Chapter 12

Summary and conclusions

SUMMARY AND CONCLUSIONS

The work presented in this thesis focuses on the assessment and monitoring of health and imaging outcomes in axial spondyloarthritis (SpA) and the relationship between these outcomes. Four major contributions to the understanding of axial SpA and to its management have been made: 1) we have contributed to improving and facilitating the assessment of disease activity in axial SpA using the Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS), for which we have defined cut-off levels for disease activity states and improvement criteria and in addition we have studied mathematical properties of the ASDAS formula resulting in further practical advice about its calculation; 2) we have contributed to increasing the knowledge about the mutual relationships between health outcomes in axial SpA, having looked at treatment responses and a comprehensive list of assessments and related health outcomes, namely health related quality of life (HRQoL), physical function, clinical disease activity, spinal mobility, structural damage and magnetic resonance imaging (MRI) of the spine; 3) we have contributed to increasing the knowledge about the factors that influence phenotypic variability in axial SpA, namely Human Leukocyte Antigen B27 (HLA-B27) positivity (a genetic factor), smoking (an environmental factor) and the presence of psoriasis (an extra-articular manifestation); and 4) we have provided further insight into understanding the processes that drive structural progression in axial SpA and into elucidating the link between inflammation and structural damage, by specifically looking at the relationship between MRI inflammation, MRI fat deposition and new bone formation in axial SpA.

The studies presented in this thesis were conducted in three cohorts: the AS Study for the Evaluation of Recombinant infliximab Therapy (ASSERT) cohort,[1] the Norwegian Disease Modifying Anti-Rheumatic Drug (NOR-DMARD) cohort,[2] and the *Devenir des Spondyloarthropathies Indifférenciées Récentes* (DESIR) cohort.[3] ASSERT was a 24-week randomised controlled trial with a tumour necrosis factor alpha (TNF) blocker, with an open extension until 102 weeks with all patients on the TNF-blocker. Demographic, clinical and MRI data were collected at baseline, 24 weeks and 102 weeks, while radiographic data was collected at baseline and 102 weeks. ASSERT was the main population studied in this thesis. NOR-DMARD is a Norwegian register from 5 centres that includes consecutive patients with axial SpA (according to the treating rheumatologist) starting a new synthetic or biological DMARD regimen. Patients from the NOR-DMARD register are considered an appropriate representation of patients with axial SpA as seen by rheumatologists in Norway. DESIR is a longitudinal prospective cohort that includes adults aged over 18 and less than 50 years from 25 regional centres in France. Patients have inflammatory back pain with symptom duration more than 3 months and less than 3 years and symptoms suggestive of SpA according to the opinion of the local investigator.

In this final chapter we will summarise the main findings of the studies presented in this thesis and we will also discuss future perspectives as well as a research agenda for the topics that we have studied.

Assessment of disease activity in axial SpA using the ASDAS

In **chapter 2** we determined cut-off values for disease activity states and response criteria according to the ASDAS. We developed the cut-offs in the NOR-DMARD cohort,[2] and validated the cut-offs in the same population at a different time-point and in an independent cohort, the ASSERT cohort.[1] Four disease activity states were defined: inactive disease, moderate-, high-, and very high disease activity. Both the patient and physician global assessments of disease activity at pre-defined levels (<1, <3 and >6 on a 0-10 scale) were used as external anchors to define the three disease activity cut-offs: 1.3, separating 'inactive disease' from 'moderate disease activity'; 2.1, separating 'moderate disease activity' from 'high disease activity'; and 3.5, separating 'high disease activity' from 'very high disease activity'. The Assessment of Spondyloarthritis international Society (ASAS) partial remission criteria were also used as an additional external anchor for 'inactive disease'. Regarding response criteria, the external anchor in the receiver operating characteristic (ROC)-curve analysis was a 'global rating of change' after starting treatment, with the health change defined by the patient in five Likert-type categories: 'much worse', 'worse', 'unchanged', 'better' and 'much better'. This resulted in the definition of two cut-offs for the magnitude of response: 'clinically important improvement' (external construct: patients reporting to be 'better' or 'much better'), defined as a decrease in ASDAS greater or equal to 1.1, and 'major improvement' (external construct: patients reporting to be 'much better'), defined as a decrease in ASDAS greater or equal to 2.0.

In **chapter 3**, we analysed the DESIR cohort, and contributed to further standardisation of the ASDAS and to a more homogeneous and reproducible application of this new index by demonstrating that: i) when the conventional CRP (cCRP) value is below the limit of detection, a CRP value of 2mg/L should be used to calculate ASDAS with CRP (ASDAS-CRP), and ii) when the high sensitivity CRP (hsCRP) value is below 2mg/L, the constant value of 2mg/L should also be used to calculate ASDAS-CRP. This study fulfilled a gap in the methodology of ASDAS calculation, since ASDAS-CRP had been developed using the cCRP and evidence-based guidance on how to calculate the ASDAS when the cCRP is below the threshold of detection or when using the hsCRP was lacking.

Further discussion and future perspectives

Chapter 2 is an important chapter from a methodological point of view since it highlights several key aspects of cut-off development, namely the fact that the cut-off selection

procedure should be an informed decision that takes into account the clinical (eg, treatment implications of the cut-off) and epidemiological context of the disease (eg, frequency of the various disease states in the target population) and the relative consequences of false-negative and false-positive test results compared to an external anchor ('gold standard', which may differ across contexts).[4,5] Importantly, we developed the ASDAS cut-offs both on clinical and statistical grounds and found a remarkable consistency between the various external constructs that we tested. Regarding improvement cut-offs, the availability of a global rating of change questionnaire in NOR-DMARD allowed us to use an adequate gold-standard for this purpose, with the cut-off for minimal clinically important improvement being beyond the limits of measurement error according to all tested methods.[6-8] Consistency of results was also shown between ASDAS-CRP and ASDAS with erythrocyte sedimentation rate (ASDAS-ESR), with the cut-offs being applicable to both formulae (however, the formulae are not interchangeable). ASDAS cut-offs showed excellent psychometric properties, with the ASDAS response criteria being more discriminative between treatment groups than classical response criteria. The two currently available remission-like states in axial SpA were also compared, ASDAS inactive disease being more discriminative than ASAS partial remission criteria.

Cut-offs are important because they give a meaning to a continuous index, to be used in an individual patient. 'Disease activity states' may help for instance to decide about the need to change treatment, they can be used as selection criteria for patient participation in research studies or they can be used as therapeutic targets (eg, aiming at remission/inactive disease). 'Response criteria' allow measuring the impact of a treatment, namely if the treatment results in clinically relevant improvement. Therefore the development of cut-offs for the ASDAS was a critical step in the ASDAS implementation plan, allowing translating mean group-effects into individual patient effects.

The ASDAS cut-offs were subsequently endorsed by ASAS and the Outcome Measures in Rheumatology (OMERACT) group and its use in clinical practice, observational studies and clinical trials has continued to increase since then.[9-16] They have been shown to have excellent measurement properties and its widespread use across different settings will allow combining results from different studies, for example for meta-analysis, or to audit results and to define and improve standards of care. ASDAS categories will also facilitate studying the impact of disease activity states on prognosis. Subsequent evidence has also suggested that the ASDAS better reflects the inflammatory disease processes in axial SpA than the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), namely at the biological level (correlation with biomarkers of inflammation, angiogenesis, cartilage and bone turnover)[17] and at the MRI level (correlation with MRI inflammation scores).[9,18,19] Furthermore, ASDAS high disease activity (ASDAS $\geq$2.1) might be a better threshold than the historically used BASDAI elevation cut-off level

(BASDAI ≥4) for the selection of patients for treatment with TNF-blockers, particularly because it selects a higher number of patients with characteristics predictive of a good response to these therapies.[13,20-22] This threshold has already been adopted by some national rheumatology societies as an additional criterion to select patients for treatment with biological therapies[23,24] and has been included in the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of axial SpA.

Excellent examples of how ASDAS categories can facilitate studying the impact of disease activity states on prognosis are two recently published articles looking at this topic. The first article showed a longitudinal association between disease activity and progression of radiographic damage in AS.[25] This study included patients from the Outcome in AS International Study (OASIS) cohort that were clinically and radiographically evaluated every 2 years up to a period of 12 years. Radiographic progression increased in parallel with increase in the ASDAS disease activity state with for example a patient with very high disease activity (ASDAS>3.5) being estimated to have an additional progression of 2.3 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) units in the subsequent 2 years in comparison to a patient with inactive disease (ASDAS<1.3). Several measures of disease activity (ASDAS, BASDAI, CRP) were significantly associated with an increase in the mSASSS but the ASDAS statistical model was the one that best fitted the data. Another recent study using the GErman SPondyloarthritis Inception Cohort (GESPIC) showed similar findings.[26] In this study, the authors also found that disease activity was associated with radiographic spinal progression in a population in an earlier disease stage compared to OASIS. Time-averaged ASDAS was significantly associated both with mSASSS worsening by ≥2 points and syndesmophyte formation/bridging over 2 years.[26] These data add to the validity (and predictive value in terms of progression of structural damage) of the ASDAS[25] and provide an additional argument to pursue a treat-to-target strategy in axial SpA, with ASDAS inactive disease potentially being the best target.

For the purpose of defining a remission-like state in axial SpA, ASDAS inactive disease seems to provide a more appropriate definition than the ASAS partial remission criteria because ASDAS inactive disease is independent of physical function, while ASAS partial remission criteria include physical function as one of its items, which implies that some patients with long-standing disease and severe structural damage and physical limitations may never fulfil ASAS partial remission criteria despite the disease being clinically and biologically inactive.[27] In a recent study reporting the outcomes of TNF-blocker treatment over a period of 2 years, achievement of ASDAS inactive disease or ASDAS major improvement was also significantly associated with greater improvements in the 36-Item Short Form Survey (SF-36) physical and mental component scores´ as well as in work productivity compared to patients that did not meet these treatment targets.[15] These data show that an ASDAS response translates into improvements in HRQoL and

health economic outcomes and again suggest that achieving ASDAS inactive disease should be considered a major treatment goal in patients with axial SpA.[15,28]

The ASDAS formula is rather complex and it is not possible to mentally calculate the index. However, this is not different from the Disease Activity Score (DAS) that has been successfully implemented in rheumatoid arthritis and in fact, compared to the DAS, the ASDAS benefits from not requiring a joint count. Rheumatologists are already familiarised with this type of indices and with the strategies that have been put in place to overcome their complexity: the availability of online, desktop, hand-held and smartphone calculators. The ASAS group has developed such tools (available at www.asas-group.org) for the ASDAS as well as a 'quick ASDAS calculation form', a 2-page form that gives the possibility to quickly calculate the ASDAS without the need of an electronic calculator. The availability of these instruments will facilitate the implementation of the ASDAS in clinical practice.

Regarding the research agenda in this area, evidence for the benefits of a treat-to-target strategy over standard treatment in axial SpA is still scarce and further studies are required; further research is needed to confirm if selecting patients for TNF-blocker treatment according to the ASDAS instead of BASDAI will result in improved long-term treatment outcomes; the definition of flare in axial SpA needs to be further explored and flare cut-offs for the currently available indices need to be established; the role of MRI in assessing and monitoring disease activity as well in selecting axial SpA patients for TNF-blocker treatment requires further investigation; finally, it needs to be confirmed whether a reduction of disease activity according to ASDAS by therapeutic intervention will be associated with reduction of radiographic spinal progression in axial SpA.

Relationship between health outcomes in axial SpA

Progressive restriction in spinal mobility is a hallmark health outcome of axial SpA and a predictor of poor long-term prognosis. In **Chapter 4** we showed that spinal mobility impairment in AS is independently determined by irreversible spinal damage as well as by reversible spinal inflammation, a finding that is consistent with clinical data reporting the improvement of both spinal inflammation and spinal mobility after treatment with TNF-blockers[1,29-31] and with studies showing an association between radiographic damage of the spine and spinal mobility impairment at the group level[32-36] but not always at the individual level.[36]

In **Chapter 5**, we studied in detail the relationships between several AS outcome measures and proposed a stratified model for health outcomes in this disease. According to this model, HRQoL is determined by physical function and disease activity, physical function is determined by spinal mobility and disease activity, and spinal mobility is determined by structural damage and inflammation of the spine (this last relationship

being based on the data presented in **Chapter 4**).

In **Chapter 6**, we showed that, cross-sectionally, MRI inflammation correlates better with CRP than with other measures of disease activity, but also correlates with the ASDAS, which includes the CRP in its formula. Furthermore, at the longitudinal level, improvement in MRI inflammation correlated with improvements in CRP and ASDAS, and a greater improvement in spinal inflammation was seen for those with higher CRP or ASDAS values at baseline. Importantly, other measures of disease activity, namely fully patient-driven measures such as the BASDAI, individual BASDAI questions and patient global, did not correlate with MRI inflammation.

The ASSERT cohort was studied in **Chapters 4, 5 and 6**.

Further discussion and future perspectives

Data from **Chapter 4** confirmed that spinal inflammation could be an explanation for the cases of discordance between the level of spinal mobility impairment and the degree of radiographic damage. Moreover, the results of this study also showed that spinal mobility impairment is more influenced by spinal inflammation in early disease, and by structural damage in later disease, which raises the suggestion that spinal mobility may better be maintained by an early- as compared to a delayed intervention. By showing that inflammatory changes (and not only structural changes) contribute to spinal mobility impairment, this study gave a new and original meaning to MRI spinal inflammation, further elucidating its role in the burden of disease. Since the mSASSS only accounts for the structural damage in the anterior corners of the cervical and lumbar spine, future research should focus on the role of damage of the thoracic spine and of the posterior elements of the spine, as well as on the role of MRI inflammation of the facet joints, vertebral ligaments and soft tissues (none of which are included in the MRI assessment at the vertebral unit level that was done in this study), in determining spinal mobility.

The model presented in **Chapter 5** explained a large percentage of the variation in the health outcomes, but not the entire variation, suggesting that other variables such as psychological, social, cultural, ethnical and educational factors should also be taken into account in future studies. However, the relations that we described are indisputable and consistent with the conceptual 'continuum of outcome measures' proposed by Tennant,[37] and suggest that in order to optimise HRQoL, both physical function and disease activity should be considered major goals in the treatment of axial SpA and optimal physical function-preserving therapy should focus not only on improving disease activity but also on maintaining spinal mobility, which on its own requires both the elimination of spinal inflammation and the prevention of structural damage. This stratified model nicely explains why optimal treatment of axial SpA should be multimodal, not only involving non-steroidal anti-inflammatory drugs (NSAIDs) and anti-TNF therapy (drugs that have

shown to improve patient-reported disease activity, while regarding MRI inflammation of the spine the effect is only clear for anti-TNF) but also therapies more specifically addressing spinal mobility (such as physical therapy) and progression of structural damage (for which no specific therapies have been developed and regarding which there is conflicting and/or inconclusive data regarding the capacity of NSAIDs and TNF-blockers to prevent the progression of structural damage).[38-41]

The associations that we described may also serve as the framework for future longitudinal studies in which temporal relationships may be tested. An association does not necessarily imply causation and only longitudinal studies can evaluate if a change in an outcome measure translates into a subsequent change in the associated measure. As we learn more about how to measure axial SpA, our knowledge about the disease improves and we can make better decisions on how to assess and treat the disease. The model we proposed is useful not only for the design and interpretation of clinical trials but also for daily clinical practice and may contribute to guide best practice in the assessment and treatment of patients with axial SpA. Since we studied a population with established AS, future research should also focus on earlier disease stages.

Data presented in **Chapter 6**, allowed us to better understand the relationship between clinical disease activity and MRI inflammation, both cross-sectionally as well as longitudinally, by assessing treatment responses and changes in MRI inflammation after TNF-blocker therapy. We concluded that ASDAS better reflects the spinal inflammatory disease process in AS than BASDAI, both as a status- and as a response measure. These results added to the construct validity of ASDAS and provided further evidence that ASDAS is an appropriate tool for monitoring patients with axial SpA. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. Nevertheless, we found weak to moderate correlations between CRP/ASDAS and MRI inflammation scores. Therefore, these clinical and laboratory measures should not be used to replace MRI assessment of spinal inflammation, which has become a useful tool in the management of patients with axial SpA. We have shown that the various measures have additive value. In the future, it will be interesting to see if more advanced (and quantitative) MRI techniques that may be more sensitive to inflammatory changes will result in different (and potential better) correlations with clinical and laboratory measures of disease activity. Another question still under debate relates to the role of MRI in the management of patients with axial SpA, especially in cases in which there is dissociation between clinical, laboratory and imaging findings. MRI may have a role in treatment adjustments but the benefit of this approach is still to be shown. It could also be debated if MRI should be used as an additional criterion to classify patients as being in remission, rather than just using clinical and laboratory criteria (or a combination of clinical and laboratory variables in the same formula such as it happens with ASDAS

inactive disease).

Phenotypic variability in axial SpA

In **Chapter 7**, our aim was to clarify the influence of HLA-B27 status on the phenotype of axial SpA. The results provided important information about the contribution of HLA-B27 to disease spectrum manifestations in axial SpA. We found that the presence of HLA-B27 was associated with an earlier age of onset of inflammatory back pain and with less delay in diagnosis. In addition, HLA-B27 was associated with axial inflammation (spine and sacroiliac joints [SIJ]). Moreover, SIJ inflammation seemed to be an intermediate variable between HLA-B27 and radiographic sacroiliitis.

In **Chapter 8**, we aimed to clarify the impact of smoking in the axial SpA spectrum. We found that in young axial SpA patients with short disease duration, smokers had an earlier onset of inflammatory back pain, higher disease activity, increased axial inflammation and structural damage, poorer functional status and poorer quality of life.

In **Chapter 9**, we compared AS patients with and without psoriasis. We found that demographic characteristics, disease activity, spinal mobility, physical function, structural damage and quality of life measures were comparable between AS patients with and without psoriasis.

The DESIR cohort was studied in **Chapters 7 and 8**, and the ASSERT cohort was studied in **Chapter 9**.

Further discussion and future perspectives

HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging. Previous studies had looked at patients with longer duration of symptoms[42,43] and also reported an association between HLA-B27 and an earlier age of disease onset, supporting the concept of axial SpA as a continuous spectrum. Our imaging analyses yielded new and relevant findings. Our models showed that HLA-B27 positivity was independently associated with MRI inflammation of the SIJ (and the spine), while MRI inflammation of the SIJ was independently associated with radiographic sacroiliitis. Interestingly, when MRI inflammation of the SIJ was removed from the models, HLA-B27 positivity was also found to be associated with radiographic sacroiliitis, suggesting that HLA-B27 may contribute to SIJ inflammation which in turn may lead to subsequent structural damage; inflammation as an intermediate factor between HLA-B27 and SIJ structural damage. In this study it was also noteworthy that ASDAS-CRP was positively associated with MRI inflammation of the spine, while BASDAI was negatively associated with MRI inflammation of the SIJ. These results also add to the validity of ASDAS-CRP as a measure for clinical disease activity in early axial SpA, and are in line with results from **Chapter 6**, obtained in a population with AS.

The adverse effects of smoking on AS disease parameters had been reported in previous studies, and were confirmed by us more robustly in an early disease stage population. In addition, we have demonstrated a new association with the presence of MRI inflammation. On radiographs, smoking was only associated with spinal, but not with SIJ damage.

The analyses in patients with and without psoriasis can be added to previous studies performed in heterogeneous populations (early inflammatory back pain, axial psoriatic arthritis and AS patients) that had showed conflicting results.[44-49] One of the advantages of our study is the large number of disease variables that were studied. We investigated a population with AS and futures studies should focus on the entire spectrum of axial SpA patients, including patients with not only radiographic but also non-radiographic axial SpA.[50] This topic was subsequently studied by other authors in the DESIR cohort.[51] In this more recent study psoriasis was associated with more active axial disease and frequent concomitant enthesitis and dactylitis. Studying the differences between patients with and without specific extra-articular manifestations (namely differences regarding treatment responses and associated comorbidities) may help us to better stratify patients and individualize treatments. Differences between TNF-blockers regarding their efficacy on extra-articular manifestations have already been described (while all TNF-blockers block TNF alpha *in vivo*, they differ significantly in structure and exact mechanism of action). New therapies to treat axial SpA are now emerging, namely therapies targeting the IL-23/IL-17 pathway, and understanding how certain extra-articular manifestations influence other disease characteristics and the response to therapies with different mechanisms of action (from the axial disease perspective as well as from the perspective of peripheral disease and the extra-articular manifestation itself) may contribute to more personalized treatment approaches.

Our studies on HLAB-27 and smoking have fuelled the discussions about gene-environment interactions in axial SpA, and particularly about the role of smoking as a prognostic factor in axial SpA, a concept that was only beginning to emerge when we published our results. Interestingly, a recently published 2-year prospective study performed also in the DESIR cohort showed that genetic (HLA-B27), environmental (smoking status) and inflammatory factors (presence of MRI inflammation of the SIJ) are independent predictors of radiographic progression of the SIJ.[52] Inflammation, represented by either abnormal CRP or MRI inflammation, had been previously reported as a predisposing factor for subsequent radiographic SIJ progression.[53] In the same previous study, the risk of progression was reported to be particularly high in case of co-existence of HLA-B27 positivity and inflammatory lesions of the SIJ.[53] The association between elevated CRP and radiographic progression of the SIJ had also been suggested in the GESPIC cohort but was not confirmed in the recently published DESIR study.[54] In another GESPIC study, smoking had been reported to be a risk factor

for structural progression at the spinal level with a potential dose related effect.[55] In the field of axial SpA, smoking has also been related to a higher incidence of the disease and a worse response to biologics. Taking into account that smoking is a potentially modifiable lifestyle factor, axial SpA patients who smoke should be strongly advised to quit this habit, since there may be disease-specific harms of smoking that go beyond the well-known risks described for the general population (axial SpA patients may have an increased cardiovascular risk by the inflammation). Of note, the demonstration of an increased risk of smoking does not necessarily imply that stopping (modifying risk behaviour) will have measurable beneficial effects.

It is interesting to speculate on the mechanisms by which smoking may confer these increased risks. Apart from rheumatoid arthritis, the pathogenic basis of the influence of smoking in rheumatic and musculoskeletal diseases including axial SpA remains largely unclear to date. Poor health behaviour, increased osteoporotic fractures and impaired cardiorespiratory function in smokers have been proposed as reasons for the negative impact of smoking on disease activity, functional status and quality of life measures.[56-58] In such explanations smoking is a risk indicator rather than a causal factor. However, this negative impact might also be mediated by a direct toxic effect of smoking. Cigarette smoke has pro-inflammatory effects, via various proposed mechanisms: smokers have an increased level of pro-inflammatory molecules such as TNF, interleukin (IL) 1, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor;[59,60] an increased concentration of free radicals;[61] augmentation of autoreactive B cells;[62] increased circulating polymorphonuclear neutrophil[63,64] and T-lymphocyte counts;[65] and smoking is associated with triggering of the nuclear factor κB pathway and promotion of pro-inflammatory cytokine gene expression.[66]

Periodontitis may also play a role in axial SpA,[67] and smoking is associated with periodontitis and its severity in a dose-dependent manner.[68] Smoking may also interfere with gut physiology, a factor that may in turn play a role in the pathogenesis of SpA.[69] Smoking was demonstrated to alter intestinal microbiota both in inflammatory bowel disease and in healthy subjects.[70] The IL-23/IL-17 pathway is pathophysiologically important in SpA[71] and in animal models, and it has been demonstrated that chronic cigarette smoke exposure is associated with an increase in lung Th17 cell prevalence and Th17-related cytokines (IL-17A, IL-6, IL-23). These data are compatible with an activation of the IL-23/IL-17 pathway by smoking.[72] In addition, some data suggest an effect of smoking on messanger ribonucleic acid (mRNA) expression of bone morphogenetic proteins (BMP) in the periosteum.[73] BMP and osteoblast signalling pathway markers (Wnt for example) and their inhibitors (dickkopf-1)[41] play a role in new bone formation in axial SpA.

Unravelling of the mechanisms underlying the relationship between smoking and health outcomes in axial SpA is an important item in the axial SpA research agenda.[74] Many questions about this topic remain unanswered. Factors linked to smoking should be investigated and, since cigarette smoking is a complex mixture of numerous agents, it needs to be determined which compound(s) in cigarette smoke is/are responsible for the deleterious effects of smoking in axial SpA. It also needs to be investigated if smoking is only a risk indicator or also a causal factor in axial SpA. Clinical trials evaluating the impact of smoking cessation in long-term health and imaging outcomes are needed, as the benefits of smoking cessation in patients with rheumatic diseases has never been prospectively assessed.

Relationship between MRI lesions and radiographic progression in axial SpA

In **Chapter 10**, we showed that MRI inflammation in a vertebral unit slightly increases the likelihood of finding a new syndesmophyte in the same vertebral unit two years later. However, the majority of syndesmophytes (in absolute numbers) developed in vertebral units without any sign of inflammation on MRI, suggesting that the relationship between MRI inflammation and syndesmophyte formation is not straightforward. Furthermore, the subtle association between MRI inflammation and new syndesmophytes at the vertebral unit level did not translate into a statistically significant association at the patient level, although a trend was also observed.

In **Chapter 11**, we confirmed that MRI vertebral corner inflammation is associated with radiographic progression in AS, and we showed that vertebral corner fat deposition is also associated with radiographic progression. The combination of fat and inflammation either at the same time point or sequentially further increased the probability of radiographic progression. Furthermore, vertebral corner fat deposition that developed *de novo* was sometimes preceded by vertebral corner inflammation, and this sequence of events had an even stronger association with progression of structural damage. However, vertebral corner inflammation, vertebral corner fat deposition and this particular sequence only partially explained the development of new bone in AS, as a large number of new syndesmophytes/bridging still occurred in vertebral corners without either inflammation or fat deposition across three time points that were assessed in this study.

The ASSERT cohort was studied in **Chapters 10 and 11.**

Further discussion and future perspectives

When we started the analyses presented in **Chapter 10**, two studies had been published showing a statistical association between MRI inflammation and syndesmophyte formation at the same the site of inflammation after 2 years of follow-up.[75,76] The strength of the association was slightly higher in these studies as compared to our study, but also

in these studies there were far more new syndesmophytes in non-inflamed vertebral sites as compared to inflamed vertebral sites. A third study by Pedersen et al was subsequently published,[77] also suggesting that sites with inflammation are more likely to develop new syndesmophytes than sites without inflammation. In addition, it has been proposed that syndesmophytes are more likely to develop at vertebral corners in which inflammation resolves compared to those where inflammation persists.[76,77] Resolving inflammation has also been associated with fat deposition.[78] In turn, fat deposition, with or without concomitant inflammation, has been associated with the formation of new syndesmophytes.[79-81]

Given the extensive debate and controversy about this topic, as well as the new data published after we performed the analyses described in **Chapter 10**, we aimed to expand our analytical studies about the association between inflammation and new bone formation by investigating the relationship between MRI inflammation and fat deposition at a vertebral corner and the subsequent development of new bone at the same corner. We focused on a detailed sequence analysis, addressing the hypothesis that vertebral corner inflammation 'leads to' fat deposition which in turn 'leads to' bone formation, and we could indeed confirm the rationality of this sequence.

It is interesting to discuss these results in relation to the question whether TNF-blockers are capable of inhibiting the progression of structural damage in axial SpA or not. The unexpected lack of inhibition of structural damage by TNF-blockers has fuelled the discussion about the relationship between inflammation and new bone formation. Initial trial data had suggested that TNF-blockers do not have an effect on spinal structural damage.[82-84] These data have recently been challenged by observational studies suggesting a protective effect of TNF-blockers on spinal radiographic progression.[85,86] However, these observational data have important methodological limitations and this is still an unsolved question.[41] Our observation that the sequence 'vertebral corner inflammation → vertebral corner fat deposition' is a rational sequence that may contribute to new bone formation in axial SpA is in agreement with the hypothesis that TNF-blocker treatment in axial SpA will only protect from structural damage if the (new) development of vertebral corner inflammation in previously unaffected vertebrae is prevented (that means: after long-term treatment), while in contrast an immediate effect of TNF-blocker treatment could even evoke new bone formation because of the abrupt suppression of vertebral corner inflammation and the subsequent development of vertebral corner fat deposition (repair reaction) at the same vertebral corner. Undoubtedly this explanation is a simplification of the truth, because the biological effects of TNF-blockers are not limited to the suppression of inflammation and TNF-blockers have also been associated with osteoproliferation in animal models.[87]

The question whether anti-TNF may retard new bone formation in axial SpA is difficult to answer. Radiographic progression is very slow in axial SpA and ethically it would be unacceptable to perform a long-term randomised controlled trial comparing the structural outcome in patients treated with- and those not treated with a TNF-blocker as this would imply delaying effective treatment in patients who might need it. Thus, we are left with observational studies to address this question. The analysis of such cohorts requires complex statistical methods and a great deal of caution in dealing with potential biases. These considerations should be taken into account in future studies about this topic. Ideally, multiple time points (annual or biennial assessments with long duration of follow-up) with complete demographic, clinical and radiographic data should be analysed in longitudinal models, taking into account time-varying variables (including changes in treatments, disease activity and acute phase reactants), potential confounders and interactions. In sequential radiographs of the same patient structural damage is highly correlated and therefore these longitudinal models should also account for within-patient correlation in order to avoid spurious results.[41] Given that an IL-17-blocker has now been approved to treat patients with axial SpA, a randomised controlled study comparing the structural effects of TNF-blocker *versus* IL-17-blocker therapy would also be informative. Moreover, the availability of low-dose computed tomography (CT) scans may help to increase the sensitivity of the imaging methods to detect progression of structural damage potentially and to allow the reduction of the length of the trial.

Consistent with previous studies, we have shown that a significant part of new bone formation occurs in vertebral corners without traceable inflammation or fat deposition. However, this does not necessarily mean that these vertebral corners do not have inflammation/fat deposition at the microscopic level because MRI may not be sensitive enough to capture all areas of inflammation/fat deposition[88] and because the time between MRI assessments may not be short enough to capture the potential fluctuation of these lesions, particularly inflammation. Conversely, these results suggest that the mechanisms of new bone formation in axial SpA are still largely unknown and that the triggering of osteoproliferation may be completely or partially independent of inflammation (and fat deposition).[89]

Interesting future questions are how to incorporate MRI in future clinical trials and long-term observational studies, whether MRI criteria should be incorporated in future treat-to-target treatment strategies, and whether new drugs with different mechanisms of action, such as drugs targeting the IL-23/IL-17 axis, will have different effects on inflammation, fat deposition and structural damage. Studies looking at additional time-points and at shorter intervals may also help to further elucidate the relationship between inflammation and syndesmophyte formation.

Final comments

In this thesis we have studied a large number of health and imaging outcomes in axial SpA. The positive emotion with which the ASDAS has been received by the axial SpA scientific community is particularly noticeable. Such a quick and wide implementation and acceptance of a new disease activity index has rarely been seen. Our clinical research has fuelled other research in the field, with research on the effects of smoking as a particularly relevant example. Our detailed studies about the relationship between MRI lesions and new bone formation on radiographs are among the most comprehensive and robust to date as they have used a uniquely large population of patients, multiple imaging readers, fully-unbiased imaging scoring methods, and three time points of assessment with adjustment for the dependence of observations in the same patient. In conclusion, our studies have contributed to a better understanding of the disease axial SpA and of the measures that we use to evaluate it and to monitor its course.

REFERENCES

1. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.
2. Kvien TK, Heiberg, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23:S188-94.
3. Dougados M, d'Agostino MA, Benessiano J, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine 2011;78:598-603.
4. Greiner M, Gardner IA. Epidemiologic issues in the validation of veterinary diagnostic tests. Prev Vet Med 2000;45:3-22.
5. Machado PM. Measurements, composite scores and the art of 'cutting-off'. Ann Rheum Dis 2016;75:787-90.
6. de Vet HC, Terluin B, Knol DL, et al. Three ways to quantify uncertainty in individually applied "minimally important change" values. J Clin Epidemiol 2010;63:37-45.
7. Turner D, Schunemann HJ, Griffith LE, et al. The minimal detectable change cannot reliably replace the minimal important difference. J Clin Epidemiol 2010;63:28-36.
8. Tubach F, Ravaud P, Beaton D, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. J Rheumatol 2007;34:1188-93.
9. Braun J, Baraliakos X, Hermann KG, et al. Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo- controlled GO-RAISE study. Annals of the rheumatic diseases 2012;71:878-84.
10. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Annals of the rheumatic diseases 2013;72:815-22.
11. Baraliakos X, Haibel H, Fritz C, et al. Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years. Arthritis Res Ther 2013;15:R67.
12. Ciurea A, Scherer A, Exer P, et al. Tumor necrosis factor alpha inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis and rheumatism 2013;65:3096-106.
13. Vastesaeger N, Cruyssen BV, Mulero J, et al. ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy. Reumatologia clinica 2014;10:204-9.
14. Song IH, Hermann KG, Haibel H, et al. Consistently Good Clinical Response in Patients with Early Axial Spondyloarthritis After 3 Years of Continuous Treatment with Etanercept: Longterm Data of the ESTHER Trial. The Journal of rheumatology 2014.
15. van der Heijde D, Deodhar A, Braun J, et al. The effect of golimumab therapy on disease activity and health-related quality of life in patients with ankylosing spondylitis: 2-year results of the GO-RAISE trial. The Journal of rheumatology 2014;41:1095-103.
16. Poddubnyy D, Hermann KG, Callhoff J, Listing J, Sieper J. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Annals of the rheumatic diseases 2014;73:817-23.
17. Pedersen SJ, Sorensen IJ, Garnero P, et al. ASDAS, BASDAI and different treatment responses and their relation to biomarkers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis treated with TNFalpha inhibitors. Ann Rheum Dis 2011;70:1375-81.
18. Machado P, Landewe R, Braun J, et al. MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a TNF inhibitor. Ann Rheum Dis 2012;71:2002-5.
19. Pedersen SJ, Sorensen IJ, Hermann KG, et al. Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis 2010;69:1065-71.
20. Arends S, Brouwer E, van der Veer E, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther 2011;13:R94.
21. Fagerli KM, Lie E, van der Heijde D, et al. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. Rheumatology (Oxford) 2012;51:1479-83.
22. Machado P, Landewe R. Spondyloarthritis: Is it time to replace BASDAI with ASDAS? Nature

reviews Rheumatology 2013;9:388-90.

23. Machado P, Bernardo A, Cravo AR, et al. Portuguese recommendations for the use of biological therapies in patients with axial spondyloarthritis--December 2011 update. Acta Reumatol Port 2012;37:40-7.
24. Wendling D, Lukas C, Paccou J, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. Joint Bone Spine 2014;81:6-14.
25. Ramiro S, van der Heijde D, van Tubergen A, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Annals of the rheumatic diseases 2014;73:1455-61.
26. Poddubnyy D, Protopopov M, Haibel H, Braun J, Rudwaleit M, Sieper J. High disease activity according to the Ankylosing Spondylitis Disease Activity Score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. Ann Rheum Dis 2016.
27. Machado PM, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis. Best Pract Res Clin Rheumatol 2014;28:711-28.
28. Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014;73:6-16.
29. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136-46.
30. Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230-6.
31. Braun J, Landewe R, Hermann KG, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum 2006;54:1646-52.
32. Kennedy LG, Jenkinson TR, Mallorie PA, Whitelock HC, Garrett SL, Calin A. Ankylosing spondylitis: the correlation between a new metrology score and radiology. Br J Rheumatol 1995;34:767-70.
33. Viitanen JV, Kokko ML, Lehtinen K, Suni J, Kautiainen H. Correlation between mobility restrictions and radiologic changes in ankylosing spondylitis. Spine 1995;20:492-6.
34. Viitanen JV, Kokko ML, Heikkila S, Kautiainen H. Neck mobility assessment in ankylosing spondylitis: a clinical study of nine measurements including new tape methods for cervical rotation and lateral flexion. Br J Rheumatol 1998;37:377-81.
35. Spoorenberg A, van der Heijde D, de Klerk E, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. J Rheumatol 1999;26:980-4.
36. Wanders A, Landewe R, Dougados M, Mielants H, van der Linden S, van der Heijde D. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? Ann Rheum Dis 2005;64:988-94.
37. Tennant A, McKenna SP. Conceptualizing and defining outcome. Br J Rheumatol 1995;34:899-900.
38. 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.
39. 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;71:1623-9.
40. Sieper J, Listing J, Poddubnyy D, et al. Effect of continuous versus on-demand treatment of ankylosing spondylitis with diclofenac over 2 years on radiographic progression of the spine: results from a randomised multicentre trial (ENRADAS). Ann Rheum Dis 2015.
41. Machado P. Anti-tumor necrosis factor and new bone formation in ankylosing spondylitis: the controversy continues. Arthritis Rheum 2013;65:2537-40.
42. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61-6.
43. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717-27.
44. Richette P, Tubach F, Breban M, et al. Psoriasis and phenotype of patients with early inflammatory back pain. Ann Rheum Dis 2012:epub ahead of print.
45. Perez Alamino R, Maldonado Cocco JA,

Citera G, et al. Differential features between primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease. J Rheumatol 2011;38:1656-60.

46. Fernandez-Sueiro JL, Willisch A, Pertega-Diaz S, et al. Evaluation of ankylosing spondylitis spinal mobility measurements in the assessment of spinal involvement in psoriatic arthritis. Arthritis Rheum 2009;61:386-92.
47. Edmunds L, Elswood J, Kennedy LG, Calin A. Primary ankylosing spondylitis, psoriatic and enteropathic spondyloarthropathy: a controlled analysis. J Rheumatol 1991;18:696-8.
48. Taylor WJ, Harrison AA. Could the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) be a valid measure of disease activity in patients with psoriatic arthritis? Arthritis Rheum 2004;51:311-5.
49. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? Ann Rheum Dis 1998;57:135-40.
50. Rudwaleit M, van der Heijde D, Landewe R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25-31.
51. Richette P, Tubach F, Breban M, et al. Psoriasis and phenotype of patients with early inflammatory back pain. Ann Rheum Dis 2013;72:566-71.
52. Dougados M, Demattei C, van den Berg R, et al. Rate and predisposing factors of sacroiliac radiographic progression after a 2 years follow-up period in recent onset spondyloarthritis. Arthritis Rheumatol 2016.
53. Bennett AN, McGonagle D, O'Connor P, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. Arthritis Rheum 2008;58:3413-8.
54. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:1369-74.
55. Poddubnyy D, Haibel H, Listing J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72:1430-2.
56. Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. Rheumatol Int 2005;25:357-60.
57. Ward MM, Weisman MH, Davis JC, Jr., Reveille JD. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. Arthritis Rheum 2005;53:710-7.
58. Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. J Rheumatol 2002;29:1420-5.
59. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. Am J Cardiol 2002;89:1117-9.
60. Glossop JR, Dawes PT, Mattey DL. Association between cigarette smoking and release of tumour necrosis factor alpha and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatology (Oxford) 2006;45:1223-9.
61. Pryor WA, Stone K, Zang LY, Bermudez E. Fractionation of aqueous cigarette tar extracts: fractions that contain the tar radical cause DNA damage. Chem Res Toxicol 1998;11:441-8.
62. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 2002;109:1625-33.
63. Smith MR, Kinmonth AL, Luben RN, et al. Smoking status and differential white cell count in men and women in the EPIC-Norfolk population. Atherosclerosis 2003;169:331-7.
64. Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. Arch Environ Health 1973;26:137-43.
65. Tanigawa T, Araki S, Nakata A, et al. Increase in memory (CD4+CD29+ and CD4+CD45RO+) T and naive (CD4+CD45RA+) T-cell subpopulations in smokers. Arch Environ Health 1998;53:378-83.
66. Shukla A, Timblin C, BeruBe K, et al. Inhaled particulate matter causes expression of nuclear factor (NF)-kappaB-related genes and oxidant-dependent NF-kappaB activation in vitro. Am J Respir Cell Mol Biol 2000;23:182-7.
67. Ratz T, Dean LE, Atzeni F, Reeks C, Macfarlane GJ, Macfarlane TV. A possible link between ankylosing spondylitis and periodontitis: a systematic review and meta-analysis. Rheumatology (Oxford) 2015;54:500-10.
68. Azizi A, Sarlati F, Bidi M, Mansouri L, Azaminejad SM, Rakhshan V. Effects of smoking severity and moderate and severe periodontitis on serum C-reactive protein levels: an age- and gender-matched retrospective cohort study. Biomarkers 2015;20:306-12.
69. Wendling D, Vuitton L, Koch S, Prati C. Spondyloarthritis and the gut: a new look. Joint Bone Spine 2015;82:77-9.
70. Biedermann L, Brulisauer K, Zeitz J, et al.

Smoking cessation alters intestinal microbiota: insights from quantitative investigations on human fecal samples using FISH. Inflamm Bowel Dis 2014;20:1496-501.

71. Wendling D, Guillot X, Prati C. The IL-23/Th 17 pathway in spondyloarthritis: the royal road? Joint Bone Spine 2015;82:1-4.
72. Wang H, Peng W, Weng Y, et al. Imbalance of Th17/Treg cells in mice with chronic cigarette smoke exposure. Int Immunopharmacol 2012;14:504-12.
73. Chassanidis CG, Malizos KN, Varitimidis S, et al. Smoking affects mRNA expression of bone morphogenetic proteins in human periosteum. J Bone Joint Surg Br 2012;94:1427-32.
74. Wendling D, Prati C. Smoking and spondyloarthritis: a bad connection. Rheumatol Int 2015;35:1951-3.
75. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther 2008;10:R104.
76. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Ostergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.
77. Pedersen SJ, Chiowchanwisawakit P, Lambert RG, Ostergaard M, Maksymowych WP. Resolution of inflammation following treatment of ankylosing spondylitis is associated with new bone formation. J Rheumatol 2011;38:1349-54.
78. Song IH, Hermann KG, Haibel H, et al. Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48. Ann Rheum Dis 2011;70:1257-63.
79. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych WP. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum 2011;63:2215-25.
80. Baraliakos X, Heldmann F, Callhoff J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819-25.
81. 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;72:23-8.
82. 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.
83. 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.
84. 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.
85. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.
86. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. Ann Rheum Dis 2014;73:710-5.
87. Zwerina J, Tuerk B, Redlich K, Smolen JS, Schett G. Imbalance of local bone metabolism in inflammatory arthritis and its reversal upon tumor necrosis factor blockade: direct analysis of bone turnover in murine arthritis. Arthritis Res Ther 2006;8:R22.
88. Gong Y, Zheng N, Chen SB, et al. Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. Arthritis Rheum 2012;64:1399-406.
89. Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.