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Spontaneous, drug-induced, and drug-free remission in peripheral and axial spondyloarthritis

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Abstract

In Spondyloarthritis (SpA), spontaneous remission is best described in Reactive Arthritis, a form of peripheral SpA. Prior SpA observational studies suggested a significant percent of patient reached spontaneous remission; however, these patients were followed under older, broader European Spondyloarthropathy Study Group (ESSG) criteria or were not defined by specific criteria. In general they were mixed populations of peripheral and axial disease and subsets were not differentiated when assessing endpoints like remission. There is limited data on the natural history of axial SpA, in part because of the evolution of the criteria with the more recently developed Assessment of SpondyloArthritis international Society (ASAS) criteria, including the designation of non-radiographic Axial SpA and peripheral SpA. Clinical trials have been done with various remission endpoints including withdrawal of therapy to determine remission maintenance. The following review will address the potential for remission in axial and peripheral SpA based on the data from both observational studies and clinical trials.

Keywords

ankylosing spondylitis; non-radiographic axial spondyloarthritis; peripheral spondyloarthritis; reactive arthritis; treatment; remission

1. Introduction

Spondyloarthritis (SpA) is an umbrella term for a group of diseases sharing common clinical and genetic features, such as involvement of the axial skeleton (sacroiliac joints and spine), certain patterns of the peripheral joint involvement (asymmetrical mono- or oligoarthritis, predominantly of the lower limbs), presence of enthesitis, dactylitis, characteristic extra-articular manifestations (acute anterior uveitis, psoriasis, inflammatory bowel disease), and

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association with the presence of HLA-B27. Depending on the predominant clinical manifestations, SpA patients can be classified either as axial SpA (predominant axial manifestations with involvement of the spine and/or sacroiliac joints), or as peripheral SpA (predominant peripheral joint involvement: arthritis and/or enthesitis and/or dactylitis) [1]. Axial SpA includes two major forms of the disease, which are covered by the Assessment of SpondyloArthritis International Society (ASAS) classification criteria [2] with the latter stage meeting the 1984 modified New York criteria [3]: non-radiographic axial SpA - nr-axSpA (a non-radiographic form/stage of the disease, without or with only minimal structural changes in the sacroiliac joints and in the spine on X-rays), and ankylosing spondylitis (AS), a radiographic form/stage of axial SpA, with definite sacroiliitis on X-rays. An overall progression rate from the non-radiographic to radiographic stage is estimated as approximately 12% over two years [4], although there are patients who remain at the nonradiographic stage for years. The major predictor of such a progression is high inflammation (as reflected by an elevated C-reactive protein (CRP) [4] and/or presence of active inflammation in the sacroiliac joints as detected by magnetic resonance imaging (MRI) [5]), such that patients with lower inflammatory disease activity are less likely to develop structural damage in the sacroiliac joints. Indeed, a number of observational studies demonstrated that elevated CRP is less frequent among patients with non-radiographic axial SpA as compared to AS [6–8]. Also, the proportion of females is significantly higher among patients with non-radiographic disease as compared to AS [6–8] indicating that females are more likely to have a milder radiographic, disease course, though with similar patient-reported outcomes [6–8]. Regarding other disease-related parameters there are no reported differences between nr-axSpA and AS supporting the concept of axial SpA as one disease [9]. Importantly, treatment trials with tumor necrosis factor α (TNFα) inhibitors demonstrated that clinical response to therapy is nearly equal in nr-axSpA and AS if patients in both groups are comparable regarding the presence of objective signs of inflammation (elevated CRP and/or active inflammation on MRI) at the beginning of the treatment [10, 11]. In Europe, TNFα inhibitors are approved by the European Medicines Agency (EMA) currently for treatment of clinically active nr-axSpA not responding to non-steroidal anti-inflammatory drugs (NSAIDs) only if objective signs of inflammation (elevated CRP and/or positive MRI) are present. In the United States, however, the Food and Drug Administration (FDA) did not approve TNFα inhibitors for this indication with several concerns, including the possible self-limiting disease course of nr-axSpA with a rather undetermined rate of spontaneous remissions.

Another two important and closely related questions in the context of the current discussion around axial SpA are 1) whether early treatment with TNFα inhibitors might increase response / remission rates and 2) whether a drug-free remission (meaning no flare after discontinuation of the drug therapy) could be achieved with early treatment. In this review we summarize the recent data on spontaneous, drug induced and drug-free remission in axial and peripheral SpA from clinical trials and observational studies. Remission in psoriatic arthritis was out of the scope of this work and is discussed elsewhere.

2. Definition of remission in spondyloarthritis

The definition of remission in axial and peripheral SpA is quite challenging. Ideally, remission of a disease is achieved if no signs and symptoms are present. In reality, however, a reasonably low level of symptoms (most likely corresponding to the “background noise” – the level of symptom that could be observed in healthy individuals) is usually chosen in order to define remission. Currently, there is no widely accepted definition of remission in peripheral SpA (except psoriatic arthritis, which is not in the focus of the current review), while in axial SpA remission can be defined in several ways (table 1). The first definition of remission is based solely on the level of clinical symptoms and does not consider objective signs of inflammation. The most widely used definition of that kind in the ASAS (Assessment of SpondyloArthritis International Society) partial remission criteria [12]. This is defined as a value ≤ 2 (on a 0 to 10 scale) in each of the following 4 domains: patient global, pain, function (the Bath Ankylosing Spondylitis Functional Index – BASFI [13]) and inflammation (mean of the Bath Ankylosing Spondylitis Disease Activity Index – BASDAI questions 5 and 6 – related to morning stiffness). This definition has been used in the majority of clinical trials in AS and axial SpA performed in the past decade. However, the ASAS partial remission criteria are composed of purely subjective measures without the presence of objective disease activity like the CRP or inflammation on the MRI. In addition, some AS patients demonstrate presence of objective signs of inflammation despite minimal clinical symptoms. This resulted in the development of a harder definition of remission, which consists of the ASAS partial remission criteria plus absence of inflammation on MRI of the sacroiliac joints and of the spine. Such a definition was used in the ESTHER (Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI) trial [14].

Recently, an ASAS endorsed AS disease activity index (ASDAS), which includes 4 clinical (spinal pain, morning spinal stiffness, peripheral arthritis, and patient global assessment of disease activity) and one objective (CRP or erythrocyte sedimentation rate – ESR) disease activity parameters has been developed [15]. ASDAS of <1.3 indicates inactive disease in AS / axial SpA that corresponds to remission [16]. Achievement of a remission or inactive disease was recently emphasized as a major treatment target in SpA in the treat-totarget recommendations [17].

3. Rates of the drug-induced and drug-free remission in axial and peripheral spondyloarthritis in the clinical trials

According to the current treatment recommendations only two drug classes plays a major role in the treatment of patients with axial and peripheral SpA: non-steroidal anti-inflammatory drugs (NSAIDs) and TNFα inhibitors [18]. Classical disease modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine or methotrexate are usually ineffective in axial disease but may be beneficial in peripheral disease. Systemic glucocorticoids in SpA are generally not recommended and should only be considered as a short-term (i.e., bridging) treatment option, usually with high doses necessary for efficacy [19].

NSAIDs are considered as a first line therapy in both axial and peripheral SpA, although the vast majority of clinical trials in support of their efficacy were performed in established AS. Good or very good improvement of the AS symptoms is usually reported by 60–80% of the patients treated with NSAIDs, while in patients with chronic low back pain of noninflammatory causes such a response is only reported by about 15% of patients [20]. In a recent survey performed in Germany, almost 20% of the AS patients reported complete pain control with NSAIDs and another 60% of the patients reported a level of pain reduction from one quarter to one half [21]. There are few NSAID trials in axial SpA / AS rarely used remission as an outcome parameter. In a study by van der Heijde, et al, ASAS partial remission criteria was achieved by 14.7%, 17.6%, and 9.1% of the AS patients who received etoricoxib – a selective cyclooxygenase-II inhibitor, not approved in the United States – 90 mg, etoricoxib 120 mg, and naproxen 1000 mg per day, respectively, for 6 weeks (table 2) [22]. In contrast, only 3.2% of the placebo treated patients achieved partial remission in this study.

In the recently published Infliximab as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST), patient with early axial SpA (both AS and nr-axSpA with symptom duration up to 3 years) not refractory to NSAIDs were randomized in a double-blind fashion at a 2:1 ratio to receive either intravenous infliximab 5 mg/kg at weeks 0, 2, 6, 12, 18, and 24 plus naproxen 1000 mg per day or intravenous placebo plus naproxen 1000 mg per day. In the placebo plus naproxen arm, 15.7% of the patients achieved ASAS partial remission at week 6, while at week 28 the proportion of patients in remission in this arm was 35.3% [23]. ASDAS inactive disease state at week 28 was achieved by 19.6% of naproxen-treated patients. These data indicate that achievement of remission with NSAIDs is possible in some patients with axial SpA.

Despite good efficacy of NSAIDs in axial SpA, a large proportion of patients have inadequate clinical response. TNFα inhibitors are currently the only other approved treatment option. In the pivotal phase III studies with TNFα inhibitors (infliximab, etanercept, adalimumab, and golimumab) in more advanced AS (mean disease duration around 10 years throughout the studies), 17 to 23 percent of patients achieved ASAS partial remission after 24 weeks of treatment (table 2) [24–27]. For comparison, the rate of remission in the placebo arms of these studies ranged between 1.3% and 5.6% with statistically significant differences across the studies [24–27]. The placebo group partial remission frequencies can be considered as the rate of spontaneous remissions in patients with more advanced AS who do not respond to conventional therapy (NSAIDs).

There are factors found to be associated with good clinical response to TNFα inhibitors in patients with AS, including short disease duration, younger age, lower level of functional disability (as reflected by lower BASFI), elevated CRP and active inflammation in the axial skeleton on MRI [28, 29]. In addition, HLA-B27 positivity and TNFα inhibitor naivety were identified to be predictors of good clinical response in a large open-label study with adalimumab in AS patients (RHAPSODY) [30]. In the light of these data several trials with TNFα inhibitors in patients with early axial SpA were performed.

In a study by Barkham et al., patients with early axial SpA (symptom duration ≤3 years, ~80% of the patients were in the non-radiographic stage) with presence of active sacroiliitis on MRI were treated with infliximab. At week 16, 55.6% of the infliximab-treated patients (12.5% in the placebo arm, p = 0.009) achieved ASAS partial remission [31]. Similar results were obtained in the INFAST trial, in which patients with early axial SpA (symptom duration ≤3 years and 40% with non-radiographic disease) demonstrated a 62% ASAS partial remission responses and 51.4% ASDAS inactive disease rate at 28 weeks of treatment with infliximab plus naproxen [23]. In an investigator-initiated open-label trial (ESTHER) with etanercept versus sulfasalazine in early axial SpA (symptom duration <5 years, about half of the patients had non-radiographic disease), a 50% ASAS partial remission rate was achieved with etanercept at week 48 (19% with sulfasalazine. P = 0.006) [14]. A stricter defined remission based on a combination of clinical (ASAS partial remission) and imaging (no inflammation in the sacroiliac joints and in the spine on MRI) was achieved by 33% of etanercept-treated patients – table 2 (as compared to 11% in the sulfasalazine arm, p = 0.03) [32]. These data confirmed that earlier anti-inflammatory treatment of active axial SpA is indeed associated with a better clinical response (with a clinical remission rate of about 50% as compared to 20–25% in more advanced disease).

In the most recent studies, the early disease stage in axial SpA was defined as an absence of structural damage in the sacroiliac joints (no definite radiographic sacroiliitis) or a combination of no damage with short disease duration. In the first trial of that kind (ABILITY-I – a phase III trial with adalimumab in patients with nr-axSpA) adalimumab treatment for 12 weeks was associated with a somewhat disappointing ASAS partial remission rate of 24% and ASDAS inactive disease rate of 16% (in the light of the data from trials in early axial SpA) – table 2 [33] (placebo response: 5% and 4% respectively, p<0.05 for both endpoints). Remarkably, the mean symptoms duration in this study population was 10 years and only 40% of the patients had elevated CRP that might at least partly explain the weaker results. In this trial, in patients with shorter disease duration, elevated CRP and/or active inflammation on MRI (factors identified as good predictors of clinical response to TNFα inhibitors in more advanced AS), the clinical response to adalimumab was significantly better [33]. This resulted in the approval of adalimumab by the EMA for treatment of nraxSpA with both clinical and objective (elevated CRP and/or inflammation on MRI) signs of disease activity and inadequate response to NSAIDs.

In another study (RAPID-axSpA, a phase III trial), a mixed population of patients with active axial SpA (~55% with AS and ~45% with nr-axSpA), were treated with certolizumab pegol. In this study, no limitations regarding symptom duration were applied (mean symptom duration was 7.7 years), but all patients had either an elevated CRP and/or active sacroiliitis on MRI. At week 24, about 24% of the certolizumab-treated patients achieved ASAS partial remission and about 31% had ASDAS inactive disease state – (table 2) [11]. In the placebo arm, 3.7% achieved these responses, p<0.05 for all comparisons of certolizumab vs. placebo). Based on these data certolizumab pegol was granted with an approval for AS and nr-axSpA in Europe with the same limitations regarding objective signs of active inflammation on MRI as adalimumab.

Importantly, response rates in the RAPID-axSpA study were comparable in nr-axSpA and in AS patients [11, 34]. Similar data on equal clinical response to anti-TNFα therapy in AS and nr-axSpA were observed earlier in the ESTHER study [10]. Therefore patients with nr-axSpA and AS respond similarly well to therapy with TNFα inhibitors if the level of inflammation at baseline is similar.

In the most recent TNFα inhibitor study in nr-axSpA, (B1801031, phase III trial), etanercept was given to patients with active axial SpA with symptom duration of less than 5 years. At week 12, 40% of the etanercept treated patients achieved ASDAS inactive disease state (table 2), [35] (17.4% in the placebo group, $p<0.001$). Again, the response was in general better in patients with elevated CRP and active inflammation on MRI [35]. An approval for etanercept for the indication “nr-axSpA” is expected this year in Europe. A similarly designed phase III study with golimumab in nr-axSpA is currently ongoing. Thus, based on the available data, drug induced remission is possible in up to one third of patients with axial SpA treated with NSAIDs and more than 50% of the patients treated with TNFα inhibitors, especially if treated early. The next question is, whether the remission achieved would sustain upon discontinuation of the anti-inflammatory therapy (drug-free remission), first in relation to anti-TNFα therapy. In AS the relapse rate after discontinuation of TNFα inhibitors ranges from 73% in a study with the follow-up period of 18 weeks [36] to 100% in case of a longer follow-up (up to 1 year) [37, 38]. It appears that duration of previous therapy has no impact on the probability of disease relapse in AS. In the vast majority of cases a good clinical response is observed after re-administration of TNFα inhibitors in case of flare, though there is concern that repeated drug holidays would result in anti drug antibodies formation and subsequent secondary loss of response similar to what was seen in Crohn’s disease [39].

In early axial SpA, drug-free remission rates might be better than in more advanced disease. In the ESTHER trial, patients who achieved a remission (ASAS partial remission plus no inflammation on MRI) at week 48 (13 patients in the etanercept arm and 4 patients in the sulfasalazine arm) entered a 48-week follow-up period. After 48 weeks, 23% (3/13) of the patients from the etanercept arm and 25% (1/4) from the sulfasalazine arm, remained in remission [32]. These data indicate that treatment modality used for remission induction (i.e., TNFα inhibitors with NSAIDs versus NSAIDs alone) does not predict remission maintenance after drug discontinuation. All patients who flared received etanercept with a good clinical response [32].

In the INFAST study, patients achieving ASAS partial remission at week 28 (end of Part 1 of the study) continued to Part 2 and were randomized (1:1) to naproxen or no treatment until week 52. At week 52, similar percentages of patients in the naproxen group (47.5%, 19/40) and in the no-treatment group (40.0%, 16/40) maintained partial remission [40]. A relatively high proportion of patients who remained in the remission might be explained by a shorter follow-up period (24 weeks), in comparison to ESTHER study, for example, in which mean time to flare was 24.4 weeks for etanercept and 39.6 weeks for sulfasalazine patients [32]. Nonetheless, INFAST data indicates that use of NSAIDs does not protect patients with axial SpA from flare after discontinuation of TNFα inhibitors.

Although complete discontinuation of anti-TNFα therapy in axial SpA patients who are in remission cannot be generally recommended due to a high risk of a flare, a dose reduction or increase of the time interval between injections / infusions might be a reliable option for some patients in order to decrease risks related to therapy and to minimize costs [41]. Such an approach is being used by some rheumatologists in clinical practice, but many questions remain open, i.e., how long should remission sustain prior to start of the dose reduction / interval increase, what are predictors of non-relapse, what are the steps in the reduction of the dose or injection interval increase. In addition, increased dose intervals, have the theoretical risk of being associated with anti-drug antibody formation, though this is not well studied in axSpA. Several drug classes (i.e., a monoclonal antibody against interleukin-17 secukinumab [42], a monoclonal antibody against interleukin-12/23 receptor, ustekinumab [43], a phosphodiesterase-4 inhibitor, apremilast [44]) demonstrated some promising results in pilot or proof-of-concept trials in AS, but larger placebo controlled trials are needed in order to demonstrate their efficacy in remission induction in axial SpA.

So far, there is only one relatively small clinical study reporting remission rates in patients with peripheral SpA (fulfilling the European Spondyloarthropathy Study Group or Amor criteria but not the criteria for AS or psoriatic arthritis) treated with a TNFα inhibitor (adalimumab) [45]. Due to lack of specific remission for peripheral SpA, ASDAS inactive disease definition was used in this study. After 12 weeks of adalimumab treatment, 42% of the adalimumab treated patients (n=19) achieved ASDAS inactive disease (as compared to 0% in the placebo group, n=19) [45]. Until this study, no data on drug-free remission after discontinuation of TNFα inhibitors existed for patients with peripheral SpA.

Patients with reactive arthritis (ReA) can be classified as patients with peripheral spondyloarthritis [1]. Although the natural course of the disease is believed to be benign with a high rate of spontaneous remissions [46] (discussed in more details below), in some patients the disease may become a chronic disabling disorder. There is only little data regarding remission induction in ReA with conventional anti-rheumatic drugs. Egsmose et al. found no significant differences in remission rates at 6 months between sulfasalazine and placebo treated patients with ReA in a small controlled study, although there was a a non-significant trend in favor of sulfasalazine [47]. The antibiotic data for ReA is controversial and heterogeneous [48]; the use of antibiotics could be recommended only in patients with evidence of persistent infection (e.g., *Chlamydia trachomatis*). There is no evidence to support antibiotic treatment in those patients whose inciting infection is an enteropathic organism.

4. Remission rates in axial and peripheral spondyloarthritis from observational studies

The observational data in Spondyloarthritis is more heterogeneous because of the variable criteria (or lack of criteria) used for enrollment. In addition, the criteria have evolved over the last 3 decades since the first study was published in the 1980s. Older studies used the European Spondyloarthropathy Study Group (ESSG) criteria to classify patients or selected patients based on SpA related features (i.e. HLA-B27 and inflammatory back pain or oligoarthritis). Few studies were designed to study remission rates, but rather how many of

these less differentiated SpA patients evolved to a more defined SpA, like AS. Because of the nature of observational studies, patients were often lost to follow up, especially with longerterm studies. Was this because their disease remitted? Does this reflect the demographic of SpA patients (who often self-treat with over-the-counter NSAIDs and exercise), or is this within the expected rate of attrition in observational studies? Based on observational data in rheumatoid arthritis, one can expect to lose a stable 4.3% of subjects per 6 months of longitudinal follow up [49]. Therefore a 10-year study might be expected to lose more than 80% of its subjects, such that the studies referenced here have acceptable retention. Newer criteria have been developed by the ASAS group [1] to separate axial from peripheral SpA and to be inclusive of axial SpA that does not meet the modified New York criteria. There are no published data from observational studies on remission rates in patients with axSpA specifically. All studies have a mix of axial and peripheral SpA not separated by subtypes. Even in the observational studies, many patients were exposed to pharmacologic interventions, except that medications specifics were not documented in terms of dose, duration or remission induction.

Schattenkirchner et al. studied patients with HLA-B27 positive arthritis or oligoarthritis [50]. Symptom duration was not documented and 119 subjects were followed for 2–6 years. Over 90 per cent of enrolled subjects had follow up data and 21% of subjects in the cohort were reported in remission (defined as an asymptomatic state). It was not specified if this was a drug-induced, drug-free or spontaneous remission and no medication data was reported. Sampaio-Barros et al. published 2 papers 9 years apart on the natural history of their Brazilian cohort of patients with “undifferentiated” SpA [4,5]. These patients met the ESSG criteria but not specific sub types at the time defined as AS or Psoriatic Arthritis. The frequency of HLA B27 was lower than is expected for patients with axial SpA (54% and 61% in the 2001 and 2010 studies respectively). The cohort was not defined by axial or peripheral predominant disease. In the initial study, the authors followed 68 patients with an average of 5 years disease duration for 2 years to assess for evolution to a defined subtype and whether patients went into a drug-free remission [4]. Remission was defined as an asymptomatic state without medications for at least 6 months and a normal pelvis radiograph. Of the 68 subjects, 13% went into remission. It is unclear whether a portion of patients reaching remission did this spontaneously as no medication data was reported. In a second study, the authors reported data from 111 patients with SpA, who were followed for 5, 7 or 10 years [5]. All patients took NSAIDs, though the dose and duration was not defined. One third of patients took systemic glucocorticoids; one third took methotrexate and almost two-thirds took sulfasalazine during the study period. No patients were placed on biologic agents. Subjects were considered in remission if they were in an asymptomatic state for at least one year without medications. Of the 111 subjects, 22.5% reached a remission state at some point during the follow up period, presumably drug-induced. It is, therefore unclear, how many of these patients achieved their remission spontaneously.

Spontaneous remission has not been formally defined in the literature. However, it is generally accepted that resolution of symptoms and signs of disease activity without the use of pharmacologic intervention would be consistent with a spontaneously remissive state. There are no studies that specifically address spontaneous remission in axial SpA. The few observational mixed studies did not document medication intake and when there was report

of pharmacologic intervention, details were absent. In ReA, most studies do not specifically document the absence of pharmacologic intervention to address the question of spontaneous remission. Because first line therapy in ReA is NSAIDs, and these are may be available without prescription, we are not able to address this question fully.

Noer studied 10 cases of ReA following a Shigella outbreak. Of these subjects, 6 returned to full active duty - the assumption that they were in a spontaneously remitted state [51]. Calin et al. followed up these subjects at 13 years. The authors were only able to contact 5 of the 10, but of these, 4 had developed a chronic arthritis (and all of these more persistent cases were HLA B27 positive) - table 3 [52].

In a 25-year follow-up study in 155 subjects with ReA, approximately 75% had reached complete remission by 2.5 years, though flares did occur in some after initial remission [46].

The same group assessed the natural history of salmonella associated ReA in hospitalized subjects. There were 63 cases and 50 of these were evaluated in follow up at a mean of 11 years. Forty percent were in complete remission and another 20% had mild joint symptoms, while 16% had developed a chronic SpA (table 3) [53].

In 2011, Thomson et al. studied the 27 subjects that had developed ReA 5 years after a salmonella outbreak. One third had gone into complete remission within 4 months of onset. On physical examination 37% were found to have some articular changes consistent with arthritis, though specifics of this are not documented [54]. Uotila et al. studied 21 subjects that had developed salmonella associated ReA at one year. Though most subjects were in remission, one-third required traditional DMARDs at one year (table 3) [55]. There is little data on the remission rates in Chlamydia associated ReA.

Based on these heterogeneous studies (both because of associated microorganisms and study design), approximately 60% of patients go into remission within 6 months of arthritis onset.

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Practice points

- Remission is an attainable treatment target in patients with Spondyloarthritis with the majority of data coming from clinical trials in axial Spondyloarthritis and observational studies in peripheral Spondyloarthritis.
- Drug-induced remission can be achieved in up to a third of the patients with axial Spondyloarthritis treated with NSAIDs and in up to a half to two-thirds of the patients treated with TNFα inhibitors, especially if the treatment is initiated early (within first 3–5 years of disease).
- Discontinuation of anti-TNFα therapy upon achievement of the remission in Ankylosing Spondylitis leads to disease flare in the majority of patients within 12 months after treatment cessation. Increased drug intervals and/or dose reduction may be an alternative to complete drug discontinuation for patients in remission. The same may be true for patients with non-radiographic Axial Spondyloarthritis, but more data are needed to confirm this.
- Reactive arthritis as a form of peripheral Spondyloarthritis is characterized by a high rate of spontaneous remissions, while data on the use of antibiotics for remission induction in acute and chronic arthritis are controversial.

Research agenda

- A remission definition in peripheral SpA as well as data on remission induction and maintenance in these patients are urgently needed.
- Early initiation of anti-TNFα therapy might increase the rate of drug-free remission in axial SpA, though it is unclear whether some patient would spontaneously remit (even temporarily) early in disease. More studies aimed at identification of predictors of drug-free remission and predictors of flare if remission is achieved are required.
- The true rates of spontaneous remission in axial Spondyloarthritis (in both nonradiographic and radiographic forms of the disease) as well as factors associated with spontaneous remission should be determined.
- Although there is a concept of “treat-to-target” in axial Spondyloarthritis, no studies have been conducted to date in order to show benefits of such an approach. Furthermore, the number of therapeutic options, which could be used in such an approach, is currently limited in axial Spondyloarthritis.

Summary

There is currently no clear data to support spontaneous remission in axial SpA, but a drug-induced remission may be an achievable target for many patients.. It is not yet clear, whether a patient can maintain drug-free remission if the drug is introduced early enough. There is emerging data that dose reduction may be an option for some patients with axial SpA, including AS. In peripheral SpA, excluding Psoriatic Arthritis, less clinical trial data exists overall. However, based on observational studies using European Spondyloarthropathy Study Group criteria, in patients with a high proportion of peripheral involvement and lower frequency of HLA-B27 than is expected in AS, SpA may be a more remitting disease.

Table 1

Definitions of remission in axial SpA used in the clinical studies.

Type of remission definition	Definition	Definition description	Reference
Clinical	ASAS partial remission	A value of not above 2 (on a 0 to 10 scale) in each of the following 4 domains: • patient global • pain • function (BASFI) • inflammation (mean of the BASDAI questions 5 and 6)	[12]
Clinical plus imaging	ASAS partial remission plus imaging remission	ASAS partial remission criteria as described above plus absence of inflammation on MRI in the sacroiliac joints and in the spine	[14]
Clinical plus lab	ASDAS inactive disease	ASDAS <1.3	[16]

ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = the Bath Ankylosing Spondylitis Functional Index; MRI = magnetic resonance imaging.

Table 2

Drug-induced remission rates in patients with axial spondyloarthritis in the clinical trials

Trial	Population	Remission definition	Drug and dose	N in the respective study arm	Assessment time-point	Remission rate	Reference
NSAIDs							
van der Heijde, et al, 2005	Ankylosing spondylitis with a history of positive therapeutic benefit with NSAIDs	ASAS partial remission	Etoricoxib 90 mg/d	103	Week 6	14.7%	[22]
			Etoricoxib 120 mg/d	92		17.6%	
			Naproxen 1000 mg/d	99		9.1%	
INFAST, 2014	Axial spondyloarthritis (~60% with AS and ~40% with nr-axSpA) with active sacroiliitis on MRI, symptom duration ≤3 years, not refractory to NSAIDs	ASAS partial remission	Naproxen 1000 mg/d	52	Week 6	15.7%	[23]
					Week 28	35.3%	
		ASDAS inactive disease			Week 28	19.6%	
TNFα Inhibitors							
ASSERT, 2005	Ankylosing spondylitis	ASAS partial remission	Infliximab 5 mg/kg iv at weeks 0, 2, 6, 12, and 18	201	Week 24	22.4%	[24]
Davis, et al, 2003	Ankylosing spondylitis	ASAS partial remission	Etanercept 25 mg subcutaneously twice weekly	138	Week 24	17%	[25]
ATLAS, 2006	Ankylosing spondylitis	ASAS partial remission	Adalimumab 40 mg sc every other week	208	Week 24	22.1%	[26]
GO-RAISE, 2008	Ankylosing spondylitis	ASAS partial remission	Golimumab 50 mg sc every four weeks	138	Week 24	23.2%	[27]
RAPID-axSpA, 2014	Axial spondyloarthritis (~55% with AS and ~45% with nr-axSpA) with elevated CRP of active sacroiliitis on MRI	ASAS partial remission	Certolizumab pegol 200 mg s.c. every other week	111	Week 24	23.4%	[11]
		ASDAS inactive disease				29.7%	
		ASAS partial remission	Certolizumab pegol 400 mg s.c. every four weeks	107	Week 24	24.3%	
		ASDAS inactive disease				30.8%	
Barkham, et al, 2009	Axial spondyloarthritis (~80% with nr-axSpA) with active sacroiliitis on MRI and symptom duration ≤3 years	ASAS partial remission	Infliximab 5 mg/kg weeks 0, 2, 6, and 12	20	Week 16	55.6%	[31]

Trial	Population	Remission definition	Drug and dose	N in the respective study arm	Assessment time-point	Remission rate	Reference
INFAST, 2014	Axial spondyloarthritis (~60% with AS and ~40% with nr-axSpA) with active sacroiliitis on MRI, symptom duration ≤3 years, not refractory to NSAIDs	ASAS partial remission	Infliximab 5 mg/kg i.v. at weeks 0, 2, 6, 12, 18 and 24	106	Week 28	61.9%	[23]
		ASDAS inactive disease				51.4%	
ESTHER, 2011	Axial spondyloarthritis (~50% with AS and ~50% with nr-axSpA) with active inflammation on MRI in the sacroiliac joints or in the spine, symptom duration <5 years	ASAS partial remission	Etanercept 25 mg s.c. twice weekly	40	Week 48	50%	[14]
		ASAS partial remission plus no inflammation on MRI				33%	[32]
ABILITY-I	Nr-axSpA, no limitations regarding symptom duration and CRP/MRI	ASAS partial remission	Adalimumab 40 mg s.c. every other week	91	Week 12	16%	[33]
		ASDAS inactive disease				24%	
B1801031	Nr-axSpA, no limitations regarding CRP/MRI, symptom duration <5 years	ASDAS inactive disease	Etanercept 50 mg s.c. weekly	106	Week 12	40%	[35]

ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; CRP = C-reactive protein; i.v. = intravenously; MRI = magnetic resonance imaging; nr-axSpA = non-radiographic axial SpA; NSAIDs = non-steroidal anti-inflammatory drugs; s.c. = subcutaneously.

Table 3

Remission rates in patients with axial and peripheral spondyloarthritis in observational studies

Study	Population	Classification*	Baseline Symptom duration	HLA B27 (%)	Remission definition	N initial evaluation	%N follow up	Assessment time-point (years)	Remission rate	Ref.
General Spondyloarthritis Studies										
Schattenkirchner et al.,1987	HLA B27 arthritis or oligoarthritis	-	ND	100	Asymptomatic state	119	93–96%	2–6	21%	[50]
Sampaio-Barros et al., 2001	uSpA in Brazilian cohort	ESSG	5 years	54	Asymptomatic ≥ 6 months without medications & a normal pelvis x-ray	68	100%	2	13%	[56]
Sampaio-Barros et al., 2010	uSpA in Brazilian cohort	ESSG & Amor	ND	61.3	Asymptomatic ≥ 1 year without medications	111	37.8%	10	22.5%	[57]
Reactive Arthritis Studies										
Noer 1966	Shigella	--	n/a	ND	Full duty (asymptomatic)	10	100	0.5	40–60	[51]
Amor 1979	Salmonella	--	n/a	ND	“complete remission”	155		2.5	75	[46]
Leirisalo et al. 1997	Salmonella	--	n/a	88	Asymptomatic	64	100%	11	50–63	[53]
Thomson et al. 2011	Salmonella	--	n/a	22	Asymptomatic	27	n/a	5	1/3 – 2/3	[54]
Uotila et al. 2013	Campylobacter & Salmonella	--	n/a	4.8	“complete remission”	n/a	21	1	50–60	[55]

SpA = Spondyloarthritis; IBP = Inflammatory Back Pain; uSpA = Undifferentiated Spondyloarthritis; ESSG = European Spondyloarthropathy Study Group; AS = Ankylosing Spondylitis; ND = Not documented; ReA = Reactive Arthritis

*No classification criteria for ReA