Withdrawal of medical therapies in axial spondyloarthritis: what would be the optimal trial design?

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ABSTRACT

Remission or low disease activity is achievable in patients with axial spondyloarthritis (SpA), and remission has been defined as one of the main targets in treating patients with axial SpA. However, it is unclear what actions should be taken once remission has occurred. Very little data are available concerning the effect of TNF inhibitors (TNFi) dosage adjustment or on withdrawal strategies in patients with axial SpA and/or in patients with ankylosing spondylitis (AS). Most issues relating to withdrawal of treatment in patients who are in remission cannot be addressed with traditional randomised placebo-controlled trials (RCT). Facing these challenges, there is a need for conducting trials with an innovative trial design to reflect real-life practice. Possible strategies upon remission include continuation, dose reduction or withdrawal of the effective therapy. Future scenarios should recognise heterogeneity in patients with axial SpA, which makes it questionable whether different trial designs will be applicable for the whole group of axial SpA. Several questions should be addressed before conducting a trial to study remission in patients with axial SpA: definition of remission (clinical and/or imaging remission), duration of remission as a defining inclusion criterion, predictors of remission, definition of subgroups (e.g. TNFi naïve patients or patients who will most likely remain in remission), when to restart and finally dose-adjustment after restart of the therapy.

Introduction

Disease course and remission in patients with axial spondyloarthritis

The concept of spondyloarthritis (SpA) characterises a disease group with chronic spinal inflammation and extraspinal manifestations such as arthritis, enthesitis, uveitis and inflammatory bowel disease (1). Ankylosing spondylitis (AS) is the main subgroup of SpA and is characterised by established radiographic changes in the sacroiliac joints (SIJ) according to the modified New York criteria (2). Because radiographic damage reflects chronic structural changes, these criteria have considerable limitations in early disease stages. Therefore, new classification criteria for axial and peripheral SpA have been recently developed (3, 4). The Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA require a history of chronic back pain ≥3 months and an age at onset <45 years as entry criteria. Next, either sacroiliitis on x-rays or MRI in addition to at least one typical SpA feature or presence of HLA-B27 in addition to at least two typical SpA features need to be present. Using this set of criteria, two groups of patients can be classified: *a*) having established radiographic changes in the SIJ, *i.e.* classified as AS; or *b*) having not developed radiographic changes in the SIJ, *i.e.* classified as non-radiographic axial SpA (nr-axSpA). At this time, however, most of the knowledge about disease course and effects of treatment options is available for patients with AS.

The disease course of axial SpA is characterised by ongoing axial inflammation and radiographic progression associated with restricted mobility of the spine and decreased function (5). Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and exercise are recommended as first line therapies in patients with axial SpA (6). For those patients who have persistent active disease, the introduction of tumour necrosis factor inhibitors (TNFi) was a major advance in the management of axial SpA (7). The good clinical response to this therapy in the majority of patients correlates with improvements in physical function and health-related

quality of life (HRQoL) (8, 9). In many trials a 20–50% reduction in disease activity could be demonstrated in around 60% of patients (10). Moreover, it has been shown that remission in patients with SpA is achievable. The rate of remission depends on the patient characteristics such as duration of disease, levels of inflammatory markers, and functional status – but studies of this topic are limited to date (11).

In contrast to rheumatoid arthritis (RA), clinical remission and low disease activity has until recently not been defined very well in SpA. Clinical remission/inactive disease should be a major treatment target, as has been defined in the treat-to-target (T2T) recommendations for patients with axial SpA (12). Frequently, the term 'partial remission' is used as defined by the ASAS remission criteria, *i.e.* as defined by the domains of patient global, pain, function and morning stiffness (13). When these criteria are applied, remission can be achieved in about 12–15% of patients with AS treated with NSAIDs, in about 25% of patients with AS treated with TNFi and in about 50% of patients with early axial SpA treated with TFNi (14-18).

In addition to clinical remission, normalisation of inflammatory markers or complete clearance of magnetic resonance imaging (MRI) inflammation ('imaging remission') might be an important outcome in treatment trials as well. It has been shown that CRP is elevated in one third of patients with AS, and that elevated CRP can be used as a predictor for development of structural changes in patients with axial SpA (19). CRP is included in the ASAS-endorsed ankylosing spondylities disease activity score (ASDAS), a new measurement tool for assessing disease activity in patients with axial SpA. Recently, ASDAS thresholds for disease activity states, including inactive disease (equivalent to remission), have been defined (20). In therapeutic trials, it is important to know not only the actual disease status but also the change in disease status, which can be assessed by using improvement scores. With the ASDAS threshold for clinically important improvement as well as the threshold for major improvement, a validated tool has been endorsed to assess the degree of improvement in individual patients.

Although the field of remission in patients with axial SpA is growing, several questions cannot yet be answered, due to lack of evidence. At the moment, there is no agreement about the best definition of remission for patients with axial SpA. Although the ASAS definition of partial remission often is used, its applicability in clinical practice is limited. A major possible limitation is the fact that physical function is included. Consequently, patients with inactive but longstanding disease are not labelled as fulfilling the ASAS partial remission criteria. However, the T2T initiative for SpA defined remission as the combination of a low BASDAI and normal CRP or inactive ASDAS (ASDAS cut-off <1.3) (12). This was based on the notion that normalisation of inflammation is important. Furthermore, it is not clear for how long the patients should be in remission before stoping a treatment.

Controlled trials

While remission is possible in patients with axial SpA, it is unclear what actions should be taken once remission has occurred. Possible strategies include continuation of therapy without change, dose reduction by longer intervals of lower doses, or withdrawal of the effective therapy. If successful, strategies to reduce/withdraw treatment are important not only from the patient's point of view (reduced drug exposure risk) but also because of ethical considerations (reducing costs with no worsening of patient quality of life). Very few data are available on the effect of TNFi dosage adjustment or on withdrawal strategies in patients with axial SpA and/or in patients with AS (21-24).

The issue of withdrawal of an effective treatment is frequently discussed in usual care, but seldom addressed in prospective controlled trials because the optimal trial design is not known. Schwartz and Lellouch suggested that controlled trials can be categorised into two different approaches: the explanatory (also called the efficacy trial) and the pragmatic trial (also called strategy or comparative effectiveness trial) (25). The explanatory approach seeks to understand a biological process by testing the hypothesis that the specified biological response is explained by exposure to a particular treatment. By contrast, the pragmatic approach seeks to compare two treatments under the conditions in which they would be applied in practice.

Most of the issues relating to withdrawal of treatment in patients who are in remission cannot be addressed with explanatory randomised placebo-controlled trials (RCT). There is little argument that the classic parallel RCT with placebo remains the gold standard for establishing the efficacy and short-term safety of an experimental agent. But since information from an explanatory trial often is unlikely to inform a pragmatic question, RCTs need to be adapted for choosing between treatment options (withdrawal or dose reduction strategies).

Clinical trials with an innovative trial design to reflect real-life practice are needed to improve knowledge concening possible withdrawal of therapies in AS. In patients with juvenile idiopathic arthritis (JIA), a RCT with a withdrawal design is often used to test a new drug. In such trials, eligible patients are treated in an open-label manner with the experimental therapy to be tested in the trial for a few months, after which responders are randomised in a double-blind manner either to continue the experimental therapy or to switch to placebo. In this double-blind withdrawal phase, patients who demonstrated a predefined definition of disease worsening are withdrawn from the double-blind withdrawal phase and usually re-treated with the experimental therapy in an open-label manner. Although this trial design is patient- and physician-friendly, the disadvantage is a bias towards responders. Nevertheless, this trial design has proven to be very effective and has been used especially in nearly all recent trials of biologic agents in children with JIA (26). Until now, no such trial conducted in patients with axial SpA has been reported. Nevertheless, RCT with a withdrawal design can be

used in patients with axial SpA to study at least two issues: (i) which patients are most likely to flare with discontinuation of therapy, and (ii) whether dose reduction is an option in patients with axial SpA. Using this trial design, attention should be directed to the possible differences in an optimal strategy between patients with early axial SpA *versus* those with longstanding AS, the likelihood of remission is much higher for patients with early axial SpA than for patients with longstanding disease.

Comparative and adaptive trials

Comparative and adaptive trials are examples of new approaches to complement the classical efficacy RCT. Examples of comparative studies with randomised arms representing two treatments (head-to-head comparisons) have been published in RA (27, 28). Both studies illustrate the motivating feature for clinician and patient that a previously tried and failed therapy was not used as the comparator. Studies in SpA are pending. The enthusiasm for more comparative studies is countered by the recognition of the impact of the required sample size when moving from placebo to active comparator arm with a non-inferiority design. A reduced dosage of an effective drug as an active comparator is an option to further evaluate. A withdrawal trial with three arms (continuation of medication, reduced dose of a medication, and stop of a medication) may be considered as a trend-setting trial design.

Adaptive trials allow adaptation to a trial after its initiation without undermining the validity and integrety of the trial (29). Adaptive trials provide a prospectively planned opportunity for modification of one or more specific aspects of the study design. In patients with RA, a DAS-driven treatment adaptation used in randomised trials showed a significantly greater DAS reduction and higher likeliness to achieve remission in the intensive disease management compared to the standard of care treatment (30). There are various adaptive trial designs of which biomarker-driven studies could be important also in patients with SpA. Since biomarker-driven studies face substantial challenges for the trial design (correct patient population, inaccuracy of disease phenotype in heterogeneous diseases, variability in patient profiles), the use of adaptive designs and biomarker-driven studies is not established in patients with SpA. Examples from studies in oncology illustrate the potential benefit in matching drugs with predictive biomarkers for future application to smaller but more focused phase III studies (31). But the biomarkers reported so far in patients with SpA are far behind predictive properties to be fulfillled if used in adaptive trials in patients with SpA.

Future scenarios

Numerous questions should be addressed before conducting a trial to study aspects of remission in patients with axial SpA: definition of remission (clinical and/or imaging remission), duration of remission as a defining inclusion criterion, predictors of remission, how to deal with patients with low disease activity, definition of subgroups (*e.g.* TNFi naïve patients or patients who will most likely remain in remission), definition of when to restart, and finally dose-adjustment after restart of the therapy. One of the first topics for research seems to be the predictors of subgroups of patients who are most likely to remain in remission after dose reduction or withdrawal. Such a possible subgroup might be patients naïve to TNF inhibitors compared to patients who have already failed to respond to TNF inhibitors. In a non-controlled/non-randomised trial with rituximab in patients with AS, the subgroup of TNFi-naïve patients performed better compared to the TNFi-failure group (16). In the future there might be some other subgroups of patients who will be able to reduce or to stop a treatment regimen.

One way to address this topic is to define predictors of the benefit of a treatment. Some trials that have been published recently showed that short disease duration, signs of inflammatory activity and early achievement of remission are promising variables (32-34). These factors could also be investigated as predictors for sustained remission after dose reduction/withdrawal.

At this time, there is no agreement on the period of time a patient should be in remission when considering to stop or to reduce the medication. Again, this is an important topic for research: does the duration of being in remission predict the propability of sustained remission after withdrawal?

A definition of when to restart treatment is also an important consideration in a withdrawal design. In principal, this is the primary outcome of the trial: the number of patients failing sustained remission. If ASDAS is the definition of remission, no longer being in inactive disease (ASDAS >1.3), reaching high disease activity (ASDAS >2.1), or showing a worsening of 1.1 (the reciprocal of a clinical important improvement) are all options with advantages and disadvantages. For patients who relapse after being in remission, adequate trial designs should address the questions regarding the optimal dose after restart of a specific treatment, and investigators should examine whether a specific treatment is efficacious again after restart. Trials comparing three arms – continuation, dose reduction, or withdrawal of the effective therapy – appear to be a valid withdrawal design in patients with axial SpA. Ideally, these trials should be placebo controlled so they can be double-blind. However, a strategy, "adaptive" trial, with prespecified protocol, can be more informative – perhaps double-blind is less needed with patient outcomes.

Conclusion

The investigation of withdrawal strategies is important for patients with axial SpA but the concept is not easily assessed in this patient population. RCTs with a placebo-arm are useful to assess efficacy of drugs but are not aligned to follow a strategic approach. Thus, innovative approaches to trial design are needed to complement the efficacy trials. RCTs with a withdrawal design are a step forward to test withdrawal in patients with axial SpA. Comparative and adaptive trials offer the opportunity of realising more targeted management in explanatory and pragmatic trials. In that light, well-designed and effective pragmatic trials offer an additional

opportunity to optimise use of current and future treatments. Future scenarios should recognise heterogeneity in patients with axial SpA, define subgroups of patients who are more likely to respond better to a specific treatment strategy, and might use a three-arm double-blind placebo-controlled trial design comparing continuation, dose reduction, and withdrawal of the effective therapy in patients with axial SpA.

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