNFi or methotrexate between baseline and 1 year. This figure is only reproduced in colour in the online version. This figure is only reproduced in colour in the online version.

we found that those lesions that showed either progression ($p=0.010$) or regression ($p=0.011$) were significantly larger than those lesions showing arrest (figure 4). With respect to methotrexate-treated PsA patients, we found similar differences, with those lesions showing regression being significantly larger at baseline ($p=0.033$) compared the ones with no change over time (figure 4).

DISCUSSION

Our data show that neither methotrexate nor TNFi inhibits osteophyte formation in PsA. These data translate previous observations on the failure of TNFi to block syndesmophyte formation in AS^{18–20} to the appendicular skeleton. In fact, these

data support the concept that mechanistic factors, which are attributed to the entire skeleton rather than specific anatomical factors of the spine explain the failure of TNFi to inhibit osteophytes. The formation of bony spurs is based on rather rapid apposition of bone supported by the proliferation and differentiation of periosteal mesenchymal cells into hypertrophic chondrocytes and osteoblasts. This process is tightly regulated by a number of anabolic pathways, which control the differentiation of mesenchymal precursors into hypertrophic chondrocytes and osteoblasts. Whereas hypertrophic chondrocyte formation depends on hedgehog proteins, osteoblast differentiation is regulated by the BMP and the Wnt-pathway.^{9 21 22} Activation of hedgehog, BMP and Wnt proteins is required to trigger a solid anabolic response leading to endochondral ossification, which results in the deposition of bone in the vicinity of the affected joint. Although not finally proved, it can be speculated that these anabolic pathways are shared during bony spur formation in the axial and the appendicular skeleton.

Data from animal models of arthritis as well as from clinical studies have not supported a strong link between inflammation and new bone formation. Therefore, some animal models of arthritis show profound new bone formation despite minimal inflammatory processes.²³ Also, TNF blockade shows no signs of interference with new bone formation and osteophyte formation in animal models of arthritis despite good effects on inflammation and bone erosion.^{24 25} As mentioned, the situation in human spondyloarthritis patients is very similar: TNFi are not able to block new bone formation in patients with AS.^{18–20} This finding is not surprising, as TNF itself is an inhibitor of bone formation.^{26 27} TNF has been shown potently to induce key factors, which block the anabolic Wnt pathway and presumably also the BMP pathway. TNF thus induces the expression of Dkk-1,⁹ which is among the most potent Wnt inhibitors, as well as sclerostin,^{28 29} which blocks both the Wnt and BMP pathway. Importantly, serum levels of both Dkk-1 and sclerostin are associated with radiographic progression in patients with AS.^{30 31} The lack of effect of TNFi on new bone formation in axial spondyloarthritis is thus not surprising,

Figure 4 Baseline size and dynamics of osteophytes. Baseline size of osteophytes in psoriatic arthritis patients treated with tumour necrosis factor inhibitors (TNFi) or methotrexate (MTX), showing either arrest, regression or progression in their size at follow-up.

Clinical and epidemiological research

despite recent evidence suggesting that very early intervention with inflammation could create a window of opportunity allowing the blockade of the skeletal effects of inflammation in spondyloarthritis.³² Drugs that directly inhibit bone formation in addition to anti-inflammatory effects, such as non-steroidal anti-inflammatory drugs, have indeed been shown to retard structural progression in axial spondyloarthropathy,^{33–34} suggesting that it may be necessary to interfere directly with bone anabolic pathways to achieve retardation of new bone formation in spondyloarthropathies.

In PsA, anti-inflammatory effects have been documented for methotrexate as well as TNFi. The latter also retard the erosions in PsA, whereas no such data exist for methotrexate at the moment.^{15–35} Although a radiographic score has been developed, which allows simultaneous scoring of erosions and osteophytes in arthritis, it has not been used to document the dynamics of new bone formation in PsA,³⁶ and the effect of TNFi on new bone formation in PsA has therefore been unclear so far. Our data show that osteophytes progress in PsA patients treated with TNFi or methotrexate despite successful improvement of disease activity reaching a low disease activity state. Also, progression of osteophytes was not related to the decrease in disease activity in PsA patients (Spearman $r=0.07$; $p=0.67$). These results suggest that despite the clinical efficacy of TNFi and methotrexate to treat the signs and symptoms of PsA, osteophyte formation is not affected. Also, the progression of osteophytes was uncoupled from bone erosion, which showed no evidence of progression in both groups of PsA patients and even some evidence of regression in TNFi-treated PsA patients.

These findings are not entirely surprising if one follows the concept that new bone formation in the axial and appendicular skeleton share common pathways. At the same time, they are interesting as they foster the concept of indirect rather than direct interaction between inflammation, bone erosion and new bone formation in the spondyloarthropathy disease cluster.³⁷ The data also show that the effects of TNFi on new bone formation are limited, and the results obtained in the axial skeleton also hold true in the periphery. Nonetheless, these findings do not limit the strong anti-inflammatory and anti-erosive potential of TNFi in patients with PsA, which is important for improving the patients' disease state by limiting signs and symptoms of disease as well as bone erosions. Further studies, however, will be necessary to decipher the interaction between bone erosion and new bone formation in PsA.

Funding This study was supported by the Deutsche Forschungsgemeinschaft (SPP1468-IMMUNOBONE), the Bundesministerium für Bildung und Forschung (BMBF; project ANCYLOSS), the MASTERSWITCH project of the European Union and the IMI-funded project BTCure.

Competing interests None.

Ethics approval Approval from the local ethics committee and national radiation safety agency (Bundesamt für Strahlenschutz) was obtained for the study.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- McInnes IB, Schett G. Pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;**365**:2205–19.
- Lam J, Takeshita S, Barker JE, et al. TNF- α induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000;**106**:1481–8.
- Redlich K, Hayer S, Ricci R, et al. Osteoclasts are essential for TNF- α -mediated joint destruction. *J Clin Invest* 2002;**110**:1419–27.
- Ritchlin CT, Haas-Smith SA, Li P, et al. Mechanisms of TNF- α - and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003;**111**:821–31.
- Schett G, Stach C, Zwerina J, et al. How antirheumatic drugs protect joints from damage in rheumatoid arthritis. *Arthritis Rheum* 2008;**58**:2936–48.
- van der Heijde D, Landewe R, Einstein S, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008;**58**:1324–31.
- van der Heijde D, Landewe R, Baraliakos X, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;**58**:3063–70.
- van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009;**11**:R127.
- Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007;**13**:156–63.
- Walsh NC, Reinwald S, Manning CA, et al. Osteoblast function is compromised at sites of focal bone erosion in inflammatory arthritis. *J Bone Miner Res* 2009;**24**:1572–85.
- Benjamin M, McGonagle D. The enthesis organ concept and its relevance to the spondyloarthropathies. *Adv Exp Med Biol* 2009;**649**:57–70.
- Finzel S, Englebrecht M, Engelke K, et al. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. *Ann Rheum Dis* 2011;**70**:122–7.
- Gladman DD, Stafford-Brady F, Chang CH, et al. Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990;**17**:809–12.
- Kavanaugh A, Antoni CE, Gladman D, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis* 2006;**65**:1038–43.
- Mease PJ, Kivitz AJ, Burch FX, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006;**33**:712–21.
- Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study (CASPAR). *Arthritis Rheum* 2006;**54**:2665–73.
- Stach CM, Bäuerle M, Englebrecht M, et al. Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. *Arthritis Rheum* 2010;**62**:330–9.
- van der Heijde D, Landewe R, Baraliakos X, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;**58**:3063–70.
- van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009;**11**:R127.
- Baraliakos X, Listing J, Brandt J, et al. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF- α antibody infliximab. *Rheumatology (Oxford)* 2007;**46**:1450–3.
- Ruiz-Heiland G, Horn A, Zerr P, et al. Blockade of the hedgehog pathway inhibits osteophyte formation in arthritis. *Ann Rheum Dis* 2012;**71**:400–7.
- Lories RJ, Derese I, Luyten FP. Modulation of bone morphogenetic protein signalling inhibits the onset and progression of ankylosing enthesitis. *J Clin Invest* 2005;**115**:1571–9.
- Lories RJ, Daans M, Derese I, et al. Noggin haploinsufficiency differentially affects tissue responses in destructive and remodeling arthritis. *Arthritis Rheum* 2006;**54**:1736–46.
- Lories RJ, Derese I, Luyten FP. Inhibition of osteoclasts does not prevent joint ankylosis in a mouse model of spondyloarthritis. *Rheumatology* 2008;**47**:605–8.
- Schett G, Stolina M, Dwyer D, et al. Tumor necrosis factor α and RANKL blockade cannot halt bony spur formation in experimental inflammatory arthritis. *Arthritis Rheum* 2009;**60**:2644–54.
- Bertolini DR, Nedwin GE, Bringman TS, et al. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;**319**:516–18.
- Gilbert L, He X, Farmer P, et al. Inhibition of osteoblast differentiation by tumor necrosis factor- α . *Endocrinology* 2000;**141**:3956–64.
- Vincent C, Findlay DM, Welldon KJ, et al. Pro-inflammatory cytokines TNF-related weak inducer of apoptosis (TWEAK) and TNF α induce the mitogen-activated protein kinase (MAPK)-dependent expression of sclerostin in human osteoblasts. *J Bone Miner Res* 2009;**24**:1434–49.
- Heiland GR, Zwerina K, Baum W, et al. Neutralisation of Dkk-1 protects from systemic bone loss during inflammation and reduces sclerostin expression. *Ann Rheum Dis* 2010;**69**:2152–9.
- Heiland GR, Appel H, Poddubnyy D, et al. High level of functional dickkopf-1 predicts protection from syndesmophyte formation in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;**71**:572–4.
- Appel H, Ruiz-Heiland G, Listing J, et al. Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2009;**60**:3257.
- Maksymowych WP, Morency N, Conner-Spady B, et al. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. *Ann Rheum Dis* Published Online First: 5 May 2012. doi:10.1136/annrheumdis-2011-200859.

33. **Wanders A**, Heijde D, Landewe R, *et al*. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005;**52**:1756–65.
34. **Poddubnyy D**, Rudwaleit M, Haibel H, *et al*. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Ann Rheum Dis* Published Online First: 29 March 2012. doi:10.1136/annrheumdis-2011-201252.
35. **van der Heijde D**, Kavanaugh A, Gladman DD, *et al*. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2. *Arthritis Rheum* 2007;**56**:2698–707.
36. **Wassenberg S**, Fischer-Kahle V, Herborn G, *et al*. A method to score radiographic change in psoriatic arthritis. *Z Rheumatol* 2001;**60**:156–66.
37. **Pedersen SJ**, Sørensen IJ, Lambert RG, *et al*. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor α inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. *Arthritis Rheum* 2011;**63**:3789–800.

Bone anabolic changes progress in psoriatic arthritis patients despite treatment with methotrexate or tumour necrosis factor inhibitors

Stephanie Finzel, Sebastian Kraus, Sarah Schmidt, Axel Hueber, Juergen Rech, Klaus Engelke, Matthias Englbrecht and Georg Schett

Ann Rheum Dis 2013 72: 1176-1181 originally published online August 21, 2012
doi: 10.1136/annrheumdis-2012-201580

Updated information and services can be found at:
<http://ard.bmj.com/content/72/7/1176>

These include:

References

This article cites 35 articles, 8 of which you can access for free at:
<http://ard.bmj.com/content/72/7/1176#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Degenerative joint disease](#) (4621)
[Musculoskeletal syndromes](#) (4930)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>