The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis

J. Zochling, J. Brandt and J. Braun

Key words: Undifferentiated spondyloarthritis, Spondyloarthritis, Management, Anti-TNF therapy.

In a recent international workshop for ankylosing spondylitis (AS), a consensus was reached that the term ‘spondyloarthritis’ is preferable to ‘spondyloarthropathy’, to emphasize the inflammatory nature of these diseases [1]. The term is often quoted in the plural form, ‘the spondyloarthritides’, accentuating that this is a group of similar diseases with distinct clinical features and a common genetic predisposition, rather than one disease with different clinical presentations. The main association recognized is with HLA B27 but it is clear that there are other genes involved, including the interleukin-1 family gene cluster [2, 3].

Irrespective of the subtype of spondyloarthritis (SpA), the main clinical manifestations of this group are inflammatory back pain (IBP), peripheral arthritis, enthesitis and anterior uveitis, while other organ manifestations are rare. Psoriasis and inflammatory bowel disease (IBD)-associated colitis should be considered as basic subtype-defining entities with their own genetic background, rather than as disease manifestations.

Five major subtypes of SpA are recognized on the basis of recently proposed classification criteria (European Spondyloarthritis Study Group [ESSG]). In recent years we and others have defined the subgroups as AS, psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD) and ‘undifferentiated’ SpA (uSpA). This terminology suggests that it is intended to, for example, include the whole group of patients with psoriasis-associated arthritis. Even on the basis of the ESSG criteria, this is certainly not correct and it is well recognized that there are different subtypes of PsA, including patient groups that rather resemble rheumatoid arthritis or osteoarthritis. Therefore, it is much clearer to choose another terminology, which is hereby introduced. The subtypes are ankylosing spondylitis, psoriatic SpA (PsSpA), reactive SpA (ReSpA), SpA associated with inflammatory bowel disease (SpIBD) and uSpA.

Alongside AS, uSpA is the most common subtype of the spondyloarthritides [4, 5] with a prevalence between 0.7% and 2.0% [5–7], and yet we know less about it than the other subtypes. This is often the case when new disease classifications emerge, and it can be difficult to retrospectively assess disease prevalence and associations from studies designed to address different disease classifications. This review aims to outline the current concept of SpA and uSpA, the latter in more detail, looking at its clinical features and natural history and the current evidence for therapy.

Classification of spondyloarthritis

The clear definition of uSpA as a clinical entity separate from other spondyloarthritides is a part of the current disease classification schema. Historically, there have been numerous changes in the classification of what we now recognize as SpA, as we have learned more about disease mechanisms and the effects of therapy. In 1957 the International League against Rheumatism (ILAR) first described a group of ‘atypical rheumatoid arthritis’ [8] including AS, arthritis associated with psoriasis (PsA) and ReA, grouped together as a pot pourri of inflammatory arthritides that did not conform to the symmetrical polyarthritis phenotype of rheumatoid disease, rather than as a group with common features. Over the years it was realized that this classification did not address the clinical similarities of the atypical group, including a predilection for spondylitis and sacroiliitis, enthesitis and extra-articular manifestations such as acute uveitis and inflammatory bowel lesions. Moll et al. [9] first described the ‘seronegative spondyloarthropathies’, being rheumatoid factor-negative but sharing common clinical, radiological and genetic features.

The changing scope of SpA terminologies has made it difficult to compare studies. It is very likely that the incomplete Reiter’s syndrome described by Arnett et al. in the 1970s [10] would today be reclassified as uSpA; in the absence of evidence of preceding infection, it is unknown if such patients were really ReA with an undefined trigger, or what we now recognize as uSpA.

The need for a standardized, evidence-based approach to classification led to the development of the ESSG preliminary classification criteria for spondyloarthropathy [11]. This introduces the unifying concept of SpA as a group of related diseases with common features (Table 1). In the last 10 yr the work of this historical group has been taken over by the Assessments in AS (ASAS) working group, which is currently working on a novel set of criteria on the basis of recent statistical calculations and a probability model [12]. One aim of this enterprise is to include magnetic resonance imaging (MRI) in the criteria set.

The ESSG classification criteria for SpA have been well studied and validated in population studies [13–16] and have a good sensitivity of 75% and a specificity of 87%. An alternative classification scheme was put forward by Amor et al. [17] (Table 2), which is more complicated but gives improved sensitivity (85%) and specificity (90%), due to the incorporation of common extra-articular manifestations of disease, including...
A patient is considered as having a spondyloarthopathy if the sum of the scores is 6 or more. The basic concepts underlying each classification set are nevertheless similar.

It is important to remember that these were developed as classification criteria, not diagnostic criteria. Although they are useful for epidemiological studies they are not necessarily ideal for daily clinical practice, where the spectrum of disease is wider and where it is especially important to include patients in very early disease stages. Therefore, it is important to stress that the ESSG criteria have been shown to lose both sensitivity and specificity when disease has been present for less than 12 months. Nevertheless, it has been suggested and it seems clear by the way rheumatologists refer to it that the classification might be a useful guide in a clinical setting [18, 19], depending on the underlying prevalence of disease. Thus, for practical and pragmatic reasons the criteria are often used in clinical practice and it can be expected that the new criteria set will also be used in clinical practice, provided it is easier to use than the previous set.

Clinical manifestations of uSpA

A patient is considered as suffering from uSpA if he/she fulfils the criteria for SpA as defined by either the ESSG or the Amor criteria, without evidence suggesting a more specific disorder, such as AS (as classified by the modified New York criteria; Table 3 [20]), psoriasis, IBD or evidence of a preceding bacterial infection trigger. More simply, a patient with either IBP or peripheral arthritis who also has evidence of current or previous enthesopathy or alternating buttock pain would be classified as uSpA. There are no pathognomonic clinical features for uSpA, and the absence of diagnostic tests for any of the spondyloarthritides requires diagnosis to be made on a combination of history, clinical examination and supportive laboratory tests. The absence of rheumatoid factor is not diagnostic and therefore rarely mentioned, and the term ‘seronegative’ is being increasingly abandoned.

IBP, peripheral arthritis and, less frequently, enthesitis are the main clinical features of uSpA [5]. In the original definition by Calin [21], IBP occurs in patients less than 40 yr of age, lasts more than 3 months, has an insidious onset, is associated with morning stiffness and is reduced by physical activity. Other authors have since reported that alternating buttock pain and nocturnal spinal pain are also important [22]. Since uSpA as it stands now is mainly a clinical diagnosis with IBP as the prominent clinical feature, there is a need to re-evaluate the proposal originally published in 1977 [21]. A study recently performed in Berlin included 214 AS patients with a disease duration of 12 yr and controls with mechanical back pain of more than 3 months. Morning stiffness for longer than 30 min, improvement by exercise but not by rest, nocturnal pain and alternating buttock pain were the best discriminating features (Rudwaleit M, unpublished data). If two of the four criteria are fulfilled, the set had sensitivity of 70% and a specificity of 80%. These criteria need to be tested in uSpA and early AS patients.

In patients with uSpA, overt radiological spinal disease is usually not present [23], since most SpA patients with involvement of the spine will have sacroiliac changes indicating AS. Inflammatory involvement of the spine ([24]; Braun J and van der Heijde D, unpublished data) and occasionally single syndesmophytes may occur. However, if there is a larger number of syndesmophytes or other evidence of definite clinically relevant spinal disease with a clear impact on the patient, a diagnosis of AS should be made by the expert. Very much along this line, it is well established that a small percentage of AS patients do not have clearcut sacroiliac changes.

In uSpA, sacroilitis is milder than in definite AS cases, often due to an earlier stage of disease [by definition, if sacroilitis of radiological grade 2 or more bilaterally is present, the patient has AS (Table 4) [25]]; Sacroilitis may not be present at all [22]. Peripheral arthritis is typically asymmetrical, often involving only one to three joints and preferentially involves larger joints in the lower limbs. Enthesitis, defined as an inflammation of tendinous or ligamentous attachments to bone, is common and can occur at any site, including the spine, commonly (but certainly not exclusively) at the Achilles tendon insertion, plantar fascial insertion on the calcaneus and the tibial tuberosity. Dactylitis, a soft-tissue swelling of one or more digits, can also occur, although not as frequently as might be seen in PsSpA or

### Table 1. European Spondyloarthropy Study Group (ESSG) classification criteria for spondyloarthritis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory spinal pain, or synovitis (asymmetrical, predominantly in lower limbs), and any one of the following:</td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Alternate buttock pain</td>
<td></td>
</tr>
<tr>
<td>Enthesopathy</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Amor classification criteria for spondyloarthropathy

<table>
<thead>
<tr>
<th>Clinical symptoms or past history of:</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar or dorsal pain at night, or lumbar or dorsal morning stiffness</td>
<td>≥1</td>
</tr>
<tr>
<td>Asymmetrical oligoarthritis</td>
<td>2</td>
</tr>
<tr>
<td>Buttock pain (buttock pain = 1, alternating buttock pain = 2)</td>
<td></td>
</tr>
<tr>
<td>Sausage-like finger or toe</td>
<td>2</td>
</tr>
<tr>
<td>Heel pain</td>
<td>2</td>
</tr>
<tr>
<td>Iritis</td>
<td>2</td>
</tr>
<tr>
<td>Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Presence of history of psoriasis and/or balanitis and/or of inflammatory bowel disease (ulcerative colitis, Crohn’s disease)</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3. Modified New York Criteria for AS (1984)

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest</td>
<td></td>
</tr>
<tr>
<td>Limitation of motion of the lumbar spine in both the sagittal and frontal planes</td>
<td></td>
</tr>
<tr>
<td>Limitation of chest expansion relative to normal values correlated for age and sex</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiological criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroilitis grade ≥2 bilaterally or grade 3–4 unilaterally</td>
<td></td>
</tr>
</tbody>
</table>

**Definite AS is present if the radiological criterion is associated with at least one clinical criterion [20]**
ReSpA. Extra-articular features of SpA are less frequent [26], including acute anterior uveitis or conjunctivitis (33%), mucocutaneous involvement (16%) and cardiac manifestations (8%), and may have preceded the more characteristic spinal or joint symptoms by years.

As already pointed out, on a cautionary note, the classification of uSpA relies heavily on the presence of IBP or peripheral oligoarthritis. It does not include, for example, a patient with only enthesitis, dactylitis or anterior uveitis as major clinical symptoms; there still remain a large number of clinical scenarios that are not classifiable by current schema. Some of these SpA manifestations can be considered as early disease, some as ‘forme fruste’ spondyloarthritides. Moreover, there are some patients with IBP who did not have or develop features of SpA, but have isolated moderate unilateral sacroiliitis documented by dynamic MRI without definite sacroiliitis on X-ray. They were classified as undifferentiated sacroiliitis. All of them were HLA B27-negative women [5]. As with any classification criteria, there will always be patients who do not fit. For this reason, comprehensive lists of all possible disease-defining symptoms and algorithms [12] are important in making a diagnosis in individual patients (Table 5).

As with all ‘seronegative’ spondyloarthritides, there is a high incidence of HLA B27 positivity in uSpA. Population studies estimate the prevalence of HLA B27 in uSpA to be between 70 and 84% [27–29], varying between studies as a result of differing underlying population HLA B27 prevalence. In individuals with IBP, HLA B27 positivity brings a 20-fold higher risk of SpA and a 15-fold higher risk of radiological sacroiliitis than when B27 is negative [6]. No other genes have been identified to contribute to uSpA.

A significant number of patients with SpA do not have elevated inflammatory markers [26, 27, 30], even though it is characterized by IBP and peripheral inflammatory arthritis. An elevated C-reactive protein or erythrocyte sedimentation rate (ESR) has therefore no diagnostic value, and should be used to monitor disease activity in individual patients rather than to establish a differential diagnosis.

Imaging in SpA can aid in diagnosis if syndesmophytes are present, but normal X-rays do not exclude the disease. Radiographic changes of the sacroiliac joints are by definition minimal and may often be unilateral. The radiological borderline between uSpA and AS is the presence of two or more chronic bilateral sacroiliac joint changes, and more than one clear-cut syndesmophytes. CT or MRI imaging is more sensitive than plain radiography in monitoring active and chronic inflammatory sacroiliac changes, and may confirm early SpA-defining sacroiliac disease. A recent study of MRI findings in 111 uSpA patients confirmed a high prevalence of sacroiliitis (78%). Of interest, some patients did also have evidence of spondylitis (9%) [24]. Thus, MRI is clearly helpful in early diagnosis of SpA but the expense of such imaging precludes regular use for diagnosis or monitoring of SpA.

X-rays of involved peripheral joints are often normal, or show evidence of soft tissue swelling in the acute case. Joint margin erosions are not prominent in AS or uSpA, unlike the classical ‘pencil in cup’ changes seen in advanced PsA. Fluffy erosions can often be seen at sites of chronic enthesitis (for example, the hind foot), and periosteal spurs at the ischial tuberosity, fibula, tibial tuberosity or greater trochanter. Ultrasound is an inexpensive imaging technique particularly suited to detecting the local changes of enthesitis, bursitis, tendonitis and synovitis, which are frequently associated with SpA.

Since IBP is the most impressive clinical finding in uSpA and since these patients are most likely to develop into AS (although this has never been shown), the use of MRI in early disease has led to the proposal of axial SpA as a separate clinical entity. Since peripheral arthritis and enthesitis are known to occur before, later and in parallel to IBP [5], we prefer the term ‘predominant axial SpA’, which leaves some leeway in the diagnosis.

Natural history of uSpA

Basically, there are at least two subsets of uSpA patients: one progresses into AS and one remains uSpA. The patients who progress into AS may do so rather rapidly or it may take many years until definite chronic spinal changes have occurred. Most probably, there are prognostic factors that affect the period between initial symptoms and the detection of definite chronic changes. Since patients with inflammatory spinal changes detected both clinically and by MRI at early disease stages are most likely to develop into AS (although this has never been shown), the use of MRI in early disease may help to diagnose or classify a patient as uSpA. However, since it is known that the mean duration of symptoms before diagnosis in AS exceeds 5 yr, the concept of SpA and uSpA should have special value in this patient group. As already stated, we clearly need to improve the criteria for early SpA to aid in early diagnosis.

Thus, the most important feature of uSpA is the risk of progression to AS or other well-defined subsets of SpA. Oostveen et al. [33] have reported on 25 Dutch SpA patients with MRI-proven sacroiliitis with no chronic X-ray changes at baseline. After 3 yr, 60% of the patients had developed into

---

**Table 4. Grading of radiographic sacroiliitis (1966)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Suspicious changes</td>
</tr>
<tr>
<td>2</td>
<td>Minimal abnormality: small localized areas with erosion or sclerosis, without alteration in the joint width</td>
</tr>
<tr>
<td>3</td>
<td>Unequivocal abnormality: moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis</td>
</tr>
<tr>
<td>4</td>
<td>Severe abnormality: total ankylosis</td>
</tr>
</tbody>
</table>

Adapted from reference 25.

**Table 5. Clinical, imaging and laboratory findings in SpA**

<table>
<thead>
<tr>
<th>SpA-associated clinical symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory back pain</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Enthesitis</td>
</tr>
<tr>
<td>Dactylitis</td>
</tr>
<tr>
<td>Anterior uveitis</td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td>Aortitis</td>
</tr>
</tbody>
</table>

**Imaging findings**

| Acute sacroiliitis |
| Chronic sacroiliac changes |
| Spondylitis |
| Syndesmophytes |
| Enthesitis |
| Synovitis |

**Laboratory findings**

| HLA B27 |
| Acute-phase reactants (CRP, ESR) |
radiological AS. In an earlier clinical study, 59% of 54 German uSpA patients were reported to have progressed to AS over 10 yr [27], with significant associated morbidity and increased mortality [34]. A more recent prospective study of the natural history of Indian uSpA patients [35] found an even higher proportion: 15 of the 22 patients (68%) showed progression to AS after 11 yr. This group had established disease at a young age (median age at disease onset 17 yr), uSpA being defined by the ESSG criteria. Uveitis was seen in four patients, one had developed psoriatic skin disease and four patients remained undifferentiated. The overall outcome was mostly benign with rather normal function in most patients (n = 19) at follow-up, but the majority had evidence of bilateral sacroiliac changes (grade 2 or more). There were few patients with syndesmophytes and none had developed a bamboo spine in the 11-yr follow-up period. Sampaio-Barros et al. [36] found that only 10% of a Brazilian cohort of 68 patients with uSpA (mean disease duration 5 yr) had progressed to AS within 2 yr of follow-up, one patient developing PsSpA in this time and 75% of patients remaining undifferentiated. As already shown, this proportion is known to increase over time. These data may well simply reflect the slow progression of structural changes to AS in some uSpA patients. To date there is only one study following patients for more than 11 yr [37], which would suggest that even after 18 yr function is well maintained, but numbers were small and prospective studies are needed to give a complete picture of long-term prognosis. Other studies of SpA that may retrospectively be considered to fit the uSpA definition have reported varying rates of progression to AS from 2% to 25% [38–40].

Importantly, progression from uSpA to AS is not the only possible transition between SpA subtypes. It is also possible that patients initially classified as uSpA will later develop psoriasis, to then fit the diagnosis of PsSpA. There may be new onset of colitis or an outbreak of silent IBP [41, 42] resulting in SpAIBD, or new onset of ‘hidden’ ReSpA after an asymptomatic triggering infection. Nevertheless, these outcomes seem to be considerably less common than the development of AS or the patient remaining in the uSpA category [35]. Furthermore, it is becoming more accepted that, despite some well-known differences in the radiographic assessment of chronic spinal changes that suggest a definite additional influence of OA, the SpA patient should be categorized according to the prominent clinical feature of spinal involvement rather than on the presence of additional skin or gut disease. Thus, a patient with AS and psoriasis has AS and psoriasis once he/she fulfils the AS criteria. Before that, he or she can be classified and diagnosed as psoriatic SpA.

There are limited data on the prognosis of SpA, uSpA and AS. One study suggests that in SpA there are certain clinical features that predict disease progression, including the presence of hip arthritis, elevated acute phase reactants (ESR), a poor response to NSAID therapy, limitation of range of movement at the lumbar spine, dactylitis, oligoarthritis and early onset, all predisposing to more aggressive disease [43]. In ReA, 35% of patients with acute arthritis will have self-limiting disease, 35% will remit with the occasional recurrence, and only 5% of patients will develop destructive arthritis or AS [44–46]. Poorer prognosis is seen in patients with post-chlamydial disease. HLA B27 positivity and/or extra-articular manifestations [47]. In connection with this, it is needed to be mentioned that the differentiation between uSpA, ReA and ReSpA may cause problems because half of the infections with chlamydia are known to be asymptomatic and antibodies are sensitive but not very specific. Thus, the clinical symptoms and the detection of chlamydia RNA by PCR or LCR remain the best tools.

In contrast to these spondyloarthritides, it is not clear which features of uSpA may be predictive of progression. Buttock pain has been shown to be associated with progression to definite SpA after 2 yr [36], with a trend towards a significant effect of HLA B27, but confirmatory studies are lacking.

With the introduction of increasingly expensive therapies for SpA in the last few years, it is important that we are able to identify those patients at highest risk of progression to severe disease who might benefit from early intervention.

MRI has been shown to be particularly useful for identifying early sacroiliitis, and can predict the development of radiographic changes of significant sacroiliitis at least 3 yr prior [33], with a positive predictive value of 60%. It correlates well with changes seen on CT, and is sensitive to change in patients with IBP and seemingly stable clinical symptoms and X-ray changes [48], making it a valuable tool in the assessment of patients with early disease, including those with uSpA. MRI is useful to detect enthesitis and synovitis not only in the axial skeleton but also in peripheral joints and entheses. The latter are also well assessed by ultrasound. The cost-efficacy of such imaging has not yet been assessed in this setting. Nevertheless, MRI is likely to be included in future classification criteria for early SpA.

**Treatment of uSpA**

Until recently there has not been a great deal of evidence to support any one therapy for uSpA, partly because the spondyloarthritides as a group have historically lacked definitive disease-modifying agents, and partly because the formal definition of uSpA itself is relatively new. It is not necessarily valid to extrapolate therapeutic strategies for AS or ReSpA when we see that not all uSpA patients will progress, and it is not yet possible to identify those individuals at high risk of developing severe disease. Therapies used for the different clinical manifestations of the spondyloarthritides, however, may be appropriate in uSpA, such as local corticosteroid therapy for enthesitis. The currently available evidence for the use of various treatments is given below.

**NSAIDs**

There are no randomized controlled trials of NSAIDs in uSpA; however, anti-inflammatory drugs have been the cornerstone of medical treatment of axial involvement in AS. Various compounds have been shown to be equally effective for IBP in AS—a pivotal study shows just under 80% of 69 patients responded with improvement in pain and function, compared with 15% of 768 patients with mechanical back pain [19]. Despite high levels of self-reported pain relief with NSAID therapy, about 50% of patients with early AS continue to have active disease [49].

**Corticosteroids**

There is no good evidence to support the use of oral corticosteroids in any of the spondyloarthritides. Pulse i.v. corticosteroid therapy has been shown in small open trials to be effective for pain in AS [50–52], and intra-articular (or even peri-articular [53]) steroids are useful in the management of painful sacroiliitis in AS patients [54–57]. Local corticosteroid injections are useful for enthesitis in other settings.

**Sulphasalazine**

A recent multicentre randomized controlled trial of sulphasalazine in uSpA and early AS suggests sulphasalazine may have a role in the treatment of axial disease [58]. Two hundred and forty-two patients were enrolled from 12 centres, the entry criteria being a Bath Ankylosing Spondylitis Disease Activity
Index (BASDAI) above 3 (indicating high disease activity) and IBP. In total, 112 patients received active drug (1 g twice a day), and 118 received placebo for up to 6 months. Half of the group was male, and 67% were HLA B27-positive. Fifty per cent had enthesitis at entry, 47% peripheral arthritis and 14% dactylitis. Those patients with IBP but no peripheral arthritis were seen to have a significantly larger improvement in BASDAI with treatment than the placebo group, but other patient subgroups were not significantly different from placebo (all groups improved). Patients receiving sulphasalazine also used, on average, fewer NSAIDs to control their symptoms than did the control group, which might have influenced the lower level of pain seen in the intervention group. It is difficult to draw further conclusions, as it may be the higher NSAID dose in the placebo group that has masked any real benefit attributable to the sulphasalazine. To date this is the only prospective study of sulphasalazine in uSpA, and further studies are needed.

In contrast to uSpA, studies of sulphasalazine in AS have been contradictory. Clegg et al. [59, 60] have shown that sulphasalazine was no better than placebo for axial disease in patients with longstanding AS, but it may be more effective than placebo for peripheral joint involvement [59–61]. The currently available evidence for peripheral arthritis in uSpA is not convincing. Sulphasalazine has been shown to reduce recurrent uveitis in AS patients [62].

**Methotrexate**

There have been no prospective studies of methotrexate in uSpA. One case report has reported a positive effect of 10 mg oral methotrexate weekly with folate in a 36-yr-old woman with acute synovitis of one knee, previous Achilles tendonitis with plantar fasciitis, unilateral asymptomatic sacroiliitis on X-ray and a polyarteritis nodosa-like cutaneous rash [63], all musculoskeletal and skin manifestations resolving over 6 months. Further case reports are lacking. Methotrexate is commonly used as a disease-modifying anti-rheumatic drug (DMARD) in rheumatoid arthritis with good results, improving symptoms and slowing the progression of radiological erosive disease. It has not enjoyed such success in AS [64], underscoring the different theoretical mechanisms of the two diseases.

**Leflunomide**

Leflunomide, another DMARD commonly used in rheumatoid arthritis [65], has not been extensively studied in SpA. There are no studies in uSpA; a pilot study in AS patients recently suggested that it is not effective for the axial manifestations of AS [66], and a larger randomized placebo-controlled trial in AS failed to find any significant disease response to leflunomide, as measured by the ASAS20 [67]. There are no available studies on the response of peripheral arthritis or extra-articular manifestations to leflunomide in the spondyloarthritides.

**Bisphosphonates**

There are to our knowledge no trials of bisphosphonates in uSpA. There is a small but growing body of evidence for the use of pamidronate, a bisphosphonate used widely in malignancy-associated bone disease, in AS. Open studies have shown short-term improvements in spinal pain with therapy [68, 69] but inconsistent effects on function [69, 70]. The only recent randomized controlled trial compared 10 mg of i.v. pamidronate monthly over 6 months compared to 60 mg i.v. pamidronate at the same frequency [71]. Both spinal pain and function Bath Ankylosing Spondylitis Functional Index (BASFI) were significantly improved in the high-dose group compared with the low-dose group. There are no placebo-controlled trials, owing to the difficulties in providing a placebo for a drug with characteristic infusion-related side effects.

**Infliximab**

The discovery of tumour necrosis factor α (TNF-α) mRNA in inflamed sacroiliac joints in AS patients [72] led to the introduction of TNF-α inhibition as a potential therapy for SpA. Biological therapy has since proved to be possibly the most important therapeutic advance in seronegative SpA to date.

Infliximab is a chimeric (mouse/human) anti-TNF monoclonal antibody of the IgG1κ isotype. Aside from case studies [73], early evidence for an effect of infliximab in uSpA can be found in prospective studies using a mix of different SpA subtypes [74–76]. Initial studies included only small numbers of uSpA patients, and although the different subtypes were not analysed separately, overall study results were encouraging. A Belgian open-label study of infliximab therapy (5 mg/kg i.v. given on weeks 0, 2, 6, 20, 34 and 48 [77]) showed good results in 21 SpA patients, of whom two had uSpA. Improvement was seen in all of the measured outcome variables (patient global health assessment, swollen joint count, pain score, C-reactive protein) in the total group analysis. Separate analyses for each disease subtype were not reported, but the authors affirm that there was no difference in response between disease classifications.

When the group was follow for 1 yr [78], there had been two withdrawals from the study, one of whom was a uSpA patient who withdrew due to disease flare at week 12 despite ongoing therapy. A recent study of 107 SpA patients treated with infliximab, 10 with uSpA, showed that efficacy persists up to 4 yr with continuing therapy [79]. The same group reported good clinical results in a randomized placebo-controlled trial of infliximab in 40 patients with active spondylarthropathy [80], but in both studies only pooled results were given.

The first prospective trial of infliximab in isolated uSpA was a small open study reported by a Berlin group [81]. Six uSpA patients with significant disease activity who had been either unresponsive to sulphasalazine or had not tolerated it received infusions of 3 or 5 mg/kg infliximab at weeks 0, 2 and 6. All patients met the ESSG criteria for SpA, but none met the criteria for a differentiated subset (AS, PsA, IBD-associated spondyloarthropathy, ReA). Median age was 36 yr and disease duration 6.2 yr. All patients had IBP in the sacroiliac region at the beginning of the study, four had radiographic unilateral sacroiliitis grade 2, three had oligoarthritis and three polyarthritis. Two patients had enthesal involvement in the feet. Clinical response was seen in five of the six patients after the first infusion. At 12 weeks, disease activity (BASDAI), functional disability (BASFI) and pain scores (measured by visual analogue scale) had improved in all patients, with improvements more marked in the three patients receiving the higher dose of infliximab (5 mg/kg). The median number of swollen joints improved by 70%, enthesitis improved in two patients, and global health, as assessed by the Medical Outcomes Study Short Form 36 (SF-36), showed significant improvements in bodily pain and vitality. Patients in this study were seen to respond similarly to those with early AS [82].

A second group has recently reported an open, short-term study of infliximab in 10 uSpA patients [83]. All patients received the study drug at a dose of 5 mg/kg, at weeks 0, 2 and 6. After 12 weeks, eight patients reported an improvement in pain, and disease activity improved in seven. The response rate to infliximab was not as dramatic as with previous AS studies, but the reason for this is unclear. Larger studies are required to define whether there is a true difference in response between the two subsets of spondyloarthropathy, or whether there are disease...
features common to both subsets that predispose to a poorer outcome with biological therapies. Studies in AS have shown remarkable clinical improvement with infliximab therapy. Disease activity is rapidly reduced with therapy [84], and both disease activity and physical function improvements persist over 2 yr with ongoing treatment [85]. Response rate is high [86] but there is early evidence of a high relapse rate on cessation of therapy [87].

Etanercept

Etanercept is a dimeric fusion protein of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human IgG1. As with infliximab, the earliest reports of the use of etanercept in uSpA are for a subgroup of a larger study in SpA. Marzo-Ortega et al. [88] reported an open study of etanercept at a dose of 25 mg twice weekly for 24 weeks in 10 patients with SpA, one of whom was defined as uSpA. Methotrexate was continued at a stable dose in those patients already receiving this therapy, but not commenced de novo. All outcomes improved over 6 months (BASFI, BASDAI, patient and physician global, joint counts; lumbar flexion, pain score, enthesopathy score) in the overall study group. The only patient with uSpA had early disease (disease duration of 8 months), and remained in clinical remission more than 9 months after stopping therapy, because of the size of the study, it is not possible to conclude that early disease gives a better treatment response, but this certainly raises the question: does early disease respond more readily or more dramatically to biological therapy, and if so, is it possible to arrest the progression of uSpA to AS or other more well-defined diagnoses with timely biological intervention? This is an important question, particularly with regard to current requirements for biological therapy in the spondyloarthritides; at present, only patients fulfilling formal criteria for AS qualify for any of the anti-TNF therapies, and there is a need to address their role in other settings, such as isolated active axial disease.

The only definitive study of etanercept in uSpA was recently published by Brandt et al. [89]. Ten uSpA patients were included in an open trial, which concluded that etanercept therapy (25 mg subcutaneously twice weekly) gave results at 12 weeks similar to those previously seen in AS [90, 91]. Patients fulfilled the ESSG criteria for SpA but none of the differential criteria. All had severe active disease for at least 6 months, with a pain score of 4 or more (on a scale of 0 to 10). Fifty per cent had oligoarthritis at the beginning of the trial, one polyarthritis, five patients had evidence of enthesitis and three had current or past uveitis. Six of the 10 patients showed more than 50% improvement in BASDAI at week 12. All measured disease manifestations improved, including IBP, peripheral arthritis and enthesitis, quality of life as measured by the Funktionsfragebogen Hannover (FFHb) and the SF-36, and functional disability as measured by the BASFI. Two patients continued to show an improvement at 6 months despite cessation of therapy. Four of the eight patients who responded to therapy relapsed once etanercept was stopped, at an average of 4.5 weeks after therapy ceased.

Three recent randomized controlled studies of etanercept in AS have shown convincing clinical improvement with therapy, with significant reductions in morning stiffness and nocturnal spinal pain [92], improvement in disease activity [90] and ASAS20 response [91].

Adalimumab

Adalimumab, a fully humanized monoclonal anti-TNF antibody, is the third anti-TNF biological therapy currently available for the treatment of rheumatoid arthritis. A recent pilot study [93] in AS suggests that adalimumab may have similar efficacy to other biologicals in AS, although controlled trials in both AS and uSpA are needed.

Anakinra

Directed at a different cytokine in the inflammatory response, anakinra is a recombinant human interleukin-1 receptor antagonist. To date, the only study of anakinra in SpA failed to show any effect of therapy on axial manifestations in AS [94].

Conclusions

As the ESSG classification criteria for SpA are becoming more widely used in clinical practice, it is important that clinicians become more familiar with the concept of uSpA, particularly if in many cases it can be considered as early AS. Can we alter the natural course of the disease? With accurate patient selection and the availability of newer biological agents that are effective in suppressing spinal and peripheral joint inflammation, the door is open for significant improvements in the early treatment of disease, and even perhaps for strategies to halt the progression of disabling SpA.

The authors have declared no conflicts of interest.

References

Undifferentiated spondyloarthritis


