A systematic comparison of rheumatoid arthritis and ankylosing spondylitis: structural outcomes

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ABSTRACT

Rheumatoid arthritis and ankylosing spondylitis are both chronic diseases with inflammation as a hallmark. Both diseases are characterized by structural abnormalities of the peripheral joints (RA) or the spine (AS) that can be visualized on conventional radiographs. RA is associated with destruction (erosions, joint space narrowing) whilst AS is dominated by bone formation (syndesmophytes). The causative relationship between inflammation and structural damage in RA is well established, whilst this relation is largely unknown but certainly less strong in AS. Progression of structural damage in RA is inhibited by disease modifying anti-rheumatic drugs and especially by TNF-blockade, whilst progression of structural damage in AS seems insensitive to TNF-blockade but sensitive to non-steroidal inflammatory drugs.

In this article, similarities and dissimilarities with respect to structural damage in RA and AS are discussed and set against a background.

Introduction

Both rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic inflammatory diseases characterized by structural changes. The word 'structural' here refers to disease-specific changes that are considered irreversible, in contrast to reversible changes that are directly associated with inflammatory signs and symptoms, such as pain and stiffness (1). Structural changes jeopardize the integrity of the human body and as such may cause functional impairment. Although you can think of structural changes in various (organ) structures, in the context of rheumatology we often refer to "bones and joints", more specifically osseous and cartilaginous tissues that are somehow affected by the inflammatory process.

Two remarks are appropriate here: the first is that plain radiography is (still) the modus of choice for the visualization of osseous structures, and thus osseous changes, and at least to some extent this remark extends to cartilaginous changes, although admittedly cartilage is not directly visualized on plain radiographs.

The second remark is that the characteristics of structural changes in RA and AS differ importantly. RA is a disease characterized by destruction of bone and cartilage whilst the predominant finding in AS is the inappropriate formation of bone rather than its destruction.

In this article we will describe the main characteristics of structural damage in RA and AS, place them in the context of other relevant outcomes, try to compare across diseases and hypothesize about the differences, with the premise that structural damage is something that can be visualized on plain x-rays. We admit that newer imaging techniques may shed different light to structural damage in these diseases, but the majority of currently available evidence has been established with conventional radiography.

Structural damage in RA

Erosions, joint space narrowing and scoring methods

The prototype lesion in RA is the bony erosion. As said, bony erosions are considered destructive lesions in which bone resorption has occurred in the joint as a consequence of chronic inflammatory processes in that joint. Another important characteristic of RA is the radiographic feature of joint space narrowing (JSN), which is broadly considered the equivalent of cartilage destruction. Corroborating evidence that JSN reflects cartilage destruction stems form studies showing an association between JSN and markers of cartilage break-down such as CTX-II (2).

Two major scoring systems were described in the 1970s to score radiographic progression in RA: The Larsen

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system (3) and the Sharp system (4). A number of modifications have been described for both systems. Most landmark trials in RA now apply the van der Heijde modification of the Sharp scoring system (SvdH) (5), because this method includes both hands and feet, both erosions and joint space narrowing, and a sufficiently broad spectrum of joints to provide sensitivity to change. In brief, the SvdH method scores the presence of erosions in 16 joints of hands and wrists (graded from 0 to 5), 6 joints of the feet (graded from 0 to 10), the presence of joint space narrowing in 15 joints of the hands and wrists (graded from 0 to 4), and in 6 joints of the feet (graded from 0 to 4). The maximal score is 280 units for erosion and 168 units for joint space narrowing, summing up to 448 units for the total Sharp score (TSS)

Pathophysiology of erosions and cartilage loss

The importance of the osteoclast as a driver of joint destruction in RA is currently undisputed. Cells with specific surface markers of osteoclasts are found in areas of pannus invasion into bone at the sites of bone erosions in animal models of arthritis (6) and in patients with RA (7). The receptor activator of nuclear factor κB-ligand (RANKL), and its naturally occurring decoy receptor osteoprotegerin (OPG) are of importance in diseases such as RA (8), erosive psoriatic arthritis (9) and multiple myeloma (10). RANKL induces osteoclastic bone destruction, and OPG protects against bone destruction by preventing RANKL to bind with its receptor RANK. Although inflammation and osteoclastogenesis are different processes in the joints, proinflammatory cytokines are major co-factors in the differentiation and activation of osteoclasts. From a clinical point of view, it is unlikely that joint destruction in RA would occur in the absence of inflammation, but inflammation may occur in the absence of joint destruction. Recently we have demonstrated that baseline OPG/RANKL-ratio as well as the first-year time-averaged ESR have distinctive effects on 5-year radiographic progression in patients with early active RA, which implies that both osteoclasts and inflammatory cytokines exert pro-erosive effects and that progression of joint damage and inflammation can at least in part be dissociated (11). The same concept has been proven by the use of a specific RANKL-inhibitor (denosumab) which exerted an inhibition of structural progression without an effect on disease activity (12).

The relationship between inflammation, damage and physical function in RA

The relationship between physical function, disease activity and structural damage in rheumatoid arthritis is well established, and there is broad consensus that physical function, as assessed by the patient, using the health assessment questionnaire, is determined both by disease activity and structural damage (13-15). Part of functional impairment is considered reversible (probably impairment due to disease activity) whereas part is considered irreversible (1). Likely, the irreversible part of functional impairment is associated with structural damage As said before, disease activity itself is a major driver of structural damage, since inflammation causes joint destruction (16). The relationship between disease activity and radiographic damage is clearly longitudinal, which corroborates the causality of this association in individual patients. The phenomenon that only part of RA patients seem to develop structural damage is still largely unexplained, but there is a strong association between markers such as anti-citrullinated antibodies (or rheumatoid factors) and erosive disease. This indicates that the propensity to develop characteristic erosions in RA is genetically determined.

The effects of non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying drugs (DMARDs) and biologicals with respect to structural damage in RA

To date, there is no indication that NSAIDs somehow inhibit the occurrence or progression of radiographic abnormalities in RA despite their well established effects on signs and symptoms of the disease.

Numerous carefully conducted clinical trials exploiting radiographic scoring methods that are sensitive to change and have discriminatory capacity have now confirmed that a number of DMARDs and biologicals are able to slow or even stop radiographic progression. TNF-blocking drugs are especially very effective in inhibiting the progression of radiographic damage, but biologicals targeting other epitopes (*e.g.* interleukin 6 receptor) are also effective. The methodological observation that TNF-blockade may induce repair in previously damaged joints is beyond doubt (17, 18) but its consequence with regard to clinical outcome is still unclear, though some observations point to less functional impairment in patients with predominantly repair as opposed to patients without (19).

Structural changes in AS

Radiographic sacroiliitis and syndesmophytes

Plain radiography of the pelvis is still a cornerstone in the diagnosis of AS. The modified New York criteria for AS require the presence of radiographic sacroiliitis in order to classify the patient as having AS (20). Radiographic sacroiliitis includes radiographic sclerosis, erosions and – importantly – ankylosis. Sclerosis is probably a secondary phenomenon of chronic inflammation. Erosions can typically be found in the lower third of the SI joints resembling the synovial part, but may occur elsewhere too. Ankylosis of the SI-joint is considered a late phenomenon of AS and reflects bony bridges in the joint. For methodological reasons, scoring of the SI joints for the purpose of quantifying progression is not performed widely.

Plain radiographs of the spine in patients with AS can show a variety of pathological features. These include erosions, squaring, sclerosis, syndesmophytes, bridging syndesmophytes, spondylodiscitis and fractures. Typical features of AS occur relatively late in the course of the disease, and are in general not contributory to the diagnosis. In a cross-sectional cohort of patients with AS, with a mean disease duration of almost 12 years, more than 60% of

patients had features attributable to AS on their spinal radiographs, but only a minority had syndesmophytes extending over multiple vertebrae. Less than 5% of patients had a characteristic "bamboo spine" which could be considered an end-stage of spinal AS.

Three methods have been described in the literature to score abnormalities in the spine. The first is the Bath Ankylosing Spondylitis Radiology Index (BASRI) (21) which is a gradual method and not broadly used in outcome studies or trials. The other two scoring methods are more detailed methods assessing the corners of the vertebrae. The Stoke Ankylosing Spondylitis Spinal Score (SASSS) (22) includes the anterior and posterior sites of each lumbar vertebra. Each corner is scored for the presence of squaring, sclerosis, erosions, syndesmophytes and bridging syndesmophytes. The maximal score is 72. The modified SASSS was published in the international literature by Creemers *et al*. (23). The main modification as compared to the SASSS is that the posterior sites of the lumbar vertebrae are not scored, and the anterior sites of the cervical vertebrae are added to the scoring method. The features that are scored are similar. The developers of this method showed that changes could be detected in 36 of 57 patients over a period of 48 weeks.

Careful psychometric analysis has shown that the mSASSS is more appropriate than either BASRI or SASSS in scoring progression of radiographic damage in patients with AS and therefore this method has been selected as the preferred method to score spinal changes in AS (ASAS) (24). However, the disadvantage of the use of radiographs to assess spinal damage is the fact that the thoracic spine can not well be visualised and consequently is not included in scoring methods.

Pathophysiology of syndesmophyte formation

Bony protrusions such as osteophytes in osteoarthritis (OA) and syndesmophytes in AS are based on endochondral ossification, which leads to deposition of chondrogenic matrix and later to remodeling into bone. Bony spurs emerge from the periosteum close to joints or intervertebral spaces, where mesenchymal cells are localized, which have the ability to differentiate into cartilage and bone, when receiving the appropriate signals. Emergence of osteophytes depends on stress towards the joint and apparently both mechanical stress (as evident from the abundance of such lesions in OA) and inflammatory stress can precipitate their formation in diseases such as AS. From a pathophysiological viewpoint these lesions can be seen as an attempt of repair or stabilization mechanism to reduce motion in the affected joint. Bony spurs can even bridge joints leading to bone ankylosis and complete stabilization of joints. Longstanding sacroiliitis is a typical example, which, after complete ankylosis and immobilization of the joint, leads to a marked reduction of clinical symptoms. Bridging of syndesmophytes in AS is another clear example.

The relationship between disease activity, damage and physical function in AS

It is generally accepted that structural damage interferes with spinal mobility. Wanders et al showed acceptable correlations between measures of spinal mobility and measures of structural damage visualised on radiographs of the spine (25). However, the relationship was not linear and it appeared that the correlation increased with increasing level of damage. Radiographic data like this suggest that the spectrum of AS is heterogeneous, including patients with and without the propensity to develop characteristic structural abnormalities of the spine, and that progression of structural damage may extend over a long time interval.

A recent analysis in the OASIS cohort has shown that physical function, measured by two different patient-reported questionnaires (BASFI and DFI), is determined by the level of patient-reported disease activity (BASDAI) and independently of that by the level of structural damage (mSASSS) (19). BASDAI reflects patient-reported outcomes such as pain in back and joints, fatigue and stiffness, and has shown to be reversible upon treatment with NSAIDs (26) and especially TNF-blocking drugs (27). mSASSS primarily reflects syndesmophyte formation and bridging, which is structural and irreversible. The analysis showed that if BASDAI is at a low level (patients report no complaints), structural damage may cause important impairments in physical functioning, which is a strong justification for the assessment of structural damage by regular x-rays of the spine and the development of therapy that may interfere with the formation of syndesmophytes. Even if drugs are able to bring a patient in a complete symptomatic remission, physical function will remain impaired due to the structural damage in the spine.

Another interesting finding of this study was that erosions, sclerosis and squaring (all assessed by the mSASSS) also contribute to functional impairment, though the effect of syndesmophytes is stronger. In conclusion, the data indicate that any radiographic abnormality that is attributable to AS may independently contribute to impaired physical function.

The relation between disease activity and syndesmophyte formation (or other AS-specific abnormalities) is less obvious. Careful analysis in the OASIS cohort has failed to demonstrate a positive association between measures of disease activity and the occurrence or progression of structural damage in AS (28); the only positive assocation was with existing structural damage and MMP3 (29).

The effects of disease modifying drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and biologicals with respect to structural damage in AS

Recently the results of a trial comparing two strategies of non-steroidal anti-inflammatory drugs (NSAIDs) were presented. The two strategies were continuous versus on-demand use of NSAIDs (30). Radiographic progression in the continuous NSAID group was statistically significantly lower as compared to the on-demand group. This finding, which is still unconfirmed by independent studies, suggests that prostaglandin-related mechanisms may play a role in explaining the formation of syndesmophytes.

DMARDs such as sulfasalazine and methotrexate are considered ineffective in reducing spinal signs and symptoms of AS, and there is no indication that they are effective in slowing radiographic progression in AS, although this has never been investigated thoroughly.
What is known about the relationship between TNF-blockade and clinical disease activity, findings on MRI and structural damage on radiographs in AS? Beyond argumentation, TNF-blockade reduces clinical disease activity, acute phase reactants and inflammation visible on MRI (31). However, this does not lead to inhibition of radiographic progression, as unequivocally shown in recent analyses including the 3 currently available TNF-blocking drugs (32, 33). In these comparisons, radiographs from the OASIS cohort were used as a comparator and there was no difference in radiographic progression over a 2-year time frame between patients from OASIS (without a TNF-blocker), and patients treated with etanercept, infliximab or adalimumab. Limiting the analysis to patients from OASIS that would have fulfilled entry criteria for the trial resulted in completely comparable results. Also adjustment for all possible differences in baseline variables did not change the results.

Similarities and dissimilarities

Comparing structural radiographic outcomes in RA and AS there are more differences than similarities. Among the main similarities is that both diseases are diagnosed and treated by rheumatologists, that both affect bone (which makes them accessible to radiographic evaluation), and that in both structural damage results in significant functional impairment. Among the main differences is that in RA destruction predominates while in AS bone formation prevails, that in RA the relation between inflammation and structural damage is crystal clear whilst in AS it cannot be proven, and that in RA TNF-blockade stops damage progression and NSAIDs do not, whilst in AS TNF-blockade has no effect on damage progression whilst NSAIDs may inhibit progression.
The scientific developments in the field of RA have preceded those in the field of AS, and the "pre-test hypothesis" of many with regard to syndesmophyte formation in AS may have been biased by knowledge about the status in RA. This is probably the best explanation for the fact that so many were surprised by the absence of any effect of TNF-blocking drugs on the progression of syndesmophytes in AS. One may however argue that – given a better understanding of pathophysiology, and with reference to methodology – such an effect was not at all entirely expectable.

A pathophysiological argument

As said, in contrast to AS, RA is the prototype of a disease that is not associated with osteophyte formation despite severe joint damage. The pathophysiological picture of RA is characterized by osteoclast formation and bone destruction with only mild signs of bone repair. This is based on the dominance of bone resorption in RA, which rapidly destroys the periosteal lining and invades bone. This process is fueled by rapid generation of osteoclasts through TNF and RANKL (resulting in bone resorption) combined with a blunted response of bone formation, which involves inhibitors of Wnt- proteins, such as Dickkopf-1 (34). The activating role of TNF on osteoclast formation has been defined in the past 5 years, whereas the role of TNF in decreasing osteoblast formation is known for many years but its molecular regulation has been poorly defined until recently. RA combines rapid bone resorption with inhibition of bone formation leading to rapid development of erosions. Structural damage in RA at least partly mimics bone damage of multiple myeloma, since both diseases are characterized by "holes" in the bone with no major reparative response. Importantly, the structural damage measured by radiological scores in RA is a direct consequence of the inflammatory process, which makes the good relation between clinical disease activity and structural damage in this disease conceivable (16).
In contrast, the pathological and in part also the radiographic picture of SpA is dominated by response-to-stress. Despite chronic inflammation, which is a well-known precipitator of trabecular bone loss that also affects patients with AS, there is evidence for a dramatic bone formation in the periosteal compartment in AS but not in RA. It appears that in AS an initial bone resorptive phase may act as a stress factor which is followed by profound endochondral bone formation originating from the periosteum and leading to bone spurs, which can even bridge the joints and fuse the vertebrae. Molecularly these lesions depend on increased bone formation, which is most likely governed by members of the TGF/BMP protein family as well as the group of Wnt proteins. In addition, Wnt proteins appear to be regulators of osteophyte formation (35). Moreover, there is a cross talk with the RANKL-OPG system, since Wnt- signaling activates OPG, which balances RANKL induced osteoclast activation (36). Inhibitors of Wnt, such as DKK-1 are key target genes of TNF, which likely explains the negative effects of TNF and other proinflammatory cytokines on bone formation. In line, DKK-1 levels are low in AS, but high in RA, suggesting that the Wnt signaling cascades are turned on in the joints of AS (34). These findings suggest that early developmental programs are switched on, when joints form osteophytes to bridge and stabilize the diseased joint space. It also suggests that TNF negatively regulates bone formation and that inhibition of bone formation and osteophyte growth by TNF- blocking agents is unlikely.

A methodological argument

Some have claimed that AS patients in whom TNF-blockade did not have an effect on structural damage had already established disease and that reduction in radiographic progression could be seen only during the early phases of the disease. This theoretical argument has gained some robustness by the mutually independent observations in 3 cohorts that there is a statistical association between inflammation on MRI of individual vertebrae and the subsequent evolution of a new syndesmophyte at the same level 2 years later. A few important remarks seem appropriate here: First, it is theoretically possible and even likely that the

aforementioned repair process requires an initial boost of inflammatory activity before it becomes independent of inflammatory triggers. It will however be very difficult to prove this mechanism as well as to pharmaceutically interfere with it like in RA. Second, though statistically indisputable, the weak relationship between inflammation and syndesmophyte formation implies that in the majority of vertebrae this association could not be demonstrated, and new syndesmophytes did occur without preceding inflammation, or vice versa inflammation was not followed by syndesmophyte formation. Third, and related to this, the factor time has shown to be of crucial importance in AS. Where radiographic progression in RA can appropriately be demonstrated in a cohort with 3 months follow-up (37), a 2-year follow-up period seems the absolute minimum for AS. Such a long follow up period hampers the demonstration of subtle associations importantly, and methodological factors such as assessment precision and co-interventions may be of decisive importance.

Having said this, one issue emerges from the discussion: It is obvious that in RA and structural damage in AS have a different background, which explains why "logical associations" in the context of RA do suddenly not seem to be logical anymore in the context of AS.

Conclusion

Structural outcomes in RA and AS are clinically relevant because of the well established relationship between damage and physical function. The pathophysiology of structural damage in RA and AS is probably fundamentally different, implying that the way of therapeutically intervening in its occurrence and progression is fundamentally different.

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