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Editorial

Radiographic progression in axial spondyloarthritis: Is it the expression of a helpful measure of structural involvement outcome?☆

Progresión radiográfica en espondiloartritis axial: ¿es el reflejo de una medida útil de desenlace de compromiso estructural?

Wilson Bautista-Molano[a,b]

[a] *Sección de Reumatología, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia*
[b] *Facultad de Medicina, Universidad Militar Nueva Granada, Bogotá, Colombia*

The term spondyloarthritis (SpA) includes a group of diseases which are closely interrelated in terms of the predominant clinical manifestations and from the genetic point of view.[1] Ankylosing spondylitis (AS), non-radiographic axial SpA (nr-axSpA), psoriatic arthritis and other subtypes with predominance of extra-articular manifestations, such as inflammatory bowel disease and uveitis are included in this group. Recently, the corresponding terminology for all Spanish-speaking countries has been updated, in order to homogenize the nomenclature and abbreviations used in scientific publications related to this pathology.[2]

The classification criteria defined and validated by the Assessment of SpondyloArthritis International Society (ASAS)[3] establish the stratification of the presentation form based on axial or peripheral predominance, and allow to integrate and optimize the classification of these patients in whom the rheumatologist has previously made the clinical diagnosis.[4] The clinimetric evaluation allows to assess the functional deterioration observed in these patients, which is closely related to the previous inflammatory process that is documented not only in the sacroiliac (SI) joints, but also in the vertebral bodies.

The structural commitment in axial SpA (axSpA) is directly related with the functional loss and the clinical impact that it entails. This structural damage is the consequence of osteoproliferative phenomena that involve the participation of osteoblastic cells and multiple mediators which allow the expression of a phenotype that is observed in the simple radiography, through the visualization not only of the osteophytes, but also of other findings such as sclerosis, erosion or ankylosis. However, the reading of these images can sometimes be difficult, which is related to the anatomical complexity in the specific case of the SI joints. In this context, some studies have demonstrated that there is a modest sensitivity and specificity in the reading and interpretation of the simple radiographs associated with a great variability when they are evaluated both by rheumatologists and radiologists.[5]

This concept of structural commitment or damage has had special relevance during the last years. Not only because of the close relationship with the pathophysiology of the

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E-mail address: wilson.bautista@gmail.com

disease, but also because it constitutes an outcome of interest to be evaluated for all interventions, whether pharmacological or non-pharmacological. It has been estimated that the radiographic progression rate observed in the spine in patients with axSpA is dependent on several risk factors such as the presence of syndesmophytes, increased titers of acute phase reactants – especially C-reactive protein – and cigarette smoking.[6] Therefore, there are clinical predictors that allow us to support clinical decisions in the management of these patients.

Although the association between structural damage in the spine and reduced spinal mobility and functional loss is widely accepted, the association between the spinal radiographic progression and reduced spinal function and mobility is less well known. This editorial presents the most relevant data about the concept of radiographic progression in patients with AS and axSpA and its clinical relevance as a measure of structural outcome including the role of images.

Images in axial spondyloarthritis

In the diagnostic and prognostic approach of patients with axSpA, the evaluation of the structural damage provides relevant information. The radiological evaluation of the SI joints and the spine is the primary imaging modality most frequently used in the evaluation of patients with axSpA. Despite the notable advances related to new imaging modalities, such as nuclear magnetic resonance (NMRI), the simple radiography remains the cornerstone of diagnosis, evaluation and classification of these patients. The evaluation of the structural commitment by images constitutes one of the main outcomes for the evaluation of disease modifying therapies, together with the prognostic factors that determine this structural damage. The interest in simple X-ray images in axSpA has substantially improved in the last decade, mainly due to the development, validation and application of radiographic scoring methods in clinical trials and research studies.[7]

However, there are points of controversy and interest in clinical practice related to the imaging technique for the SI joint and the usefulness of the radiography in the diagnosis, especially in early disease in the context of the ASAS classification criteria. In addition, it has been discussed the role of the radiography in the follow-up, evaluation and management of this pathology. While the simple radiography remains the mainstay of diagnosis, its limitations are increasingly clear. In particular, cohort studies have shown that only a minority of patients with early SpA will have clearly defined radiographic sacroiliitis.[8–10] In this particular context, the role of NMRI takes on greater importance.

The modified Stoke Ankylosing Spinal Score (mSASSS), a radiographic scoring tool, has become the preferred method for the evaluation of radiographic progression, mainly due to its higher sensitivity to change compared with other described methods. This scoring system consists of a sum of the scores of the findings observed in the simple radiograph of the lumbar and cervical spine, from a lateral view, ranging from 0 to 72. The SASSS scoring method evaluates the anterior and posterior corners of each lumbar vertebra from the lower edge of T12 to the upper edge of S1. In these anatomical locations, a score of 1 is assigned for the presence of quadrature, sclerosis or erosions, a score of 2 for syndesmophytes, and a score of 3 for ankylosis. If there is a combination of erosions, sclerosis or quadrature, the score assigned for that vertebral corner is still 1.[11,12] In the mSASSS scoring method (modified version), the posterior corners of the lumbar vertebrae are not evaluated and the anterior corners of the cervical vertebrae from the lower edge of C2 to the upper edge of T1 are added to the scoring method, giving rise to the same score range.[13]

However, the widespread use of this method has exposed its important limitations with respect to the lack of reliability associated with insufficient methodological standardization.[14] The images by simple radiography are not a very sensitive tool and cannot adequately differentiate the quadrature of the vertebral bodies. It is probable that additional modifications to this score will be required in order to optimize its operational performance, while the search for new tools for the evaluation of the structural progression in axSpA should continue.

Modification of the disease

The concept of "disease modification" makes reference to the improvement in symptoms in combination with associated changes in the course of the disease.[15] This concept is closely related to the pathophysiological process of the disease and constitutes the center of the immediate patient's expectations associated with short-term interventions. All of the above is reflected in the outcome of the disease and in the main focus of the rheumatologist who defines a therapeutic strategy.

Medications can influence the process of evolution of the disease and give rise to a short-term control of symptoms that are caused by inflammation (symptom-modifying drugs). They can also have an impact on the disease with long-term results (medications that modify or control the disease).[16] The combination of the control of the symptoms together with the prevention of permanent structural damage and disability will have a clear effect on the functionality of the patient, for which there are additional measures or measuring instruments.[17] At any point in time during the evolution of the disease, the function will be determined by a series of factors that include not only the inflammatory symptoms and the disability caused by the structural damage in the tissues involved, but also by other consequences of the disease, such as the loss of muscle strength, the general physical condition and the psychological impact.[18] The influence of each of these variables varies over time in patients on individual basis. In this context, the modification of the disease results in an improvement in the function and constitutes an aspect of greater complexity to be evaluated in the presence of the existing interventions. However, this inclusive model often comes down to the prevention of structural damage as a defining factor to categorize and evaluate the impact of pharmacological interventions.

The majority of the studies on pharmacological interventions and their effects on the long-term outcome of the disease have been carried out in patients with rheumatoid arthritis (RA). Several studies have evidenced treatments that can modulate the structural commitment in RA, which is

evaluated by radiographic methods and is characterized by joint space narrowing and bone erosions.[19] However, it is less clear that the structural modification constitutes a *sine qua non* condition for the modification of the disease in axSpA. The modification of the disease from a clinical point of view should focus on the factors that affect the function, including inflammatory symptoms and structural damage.

The effect and the type of structural damage are expressed differentially in patients with axial predominance compared to those who present predominantly peripheral symptoms. In axSpA the patients have rigidity and their axial mobility is limited. Although this is partially reversible, since inflammation also contributes to these manifestations, the progressive loss of mobility is associated with the neoformation of cartilage and bone that leads to ankylosis of the SI joint and the spine. For this reason, progressive ankylosis of the spine is an important determinant of disability in AS.[20] In this sense, the modification of the disease in SpA should focus on the rapid control of inflammatory symptoms, and address the short and long term consequences of both types of structural compromise: new formation of cartilage/bone and joint destruction. In synthesis, the modification of the disease in SpA refers to the maintenance or improvement of the function over time, and is not determined solely by the structural damage, but by many factors related to the inflammatory process and the activity of the disease.[21]

Pathophysiology of the osteoproliferative phenomenon in SpA (osteoclastic and osteoblastic differentiation)

One of the most relevant manifestations in AS is the bone formation that coexists with the process of bone resorption. Similarly to that is found in other inflammatory diseases, there is an imbalance in these pathophysiological processes that results in the appearance of syndesmophytes and bone erosions in AS.[22] The formation of new bone often limits the embryonic development and the process of fracture repair, even at the cellular and molecular level. One of the main differences between the process of bone development and the process of bone neoformation in SpA is the heterotopic growth observed in patients with SpA.[23] It has been observed in these patients that the process of bone proliferation and finally the ankylosis are originated in the enthesis organ. Conversely, the osteophytes observed in osteoarthritis have their origin in the articular cartilage and the subchondral bone.[24]

Several molecular signaling pathways that are critical within the process of tissue homeostasis, development and formation have been described.[25] The bone morphogenic proteins, which are secreted by macrophages, are related to growth and differentiation factors.[26] In this context, they could play an important role in the process of joint remodeling, particularly in the formation of enthesophytes. However, the regulatory mechanisms and their relationship with other triggering factors are not clearly defined.

IL-17 has an important role in the promotion of osteoclastogenesis directly and by the activation of the receptor activator of nuclear factor kappa B (RANK).[27] However, it functions in combination with the TNF-α. The latter cytokine stimulates the bone destruction through the RANK-RANK ligand system (RANK-RANKL) and inhibits the bone formation through the overexpression of the Dickkopf-related protein 1 (DKK1),[28] which suppresses the WNT pathway in the bone.[29] The signaling of the WNT/B-catenin pathway is a regulator of osteogenesis and its high levels promote the formation of osteoblasts and reduce osteoclastogenesis (and, therefore, bone resorption).[30] Unlike the TNF-α, IL-17 seems to exert a dual effect in this context, because it can promote not only bone destruction by acting in a complementary manner with the TNF-α, but also promotes the formation of bone in sites of inflammation or exposed to mechanical stress.[31]

Conclusion

In summary, the progression of radiographic damage in the spine in axSpA is clinically relevant due to the clear association with the physical function. The progression rate depends on the structural damage present (syndesmophytes), the degree of activity of systemic inflammation (acute phase reactants) and the presence of smoking habit. Therefore, it constitutes an outcome of interest to evaluate in relation to the interventions carried out in patients with SpA with the effect of measuring their impact as disease modifiers. Further studies in this area will allow us to clarify the molecular signaling pathways that are involved in the process of bone remodeling and the validation of biomarkers of bone resorption/formation.

It is clear that the evaluation of the progression of structural damage in SpA has generated controversy based on the results of studies conducted during the past few years. In particular, the measurement of structural damage and its application in the context of daily clinical practice generates concerns related to its routinely and periodic application in patients with SpA. The difficulty for its reproducibility and the time it takes to perform these measurement scores make that its systematic application is not generalized in the clinical scenario. Likewise, all pharmacological interventions evaluated so far have shown a marginal benefit in the modification of radiographic progression. Even in the case of the anti-TNFs, their effect can be observed after 4–8 years of exposure and is related to an indirect mechanism, that is, through the modification of the disease activity. In that sense, it would be very interesting to evaluate the role that the NMRI or even the tomography could have in relation to the evaluation of axial structural changes and the possible generation of simplified evaluation scores that allow us to measure this outcome. Therefore, we need additional information in this regard, which should be validated in prospective long-term follow-up cohorts.

Conflict of interest

The authors declare they do not have any conflict of interest.

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