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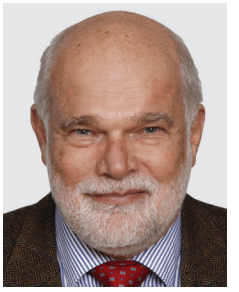
Editorial



The Early Course of Radiographic Progression in Axial Spondyloarthritis: Have We Missed Something?

Jürgen Braun[1]

The DESIR (*Devenir des spondylarthropathies indifférenciées récentes*) cohort is a rather successful 10-year follow-up study of 708 patients with early inflammatory back pain lasting > 3 months and < 3 years, and recruited within 26 months in 25 centers in France. Patients were followed up every 6 months during the first 2 years and then once every year.[1] The mean age at baseline was 34 (SD 9) years, 54% were female, and 57% were HLA-B27 positive. Very recently, the 10-year data on radiographic progression of patients from this cohort, classified as having either nonradiographic axial spondyloarthritis (nr-axSpA) or radiographic axSpA (r-axSpA; also known as ankylosing spondylitis [AS]), were published.[2] In axSpA, the axial skeleton is mainly affected through inflammation and new bone formation; this is well known to mostly start in the third decade of life, with patients often presenting with the characteristic feature of inflammatory back pain. The difference between the classification as r-axSpA or nr-axSpA is historically based on the presence or absence of definite radiographic changes in the sacroiliac joints (SIJ) of patients with axSpA, which is equivalent to fulfilling the radiographic criterion of the 1984 modified New York (mNY) criteria for AS. Since back pain is a frequent symptom, there is often a considerable delay in diagnosis between 5 to 10 years after the onset of symptoms. Clearly, reduction of pain and maintenance/improvement of function are important factors for patients, and spinal radiographic progression is considered an important long-term outcome of axSpA, which can be predicted—next to male sex and smoking—by the persistence of inflammation.[3]

In DESIR, the net radiographic progression rate was only 8.7% in 10 years.[4] Several other cohort studies have reported somewhat different, but usually low rates, of radiographic progression for time periods between 2 and 10 years from nr-axSpA to r-axSpA or from 1 mNY grade to another.[5,6] One study suggested an inhibitory effect of tumor necrosis factor inhibitors,[7] similar to what was observed in DESIR.[2] However, these low progression rates are in contrast to earlier data indicating that most radiographic progression in AS occurs within the first 10 years, but these data were collected in a time when biologic disease-modifying antirheumatic drugs (bDMARDs) were not yet available.[8]

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There are 2 points that, in my opinion, need to be discussed in this regard: (1) Are we performing the right studies with the appropriate cohorts? (2) Is the progression from nr-axSpA to r-axSpA the best outcome to choose?

Can we improve study designs?

There is no doubt that cohort studies are valuable for learning about the course of a disease. Theoretically, we would like to include all patients with possible axSpA, but is this the case in the cohort studies performed to date? From textbooks, we know that the mean age of onset of first symptoms related to AS is 26 years old. This was confirmed by a study performed in Leeds, UK, some years ago,[9] in which patients with a mean age of 28 years and who had symptoms for < 2 years (all positive for HLA-B27 and sacroiliitis as assessed by magnetic resonance imaging [MRI]) were included; this is still the earliest axSpA cohort ever reported. Similarly, in the Infliximab as First Line Therapy in Patients With Early Active Axial Spondyloarthritis Trial (INFAST),[10] patients were about 30 years old with < 2 years of symptom duration. Importantly, in that study, > 50% of patients were already mNY positive at baseline. In DESIR, it was nearly 25%,[2] but the baseline demographic data are also worth mentioning, since the percentage of female individuals was higher and the percentage of HLA B27-positive subjects was lower than what could have been expected. What this suggests is that patients in observational cohorts can be somewhat different from those in treatment studies: they are older, more often female, less often HLA-B27 positive and fulfilling mNY criteria, and they show less radiographic progression.[11] The latter is backed by different data looking at spinal radiographic progression, which is largely absent in nr-axSpA.[12]

For inclusion in DESIR, patients were recruited if they had inflammatory back pain for > 3 months and < 3 years.[1] Thus, although it was not planned for DESIR to exclude severe patients, this is indeed what probably happened. It is conceivable that a 30-year-old patient who has already had axSpA for some years, including ankylosis, will not be included in an inception cohort that was planned to include early patients because the outcome planned for is already there. For example, a 30-year-old patient with a symptom duration of 4 years with mNY grade 4 and syndesmophytes would not have been included in the DESIR cohort.

Taken together, inception cohorts such as DESIR may not

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include the most severe patients. Thus, the results of these studies should not be interpreted in such a way that axSpA is now considered as a rather benign disease with limited radiographic progression.

Are there better outcomes?

It has been shown many times that the degree of radiographic changes in the SIJ is subject to individual author interpretation,[13,14] and therefore not suitable for a meaningful clinical diagnosis.[15] The differentiation of r-axSpA and nr-axSpA is historically explained by the fact that once a pharmaceutical company had received an approval for AS, it had to also get an approval for "non-AS" axSpA, which implied that authorities—such as the US Food and Drug Administration—checked whether patients were erroneously included in a nr-axSpA trial by looking at the SIJ radiographs. If the central reader judged a patient as mNY positive, the patient was out of the analysis; for example, this happened in ABILITY-1.[16] Thus, there is no medical or scientific need for this differentiation in terms of diagnosis, nor as an outcome variable. Previous reports on the ability of bDMARDs to diminish the number of erosions in the SIJ have also shown to be critical in this regard. However, new techniques to better detect erosions in the SIJ by MRI are indeed promising.[17,18]

What is the functional relevance of being first mNY negative and then mNY positive on follow-up? To my knowledge, there is only one study that answered this question,[19] by showing an independent but rather small though significant association of the SIJ sum score with the Bath Ankylosing Spondylitis Functional Index (BASFI; $b = 0.10$) and the Bath Ankylosing Spondylitis Metrology Index (BASMI; $b = 0.12$), indicating that a change by 1 radiographic SIJ grade is associated with BASFI and BASMI worsening of 0.10 and 0.12 points, respectively. Thus, we are looking at an outcome that is difficult to assess and functionally almost irrelevant.

Further, there are better options than radiographs, such as MRI.[20] New techniques such as synthetic MRI[18] may even further improve the performance of MRI in the SIJ and the spine. For the spine, we already know that low-dose computed tomography performs better than conventional radiography,[21] with the advantage of also including the spine, which is not possible with the conventional evaluation using modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[22]

Conclusion

Taken together, it is time to design new cohort studies and choose better outcomes. Most importantly, young patients with severe disease should not be excluded from cohorts. Further, mNY SIJ grades are neither suitable for diagnosis nor a meaningful outcome.

As a possible solution, all patients with possible axSpA should be included, who are, for example, < 35 years old. Regarding outcome, I would rather choose new bone formation in the spine, as indicated by new onset or worsening of syndesmophytes using superior techniques, or new onset or spreading of spinal inflammation as assessed by MRI.

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COMPETING INTERESTS

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