Chapter 8

Summary and general discussion

M.A.C. van der Weijden

Summary

Chapter 1 introduces the focus and aims of this thesis. This chapter starts with an overview of Spondylarthropathies and Ankylosing spondylitis, osteoporosis and vertebral fractures and finally it represents the relation between these topics. In this respect the diagnostics, epidemiology and pathogenesis are discussed. Furthermore, reference is made to new methods to diagnose AS in an earlier stage and work participation is outlined.

Chapter 2 reviews the literature investigating the prevalence of low bone mineral density in early AS. We included articles which used the modified New York criteria for the diagnosis of AS, included patients with a disease duration of less than 10 years and used the WHO criteria for osteopenia and osteoporosis. Decreased BMD was defined as a T-score <-1.0, including both osteopenia and osteoporosis. Seven articles matched the aforementioned criteria. The overall prevalence of decreased BMD of the articles reviewed is 54% (n=229/424) for lumbar spine and 51% (n=224/443) for femoral neck. The prevalence of osteopenia respectively osteoporosis for lumbar spine is 39 respectively 16% and for femoral neck 38 respectively 13%.
In conclusion, this review showed with seven articles that in a relatively young and predominantly male population there is considerable low BMD. The total prevalence of low BMD measured was 51-54% and osteoporosis was present in 13-16% of the AS patients with a short disease duration.

Chapter 3 describes the prevalence and risk factors of low bone mineral density in patients with a recently diagnosed Spondylarthropathy. In this cross-sectional study, BMD of lumbar spine and hips was measured in 130 consecutive early (time until diagnosis 6.6 months) SpA patients. The outcome measure BMD was defined as osteoporosis, osteopenia and normal bone density. In total, 9% of the early SpA patients had osteoporosis, 38% osteopenia and 53% had a normal BMD. To investigate the risk factors for low BMD, uni- and multivariate logistic regression was performed. With univariate analyses, male gender, diagnosis of Ankylosing spondylitis, increased CRP, high BASFI and high BASMI were significantly associated with low BMD. Factors showing a relation with low BMD in the multivariate model were male gender (OR 4.18, 95% confidence interval (CI) 1.73-10.09), high BASMI (OR 1.54, 95% CI 1.14-2.07) and high BASFI (OR 1.18, 95% CI 1.00-1.39).

In conclusion, in our early SpA cohort with relative young SpA patients (mean age of 38 years) a high frequency (47%) of low BMD in femur as well as in lumbar spine was found. Low BMD was associated with male gender and decreased functional capacity (measured by BASMI and BASFI). These findings emphasize the fact that low BMD is already a common complication in early stage disease and is associated with disease-activity. There is need for further investigation of the clinical relevance of this finding concerning low BMD.

In **Chapter 4** the prevalence of vertebral fractures (VF) in early SpA patients was studied as well as the associations between vertebral fractures, and demographic and disease-related variables. Consecutive, recently diagnosed SpA patients (from the Early SpA cohort) were included when both BMD-measurements and radiographs of the spine were available. VF were assessed according to the method of Genant et al.: fractures were defined as reduction of ≥20% of the vertebrae. Descriptive statistics, t-tests and logistic regression analyses were used to study the relationship between VF and demographic and disease-related variables, radiographic damage and BMD. A total of 113 early SpA patients were included with a disease duration of 7 months and a mean age of 37 years. Seventeen patients (15%) had at least one VF; fourteen patients had one VF and three patients had two VF. Most VF were located at Th6-Th8. In patients with VF, BMD of lumbar spine was lower than BMD of patients without VF (t-test: p=0.043). Axial Psoriatic arthritis (PsA) was significantly associated with a higher risk for VF (odds ratio [OR]: 4.62, 95% confidence interval [CI] 1.15-18.58, p=0.031).
In conclusion, in the early SpA group of 113 patients with young age and a disease duration of only 7 months, 15% already had at least one VF. The VF were associated with low BMD of the lumbar spine and with axial Psoriatic arthritis. Furthermore, this study demonstrated that most vertebral fractures were asymptomatic and undetected by routine diagnostic procedures, which can lead to under treatment of early SpA patients.

Chapter 5 studies the effects of TNF-blocker etanercept in AS patients with high disease activity on BMD and VF after two years of treatment. In addition, changes in bone-markers (CTXI, CTXII, RANKL, OPG, Osteocalcin) and radiological damage were taken into account. The BMD lumbar spine and hips were measured at baseline and after two years, as well as the radiological damage (mSASSS, including thoracic spine), VF (by the semi-

quantitative Genant method) and change in bone-markers. Forty-nine active AS patients showed after two years of etanercept therapy an increase of BMD hip with 2.2% ($p=0.014$) and an increase of BMD lumbar spine of 7.0% ($p<0.001$). The disease activity showed a clear decrease: BASDAI decreased significantly ($p<0.001$) as well as the level of inflammation parameters (CRP and ESR) ($p<0.001$). However, despite etanercept therapy, the number of patients with VF more than doubled (from 6 to 15 patients, $p=0.004$) and radiological damage increased significantly over time (from 12.1 to 18.5, $p<0.001$). No significant changes in bone-marker levels were found.
In conclusion, in this prospective longitudinal cohort study it was showed that after two years of etanercept treatment the BMD of hip and spine raised significantly, but the number of patients with VF and the severity of VF increased as well. Besides that, radiological progression, including the thoracic spine, increased significantly. Thus, the favourable bone preserving effect of anti-TNF was accompanied by unfavourable outcomes on VF and radiological damage.

In order to find new techniques for early detection of SpA **Chapter 6** describes a pilot study in which the potential of PET-CT in imaging AS activity was tested. In a stepwise approach different PET tracers were investigated. First, whole-body [18F]FDG and [11C](R)PK11195 (tracers for inflammation) PET-CT scans were obtained of 10 AS patients fulfilling the modified New York criteria. Five of these patients had low disease activity according to the BASDAI and five had high activity and were eligible for anti-TNF treatment. Secondly, an extra PET-CT scan using [18F]Fluoride (bone tracer) was made of two AS patients with high disease activity. MRI scans of the total spine and sacroiliac joints were performed and conventional radiographs of the total spine and sacroiliac joints were available for all patients as reference method. Results showed no increased uptake of the inflammatory markers [18F]FDG and [11C](R)PK11195 on PET-CT scans of the first 10 patients. In contrast, MRI demonstrated a total of five bone edema lesions in three out of 10 patients. In the two additional AS patients scanned with [18F]Fluoride PET-CT, [18F]Fluoride depicted 17 regions with increased uptake in both vertebral column and sacroiliac joints. In contrast, [18F]FDG depicted only three lesions, with an uptake of five times lower compared to [18F]Fluoride, and again no [11C](R)PK11195 positive lesions were found. In these two patients, MRI detected nine lesions and six out of nine matched

with the anatomical position of [18F]Fluoride uptake. Conventional radiographs showed structural bony changes in 11 out of 17 [18F]Fluoride PET positive lesions.
In conclusion, our PET-CT data suggest that AS activity is reflected by bone activity (formation) rather than by inflammation. The results also show the potential value of PET-CT for imaging AS activity using the bone tracer [18F]Fluoride. In contrast to active RA inflammation tracers [18F]FDG and [11C](R)PK11195 appeared to be less useful for AS imaging.

Chapter 7 explores the impact of early Spondylarthropathies on work participation and investigates variables associated with work outcomes. Due to pain, fatigue, spinal and extra-spinal manifestations of SpA, many patients experience functional and social impairment which can lead to reduced quality of life. Impairment of function leads to work disability and has serious economic consequences for patient and society. More insight into the magnitude and determinants of social and work related problems might help to keep patients in the labor force by adequate professional counseling and vocational rehabilitation [1]. Patients already participating in the Early Spondylarthropathy cohort, aged between 18-65 years, received a postal questionnaire about work participation. In the 140 patients, with a mean age of 41 years and a disease duration of <5 years, 19% was not employed due to SpA. Sick leave was reported in about 30% of the working population in one or more occasions in the previous year due to SpA. Moreover, a substantial portion of the SpA patients experienced work-related (21%) and career-related (31%) problems. Fifty-nine percent of the patients reported normal productivity while at work, while 41% reported reduced productivity due to SpA. Multivariable regression analyses showed that high BASMI and ASQoL were significantly associated with not being employed and with reduced productivity while at work. Patients reported in 42% of the cases that the rheumatologist had no attention for work or work related problems and 47% sought regular medical attention elsewhere in addition to the rheumatologist. Especially patients who reported sick leave in the last year, paid more visits to the rheumatologist and other healthcare providers, and needed more help in daily activities compared with those who work without sick leave.
In conclusion, withdrawal from labour force in early SpA is substantial. In relatively young SpA patients, with mild disease activity and short disease duration of <5 years, there is already 19% withdrawal from work, 30% sick leave and in 40% productivity loss at work.

Moreover, a substantial portion of the SpA patients already experience work-related and career-related problems as a result of SpA complaints. These problems can be recognized when a proper occupational history is performed. Early referral and good cooperation between different specialists, like occupational physicians, insurance physicians or occupational therapists can make important differences for these patients. So more attention, not only for the physical suffering of SpA patients, but also for work related aspects of this disease is urgently needed already in an early stage of disease.

General discussion

In summary, this thesis emphasizes that already in an early stage of SpA a lot of problems do occur. Many early SpA patients were found to suffer BMD loss, often complicated with 'undetected' vertebral fractures. Treatment with a TNF blocker increases the BMD, but such treatment was not found to delay the onset of new vertebral fractures or radiographic progression. Furthermore, despite the low disease activity measurable in the early stage disease, considerable 'silent' loss in social participation due to the SpA could already be observed in this early stage. At last, new imaging tools, like PET-CT scans seem to be a promising diagnostic method to diagnose patients in an earlier stage.

Bone

Usually, patients with a SpA or AS are not routinely assessed for osteoporosis, since there are no existing guidelines and most patients are young men who are less likely to be screened [2]. However, we demonstrated with our review that half of the patients with definite AS and a disease duration of <10 years had low BMD (T-score <-1.0), not only in the hips but also in lumbar spine (51 respectively 54%). Moreover, osteoporosis was already present in 16% in lumbar spine and 13% in the hips. We confirmed these numbers in our Amsterdam Early SpA cohort with a disease duration even shorter, only 6.6 months (and a median symptom duration of 6.3 years). We showed in this group comparable numbers of low BMD (47%) and osteoporosis (9%), which means that low BMD and osteoporosis are already present in a much earlier disease state. Risk factors for low BMD were male gender and decreased functional capacity (by high BASMI and BASFI scores). The identification of these risk factors for low BMD in SpA is important, not only in order

to develop more insight in the pathogenesis but also to develop strategies to prevent its occurrence.

The clinical relevance of the above mentioned high percentage low bone mineral density depends on whether this will lead to future fractures. As the literature learns that longstanding AS is often accompanied by vertebral fractures, the question raised whether this was already present in the early stage disease in the Amsterdam Early SpA cohort. Our investigation of this group resulted in 15% (17/113) with at least one vertebral fracture, whereby the occurrence of VF was associated with low BMD spine (and PsA). Most vertebral fractures were found in the mid-thoracic spine and most were undetected by routine procedures. These results emphasize the need for more attention for early complications of low BMD in SpA. Low BMD increases the risk for vertebral fractures and, moreover, these vertebral fractures are often undetected because the symptoms (back pain) are difficult to differentiate from the common 'inflammatory' back pain in SpA. In addition, most vertebral fractures occur in the thoracic spine, which is not incorporated in the routine spinal X-rays performed in SpA. Therefore, we propose to include X-rays of the thoracic spine in addition to the cervical and lumbar spine in follow-up procedures of axial SpA patients in order to detect these vertebral fractures. Knowledge of existing fractures is necessary for the optimal assessment of risk for future fractures.

The etiology of bone loss in SpA is complex and probably multifactorial: besides genetic predisposition and hormonal factors [3], it was suggested in older literature that immobility due to pain, stiffness and ankylosis could be the cause of bone loss in AS [4]. However, now that it is shown that important bone loss is already present in patients with early disease, even in patients without serious increased functional disability or radiographic damage, it seems likely that systemic factors also contribute a great deal to bone loss in AS [5, 6]. Several studies suggest that systemic inflammatory mediators may play a role in modulating bone turnover in AS, correlations have been shown with proinflammatory cytokines, with acute phase reactants and conflicting results of bone turnover markers [3, 7].

Since SpA is characterized by chronic inflammation, it would be expected that treatment with TNF blockers, which decrease inflammation, should increase BMD and could prevent the occurrence of new VF. We indeed showed that anti-TNF therapy is favourable for BMD in AS, but does not seem to prevent the occurrence of vertebral fractures and progression of radiological damage. It is possible that in more mature inflammatory lesions in active AS

the reparative process is already started and new bone will be formed once the signaling pathways have been activated. The timing of the anti-TNF treatment might be too late when the induction of reparative changes has already started [8-10]. Another explanation could be that TNF-alpha is not the right inflammatory mediator to target and other inflammatory mediators might probably have more influence on the quality and/or quantity of bone, for instance interleukines (IL-1, IL-6 or IL-17) [11, 12]. However, the studies performed so far with a few drugs that interfere with these interleukine pathways were not designed for bone outcome parameters. Anti-IL1 (anakinra) has until now not proven to be highly effective in reducing inflammation in AS and therefore is not tested in larger groups for effects on bone metabolism [13]. Anti-IL17 (secukinumab) however, does inhibit inflammation in AS but data on bone quality so far are lacking [14]. Treatment options of osteoporosis in SpA so far have not been studied extensively. Currently, there is no general consensus for treating osteoporosis in AS and inhibition of TNF-alpha is thought to be the most effective approach for reducing symptoms of inflammation in AS patients, although it is apparently not the best approach to increase the quality of bone. Bisphosphonates are widely used to treat osteoporosis in the general population, as well as in patients with inflammatory rheumatic diseases (RA, SLE) and have been considered as an alternative to improve the BMD in AS. However, the concomitant occurrence of local bone growth with systemic bone loss represents a paradox in AS of which the pathophysiology still has to be unraveled. Until now, no extensive study has been published regarding the effects of bisphosphonates in AS on BMD, extra bone formation and the risk of progression of vertebral fractures [12].

Apparently, intervening in a progressing disease is very difficult, which makes it even more important to intervene very early in the disease process of SpA, before early changes of bone metabolism take place. In this way we might prevent the progression of the disease with concomitant problems like osteoporosis, vertebral fractures and ongoing radiological progression. Unfortunately, it is not so easy to detect and diagnose patients with typical symptoms and features of a SpA due to limitations of our diagnostic arsenal available.

Imaging

Until recently, plain radiographs were obligatory for the diagnosis of AS according to the modified New York criteria [15]. The disadvantage of this imaging technique is that it

usually takes many years before the disease comes to full expression and definite radiographic sacroiliitis appears [15]. Consequently, the diagnosis is often delayed by 5 to 10 years, especially in patients with an early or incomplete clinical picture. To enable earlier diagnosis, highly reliable and sensitive imaging techniques are needed. Nowadays, magnetic resonance imaging (MRI) is increasingly being used for the detection of sacroiliitis and inflammation of the spine in early AS. At MRI images (early) inflammation can be visualized by bone marrow edema or enhanced gadolinium contrast uptake or both. However, these signs are non-specific indicators of increased free water content and increased vascularization, respectively [16, 17]. Moreover, chronic AS changes such as new bone formation in the spine (syndesmophyte formation) can be less well visualized on MRI than on radiographs [18]. Finally, although validated scoring methods are available, conflicting data on the sensitivity and specificity of MRI in (suspected) early SpA have been published [19-22]. Only about 30% of the patients with suspected axial SpA show typical signs of inflammation [20]. Therefore, the precise role of MRI in visualizing disease activity of AS has not yet been fully elucidated. In our small pilot study with PET-CT the data suggest that AS activity is reflected by bone activity (formation) rather than inflammation. The results also show the potential value of PET-CT for imaging AS activity using the bone tracer [18F]Fluoride. In future, this imaging modality might be valuable for early diagnosis of SpA and it might increase the possibility to intervene before complications of the disease occur.

Work participation

The symptoms and complications of SpA can lead to much 'unrecognized' social and work related participation problems, even in an early stage of the disease. We investigated problems with work participation, absenteeism, presenteeism and resource utilisation in patients with an early SpA of whom most were not yet treated with TNF blockers. In the Early SpA cohort 20% of the patients did not have a paid job due to the Spondylarthropathy and 30% of the patients reported one or more occasions of sick leave in the last year. Most problems remain undisclosed since many patients also experience work-related (21%) and career-related (31%) problems due to their disease. Early diagnosis and early treatment with NSAIDs, physical therapy and patient education might reduce these numbers. In addition, the positive effect of TNF blockers on work participation, considering the high cost of these

drugs, should be taken into account in future studies to make a proper analysis of the financial benefit/risk ratio.

Future perspective

Over the past decades rheumatology has made great progress in diagnosing and treating patients with AS. Decades ago treatment was restricted to relieving pain and preserving mobility by physical therapy because effective medicine was hardly available. Nowadays, patients can be offered more with the development of the TNF-alpha blocking drugs, which appear to be able to suppress the symptoms of inflammation in AS. Also great progress is made in diagnosing AS in an earlier stage. Whereas a few decades ago, AS was diagnosed with a mean delay of 8-10 years, today a 'probable' diagnosis can be made in an earlier stage with help of clinical algorithms and more sensitive imaging methods. The ASAS (Assessment in Ankylosing Spondylitis) working group, a group of international experts in the field of AS, has made tremendous progress in setting criteria for diagnosis, treatment, response and disease activity in AS. However, there is still a lot to explore and to investigate in the total group of early Spondylarthropathies.

Early diagnosis

The challenge to make an earlier diagnosis in SpA remains an important field of interest. For many years an early diagnosis was not particularly relevant, since efficacious drugs that could potentially influence the course of disease were lacking. Although, it has yet been proven that the radiological progression continues under the best treatments we have, the patients do well under treatment with anti-TNF by better functional ability, less pain and keeping them in labor participation. Since MRI has its limitations in diagnosing early SpA and as patients seem to benefit most if treatment with TNF blockers is started early in the course of the disease, it is important to find new techniques to diagnose SpA in early stage [23, 24]. As we showed promising results from our small pilot study with PET-CT, a more extensive study has been started at the VU University Medical Center to investigate whether the pilot results presented in this thesis can be repeated, providing more insight in the potential of PET-CT in diagnosing AS in the earliest stage.

Early treatment

Furthermore, we started in the VU University medical center a double blind placebo controlled trial (PREVAS-study) to investigate the efficacy of very early treatment with anti-TNF in non radiographic axial SpA. The aim of this study is to determine the efficacy of 16 weeks of anti-TNF treatment and to investigate whether radiological progression will be decreased in the TNF treated patients compared to the placebo group on longer term.

Also more research on the role of NSAIDs in early SpA is needed. The role of NSAID's in bone changes of AS is still under debate. Prostaglandins play an important role in the regulation of osteoblast and osteoclast functions, and inhibition of prostaglandin production retards bone formation. Therefore, NSAIDs could be expected to have consequences in different clinical situations of bone formation or remodeling [25]. Several studies described a delay in radiographic progression in AS patients who continuously used NSAIDs in an anti-inflammatory dosage, compared to AS patients who used a lower dose [26, 27]. However, the effects in early non radiographic SpA is not fully elucidated yet [28, 29]. Possibly more intensified treatment (high dose and long term) instead of on demand treatment might have positive long term effects on radiological progression to AS. So far, no clear information is available whether bone mineral density is influenced by chronic NSAID use [30].

Another important focus area is the concomitant occurrence of local bone growth with systemic bone loss known as a paradox in AS. It is a true challenge to unravel the pathophysiology of bone loss in AS on the one hand and the extensive bone-formation on the other hand by more fundamental and translational research. We showed that both complications occur and that especially low BMD is already present in early stage disease. Therefore, it is also a challenge to develop new therapies, which unlike current anti-cytokine strategies, also have an effect on ankylosis. The combination of a decreased quality of bone (visualized by changes like syndesmophytes and ultimately ankylosis of the spine) and decreased quantity of bone (measured by low bone mineral density and ultimately by osteoporosis) is likely the cause of the increase of vertebral fractures in this patient group because the biomechanical adaptation range of the spine upon loading or trauma is limited [12]. Since treatment of TNF-alpha seems not to have a positive effect on the number and severity of vertebral fractures, more investigation is urgently needed because of the association with more back pain, reduced quality of life, and increased risk

of future vertebral and non-vertebral fractures. Therefore, early recognition of the low BMD and vertebral fractures in daily practice is necessary. Rheumatologists should routinely assess patients with a SpA for osteoporosis by DXA and vertebral fractures by assessment of the lumbar spine but also of the thoracic spine, since most vertebral fractures were found at this location.

Optimal treatment strategies of these patients are a challenging topic for future research. Bisphosphonates are the first choice in treatment of osteoporosis and vertebral fractures in the general population, but also in other rheumatic diseases like RA and SLE. However until now, no placebo controlled trial has been performed with bisphosphonates in AS. It seems worthwhile to perform such a RCT to investigate whether bisphosphonates will also have a therapeutic effect on osteoporosis and associated VF in AS, and further to study what the consequence will be on the extensive bone formation of the disease itself.

As mentioned before, for many years NSAIDs and physical exercise were the only available effective treatments for Spondylarthropathies. Tumor necrosis factor (TNF) inhibitors have showed considerable beneficial effects on pain and function in especially patients with AS. However as mentioned above, evidence of a disease modifying effect by reducing the radiological progression is lacking. The high costs of these TNF blocking treatments makes a more detailed investigation of the (economic) impact of AS necessary [31]. Furthermore, better insight into predictors of patients with a bad prognosis and into variables that predict response to these therapies will help us to select patients for whom these treatments are not only effective but also cost-effective [31]. Therefore more cost-effectiveness studies are needed. In addition, more attention from the specialist is needed and when required professional counseling for the social and work related impact of the disease, especially already in the early stage of the disease.

The Amsterdam Early SpA cohort described in this thesis forms the framework for a lot of investigation still to be performed to clarify much of the topics described above. Hopefully the continuation and further elaboration of the Early SpA cohort (as an inception cohort) will give more insight into the prognosis and prognostic factors for SpA, the value of different diagnostic methods like MRI and PET-CT in diagnosing in earlier stage, progression of co-morbidity (like osteoporosis and vertebral fractures), quality of life and

social participation and how we can optimize our current treatment arsenal and strategy in treating osteoporosis but finally and foremost also SpA itself.

Reference list

[1] Boonen A, de Vet H, van der Heijde D, van der Linden S. Work status and its determinants among patients with ankylosing spondylitis. A systematic literature review. J Rheumatol 2001 May;28(5):1056-62.

[2] Magrey M, Khan MA. Osteoporosis in ankylosing spondylitis. Curr Rheumatol Rep 2010 Oct;12(5):332-6.

[3] Franck H, Meurer T, Hofbauer LC. Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in patients with ankylosing spondylitis. J Rheumatol 2004 Nov;31(11):2236-41.

[4] Rubinstein HM. Osteoporosis in ankylosing spondylitis. Br J Rheumatol 1991 Apr;30(2):160.

[5] Gratacos J, Collado A, Filella X, Sanmarti R, Canete J, Llena J, et al. Serum cytokines (IL-6, TNF-alpha, IL-1 beta and IFN-gamma) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. Br J Rheumatol 1994 Oct;33(10):927-31.

[6] Gratacos J, Collado A, Pons F, Osaba M, Sanmarti R, Roque M, et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a followup study. Arthritis Rheum 1999 Nov;42(11):2319-24.

[7] Ghozlani I, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. Bone 2009 May;44(5):772-6.

[8] Kang KY, Ju JH, Park SH, Kim HY. The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis. Rheumatology (Oxford) 2013 Apr;52(4):718-26.

[9] Maksymowych WP. Disease modification in ankylosing spondylitis. Nat Rev Rheumatol 2010 Feb;6(2):75-81.

[10] Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis 2013 Jan;72(1):23-8.

[11] Braem K, Lories RJ. Insights into the pathophysiology of ankylosing spondylitis: contributions from animal models. Joint Bone Spine 2012 May;79(3):243-8.

[12] Carter S, Lories RJ. Osteoporosis: a paradox in ankylosing spondylitis. Curr Osteoporos Rep 2011 Sep;9(3):112-5.

[13] Haibel H, Rudwaleit M, Listing J, Sieper J. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis 2005 Feb;64(2):296-8.

[14] Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013 Nov 23;382(9906):1705-13.

[15] Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984 Apr;27(4):361-8.

[16] Maksymowych WP, Lambert RG. Magnetic resonance imaging for spondyloarthritis-avoiding the minefield. J Rheumatol 2007 Feb;34(2):259-65.

[17] Weber U, Hodler J, Kubik RA, Rufibach K, Lambert RG, Kissling RO, et al. Sensitivity and specificity of spinal inflammatory lesions assessed by whole-body magnetic resonance imaging in patients with ankylosing spondylitis or recent-onset inflammatory back pain. Arthritis Rheum 2009 Jul 15;61(7):900-8.

[18] Braun J, Baraliakos X, Golder W, Hermann KG, Listing J, Brandt J, et al. Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. Ann Rheum Dis 2004 Sep;63(9):1046-55.

[19] De Hooge M, van den Berg R, Navarro-Compan V, van Gaalen F, van der Heijde D, Huizinga T, et al. Magnetic resonance imaging of the sacroiliac joints in the early detection of spondyloarthritis: no added value of gadolinium compared with short tau inversion recovery sequence. Rheumatology (Oxford) 2013 Jul;52(7):1220-4.

[20] Molto A, Paternotte S, van der Heijde D, Claudepierre P, Rudwaleit M, Dougados M. Evaluation of the validity of the different arms of the ASAS set of criteria for axial spondyloarthritis and description of the different imaging abnormalities suggestive of spondyloarthritis: data from the DESIR cohort. Ann Rheum Dis 2014 Jan 3.

[21] Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009 Jun;68(6):770-6.

[22] Van Onna M, van Tubergen A, van der Heijde D, Jurik AG, Landewe R. Gadolinium contrast-enhanced MRI sequence does not have an incremental value in the assessment of sacroiliitis in patients with early inflammatory back pain by using MRI in combination with pelvic radiographs: a 2-year follow-up study. Clin Exp Rheumatol 2014 Jan 14.

[23] Haibel H, Sieper J. Editorial review: how early should ankylosing spondylitis be treated with a tumor necrosis factor-blocker? Curr Opin Rheumatol 2010 Jul;22(4):388-92.

[24] Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004 Jun;63(6):665-70.

[25] Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. Basic Clin Pharmacol Toxicol 2008 Jan;102(1):10-4.

[26] Kroon F, Landewe R, Dougados M, van der Heijde D. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis 2012 Oct;71(10):1623-9.

[27] Wanders A, van der Heijde D, Landewe R, Behier JM, Calin A, Olivieri I, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005 Jun;52(6):1756-65.

[28] Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler 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 2012 Oct;71(10):1616-22.

[29] Song IH, Poddubnyy DA, Rudwaleit M, Sieper J. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. Arthritis Rheum 2008 Apr;58(4):929-38.

[30] Konstantinidis I, Papageorgiou SN, Kyrgidis A, Tzellos TG, Kouvelas D. Effect of non-steroidal anti-inflammatory drugs on bone turnover: an evidence-based review. Rev Recent Clin Trials 2013 Mar;8(1):48-60.

[31] Boonen A. A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. Nat Clin Pract Rheumatol 2006 Oct;2(10):546-53.