Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

New considerations in the design of clinical trials for spondyloarthritis

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Inflammation in spondyloarthritis (SpA) primarily affects the axial skeleton including the sacroiliac joints, the spine and the peripheral joints. Currently, axial and peripheral SpA can be distinguished, and new criteria have been developed to classify these subtypes. Ankylosing spondylitis (AS; Bechterew's disease) belongs to the spectrum of axial SpA. To date, randomized clinical trials in this field have usually been conducted in patients with AS, showing efficacy of non-steroidal anti-inflammatory drugs and of TNF-α-inhibiting biologicals on signs and symptoms of AS, on acute phase reactants and on inflammation on MRI of the spine and sacroiliac joints. In this article, classic trial design in AS is discussed, as well as the implications of the development of the new Assessment in Spondyloarthritis international Society criteria and new outcome measures in the field of SpA on future trial designs with regard to new drug development.

Keywords: ankylosing spondylitis • axial spondyloarthritis • imaging • MRI • peripheral spondyloarthritis • radiography • randomized clinical trial

Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease primarily, but not exclusively, affecting the axial skeleton including the sacroiliac joints (SI-joints), the spine and the peripheral joints [1]. The broader concept of SpA includes the disease ankylosing spondylitis (AS) as a classic pendant. Patients with SpA may have musculoskeletal symptoms such as inflammatory back pain and arthritis, but also extra-skeletal manifestations such as acute anterior uveitis, psoriasis and inflammatory bowel disease (Crohn's disease or ulcerative colitis).

Currently, the clinical subtypes axial SpA (to which AS belongs) and peripheral SpA are distinguished on the basis of predominant presenting features. Patients with axial SpA present with chronic back pain [2], whilst patients with peripheral SpA present with arthritis, enthesitis or dactylitis [3]. This article is written from the perspective of SpA, knowing that it may be difficult, if not impossible, to distinguish some patients with peripheral SpA and patients with (oligoarticular) psoriatic arthritis. Further research and discussion, beyond the scope of this article, will shed more light on these nosological differences.

To date, the cause of SpA is unclear, but there is ample evidence that both the adapted and the innate immune system are involved in the initiation and maintenance of the chronic inflammatory process, that preferentially originates from the bone–tendon junction (enthesitis) [1]. There is a strong genetic trait via HLA-B27, but polymorphisms in other genes, such as the gene encoding for the IL-23 receptor and for the ARTS-1 enzyme, are also contributory [4].

Unlike the situation in rheumatoid arthritis (RA), where inflammation may lead to bone loss (erosions) and cartilage loss, (axial) SpA is characterized by new bone formation rather than degradation, and bony spurs, called syndesmophytes, emerge from the edges of the vertebral bodies. These syndesmophytes have a tendency to fuse and form bony bridges spanning adjacent vertebral bodies, which may give the

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characteristic radiographic appearance of 'bamboo spine' as in AS. The triggers initiating the new bone formation have not been elucidated yet, but many believe that the inflammatory response must somehow be responsible for this process. Evidence supporting this view stems from carefully conducted imaging studies unravelling the association between inflammation on MRI and syndesmophyte formation on conventional radiographs, which report odds ratios between 1.5 and 3 [5–7]. The same studies, however, show that most syndesmophytes occur at levels without visible inflammation, whilst many levels with visible inflammation do not show syndesmophyte formation, pointing to the still poor understanding of this typical phenomenon.

Diagnosis & classification of SpA

An appropriate diagnostic test for SpA is lacking. Available classification criteria such as the modified New York criteria for AS [8] were usually applied to confirm a diagnosis of AS in the clinical situation. Since the modified New York criteria include radiographic sacroiliitis as an obligatory but rather late feature, these criteria lack sensitivity and AS was usually diagnosed with a significant delay [9]. Such a delay was considered increasingly unwarranted in view of the availability of effective medicines that may suppress the inflammatory response. Furthermore, the modified New York criteria do not recognise the clinical syndrome of peripheral SpA. The European Spondylarthropathy Study Group (ESSG) criteria [10] and the Amor criteria [11] for SpA were considered more sensitive to recognizing SpA at an earlier stage, and included peripheral symptoms, but did also did not distinguish between axial and peripheral SpA.

Recently, clinical investigators in the field of AS have proposed the concept of early non-radiographic SpA as a condition in which symptoms and signs of sacroiliitis are already present at an early stage, but radiographs are (still) normal [12]. These symptoms of sacroiliitis can be made visible by MRI years before radiographic changes may occur. To date, it is unclear how long this lag time between changes on MRI and on radiographs actually is, but there is a strong suspicion that only a proportion of the patients with sacroiliitis on MRI will ultimately develop radiographic abnormalities that suffice for a classifying diagnosis of AS. There is some evidence that such an evolution primarily –but not exclusively- takes place in HLA-B27-positive male patients [13]. Conclusive clinical data obtained in patients with non-radiographic SpA, though, show that the burden of disease – in terms of signs and symptoms – is as high in early non-radiographic SpA as in AS [14].

The same investigators that have proposed the concept of early non-radiographic SpA have been at the basis of the new axial SpA criteria that aim at an earlier diagnosis, so that an effective treatment can be started much earlier than before [2]. These axial SpA criteria give justice to the appreciation that SpA covers a spectrum of different, but often associated clinical symptoms, which each in itself may help to make a diagnosis. Furthermore, the axial SpA criteria recognize the clinical feeling that some patients with typical symptoms of SpA will not have demonstrable inflammation of the sacroiliac joints but yet follow a clinical course that is typical for SpA. In brief, a patient with chronic (>3 months) back pain can fulfil the axial SpA criteria in two manners (Figure 1). Firstly, by showing sacroiliitis on MRI and/or radiographs and having at least one SpA feature; and secondly, by showing HLA-B27 presence and having at least two SpA features.

These investigators have also developed criteria for peripheral SpA in order to be better able to distinguish this important clinical subset of SpA, and make it accessible for clinical research [3]. In brief, the criteria for peripheral SpA starts with a patient presenting with arthritis, enthesitis and/or dactylitis (Figure 1). These presenting symptoms are characteristic features of patients with SpA, and they can occur without axial symptoms. Then, a patient has to fulfil either at least one of the set of higher weighted SpA features (e.g., uveitis or psoriasis), or at least two of the set of lower weighted SpA features, in order to make a classification of SpA.

Current clinical trials in SpA

Randomized clinical trials (RCTs) in the field have been boosted by the advent of the TNF-α inhibiting biologicals (TNF-inhibitors). To date, most RCTs with TNF inhibitors have been performed in populations with patients fulfilling the modified New York criteria for AS.

These patients had to have active disease, usually defined as a patient-reported outcome above a certain threshold (e.g., A Bath Ankylosing Spondylitis Disease Activity Score [BASDAI] >4), and initially were not allowed to have complete spinal fusion, as it was believed that those patients would have end-stage disease that would not clinically respond to otherwise effective medication. Later, it turned out that even patients with end-stage disease could improve a lot on a variety of clinical measures.

The primary outcome parameter in those trials was (and still is) the ASAS20 response [15]. The ASAS20 response measure is, in analogy of the American College of Rheumatology (ACR)-20 response for RA, a thoroughly validated response index that, out of a large set of candidate response measures, best discriminated between placebo and active drug, with an acceptably

low placebo response rate. An ASAS20 response constitutes a 20% improvement in at least three out of four patient-reported outcomes (domains; pain, inflammation, patient global and function), whilst the fourth should not have worsened more than 10%.

The RCT scenario outlined here forms a default scenario for testing new treatments in patients with AS that has been successfully applied since then in a number of RCTs testing non-steroidal anti-inflammatory drugs (NSAIDs) [16,17], disease modifying antirheumatic drugs (DMARDs) [18,19] and TNF-inhibitors [20–23] with respect to their potential to reduce 'signs and symptoms' of AS. To some extent, these RCTs even provide a predictable response pattern for TNF-inhibitors (the '60–20 rule' referring to 60% ASAS20 response in the active drug arm versus 20% ASAS20 response in the placebo arm), adding to the appreciation of certain class specificity in AS for this group of treatments. Needless to say that this default trial plan has importantly attributed to achieving regulatory approval for NSAIDs and TNF inhibitors, and subsequent reimbursement, for patients with AS in clinical practice.

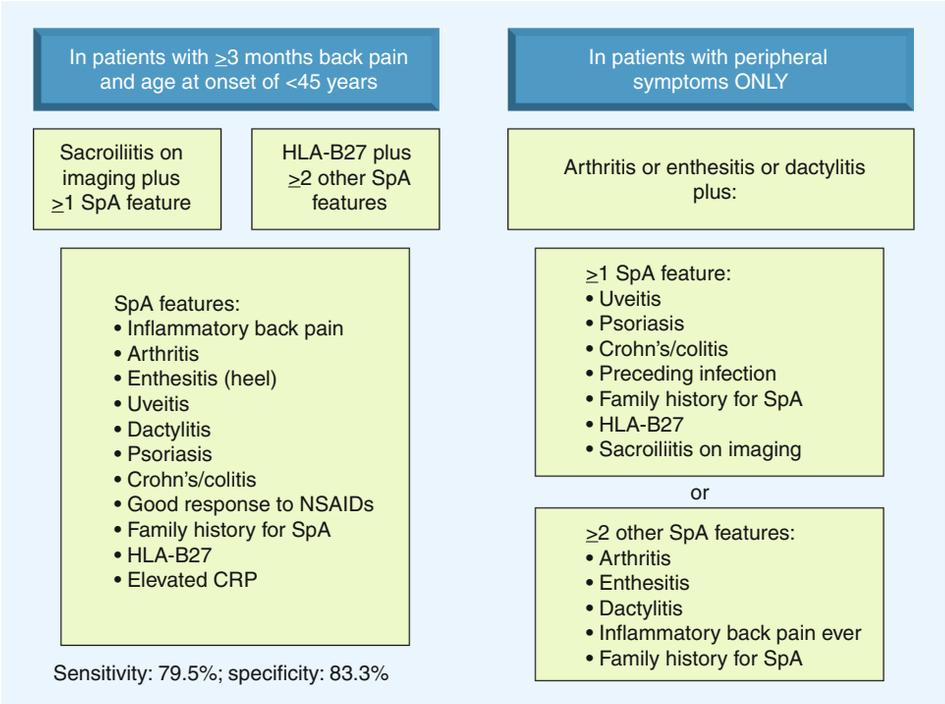

Figure 1. The new Assessment in SpondyloArthritis international Society (ASAS) criteria for axial spondyloarthritis and peripheral spondyloarthritis.
CRP: C-reactive protein; SpA: Spondylosing arthritis.

Disadvantages of conventional AS trial design

By doing these trials in AS and reading their results, increasing concerns arose with regard to the appropriateness of these trials in a number of facets. These concerns were that the ASAS20 response measure is too heavily weighted by patient-reported outcomes (PROs); that the usual trial duration of 6 months, being ethically justifiable, is too short to measure structural changes of the spine; and that the inclusion of only AS patients (with an average disease duration of 5–7 years at diagnosis) implies that early AS trials are impossible. We will briefly discuss these three arguments.

■ Overweighting PROs: underweighting inflammation

Many experts in the field believe that it is inappropriate to base a conclusion of drug efficacy solely on PROs. Undoubtedly, this belief has been fuelled by the fact that TNF-inhibitors have shown to be very effective in reducing levels of acute phase reactants (e.g., C-reactive protein [CRP]) [20–23], and in reducing signs of spinal inflammation on MRI [24,25]. But more importantly, there is an almost dogmatic conviction in rheumatology nowadays that chronic inflammation causes adverse long-term effects such as accelerated atherosclerosis, such as in RA, that should be suppressed thoroughly by treatments if possible, in order to improve long-term outcome [26]. Preferably, the impact of treatments on inflammation should be expressed in the primary outcomes of future clinical trials. It is for these reasons that the Assessment in SpondyloArthritis International Society (ASAS) has decided a few years ago to develop a new disease activity measure that includes an acute phase reactant as well as PROs. This measure, called the ankylosing spondylitis disease activity score (ASDAS), that has been designed in analogy of the disease activity score (DAS) for RA, has recently been published after subjection to a thorough validation program [27,28]. The final version of ASDAS includes four PROs (pain spine, fatigue, morning stiffness and patient global) as well as CRP. Subsequently, ASAS has developed important cut-off levels for several disease activity states and for meaningful improvement (response) that can now be used in clinical trials as a primary end point [29].

Measuring structural changes of the spine

Progression of structural changes in AS (the formation of syndesmophytes and bridging syndesmophytes) can be measured in clinical trials using several scoring instruments, but after a comparative validation program under ASAS/Omeract auspices, ASAS has chosen a modification of the Stoke Ankylosing Spondylitis Spine Score (mSASSS) as the method of choice for measuring structural progression [30]. It is important to be informed about the effect of new treatments on progression of structural changes since it has been shown convincingly that these changes interfere independently with spinal mobility, physical function and quality of life (and as a consequence with economic aspects of the disease) [31,32]. A major problem though, is that these changes occur slowly over time and need at least 2 years to develop to such an extent in a group of AS patients that they can be reliably distinguished using current measurement instruments. Attempts to improve the mSASSS in terms of sensitivity to change and discrimination, or to substitute radiography by MRI, have failed thus far.

Approximately 5 years ago, we felt that conventional placebo-controlled RCTs would never give resolution with regard to the question of inhibition of radiographic progression by TNF-inhibitors in AS, and we proposed an alternative study design [33]. In the past, the 2-year radiographic progression of actively treated patients with the 2-year progression of prospectively followed AS patients was compared by doing a reading exercise, in which x-rays of patients and controls are blindly offered to x-ray readers (with unknown time order). This design was adopted by regulatory authorities and by pharmaceutical companies, and was applied three times with three different TNF-inhibitors [34–36]. Whilst the feasibility and credibility of this approach (which is second best in comparison to an approach with concurrent placebo controls) was unequivocally proven, the results clearly showed that TNF-inhibitors, when applied in patients with advanced AS, did not influence radiographic progression. Immediately, the argument of a too late start of the intervention was risen [37], a hypothesis that is waiting to be proven.

The need for early AS trials

The average disease duration of patients included in previous AS trials is more than 10 years. The average duration of complaints in patients with AS at the time of diagnosis is 5–7 years [9], so with unchanged methodology it will be impossible to exploit early AS trials. The main reason for such a late diagnosis is, as outlined above, the time needed to fulfil the modified New York criteria for its radiographic criterion of sacroiliitis. Two main lines of reasoning provide justification for RCTs with patients (far) earlier in the course of their disease. The first is the observation that patients with early non-radiographic AS seem to suffer as much from signs and symptoms of the disease as patients with established AS; the second is fuelled by the aforementioned hypothesis that syndesmophyte development, being insensitive to treatment by TNF inhibitors in classic AS, may be sensitive to TNF inhibition if this is started before the assumed shift from a primary inflammatory reaction into an inflammation-independent repair reaction, that is at the basis of syndesmophyte formation, has taken place. This essentially means a treatment start 'as early as possible'.

Future clinical trials in SpA

How do these limitations of classic trials design in AS accommodate into more appropriate trial designs in the future?

The elements necessary for such new designs have partly been outlined above. The new ASAS criteria for axial [2] and peripheral [3] SpA will help tremendously to identify patients with SpA at a much earlier stage than before. Importantly, it will be possible now to not only focus on patients with primarily axial symptoms, but also on patients with peripheral SpA that, until now, have been neglected in clinical trials.

These trials, especially in patients with axial SpA, will have the ASDAS as a primary outcome measure, having a better face validity, and providing a higher level of sensitivity to change and discrimination [27,28].

Although syndesmophyte formation measured on x-rays of the spine will remain an important standard for judging drug-effects on structural changes, there will be a more prominent place for MRI assessment in SpA trials. Whilst it has been shown that syndesmophyte formation is better detected on x-rays than on MRI [38], MRI has the advantage of showing what is considered the immediate sequels of inflammation; the fat infiltration (fatty changes) in the corners of vertebrae (and maybe the SI-joints). These fatty changes may be the basis of future syndesmophyte formation [39], and may be reliably detected within a time frame that is far shorter than 2 years, putatively allowing an assessment in a trial with concurrent control patients. Additionally, biomarkers may increasingly be applied in SpA trials as surrogate outcome markers for progression of structural damage.

Practical aspects of trial design in SpA

Inclusion criteria for SpA trials in the future will be aimed at patients that fulfil axial or peripheral SpA criteria as a starting point. Since patients with axial SpA fare a different course, as compared with patients with peripheral SpA, and treatment is different, we

foresee trials designed for axial SpA and trials designed for peripheral SpA, and the first examples of such trials will be published soon.

As pointed out above, patients with axial SpA can fulfil the criteria in two ways. Either via positive imaging (x-rays or MRI of the SI-joints) and one additional SpA feature, or via the presence of HLA-B27 and two additional SpA features. Up to now it is unclear if – and how – both subgroups differ with respect to prognosis and treatment response. More importantly, the highly effective treatments that are nowadays available may prevent us from obtaining knowledge about the natural course of axial SpA anyway, a phenomenon that we have also seen in idiopathic early arthritis. It is, therefore, highly recommended to perform stratified inclusion and randomization with a sufficient number of patients per stratum so that meaningful treatment contrasts can be statistically demonstrated per stratum. It is unwise to only include patients according to the imaging stratum as it will be at the cost of generalizability. It may jeopardize the possibility of early diagnosis, and it puts too much emphasis on the value of MRI as a diagnostic tool.

A similar reasoning may apply for peripheral SpA trials. This group of patients is far more heterogeneous than that of axial SpA, and the course of disease may vary considerably per subgroup of starting criterion. Undoubtedly, it will be far more difficult to enrol patients in a peripheral SpA trial, but stratified randomization is nevertheless highly recommended.

It is a generic principle to include patients with relatively active disease in a trial since these patients usually need treatment most. There is a methodological argument pointing to better discrimination between treatment arms if patients with high disease activity are included, but this phenomenon is sparsely investigated and may not be relevant anyway. If an entry criterion for disease activity is used though, it should be an ASDAS-based criterion for axial SpA and for example, a joint count or an enthesitis score or dactylitic joint count for peripheral SpA.

In terms of outcome assessment we think the focus will change from ASAS20 response to ASDAS and MRI response as primary outcome measures. ASDAS response is conceptually close to ASAS20 response but includes CRP and has shown to be more discriminatory. MRI provides valuable additional information about inflammation that has been shown to be partly independent of clinical information only, but more importantly MRI provides useful information about the development of fatty infiltrations as a sequel of inflammation, and potentially as a surrogate for syndesmophyte formation in the spine and ankylosis in the SI-joints. Therefore, we recommend RCTs with MRI of the sacroiliac joints as well as the spine, for example at entry and after 6 weeks and 6 months. MRI of the sacroiliac joints and the spine is an appropriately validated technique with sufficient reproducibility and appropriate scoring methods that have proven their value many times [40,41]. T1-weighted sequences and STIR sequences are sufficient, and gadolineum administration is considered redundant [42].

Furthermore, these trials should include measures for physical function and spinal mobility, as is usual in RCTs in patients with AS. At last, baseline and 2-year x-rays of the spine should be included, so that syndesmophyte formation can be monitored.

Outcome assessment in peripheral SpA requires further research. Patients presenting with arthritis may be followed by conventional disease activity and response measures used in RA and psoriatic arthritis. However, very often, these patients will only have a few joints affected, making conventional state and response measures, such as DAS28 and ACR20, less attractive. Whilst MRI is very useful in axial SpA, its value in peripheral SpA is far less obvious. Unlike the arthritis in RA, arthritis in (peripheral) SpA is usually non-erosive and often more transient. Where MRI in the field of RA has the potential of detecting synovitis in clinically otherwise normal joints, it is uncertain if such a scenario exists in arthritis in SpA.

Patients primarily presenting with enthesitis can be assessed by enthesitis measures, for example, the Maastricht Enthesitis Score (MASES) [43], which has been shown to be responsive and discriminative in AS clinical trials with TNF-inhibitors. Alternatively, the HEEL study recently explored and established the value of MRI in monitoring AS patients with heel enthesitis, demonstrated on MRI [44], but it seems unfeasible to follow up more than one or two enthesitic lesions by MRI in the same patient. Currently, research establishing the value of ultrasound in this field is ongoing [45].

In terms of trial duration, trials in axial SpA should include a placebo-controlled phase for 12 to 16 weeks, which should be sufficient to measure a contrast in ASDAS response and MRI response, and is considered ethically justifiable. Long-term extension studies on active drugs should follow this placebo controlled phase, such as in RA and AS.

Limitations

These new concepts for trial design in SpA are definitely advantageous in providing the field of SpA access to research with new treatments, and fulfilling the previously unmet need of patients with non-radiographic SpA. From a methodological point of

view, however, there are also limitations that should seriously be considered.

One of the main concerns is the diagnostic and prognostic heterogeneity of axial and peripheral SpA. We do not precisely know the natural course of patients delineated by the new criteria sets. We do not yet know which proportion of patients diagnosed with early non-radiographic axial SpA will have the same complaints after 5 to 10 years, we do not know the proportion ultimately developing syndesmophytes or other SpA related features. We also do not know which proportion of patients diagnosed with peripheral SpA will follow a chronic course with respect to their arthritis, enthesitis or dactylitis. In line with these limitations, we do not know which patients may need our best treatments and in which patients a 'wait and see' approach, or an approach with local treatments, is justified. We do not know whether the primary outcome measures proposed here are truly the best outcome measures in this field. We also do not know which subgroups of patients will respond best to different treatments, and in which patients' risks and costs may ultimately outweigh benefit, which, from the viewpoint of drug developers, is a serious concern when designing optimal RCTs.

Somewhat paradoxically, though, the only way of providing resolution for these dilemmas is to set out RCTs including the broadest array of patients in carefully chosen (and powered) strata, and the broadest set of potentially useful outcome measures. As an example of this, a future RCT in axial SpA should no longer focus on patients with AS according to modified New York criteria alone, but should include patients classified as having axial SpA, both according to the 'imaging route' as well as to the 'HLA-B27 route' (Figure 1).

Such an approach will have implications for the sample size of the trial (high patient numbers will be required) and the costs of monitoring (MRI will be an obligatory part of the assessment set), but will ultimately pay back in terms of delineating subgroups of patients that are most appropriate for specific treatments.

Concluding remarks

In light of the costs associated with trials in SpA, and the high number of potentially promising new treatments on the radar, it is likely that most of these trials will be initiated by – and performed under auspices of – the pharmaceutical industry. It is highly recommended that such trials are designed and performed in close collaboration with the experts in the field of axial and peripheral SpA, especially since – unlike RA and AS – there is not yet a clear and default framework available in this new and still evolving field of clinical science.

Future perspective

The SpA field is a field in development, which may expect a tremendous boost by the settlement of the new classification criteria for axial and peripheral SpA, and by the clinical trials with TNF-blocking drugs and 'non-TNF-biologicals'. The criteria will need fine-tuning, for example with regard to the cut-off level for a positive MRI of the SI-joints, and it is difficult to predict the efficacy of 'non-TNF-biologicals', but both developments will result in a plethora of useful data to further investigate and try to understand SpA. We believe in the value of prognostication, and better prediction algorithms will be developed based on currently ongoing cohort studies, and putatively including genetics and biomarkers. A primary target will be predicting the formation of syndesmophytes and ankylosis. In analogy to the situation in RA this may ultimately lead to personalized medicine and treat-to-target in SpA.

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Executive summary

- Most trials in the field of spondyloarthritis (SpA) have been conducted in patients with ankylosing spondylitis (AS).
- The average patient with AS in a clinical trial has 5 to 10 years of disease duration.
- TNF-blocking biologicals are effective in reducing signs and symptoms in patients with AS, but do not influence the formation and growth of syndesmophytes.
- Recently, new classification criteria for axial and peripheral SpA have been developed that allow randomized trials to be conducted in patients with early disease.
- The place of MRI and HLA-B27 in the new criteria for axial SpA is very important.
- New trials should include patients based on these new criteria, rather than only patients fulfilling classification criteria for AS.
- New trials should include new measurement instruments such as MRI and the newly developed Ankylosing Spondylitis Disease Activity Score for disease activity.

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