The Ghent Inflammatory Arthritis and Spontaneous Arthritis Cohort: First Results
The Ghent Inflammatory Arthritis and spondylitis cohort: First results

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AAU</td>
<td>Acute anterior uveitis</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>Anti-Escherichia coli outer membrane porin C</td>
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<tr>
<td>AS</td>
<td>Ankylosing spondylitis</td>
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<tr>
<td>ASAS</td>
<td>Assessment in SpondyloArthritis international Society</td>
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<tr>
<td>ASCA</td>
<td>Anti-Saccharomyces cerevisiae antibodies</td>
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<tr>
<td>ASDAS</td>
<td>Ankylosing Spondylitis Disease Activity Score</td>
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<tr>
<td>BASDAI</td>
<td>Bath Ankylosing Spondylitis Disease Activity Index</td>
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<td>BASFI</td>
<td>Bath Ankylosing Spondylitis Functional Index</td>
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<tr>
<td>BASMI</td>
<td>Bath Ankylosing Spondylitis Metrology Index</td>
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<tr>
<td>BMO</td>
<td>Bone marrow oedema</td>
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<tr>
<td>CD</td>
<td>Crohn’s disease</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>DMARDs</td>
<td>Disease-modifying antirheumatic drugs</td>
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<tr>
<td>EAMs</td>
<td>Extra-articular manifestations</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>ESSG</td>
<td>European Spondylarthropathy Study Group</td>
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<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GIANT</td>
<td>Ghent Inflammatory Arthritis and spoNdylitis cohorT</td>
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<tr>
<td>HLA-B27</td>
<td>Human Leucocyte Antigen-B27</td>
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<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>IBP</td>
<td>Inflammatory back pain</td>
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<tr>
<td>ICC</td>
<td>Intraclass correlation coefficient</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IL-23R</td>
<td>Interleukin-23 receptor</td>
</tr>
<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<tr>
<td>JAK</td>
<td>Janus Kinase</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>mSASSS</td>
<td>Modified Stokes AS Spine Score</td>
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<tr>
<td>Nr-axSpA</td>
<td>Non-radiographic axial SpA</td>
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<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>OASIS</td>
<td>Outcome in AS International Study</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>pANCA</td>
<td>Perinuclear antineutrophil cytoplasmic antibodies</td>
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<tr>
<td>PsA</td>
<td>Psoriatic arthritis</td>
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<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ROC-AUC</td>
<td>Receiver Operating Characteristic - Area Under the Curve</td>
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<tr>
<td>SIJs</td>
<td>Sacroiliac joints</td>
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<tr>
<td>SpA</td>
<td>Spondyloarthritides</td>
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<tr>
<td>SPARCC</td>
<td>Spondyloarthritis Research Consortium of Canada</td>
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<tr>
<td>STIR</td>
<td>Short tau inversion recovery</td>
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<tr>
<td>Th17</td>
<td>T helper 17</td>
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<tr>
<td>TNF-α</td>
<td>Tumor Necrosis Factor-α</td>
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<tr>
<td>TNR</td>
<td>True negative rate</td>
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<tr>
<td>TPR</td>
<td>True positive rate</td>
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<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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Chapter 1
General introduction
General introduction

1. Clinical spectrum and classification of spondyloarthritides

Spondyloarthritides (SpA) are a heterogeneous family of prevalent and disabling rheumatic diseases sharing common clinical, radiological, genetic and even therapeutic characteristics. SpA occur in 0.2% to 1% of the population. Age at onset ranges from adolescence to 40 years, or to an older age in more exceptional cases. Ankylosing spondylitis (AS), the prototype disease in this concept, was originally assumed to be an axial variant of rheumatoid arthritis (RA). However, in the 1960s rheumatologists started to realize that this disease was a distinct entity. In the 1970s Moll and Wright[1, 2] published seminal work formulating the unified concept of ‘seronegative spondarthritis’; ‘seronegative’ referred to the lack of rheumatoid factors (considered to be typical for RA), whereas the prefix ‘spond-’ was used to stress the close relationship between the different diseases and AS. In the original description (figure 1), diseases such as AS, psoriatic arthritis (PsA), reactive arthritis, and arthritis/spondylitis associated with inflammatory bowel disease (IBD) (Crohn's disease (CD), ulcerative colitis (UC)) were included. The concept was clinically characterized by peripheral arthritis (principally of the lower limb) and enthesitis, radiological sacroiliitis (with or without spondylitis), evidence of clinical overlap (including skin, gut and eye disease) and a tendency for familial aggregation. Shortly after the initial description of the SpA concept, the discovery of a strong association of these diseases with the genetic marker Human Leucocyte Antigen (HLA)-B27 was simultaneously reported by two independent research groups, providing further support to this unifying theory[3, 4].

Given the heterogeneous character of the diseases belonging to the SpA concept, classification is a major issue, with the purpose of defining homogeneous subgroups of patients that can be followed prospectively (to obtain data on the natural evolution of the disease) or in whom a specific new treatment can be tested. When discussing classification criteria, it is important to emphasize the difference with diagnostic criteria and to remember that classification should only be applied to patients who already have an established diagnosis.
Typically, however, physicians will use the different components of classification criteria and take them into account when making a diagnosis in daily life. The first classification criteria within the field of SpA were the Rome and later New York criteria for AS\[5\]; they allowed identification of a homogeneous group of patients with axial complaints and definite structural damage defined as radiographic sacroiliitis (bilateral grade 2 or unilateral grade 3–4, see section 4.1). The latter is also the major drawback of these criteria because radiographic sacroiliitis is usually developing slowly (typically over years), thus allowing only patients with rather longstanding disease to be classified. Furthermore, these criteria do not take into account the peripheral joint manifestations of SpA, nor the extra-articular manifestations (EAMs) or the response to therapy. In the 1990s, two sets of new criteria were published covering the full spectrum of SpA, namely the Amor criteria\[6\] and the European Spondylarthropathy Study Group (ESSG) criteria\[7\]. Whereas the Amor criteria are based on a list of 12 criteria, none of which is mandatory, the ESSG criteria introduced the concept of an ‘entry criterium’: in order to classify a patient as SpA, either inflammatory back pain (IBP) or synovitis (asymmetric or predominantly of the lower limbs) needs to be present, in addition to one extra typical SpA feature. Both classification sets also have, however, limitations, especially in early disease, with Amor’s criteria being rather difficult to use. They are quite specific but have a lower sensitivity, whereas ESSG criteria have higher sensitivity, but low specificity\[8, 9\].

The arrival of new, expensive treatment options such as Tumor Necrosis Factor-α (TNF-α)-blockade (see section 5.2) provoked a therapeutic revolution unknown in the field of SpA. One consistent finding in all trials with biologicals targeting TNF-α is the fact that response to treatment seems to be higher in patients with shorter disease (symptom) duration. With regard to the existing classification criteria, two problems became evident; on one hand it was clear that the modified New York criteria for AS did not allow classification in an early disease stage, thus excluding treatment at an early (possible) ‘window of opportunity’; on the other hand, there was a legitimate fear that using the less-specific ESSG criteria would result in an unnecessary high number of patients being considered candidates for this expensive biological treatment. In order to provide a solution to this problem, the Assessment in SpondyloArthritis international Society (ASAS) started a study with the construction of new classification criteria for axial and peripheral SpA as a final goal. In this study, consecutive patients presenting with either back pain or peripheral joint involvement suggestive of SpA, usually started before 45 years of age, were evaluated in depth.
Figure 1 and 2: Original and current concept of SpA (adapted from [10])
Subsequently, the ASAS classification criteria were introduced, subdividing SpA based on the predominant musculoskeletal manifestation (figure 2 and 3)[11]. In this classification patients showing mainly symptoms related to inflammation of the axial skeleton are segregated from patients who have peripheral arthritis, enthesitis or dactylitis as the prevailing symptom. For PsA, the CASPAR criteria[12] can also be applied.

Axial SpA is now the preferred term for involvement of the axial skeleton (spine and sacroiliac joints (SIJs)) and involves both patients with damage visible on radiographs of the sacroiliac joints (AS-modified New York criteria[5]), as patients in which damage is not visible radiographically (non-radiographic axial SpA (nr-axSpA)) (figure 4).

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**ASAS Classification Criteria for Spondyloarthritis (SpA)**

<table>
<thead>
<tr>
<th>In patients with $\geq$ 3 months back pain and age at onset &lt; 45 years</th>
<th>In patients with peripheral symptoms ONLY</th>
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<tbody>
<tr>
<td>Sacroiliitis on imaging plus $\geq$ 1 SpA feature OR</td>
<td>HLA-B27 plus $\geq$ 2 other SpA features</td>
</tr>
<tr>
<td>Arthritis or enthesitis or dactylitis plus</td>
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</table>

**SpA features**
- inflammatory back pain (IBP)
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn’s/coilitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

*Sensitivity: 79.5%; Specificity: 83.3%; n=975.*

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31 (with permission)

**Figure 3: ASAS criteria for classification of axial and peripheral spondyloarthritis[11]**
Recently, there has been a lot of interest for this entity of nr-axSpA. There is probably a relevant proportion of patients with axial SpA that will never evolve into the radiographic stage. This subgroup of patients has been recognized for a long time, as radiographic sacroiliitis was not required to fulfill the Amor criteria[6] in 1990 and the ESSG criteria[7] in 1991. Several studies agree that the progression rate from non-radiographic to radiographic axial SpA over 2 years is about 10%, and around 20% in patients with an elevated C-reactive protein (CRP) or with active inflammation on magnetic resonance imaging (MRI) of the SIJs[14]. Clinical features are comparable between patients with nr-axSpA and AS, except for a lower proportion of male patients and a lower burden of inflammation in the non-radiographic group. Both groups do not differ regarding signs and symptoms[15, 16].
2. Extra-articular manifestations of SpA

Several EAMs are associated with SpA. They can be subdivided in 2 groups (table 1). One group is related to the SpA concept and includes involvement of skin, eye, gut and urogenital system. The other group (non-concept related) reflects chronic, longstanding inflammation, and includes involvement of lung, heart, kidney and nerves. The concept related manifestations are quite frequent (20–60%)[17], can occur at any moment of the disease evolution (sometimes as first manifestation), and are sometimes linked to axial or peripheral joint inflammation. The non-concept related manifestations are very rare (1 to 5%), frequently happen subclinical, occur only in longstanding disease, and are not related to the locomotor manifestations[10].

<table>
<thead>
<tr>
<th>SpA concept-related</th>
<th>Non-SpA concept related</th>
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<tbody>
<tr>
<td><strong>Skin</strong></td>
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<tr>
<td>Psoriasis</td>
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<tr>
<td>Erythema nodosum</td>
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<tr>
<td>Pyroderma gangrenosum</td>
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<tr>
<td>Keratoderma blenorrhagica</td>
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<tr>
<td><strong>Eye</strong></td>
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<tr>
<td>Acute anterior uveitis</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>Inflammatory bowel disease</td>
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<td>* Crohn’s disease</td>
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<td>* Ulcerative colitis</td>
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<td><strong>Urogenital</strong></td>
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<td>Aseptic urethritis</td>
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<td>Balanitis</td>
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<td>Vaginitis</td>
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<tr>
<td><strong>Pulmonary</strong></td>
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<tr>
<td>Upper lobe fibrosis</td>
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<td>Pleural thickening</td>
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<tr>
<td><strong>Cardiac</strong></td>
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<td>Aortitis, aortic insufficiency</td>
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<td>Conduction abnormalities</td>
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<tr>
<td>(bundle branch block, AV conduction block)</td>
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<td><strong>Renal</strong></td>
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<tr>
<td>Secondary amyloidosis</td>
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<td>IgA nephropathy</td>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td>Cauda Equina syndrome</td>
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Table 1: Extra-articular manifestations in SpA (adapted from [10])
2.1 Skin

Psoriatic or psoriatic-like lesions occur frequently in SpA (±11% compared to 1-2% in the general population)[17]. The majority of the patients (circa 70%) develop psoriasis before articular involvement; arthritis precedes the onset of psoriasis by more than 1 year in circa 15% of cases, and in circa 15% the two conditions occur within 12 months. The skin and nail lesions in SpA are identical to uncomplicated skin disease, most commonly presenting as plaque psoriasis (figure 5), but sometimes the lesions can be limited to scalp or nails. There is no evidence suggesting a parallelism between the activity of skin disease and the locomotor inflammation[18].

Erythema nodosum are painful red nodules mostly localized on the distal extremities, showing focal panniculitis on biopsy. It is seen in associated IBD, in up to 15% of patients[19]. Observed in association with peripheral arthritis, it frequently parallels the activity of the IBD.

Pyoderma gangrenosum is an uncommon ulcerative cutaneous disease of unknown etiology. It is associated with an underlying systemic disease in at least 50% of cases, most commonly IBD, and causes large, painful sores, most often on the legs.

Keratoderma blennorrhagica is an unusual severe skin manifestation, mostly related to genitourinary involvement. It starts with clear vesicles, evolving to pustular keratotic lesions which are painful on pressure. Histologically, it can hardly be differentiated from palmoplantar pustulosis.
2.1 Eye

Acute anterior uveitis (AAU) (figure 6) is the most common extra-articular manifestation of SpA and is strongly linked with HLA-B27. Thirty to 40% of all AS patients develop AAU during the course of disease. Conversely, about 50% of patients with AAU as an initial presentation have or will develop a form of SpA[20].

Patients who are HLA-B27 positive have a less favorable prognosis with a significantly higher rate of recurrent inflammatory attacks[21]. Classical symptoms of AAU are pain, redness, blurred vision and photophobia. Attacks typically have a sudden onset and are unilateral, they usually last up to 6 to 12 weeks. Generally, local treatment is sufficient, but relapses frequently occur.

Extended, uncontrolled attacks can expand into the posterior part of the eye with the formation of synechiae and secondary glaucoma. Subsequently, it can be an important cause of vision loss.

2.3 Urogenital system

Aseptic urethritis vaginitis or balanitis can occur, mostly curing spontaneously.

2.4 Gut

Inflammatory bowel disease comprises two types of chronic intestinal disorders: Crohn’s disease (figure 7) and ulcerative colitis. IBD affects approximately 0.1-0.2% of the general population and its peak onset occurs between 15 to 30 years of age. In SpA, prevalence fluctuates around 6%. CD generally involves the ileum and colon, but it can affect any region of the intestine, often discontinuously. UC involves the rectum and may affect part of the colon or the entire colon. Interestingly, extra-intestinal manifestations frequently occur in patients with IBD[22]. This suggests an important and reciprocal overlap between these diseases.
3. **Pathogenesis**

*Microscopic gut inflammation*

Bacterial gut infections such as Yersinia enterocolitica, Salmonella typhimurium, Campylobacter jejuni, and Shigella spp may cause joint inflammation in genetically predisposed patients. About 20% of these patients with reactive arthritis eventually develop AS. This observation was a first suggestion of a possible role for mucosal inflammation in the pathogenesis of SpA. This role has been established by Mielants et al.[23], who described a very high frequency of microscopic gut inflammation in patients with different forms of SpA, and corroborated by several additional investigators[24-26]. Indeed, microscopic gut inflammation was observed in 60% of patients with AS, 90% of patients with enterogenic reactive arthritis, 20% of patients with urogenital reactive arthritis, 65% of patients with undifferentiated SpA, 16% of those with the pauciarticular and axial forms of psoriatic arthritis, and in 80% of patients with late-onset pauciarticular juvenile chronic arthritis or juvenile SpA[27-29]. The mucosal inflammation in SpA can affect the ileum as well as the colon. It can be subdivided into an acute type (resembling an acute bacterial enterocolitis), in which neutrophils predominate, or a chronic type (resembling CD), which is characterized by a mixed inflammatory infiltrate combined with structural remodeling of the gut mucosa (figure 8)[30].

![Mucosal inflammation in SpA: normal, acute and chronic gut histology (adapted from [31])](image)
Most patients with normal histology or acute intestinal lesions have transient arthritis, whereas the majority of those with chronic intestinal lesions have persistent joint inflammation. A tight relationship between gut and joint inflammation has been revealed in prospective follow-up studies of patients with SpA: clinical remission of joint inflammation was associated with resolution of gut inflammation, whereas the presence of gut inflammation was associated with persistent joint inflammation[31, 32]. Data from several ileocolonoscopic studies indicate that chronic gut inflammation, found in approximately 30% of patients with SpA, can be considered as an early stage of CD[31]. Most importantly, chronic inflammatory lesions were found to be a risk factor for CD; indeed, 20% of patients with chronic lesions developed clinically overt IBD over a 5 year period[32]. Besides, chronic gut lesions were associated with reduced axial mobility and a diagnosis of AS[33].

The pathogenesis of both SpA and IBD is considered to be the result of a complex interplay between the host (genetic predisposition) and environmental factors, notably microorganisms, leading to a disturbed immune system and chronic inflammation.

### 3.1 Genetic predisposition

Within the SpA concept, there is a strong genetic link with HLA-B27, especially for AS, that has been known for about 40 years. The disease prevalence also parallels the frequency of this allele in different populations. The HLA-B27 gene, however, accounts for less than 30% of the heritability, which led to an intense global effort to uncover the remaining predisposing genes[34]. Several candidate genes have been identified as being related to SpA. In addition to HLA-B27, genome wide association with AS has been demonstrated at ERAP1 and RUNX3 (antigen presentation), interleukin-23 receptor (IL-23R) and IL-12B (IL-23/T helper 17 (Th17) pathway), 2p15, and 21q2 (unknown function), KIF21B (possibly NF-κβ pathway), IL-1R2, CARD9 and PTGER4 (innate immune responses), TNFRI/LTBR (TNF pathway), ANTXR2 (possibly skeletal involvement) and TBKBP1/NPEPPS/TBX21 (TNF pathway/antigen presentation/Th1)[35]. ERAP1 codes for an endoplasmic reticulum aminopeptidase with a dual function: trimming of peptides in the endoplasmic reticulum prior to HLA class I presentation and trimming of cytokine receptors from the cell wall. ERAP-1 is not only associated with AS, but with non-AS SpA as well and predisposes to disease, only in presence of HLA-B27[36].
Also for IBD, a myriad of genetic markers are known. Genetic defects associated with IBD typically affect genes responsible for the regulation of innate immune defense against intestinal bacteria (e.g. NOD2 and ATG16L1), modulation of the adaptive immune response (e.g. IL-23R and IL-10) or epithelial cell integrity and repair (e.g. PTPRS)[22].

In an Iceland genealogy database, a remarkable overlap in the genetic background between AS and IBD was revealed because there was an elevated cross-risk ratio between either of these diseases[37]. A 3-fold increased risk to develop IBD was identified in first-degree relatives of patients with AS; conversely, equal risk was found in relatives from patients with IBD being much more susceptible to develop AS. Hence, IBD and AS share a common genetic susceptibility, of which the association with IL-23R polymorphisms is most prominent[38]. However, it is not clear whether the presence of microscopic bowel inflammation in AS patients may have influenced this overlap. Indeed, this was suggested by the results of a previously conducted study on an SpA cohort that was limited to NOD2 polymorphisms. The authors found a high prevalence in SpA patients with chronic gut inflammation, similarly to CD patients. In contrast, the prevalence was unaltered in patients lacking gut inflammation or in the group with acute inflammatory gut lesions[39].

Furthermore, additional shared associations between AS and IBD were found at chromosome 1q32 near KIF21B, STAT3, IL-12B, JAK2, PTGER4, CARD9, CDKAL1, IL1R2 and ORMDL3. As the genes IL-23R, STAT3, JAK2, PTGER4 and IL-12B all influence Th17 lymphocyte differentiation/activation, this provides further evidence implicating the Th17 lymphocyte subset in the pathogenesis of ankylosing spondylitis[40, 41].
3.2 Environmental factors

In addition to genetic susceptibility, much attention has been given to the role of environmental factors in triggering the onset of rheumatic disease. Given the prototypical link between certain bacterial infections and the onset of reactive arthritis, several studies have aimed to assess the role of intestinal flora in disease progression, as well as the resulting changes in mucosal response. The response of patients with SpA to intestinal microbes is evidenced by the presence of IBD-associated circulating antibodies that target a subset of commensal microbial antigens, including anti-Saccharomyces cerevisiae antibodies (ASCA), anti-Escherichia coli outer membrane porin C (anti-OmpC) antibodies and perinuclear antineutrophil cytoplasmic antibodies (pANCA)[42, 43]. The presence of these antibodies demonstrates a loss of tolerance to commensal intestinal microorganisms. In a small pilot study, 55% of patients with AS (but without manifest IBD) showed at least one of these IBD-associated antibodies; indeed, pANCA, ASCA (immunoglobulin (Ig)A and/or IgG), and anti-OmpC antibodies were found in 21%, 30%, and 19% of patients, respectively. As pANCA was more frequently present in patients with AS and concurrent ulcerative colitis than in those with AS alone, it seems to be an indicator for ulcerative colitis in patients with AS[44]. In another pilot study, the median anti-I2 response (associated with anti-Pseudomonal activity) was significantly higher in patients with AS than in controls[45].

Of interest, changes in mucosal responses from inflammatory cells, most notably neutrophils, have also been linked to bowel inflammation in the context of SpA. Hence, fecal markers of neutrophil influx into the mucosa are promising indicators of intestinal inflammation. Indeed, calprotectin (a complex formed of the calcium-binding proteins S100A8 and S100A9) has been used as a fecal marker of IBD for more than 10 years[46], and shows a substantial correlation with IBD activity. Similarly, significantly increased fecal concentrations of calprotectin are found in patients with AS (compared with healthy controls)[47, 48] which were comparable to the concentrations found in patients with CD. In a small ileocolonoscopic study, microscopic and/or macroscopic signs of inflammation were found in 62.5 % of patients with persistent elevation of fecal calprotectin (5/8 patients). Serum calprotectin is moderately increased to normal in AS patients[48, 49].
Transition model

At present the factors that favor chronicity of disease in SpA remain unclear. Characterizing such factors is crucially important, as better understanding of the mechanisms that promote sustenance of inflammation might have therapeutic implications. In the context of mucosal inflammation in SpA, we’ve proposed a model in which chronic gut inflammation (a risk factor for chronicity of gut and joint disease in SpA) proceeds through an initial acute inflammatory event (figure 9)[50]. Acute inflammatory episodes can be induced in any individual by a variety of factors including certain bacterial infections or biomechanical stress - involving a number of microbial or endogenous danger signals at the molecular level. Acute inflammatory episodes are likely to be mediated by cells primarily of the innate immune system, such as macrophages and neutrophils, and typically resolve with time in the majority of individuals. However, susceptible individuals who are under the influence of a variety of genetic factors that affect antigen processing, endoplasmic reticulum stress, autophagy or cytokine signaling, are unable to appropriately resolve these acute inflammatory insults. Acute inflammation can then transition into a more chronic phase. Here, cells of the adaptive immune system are also involved, and, although natural regulatory feedback mechanisms are engaged, they are unable to resolve the inflammation. We anticipate that future therapeutic strategies will need to target the transition phase to prevent the occurrence of chronic SpA. Indeed, on the basis of the underlying mechanisms of the acute, transition and chronic phases, we speculate that profoundly different strategies will be demanded to approach the chronic as opposed to the transition or acute phases of the disease.

Figure 9: Transition model (adapted from [50])
4. Imaging in SpA

4.1 Conventional radiographs

The ‘gold standard’ for assessment of structural changes in AS is still conventional radiographs, but this can only depict structural changes, which appear after a certain disease duration, and cannot directly visualize active inflammation[51]. Definite structural changes of the SIJs have been part of the diagnostic and classification criteria for almost 50 years. A grading of 0 to 4 is scored with bilateral changes ≥2 or unilateral ≥3 being considered critical for the diagnosis of AS[5]. Sclerosis, erosions and ankylosis are the main radiographic findings (figure 10).

The typical spinal changes in AS are squaring, erosions, sclerosis and syndesmophytes. The modified Stokes AS Spine Score (mSASSS)[52], evaluating lateral view X-rays of cervical and lumbar spine, is a validated scoring system, currently considered the best method for quantification of chronic spinal changes as detected by conventional radiographs[53] (figure 11).
4.2 Magnetic resonance imaging

Over the past decade a marked progress has been achieved to diagnose SpA at an earlier stage, before structural damage has occurred. New imaging modalities such as MRI of SIJs and spine have been widely validated. MRI enables us to identify early in the disease course patients with nr-axSpA by assessing active inflammatory lesions such as bone marrow oedema (BMO)/osteitis, synovitis, enthesitis and capsulitis. Among these, the clear presence of BMO/osteitis (highly suggestive for SpA) is considered essential for defining active sacroiliitis. The BMO needs to be present on at least two slices in case of one lesion. If there is more than one signal on a single slice, one slice may be enough. This is included in the ASAS classification criteria as a major criterion in the imaging part of the set[54]. Active inflammatory changes are visualized best by fatsaturated T2-weighted turbo spin-echo sequence or a short tau inversion recovery (STIR) sequence with a high resolution[55]. Structural damage lesions such as sclerosis, erosions, fat deposition and ankylosis can also be detected by MRI. At present, however, the exact place of structural damage lesions for diagnosis and classification is less clear, particularly if these findings are minor. These chronic changes are best visualized by using a T1-weighted turbo spin-echo sequence (figure 12).
There is evidence that spondylitis may also occur before or without sacroiliitis. Based on expert consensus and taking the literature review into consideration, a positive spinal MRI for inflammation is defined as the presence of anterior/posterior spondylitis in ≥3 sites. Evidence of fatty deposition at several vertebral corners was found to be suggestive of axial SpA, especially in younger adults[56]. Up until now, spinal changes are not included in the imaging part of the ASAS classification criteria. Different scoring systems for MRI of the SIJs and the spine have been published (table 2).

<table>
<thead>
<tr>
<th>Sacroiliac joints</th>
<th>Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spondyloarthritis Research</td>
<td>• SPARCC SIJ inflammation score</td>
</tr>
<tr>
<td>Consortium of Canada (SPARCC)</td>
<td>• AS spine MRI inflammation score</td>
</tr>
<tr>
<td>spine inflammation score</td>
<td>• Berlin method</td>
</tr>
<tr>
<td>• Leeds Method</td>
<td>• Danish spine MRI scoring method</td>
</tr>
<tr>
<td>• Berlin method</td>
<td></td>
</tr>
<tr>
<td>• Danish SIJ MRI scoring method</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2: Published scoring systems for MRI of the SIJs and the spine*
Until the late 1990’s, the therapeutic options for SpA patients were limited. Patients were treated with physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs), and sulfasalazine, but often the symptoms persisted. However, the introduction of TNF-α blocking agents represented a major therapeutic breakthrough for refractory SpA patients\[57, 58\]. Figures 13 and 14 give an overview of the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of AS\[59, 60\].

The **overarching principles** of the management of patients with AS are:

» AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.

» The primary goal of treating the patient with AS is to maximize long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalization of function and social participation.

» Treatment of AS should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

» The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.

1. **General treatment**

The treatment of patients with AS should be tailored according to:

» The current manifestations of the disease (axial, peripheral, enthesal, extra-articular symptoms and signs).

» The level of current symptoms, clinical findings, and prognostic indicators.

» The general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors).

» The level of current symptoms, clinical findings, and prognostic indicators.

» The general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors).
2. **Disease monitoring**

The disease monitoring of patients with AS should include:

» Patient history (e.g. questionnaires)
» Clinical parameters
» Labarotory tests
» Imaging

✔ All according to the clinical presentation as well as the ASAS core set

The frequency of monitoring should be decided on an individual basis depending on:

» Course of symptoms
» Severity
» Treatment

3. **Non-pharmacological treatment**

» The cornerstone of non-pharmacological treatment of patients with AS is patient education and regular exercise.

» Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises.

» Patient associations and self-help groups may be useful.

4. **Extra-articular manifestations and comorbidities**

» The frequently observed extra-articular manifestations, for example, psoriasis, uveitis and IBD, should be managed in collaboration with the respective specialists.

» Rheumatologists should be aware of the increased risk of cardiovascular disease and osteoporosis.

5. **Non-steroidal anti-inflammatory drugs**

» NSAID, including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness.

» Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease.

» Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAID.

6. **Analgesics**

» Analgesics, such as paracetamol and opioid(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

7. **Glucocorticoids**

» Corticoid injections directed to the local site of musculoskeletal inflammation may be considered.

» The use of systemic glucocorticoids for axial disease is not supported by evidence.
8. **Disease-modifying antirheumatic drugs (DMARDs)**
   » There is no evidence for the efficacy of DMARD, including sulfasalazine and methotrexate, for the treatment of axial disease.
   » Sulfasalazine may be considered in patients with peripheral arthritis.

9. **Anti-TNF therapy**
   » Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
   » There is no evidence to support the obligatory use of DMARD before or concomitants with anti-TNF therapy in patients with axial disease.
   » There is no evidence to support a difference in efficacy of the various TNF-inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
   » Switching to a second TNF-blocker might be beneficial especially in patients with loss of response.
   » There is no evidence to support the use of biological agents other than TNF inhibitors in AS.

10. **Surgery**
    » Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.
    » Spinal corrective osteotomy may be considered in patients with severe disabling deformity.
    » In patients with AS and an acute vertebral fracture a spinal surgeon should be consulted.

11. **Changes in the disease course**
    » If a significant change in the course of the disease occurs, other causes than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

*Figure 13: ASAS/EULAR recommendations for the management of AS (adapted from [60])*
5.1 Non-steroidal anti-inflammatory drugs

Together with exercise and physical therapy, NSAIDs remain the cornerstone of treatment in axial SpA. The effect of NSAIDs is quick (at 24–48 h after a full dose of NSAID the back pain is not present anymore or much better) but temporary, with relapse of symptoms upon discontinuation. The effect on long-term radiographic progression is still not entirely clarified. A study by Wanders et al.[61] looked at the effect on radiographic progression (cervical and lumbar spine) of continuous versus on demand celecoxib treatment in patients with AS. The progression in the continuous group was significantly decreased versus the group with on demand treatment, providing evidence that continuous treatment with NSAIDs is capable of slowing down the radiographic progression of the disease. Post-hoc analyses revealed that patients with elevated acute phase reactants benefit most from continuous treatment with NSAIDs[62]. Indeed, more recent work confirmed that a high NSAID intake (NSAID index≥50) over 2 years is associated with retarded radiographic spinal progression in AS, more specifically in patients with syndesmophytes at baseline and elevated time-averaged CRP[63].
5.2  **Tumor Necrosis Factor-α Blockade**

Advances in our understanding of the pathogenesis of SpA suggest that biological therapies may be able to inhibit the specific molecules involved in the inflammatory cascade. In particular, most of the research has focused on pharmacotherapies targeting the TNF-α pathway. TNF-α is a proinflammatory cytokine critically involved in disease pathogenesis of SpA, IBD and RA. The role of TNF-α in IBD-related SpA has been investigated in the TNFΔARE murine model, which is characterized by the high expression of TNF-α. These mice develop a phenotype dominated by IBD-like intestinal inflammation and arthritis/enthesitis, thus implicating TNF-α as a critical factor in the induction of inflammation in IBD and IBD-related SpA[64]. Several placebo-controlled trials evaluating infliximab, adalimumab and golimumab (anti-TNF monoclonal antibodies), etanercept (a dimeric soluble form of the TNF-receptor) and certolizumab pegol (PEGylated Fab’ fragment) have demonstrated substantial symptomatic benefit in NSAID-refractory patients. Reduction in pain, stiffness and fatigue may be seen as soon as 2 weeks after the start of treatment, while improvement in spinal mobility is also evident from 12 weeks onward. Maximal benefit is seen by 12 weeks and is sustained over periods of several years. Other benefits include improved quality of life, reduced sick leave, improvement in work productivity, reduced acute-phase reactants, improvement in synovial histopathology, and reduction in MRI features of inflammation that are sustained over several years. At this moment, and despite the fact that no head-to-head comparisons are available, it seems that the efficacy of the different compounds is comparable regarding both axial and peripheral/enthesal symptoms[65-69].

For adalimumab[70], infliximab[71], etanercept[72] and certolizumab pegol[69], placebo-controlled studies in nr-axSpA have shown similarly good responses. Studies with golimumab (clinicaltrials.gov) are ongoing. In all studies, responses were higher in patients with objective signs of inflammation (positive MRI and/or CRP). This was even an inclusion criterium in the studies with certolizumab pegol. Conclusive data on the long term effect of anti-TNF therapy on radiographic progression are lacking. Studies have not shown benefit regarding the progression of structural changes after 2 and 4 years of continuous treatment when compared with historical cohorts[73-77]. However, recent data suggest a possible benefit as there was less bone formation in the anti-TNF treated group after 8 years[78, 79].
As for the extra-articular manifestations of SpA, anterior uveitis associated with HLA-B27 seems to respond quickly to monotherapy with infliximab. Some patients experience relapses after a median period of 5 months, which may simply reflect the natural course of the disease. Like infliximab, adalimumab has demonstrated efficacy in the treatment of uveitis based on results of open-label trials. Adalimumab was safe and effective in 68% of refractory uveitis patients 10 weeks after study enrolment, and maintained in 39% after 1 year[80]. Results from trials of etanercept are more contradictory[81]. Psoriasis patients react well to infliximab, adalimumab and etanercept, although the latter seems to be less effective than the monoclonal antibodies. Trials have revealed promising results for golimumab and certolizumab pegol as well[82, 83].

Anti-TNFα agents with proven efficacy in treating IBD patients include infliximab, adalimumab, certolizumab pegol (CD) and golimumab (UC)[84, 85]. A special scientific challenge is that more TNF-α antagonists seem to be effective in AS than in IBD. Etanercept is an example of such a drug with discordant efficacy in both diseases. Etanercept cannot be used to treat or prevent flares of ileocolitis[86]. Subcutaneous etanercept at a dose of 25 mg twice weekly (the approved dose for AS and RA) is safe but not effective in the treatment of patients with moderate to severe CD[87]. The biological basis of this discrepancy is still under research, but it is believed that reasons for such a discrepancy may include differences in bioavailability and pharmacodynamics, as well as biological effects at the cellular level (etanercept does not induce lymphocyte apoptosis) that may differ between different TNF-α antagonists. The influence of the different anti-TNF-α agents on microscopic gut inflammation in SpA, and the possible evolution to overt IBD, has not been investigated yet.
5.3 Treatment beyond TNF-blockade

In rheumatoid arthritis, many new target therapies have been tested over the past years, often with positive outcomes. Subsequently, these therapies have been trialed in the SpA population. The results of these studies however, are often less promising. Until so far, anti-TNF therapy remains the only evidence based and approved biological therapy for SpA.

B-cell depletion therapy. In an open-label study where 20 AS patients with active disease were treated, rituximab was modestly efficacious in anti-TNF naïve patients. However, it was not in anti-TNF inadequate responder patients[88]. Conversely, a French study on eight patients with SpA receiving rituximab showed less favorable outcomes[89]. In an open-label study of 9 patients, rituximab showed some efficacy in treatment of PsA[90]. In another open-label study of rituximab for 21 patients with PsA modest improvement in arthritis and psoriasis was observed, especially in TNF inhibitor-naïve patients[91]. Larger randomized controlled clinical trials are required to confirm the potential effect of rituximab in PsA.

Costimulation blockade. In a prospective open-label pilot study, abatacept (10 mg/kg) administered intravenously in 15 TNF-inhibitor naive patients and 15 patients with inadequate response to TNF-inhibitors with active AS, failed to demonstrate efficacy[92]. In PsA however, an ACR20 response of 48% was seen in the abatacept (10 mg/kg) group. Compared with placebo, improvements were significantly higher (P <0.006)[93].

Anti-interleukin 17A. Secukinumab has shown promising results in AS, significantly improving clinical signs and symptoms. ASAS20/ASAS40 responses were comparable to treatment with anti-TNF therapy[94], but confirmation of these preliminary results is needed. In a small multicenter, double-blind, randomized, placebo-controlled trial of PsA, statistical significance was not met in the primary end point, although a larger proportion of patients who were treated with secukinumab showed improvement than placebo[95]. The fact that this molecule is ineffective for CD[96] [moreover, higher rates of adverse events were noted compared with placebo] but highly effective for psoriasis[97] challenges our current understanding of the underlying pathogenetic pathways leading to EAM. Brodalumab and ixekizumab also significantly improved plaque psoriasis in 12-week, phase II studies[98].
**IL-12/23 inhibitor (p40 subunit).** An open-label proof-of-concept study on ustekinumab in AS seemed to be effective with a significant reduction of signs and symptoms[99]. In PsA, phase 3 studies have shown significant improvement of arthritis, enthesitis and dactylitis, improved physical function and plaque psoriasis[100-102]. Patients with moderate-to-severe CD, resistant to TNF-blockers, had an increased rate of response to induction with ustekinumab[103]. Furthermore, patients with an initial response to ustekinumab had significantly increased rates of response and remission with ustekinumab as maintenance therapy.

**Interleukin 6 inhibitor.** An open-label study failed to demonstrate any clinical improvement in patients with axial SpA treated with tocilizumab[104]. The published case reports show inconsistent results[105-108]. A placebo-controlled multicenter trial on tocilizumab in active AS patients was stopped after 12 weeks because the primary end point (ASAS 20) was not met in patients who had failed to respond to TNF-blockers.

**Small molecules.** In a small pilot study efficacy of apremilast (inhibitor of phosphodiesterase 4) for patients with AS was evaluated. Significant improvement was not observed in the treatment group[109]. A phase 3 randomized clinical trial is currently ongoing (Clinicaltrials.gov). Robust data on apremilast suggesting evidence as a DMARD in PsA[110] have been published. A dose-ranging study on tofacitinib (Janus Kinase (JAK) inhibitor) in AS is currently ongoing (Clinicaltrials.gov).
General introduction


Chapter 2

Aims
In the traditional view patients with axial SpA progress from a nonradiographic into a radiographic stage. It is anticipated that a relevant proportion of patients will never evolve into this radiographic stage. Unfortunately, so far there are no long-term prospective data on the evolution of patients diagnosed with early SpA (classified according to the ASAS criteria). Therefore, one of the outstanding questions remains whether a fraction of axSpA patients could have an overall mild disease progression, in some cases even self-limiting. This is important for the initiation of new (expensive) therapies in early phases of disease and is one of the concerns raised by regulatory authorities such as the Food and Drug Administration (FDA).

On the other hand, there is an overwhelming evidence that patients with a short symptom duration treated with anti-TNF therapy have a significantly higher chance of achieving remission than patients with longer disease duration[1].

Hence, there is an urgent need for tools to differentiate between patients with mild disease and patients at risk for quick evolution, especially in times of (expensive) biologic drugs. This thesis focuses on the development of a strategy to identify early nr-axSpA patients, at risk for (quick) evolution to AS. We anticipate that gut inflammation could be such a predictor of long term outcome, as previous studies suggest that patients with microscopic gut inflammation are more prone to develop CD and AS.

We started from the hypothesis that we could predict the risk on microscopic gut inflammation, based on surrogate markers. Such model may be useful in the future to identify individuals at risk, who would benefit from an early aggressive therapeutic approach. In this respect, we know that etanercept, a biological used for the treatment of SpA, has no indication in the treatment of IBD, in contrast to infliximab and adalimumab (and certolizumab and golimumab) which are effective in both conditions. Probably etanercept may not be the best choice for SpA patients with microscopic gut inflammation, especially those with an elevated risk to develop IBD.
However, patients treated with etanercept are possibly less prone to infectious complications, compared to patients treated with monoclonal antibodies. Furthermore, we know that prevalence of clinical remission in SpA patients treated with sulphasalazine is significantly higher in patients with microscopic gut inflammation[2].

**Chapter 3** represents a multiparametric predictive model to identify the risk of microscopic gut inflammation in SpA. On the basis of genetic, radiological, clinical data and laboratory findings, such as biomarkers, we aimed to produce a clinically applicable predictive algorithm. We therefore employed a genotype-phenotype association in the Ghent Inflammatory Arthritis and spondylitis cohort (GIANT) and related this to the onset of microscopic gut inflammation. All collected data were used to produce a tailored logistic regression model for risk stratification.

**Chapter 4** examines the link between the extent of bone marrow edema and gut inflammation. The introduction of MRI has enabled us to identify active inflammation of the SIJs early in the disease course. In our own experience, patients with more severe BMO on MRI showed more frequently microscopic gut inflammation and vice versa. Ileocolonoscopy was performed in 68 consecutive patients, naive to TNFα-blockers. MRI of the SIJs was performed in all patients. We compared the extent of BMO between the patients according to histological gut classification.

Altogether, these studies lead to new insights into the identification of early axial SpA and the underlying basis of the overlap between SpA and IBD, particularly the relation to microscopic gut inflammation and the functional consequences thereof.
Aims

References


Chapter 3

Original research article - Concise report

Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model

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Objective
To assess the rates and explore predictors of microscopic gut inflammation in a cohort of patients with axial and peripheral spondyloarthritis

Methods
Ileocolonoscopy was performed in 65 patients with axial and peripheral SpA from the Gent Inflammatory Arthritis and SpinoT cohort. Histopathological analysis and scoring were performed by an experienced pathologist.

Results
Overall, 46.2% of the patients with SpA showed microscopic gut inflammation. In axial SpA, the following parameters were independently associated with gut involvement: male sex (OR=8.9, p=0.035); high disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Index (OR=2.05, p=0.032); restricted spinal mobility measured by the Bath Ankylosing Spondylitis Metrology Index (OR=1.94, p=0.009); and younger age (OR=0.85, p=0.013). No clear association was found for human leucocyte antigen-B27 status, presence of peripheral arthritis, enthesitis, uveitis, psoriasis, intake of non-steroidal anti-inflammatory drugs and family history of SpA. The prevalence of gut inflammation in non-radiographic axial SpA and ankylosing spondylitis was comparable.

Conclusions
The prevalence of microscopic gut inflammation in SpA remains unaltered over time. Younger age (shorter symptom duration), progressive disease, male sex and higher disease activity are independently associated with microscopic gut inflammation in axial SpA.
INTRODUCTION

It has been recognised for a long time that ~60% of all patients with spondyloarthritis (SpA) show microscopic inflammatory gut lesions, a fraction of which evolve into Crohn's disease. However, since the first report of these findings (1984–1985)[1], the field of SpA has experienced major developments, among them the possibility to decrease the gap between onset of symptoms and diagnosis, particularly by the introduction of MRI of the sacroiliac joints (SIJs). As a consequence of the introduction of the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria[2], it is now possible to identify early in the disease course patients with non-radiographic axial SpA. In addition, improved hygiene has resulted in altered exposure to, and colonisation by, micro-organisms (hygiene hypothesis)[3]. This has led to a shift in pathologies, possibly suggesting that the prevalence of mucosal inflammation may have declined.

This study was designed to ascertain whether the prevalence of gut involvement in SpA has changed. Furthermore, we aimed to develop a predictive model for microscopic gut inflammation in axial SpA using clinical and biological parameters.

METHODS

Study population

The Gent Inflammatory Arthritis and spondylitis cohort is a prospective observational cohort in which patients diagnosed with SpA and classified according to the ASAS criteria are prospectively followed. Ileocolonoscopy was performed in 65 consecutive patients, naive to tumour necrosis factor (TNF) blockers. None of the patients reported suggestive gastrointestinal complaints for, or had a previous diagnosis of, inflammatory bowel disease (IBD).

History and investigations

All patients were interviewed about their disease history, their family history of SpA, drug intake and smoking habits. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was defined as continuous use at the time of endoscopy or within 1 week before. Before ileocolonoscopy, all patients underwent a complete clinical examination. Radiographs of the SIJs, the spine and involved joints were obtained. MRI of the SIJs was performed in 37 out of 49 patients diagnosed with axial SpA.
In the other patients, diagnosis and classification was made on the basis of x-ray and/or human leucocyte antigen (HLA)-B27 positivity. The results were interpreted by a group of rheumatologists and a musculoskeletal radiologist (LJ). Laboratory tests included inflammatory parameters, HLA-B27 determination and peripheral blood cell examination. All patients were asked to complete the following questionnaires: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Visual Analogue Scale (VAS) global disease activity.

Ileocolonoscopy

For each patient, 4–14 biopsy samples were taken of ileum and colon, with a median number of six per patient. The biopsy specimens were classified by an experienced pathologist, who was unaware of macroscopic findings and the patient’s diagnosis.

Histological classification

Two histological types of microscopic gut inflammation can be distinguished in SpA: acute and chronic as previously reported[4]. This classification refers to the observed morphological characteristics, not the disease duration. Similarly to previous ileocolonoscopic studies[5], a diagnosis of chronic inflammation was made whenever a biopsy specimen featured chronic lesions, regardless of acute inflammation in other fragments.

Acute lesions

The normal mucosal structure is preserved and changes are limited to infiltration of the epithelium with neutrophils and eosinophils, crypt abscess formation, and infiltration of the lamina propria with polymorphonuclear cells.

Chronic lesions

The normal mucosal architecture is disturbed, with crypt distortion, villous blunting and fusion, increased mixed lamina propria cellularity, and presence of basal lymphoid aggregates.
Statistical analysis

Data were analysed using SPSS V.19. A univariate analysis was performed to compare all demographic, clinical and biochemical variables between the patients with and without microscopic gut inflammation. Normally distributed numeric variables were tested by an independent-samples t test. In the case of a skewed distribution, the Mann–Whitney U test was performed. For categorical variables, the Fisher exact test was used. Multivariate binary logistic regression analysis (backward selection) was performed to estimate the associations between patient and disease characteristics that are potential predictors of microscopic gut inflammation. Model quality was checked by calculating the area under the receiver operating characteristics curve (ROC-AUC) and the Hosmer–Lemeshow test. For all analyses, p<0.05 was considered significant. Analyses were restricted to individuals with complete data.
RESULTS

Patients
Sixty-five patients were included in the study, of which 49 were diagnosed with axial SpA (ASAS classification criteria) with or without peripheral manifestations, and 16 were diagnosed with peripheral SpA without axial involvement. Baseline characteristics of all patients are presented in table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Axial SpA (n=49)</th>
<th>Peripheral SpA (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.7±11.5</td>
<td>37.8±14.3</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
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<td>1.3 (0.2–18.6)</td>
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<td>Male gender</td>
<td>25 (51.0)</td>
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</tr>
<tr>
<td>HLA-B27 (+)</td>
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<td>7 (43.8)</td>
</tr>
<tr>
<td>Presence or history of arthritis</td>
<td>8 (16.3)</td>
<td>15 (93.8)</td>
</tr>
<tr>
<td>Presence or history of enthesitis*</td>
<td>11 (22.4)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Presence or history of uveitis</td>
<td>10 (20.4)</td>
<td>1 (6.3)</td>
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<tr>
<td>Presence or history of psoriasis</td>
<td>4 (8.2)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Family history of SpA</td>
<td>21 (42.8)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Treatment with NSAIDs</td>
<td>44 (89.8)</td>
<td>9 (56.3)</td>
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<tr>
<td>Treatment with DMARDs</td>
<td>1 (2.0)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Smoking, currently</td>
<td>12 (24.5)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.7 (0.0–2.7)</td>
<td>0.7 (0.0–10.3)</td>
</tr>
<tr>
<td>Active lesions on MRI SIJ</td>
<td>33 (89.2)</td>
<td>–</td>
</tr>
<tr>
<td>BASDAI, numeric rating scale</td>
<td>4.6 (0.4–9.6)</td>
<td>–</td>
</tr>
<tr>
<td>ASDAS</td>
<td>2.7 (0.4–5.4)</td>
<td>–</td>
</tr>
<tr>
<td>BASMI</td>
<td>2 (0–9)</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 1: Baseline demographic and clinical characteristics
In the case of numeric variables, results are given as mean±SD (normal distribution) or median and range (skewed distribution); dichotomous parameters are presented as frequencies with percentage.
*Past or present enthesitis diagnosed by a physician.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; SpA, spondyloarthritis.
Prevalence of microscopic gut inflammation in axial and peripheral SpA

Overall, 46.2% of the patients showed microscopic gut inflammation. The acute type of inflammation was present in 16.9%, and the chronic type in 29.2% of patients (figure 1). Figure 2 shows the distribution according to classification. The inflammation was located in the ileum in 50% of cases, in the colon in 23.3%, and in 26.7% both ileum and colon were affected. There was a strong similarity between the microscopic and macroscopic findings. All but two patients with a normal microscopic appearance also had a perfectly normal macroscopic aspect of the mucosa. Eighteen out of 30 patients with microscopic inflammatory involvement showed macroscopic abnormalities, ranging from erythema, oedema and friability of the mucosa to ulcerations, granulation and cobblestoning.

Prediction of microscopic gut inflammation in axial SpA

No significant differences were observed in the univariate analysis (see online supplementary data table 1) comparing patients with axial SpA with or without microscopic gut inflammation.

We next conducted a multivariate analysis. For 45 of the 49 patients with axial SpA, complete data were available. Using a backward procedure, we included five variables in our model. The model is presented in table 2. Bootstrap validation showed no indication for overfitting and confirmed the results found in our original model (data not shown). Male sex and a higher BASDAI were independently associated with microscopic gut inflammation (OR 8.9, 95% CI 1.18 to 67.37 and OR 2.05, 95% CI 1.06 to 3.95, respectively), as well as higher Bath Ankylosing Spondylitis Metrology Index (BASMI) (OR 1.94, 95% CI 1.18 to 3.19) and younger age (OR 0.85, 95% CI 0.75 to 0.97). Our final model has a sensitivity of 81.8% and a specificity of 78.3% for detecting microscopic gut inflammation in axial SpA. No indication for multicollinearity was found.

No clear association was found for HLA-B27 status, NSAID use, smoking habits, presence of peripheral arthritis, enthesitis, family history of SpA, uveitis and psoriasis.
Figure 1: Different patterns of ileal biopsy findings in SpA patients.

(A) Normal histology of ileal mucosa featuring slender villi and straight crypts; absence of inflammatory cell infiltrates (H&E; original magnification ×4). (B) Higher magnification emphasising lack of inflammatory cell infiltration in villus epithelium (H&E; original magnification ×20). (C) Focal active inflammation in mucosa with preserved architecture of villi and crypts (H&E; original magnification ×4). (D) Increased amount of granulocytes in villus and crypt epithelium with well-preserved epithelium (H&E; original magnification ×20). (E) Chronic dense inflammatory cell infiltration of lamina propria with crypt and villus alterations (H&E; original magnification ×4). (F) Active granulocytic infiltration of villus epithelium and chronic dense lymphoplasmocytic cellular infiltrate in the lamina propria (H&E; original magnification ×20).

This figure is only reproduced in colour in the online version.
Table 2: Multivariate analysis of microscopic gut inflammation in axial SpA
Statistically significant p values are given in bold.
BASDAI, the Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ROC-AUC, Receiver Operating Characteristic-Area Under the Curve; TNR, True negative rate, specificity; TPR, True positive rate, sensitivity

<table>
<thead>
<tr>
<th>Model variable</th>
<th>OR</th>
<th>CI</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.85</td>
<td>0.75 to 0.97</td>
<td>0.013</td>
</tr>
<tr>
<td>Sex, male</td>
<td>8.90</td>
<td>1.18 to 67.37</td>
<td>0.035</td>
</tr>
<tr>
<td>BASMI</td>
<td>1.94</td>
<td>1.18 to 3.19</td>
<td>0.009</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2.05</td>
<td>1.06 to 3.95</td>
<td>0.032</td>
</tr>
<tr>
<td>Presence or history of enthesitis</td>
<td>0.32</td>
<td>0.04 to 2.40</td>
<td>0.27</td>
</tr>
<tr>
<td>Constant</td>
<td>0.97</td>
<td></td>
<td>0.981</td>
</tr>
<tr>
<td>Nagelkerke R²</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPR and TNR</td>
<td>81.8% and 78.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROC-AUC</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Prevalence of gut inflammation according to classification.
DISCUSSION

In this cohort of patients with axial and peripheral SpA, nearly half showed microscopic gut inflammation. A high frequency in patients with different forms of SpA was originally discovered in the 1980s by Mielants et al[5] and has been validated by several other investigators[6–8]. Almost 30 years later, new classification criteria enable us to identify early axial and peripheral SpA. This study thus provides substantial new insights into the link between gut inflammation, symptom duration and disease activity in patients with axial SpA.

Over the past few years, striking progress has been made in our understanding of SpA and IBD. Nevertheless, the exact role of microscopic gut inflammation in SpA has not been determined, nor has the link with outcome measures been investigated. We have focused on clinical and biological parameters predictive of the presence of microscopic gut inflammation in patients with axial SpA; future work will address predictive parameters in peripheral SpA. In axial SpA, we found younger age (equivalent to shorter symptom duration), male sex, higher disease activity (BASDAI) and higher BASMI to be independently associated with microscopic gut inflammation.

We selected BASDAI for inclusion in the final model instead of Ankylosing Spondylitis Disease Activity Score (ASDAS) because we found that the value of ASDAS in predicting gut inflammation was explained by the BASDAI component, not by the C-reactive protein (CRP) component (see multivariate analysis in online supplementary data table 2). Both younger age and shorter symptom duration (with a correlation of 0.47) had a significant influence on the odds of having microscopic gut inflammation. We included age in the final model, as it was a more accurate predictive parameter (ROC-AUC and Nagelkerke $R^2$). The fact that CRP did not show a significant association with gut inflammation was surprising. However, a recent study by Soliman et al showed no significant association between CRP and disease activity measured by bone marrow oedema on MRI of the SIJ[9]. Another study by Machado et al also found weak to moderate correlations between CRP and MRI scores[10]. Future research will address the association between gut inflammation and the quantification of bone marrow oedema on MRI.
Despite the putative link between NSAID use and bowel inflammation, the association between NSAIDs and IBD flares cannot be considered definitive, because, in the only two available randomised controlled, double-blind trials in patients with quiescent IBD receiving a cyclo-oxygenase 2-selective inhibitor (celecoxib/etoricoxib) or placebo[11,12] no significant difference in the frequency of disease exacerbation was found. Considering microscopic gut inflammation, Mielants and Veys[13] observed an equal prevalence among patients receiving NSAIDs and patients not receiving anti-inflammatory drugs. In the present study, we controlled for intake of NSAIDs in our predictive model. However, no association was found with microscopic gut inflammation in either the univariate or the multivariate analysis.

Prospective follow-up studies on SpA revealed microscopic gut inflammation to be an important risk factor for developing ankylosing spondylitis[14]: evolution of non-ankylosing spondylitis SpA to full-blown ankylosing spondylitis was always associated with gut involvement at disease onset, and remission of joint inflammation was associated with disappearance of gut inflammation. The present study identified shorter symptom duration and higher disease activity to be associated with microscopic gut inflammation, suggesting its important pathogenic role. Male patients overall show more rapid radiographic progression[15], which supports our finding that male sex is a major risk factor for underlying microscopic gut involvement. Future prospective studies are needed to assess the real impact of microscopic gut inflammation on the long-term outcome of early axial SpA as defined by the new criteria, and to evaluate the impact of more aggressive therapeutic strategies, including early intervention trials based on the presence or absence of microscopic gut inflammation.

The acute and chronic types of gut involvement were pooled in this analysis, as it can be expected that the development of chronic bowel inflammation occurs through a transition phase, in which inflammation evolves from an acute to a chronic state. This has been termed the transition model[16]. In line with this, no significant differences in baseline characteristics were found between the two groups. The higher prevalence of chronic gut inflammation found in ankylosing spondylitis compared with axial SpA supports this transition model and indirectly validates the new ASAS criteria for axial SpA. Overall, our results underscore the role of bowel inflammation in SpA.
Results

**FOOTNOTES**

**Contributors** LVP, FEVdB, PJ, PC, MDV, HM, DE: study conception and design. LVP, PJ, EG, MDV, HP: acquisition of data. LVP, CC, RC, LJ, DE: analysis and interpretation of data.

**Funding** This study was supported by a grant from the Clinical Research Funding of Ghent University Hospital to LVP.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** The study protocol was approved by the ethics committee of Ghent University Hospital.

**Provenance and peer review** Not commissioned; externally peer reviewed.
References

Chapter 4

Original research article - Concise report

Degree of bone marrow oedema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort

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Introduction
Bone marrow oedema (BMO) of the sacroiliac joints (SIJs) is a hallmark of axial spondyloarthritis (SpA). However, the relationship between the extent of BMO and disease phenotype is poorly understood.

Objective
To assess the link between BMO of the SIJs and gut inflammation. We have also evaluated the correlation between BMO and established disease activity parameters.

Methods
Sixty-eight patients with axial SpA from the Gent Inflammatory Arthritis and spoNdylitis cohOrT underwent ileocolonoscopy and MRI of the SIJs. Histopathological analysis and SPondyloArthritis Research Consortium of Canada (SPARCC) scores were performed.

Results
A significant higher SPARCC score (median (range)) was observed in axial SpA patients showing chronic gut inflammation (16.9 (3.8–68.3)) compared with axial SpA patients showing normal gut histology (9.8 (0.0–45.0); p<0.05). In a multiple linear regression model, we identified, besides chronic gut inflammation (effect size of 11.3, 95% CI (2.1 to 20.4)), male sex (effect size of 10.5, 95% CI (3.3 to 17.8)) to be independently associated to the extent of BMO. There was a low to moderate correlation between the degree of BMO and C-reactive protein(r=0.39, p=0.002) and Ankylosing Spondylitis Disease Activity Score (r=0.35, p=0.007).

Conclusions
Higher degrees of BMO were observed in patients showing chronic gut inflammation. These data solidify a link between mucosal inflammation and progressive disease in axial SpA.
INTRODUCTION

In spondyloarthritis (SpA), an intriguing link between gut and joint inflammation exists. About half of the patients show microscopic inflammatory gut lesions, a fraction of which evolves into Crohn's disease. Over the past decade a marked progress has been achieved to diagnose SpA at an earlier stage before structural damage has occurred. New imaging modalities such as MRI of sacroiliac joints (SIJs) and spine have been widely validated. The results of these studies have led to new insights into how the disease emerges and are reflected by new SpA classification criteria developed by the Assessment of SpondyloArthritis international Society (ASAS) consortium[1]. Therefore, the terms axial and peripheral SpA have been introduced to define primarily axial versus peripheral joint involvement. Recently, the high prevalence of microscopic gut inflammation was confirmed in a patient cohort fulfilling the ASAS criteria for axial and peripheral SpA (Gent Inflammatory Arthritis and spoNdylitis cohOrT (GIANT)), and several risk factors for microscopic gut inflammation were identified[2].

MRI is one of the modalities that enables us to identify early in the disease course patients with non-radiographic axial SpA (nr-axSpA) by assessing bone marrow oedema (BMO) of the SIJs (imaging arm). However, the correlation between the extent of BMO and different measures of disease activity remains unclear. This study was designed to assess the link between BMO of the SIJs and gut inflammation. Furthermore, we have evaluated the correlation between BMO and established disease activity parameters.

METHODS

Study population

The GIANT is a prospective observational cohort in which patients diagnosed with SpA and classified according to the ASAS criteria are prospectively followed. Ileocolonoscopy was performed in 68 consecutive patients, naive to tumour necrosis factor-α (TNF-α) blockers. MRI of the SIJs was performed in all patients. Patients with complete ankylosis of the SIJs were excluded from the analysis as they showed no BMO.
History and investigations

MRI

Images were obtained on a 1.5 T MRI unit (Avanto/Symphony, Siemens Medical, Erlangen, Germany). The SIJs were imaged in a body flexed array coil (Siemens Medical, Erlangen, Germany). Sequence protocol included semicoronal (along long axis of the sacral bone) T1-weighted turbo spin echo (TSE) (slice thickness (ST) 3 mm; repetition time/echo time (TR/TE) 595/20 ms); semicoronal STIR (ST 3 mm; TR/TE/inversion time (TI) 5030/67/150 ms); axial T2-weighted FS TSE (ST 6 mm; TR/TE 5260/13 ms); axial STIR (ST 5 mm; TR/TE/TI 7540/67/150 ms). The SPondyloArthritis Research Consortium of Canada (SPARCC) method was used for scoring BMO in the SIJs[3]. All scores were performed by an experienced musculoskeletal radiologist (LJ), who was trained and calibrated by the SPARCC online MRI training module. As we used ST 3 mm in the semicoronal STIR sequence, we scored eight coronal slices instead of the usual six slices. All scores were converted to a maximum score of 72 by multiplying the obtained score by 3/4.

Ileocolonoscopy

In each patient, 4–14 biopsies were taken of ileum and colon, with a median number of six specimens per patient. The biopsies were read and classified by an experienced pathologist (CC), who was unaware of macroscopic findings and the patient’s diagnosis.

Other

Laboratory tests included inflammatory parameters, human leucocyte antigen-B27 (HLA-B27) determination and peripheral blood cell examination. All patients were asked to complete the following questionnaires: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and visual analogue scale (VAS) global disease activity.

Histological classification

Two histological types of microscopic gut inflammation can be distinguished in SpA—acute and chronic inflammation—as previously reported[4]. This classification refers to the observed morphological characteristics, not to the disease duration. Similar to previous ileocolonoscopic studies[5], a diagnosis of chronic inflammation was made whenever a biopsy featured chronic lesions, regardless of acute inflammation in other fragments.
Statistical analysis
Data were analysed using SPSS V.19. Non-parametric independent sample testing (Kruskal–Wallis and Dunn–Bonferroni posthoc testing with correction for multiple testing) was performed to compare the SPARCC scores between the patients according to histological classification. Subsequently, multiple linear regression analysis was performed to adjust for confounding factors (age, sex, HLA-B27 positivity). The intraobserver reproducibility was assessed by calculating an intraclass correlation coefficient (ICC). A two-way random model for absolute agreement was used. The correlations were studied with Spearman’s rank-based correlation coefficient. The data are expressed as median (range); for all analyses p<0.05 was considered statistically significant. Analyses were restricted to the individuals with complete data.

RESULTS
Patients
Sixty-eight patients were screened, of which 62 were included in the analysis. Because of total ankylosis of the SIJs, six patients were excluded from the study analysis. Median time between MRI and ileocolonoscopy was 1.44 months. Baseline demographic and clinical characteristics are presented in table 1. In total, 3 of 16 patients with histology of chronic gut inflammation had a recent or an established diagnosis of inflammatory bowel disease (IBD).
### Results

<table>
<thead>
<tr>
<th></th>
<th>Normal gut histology (n=35)</th>
<th>Acute inflammation (n=11)</th>
<th>Chronic inflammation (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>36.4±9.0</td>
<td>32.8±8.3</td>
<td>28.9±7.0</td>
</tr>
<tr>
<td>Symptom duration, years †</td>
<td>7.6±7.5</td>
<td>2.6±3.7</td>
<td>4.1±4.5</td>
</tr>
<tr>
<td>Male Gender</td>
<td>19 (54.3)</td>
<td>4 (36.4)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>HLA-B27 (+)</td>
<td>28 (80.0)</td>
<td>10 (90.9)</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>ModNY AS</td>
<td>11 (31.4)</td>
<td>3 (27.3)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>0.4 (0.0–2.4)</td>
<td>0.5 (0.0–5.4)</td>
<td>0.6 (0–2.2)</td>
</tr>
<tr>
<td>BASDAI, numeric rating scale ‡</td>
<td>3.7 (0.4–7.1)</td>
<td>6.0 (2.4–9.6)</td>
<td>5.3 (0.4–6.6)</td>
</tr>
<tr>
<td>ASDAS</td>
<td>2.3 (0.4–3.9)</td>
<td>3.0 (1.2–5.4)</td>
<td>2.8 (1.0–4.2)</td>
</tr>
</tbody>
</table>

**Table 1: Baseline demographic and clinical characteristics of the study population**

In case of numeric variables, results are given as mean with SD or as median and range; dichotomous parameters are presented as frequencies with percentage.

*Patients with chronic gut inflammation were significantly younger compared with patients with normal gut histology (one-way ANOVA—independent samples t test).
†Patients with acute gut inflammation had a significant shorter symptom duration compared with patients with normal gut histology (Kruskal-Wallis and Mann-Whitney U test). These differences reflect the conclusion of our recently published prediction model for microscopic gut inflammation.[2]
‡Although patients with normal gut histology had numerically lower values for BASDAI compared with patients with either acute or chronic gut lesions, this difference did not reach statistical significance (p=0.068).

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA, human leucocyte antigen; ModNY AS, ankylosing spondylitis according to modified New York criteria.

### Degree of BMO in patients with and without gut inflammation

The median SPARCC score of each group is presented in figure 1A. A significant difference was found between axial SpA patients showing chronic gut inflammation (16.9 (3.8–68.3)) and patients with normal gut histology (9.8 (0.0–45.0); p<0.05). This is clearly illustrated by figure 1B, showing chronic gut inflammation on ileal biopsy in a patient with extensive BMO on MRI (SPARCC score 48/72).

These results were confirmed in a multiple linear regression analysis: adjusted for age, HLA-B27 positivity and male sex, chronic gut inflammation was associated with higher SPARCC scores compared with normal gut histology, with an effect size of 11.3 (95% CI (2.1 to 20.4)). Additionally, we identified male sex to be independently associated with higher SPARCC scores, with an effect size of 10.5 (95% CI (3.3 to 17.8). No significant association with age or HLA-B27 positivity was found.
Reliability of the SPARCC scoring system

For a subset of 30 patients, a second reading was performed. The intraobserver variability was very small, with an ICC of 0.99.

Figure 1: (A) Comparison of the median SPARCC-scores of patients with normal, acute and chronic gut histology. NS, not significant. (B) Left: Active granulocytic infiltration of villus epithelium and chronic dense lymphoplasmocytic cellular infiltrate in the lamina propria (H&E; original magnification ×20). Right: Semicoronal STIR MR image shows active inflammation as bilateral bone marrow oedema of the sacroiliac joints (long arrows) and at the corners of the L5 vertebral body (short arrows).

Correlation between BMO and established disease activity parameters

As a next step, we evaluated the correlation between BMO and established disease activity parameters. These results are presented in table 2. C-reactive protein (CRP) (r=0.39, p=0.002) and Ankylosing Spondylitis Disease Activity Score (ASDAS) (r=0.35, p=0.007) showed a low to moderate correlation with the SPARCC score. No correlation with BASDAI or patient global VAS score was found.
DISCUSSION

In this study, we found that gut inflammation is linked to degree of BMO in SIJs of patients with axial spondyloarthritis. More specifically, highest levels of BMO were found in patients with chronic gut lesions. In the current analysis, patients with overt IBD (n=3) were not excluded, as we were interested in the link between disease activity and gut inflammation in general, not restricted to microscopic involvement. However, results were similar when patients with overt IBD were excluded from the analysis. Thus, our findings indirectly illustrate the evidence of a relationship between inflammation and progressive disease[6–8] as SpA patients with chronic gut inflammation are known to evolve more frequently to ankylosing spondylitis[9].

One of the major reasons for designing the new ASAS classification criteria for axial and peripheral SpA was the well-known ascertainment that by applying modified NY criteria for AS there is a rather long delay between symptom onset and definitive diagnosis[10]. This was partly alleviated by the Amor[11] and the ‘European Spondyloarthropathy Study Group’ (ESSG) criteria[12], as radiographic sacroiliitis was not longer required to fulfill these criteria. However, especially with the latter, there was the fear for less specificity[13], which is important if these criteria would be used for decisions on the use of expensive new (biologic) drugs. The ASAS criteria allow classification of both classic AS (radiographic axSpA) as well as an entity, which is named nr-axSpA. In our study, 66.1% of patients did not fulfill the modified New York criteria for AS and could thus be classified as nr-axSpA. At present, long-term data are lacking to determine which proportion of nr-axSpA patients progresses to the radiographic stage of the disease. Preliminary data suggest that the progression rate from non-radiographic to radiographic axial SpA over 2 years is about 10%, and around 20% in patients with active inflammation on MRI of the SIJ[14].

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Table 2: Spearman correlation coefficients (and p values) between disease activity parameters and SPARCC score

<table>
<thead>
<tr>
<th></th>
<th>SPARCC score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>0.39 (0.002)</td>
</tr>
<tr>
<td>BASDAI</td>
<td>0.10 (0.440)</td>
</tr>
<tr>
<td>ASDAS</td>
<td>0.35 (0.007)</td>
</tr>
<tr>
<td>Patient global VAS score</td>
<td>0.10 (0.429)</td>
</tr>
</tbody>
</table>

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; SPARCC, SPondyloArthritis Research Consortium of Canada; VAS, visual analogue scale.
Identifying patients at risk for early progression, who would benefit from more aggressive therapeutic strategies, is probably one of the greatest challenges for the future. The results of this study add a novel factor, chronic gut inflammation, to this risk stratification.

The multiple regression analysis confirmed the independent association, not related to HLA-B27 positivity or age, and additionally identified male sex as a predictor of higher degrees of BMO. Indeed, male sex is a well-established parameter of MRI inflammation and progressive disease[15–18]. Previous reports have suggested a link between HLA-B27 positivity and MRI inflammation of the SIJs[17–19]. However, in these studies, either no adjustment for confounding factors was done or only the absence or the presence of BMO was assessed (not the extent).

We have also evaluated the correlation between BMO of the SIJs and established clinical disease activity parameters. SPARCC scores correlated weakly to moderately with CRP (r=0.39, p=0.002) and ASDAS (r=0.35, p=0.007). Machado et al[20] and Konca et al[21] performed similar analyses assessing BMO in the spine and also found weak to moderate correlations with CRP and ASDAS. In a smaller study by Soliman et al[22], MRI features of activity were not related to CRP; however, BMO was not assessed quantitatively in this study, making a comparison difficult. Similar to our and previous reports[23–25], there were no correlations between MRI scores and other disease activity measures, namely BASDAI and patient global VAS score. Therefore, our data regarding clinical disease activity and BMO of the SIJs are entirely consistent with the data in the referred studies on BMO in the spine. As we did not perform MRI of the spine systematically, we cannot comment on this in our study population.

There are some limitations to our study. We clearly established the link between chronic gut lesions and BMO of the SIJs. Possibly because of the smaller number of patients with acute gut histology, we cannot draw definite conclusions on this type of gut inflammation. However, prospective follow-up studies have shown that these acute lesions resolve spontaneously in most cases[5]. Furthermore, we used the SPARCC score to quantitate BMO in the SIJs. However, this scoring method only assesses six (eight) coronal slices that demonstrate the cartilagenous portion of the SIJs, providing no information on the other parts. It would be interesting to confirm our results in future studies with other validated scoring systems (Berlin, Leeds or Danish SIJ MRI scoring method).
As chronic mucosal inflammation seems to be linked to active inflammation (BMO) on MRI of the SIJs, with the latter having an approximately twofold higher progression rate from nr-axSpA to classic AS[14], our data on the link between BMO of the SIJs and gut inflammation provide clinicians with an extra tool to stratify patients at higher risk for progression.

Results

FOOTNOTES

Handling editor Tore K Kvien

Contributors LVP, LJ, FVdB, PJ, PC, MDV, HM and DE are responsible for study conception and design. LVP, PJ, EG, MDV and HC are responsible for acquisition of data. LVP, CC, RC, LJ and DE are responsible for analysis and interpretation of data.

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Competing interests None.

Patient consent Written informed consent was obtained from all patients, prior to any study related procedure.

Ethics approval The study protocol was approved by the Ethical Committee of Ghent University Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.
REFERENCES


Chapter 5

General discussion and conclusions
SpA is a family of common chronic inflammatory disorders, affecting the spine, peripheral joints and entheses. Up until recently, the average period between the first emergence of symptoms and diagnosis of AS was about 6 to 11 years[1]. During this time, patients rarely received targeted counseling and treatment by a specialized physician. The consequences of this delay were structural damage, limitations and disability affecting patients’ quality of life and economic burdens both for the individual and society. An early diagnosis of SpA can lead to quick access to adequate treatment, improving the outcome.

This diagnostic delay in AS patients was mainly a consequence of the relatively late appearance of definite sacroiliitis on X-ray in most of the patients, a condition for diagnosis according to the Modified New York classification criteria. Recently, the field of rheumatology has experienced major developments, especially with the introduction of MRI of the SIJs. MRI can detect active inflammation of the SIJs in early stage, even when structural damage is lacking. Clinicians will now take all these different SpA characteristics into account when establishing a diagnosis. In order to define homogeneous subgroups within the SpA concept, new classification criteria have been developed for peripheral and axial SpA, with the latter consisting of classic AS and nr-axSpA, a potentially early form of axial SpA in which no definite radiographic lesions are visible[2]. These criteria are based upon the presence of either an imaging anchor (which could be classic radiographic sacroiliitis or active inflammation on MRI), or HLA-B27 positivity, in combination with other typical SpA characteristics.

In 2010, the Rheumatology department of Ghent University Hospital started the Ghent Inflammatory Arthritis and spoNdylitis cohort. Patients with a clinical diagnosis of SpA, classified according to the ASAS criteria, are followed prospectively every 6 months for at least 5 years by clinical parameters, standardized questionnaires, laboratory tests and imaging. This database has been continuously enriched with new patients ever since, and has managed to include 250 SpA patients, of which 100 with ileocolonoscopy. It’s the first prospective cohort to follow patients with a clinical SpA diagnosis, classified according to the new criteria.

The baseline characteristics of the newly diagnosed axial SpA patients in GIANT compared to other prominent cohorts[3-8] are shown in table 3.
<table>
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<th>GIANT</th>
<th>GESPIC</th>
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<th>ESPAC</th>
<th>ATLAS</th>
<th>ABILITY-1</th>
<th>Haibel</th>
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<tr>
<td></td>
<td>N =95</td>
<td>N =33</td>
<td>N =62</td>
<td>N =236</td>
<td>N =119</td>
<td>N =56</td>
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<td>Age at onset, mean</td>
<td>29.1</td>
<td>27.9</td>
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<td>30.4</td>
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<tr>
<td>Symptom duration, mean, years</td>
<td>5.0</td>
<td>6.3</td>
<td>4.4</td>
<td>5.2</td>
<td>3.0</td>
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</tr>
<tr>
<td>Male sex</td>
<td>50.5</td>
<td>63.6</td>
<td>43.5</td>
<td>64.0</td>
<td>65.5</td>
<td>42.9</td>
<td>76.8</td>
</tr>
<tr>
<td>HLA-B27 positive, %</td>
<td>77.9</td>
<td>87.9</td>
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<td>82.2</td>
<td>73.1</td>
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<td>89.1</td>
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<tr>
<td>Positive family history of SpA</td>
<td>48.4</td>
<td>45.5</td>
<td>50.0</td>
<td>37.2</td>
<td>39.3</td>
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<td>Clinical manifestations, ever</td>
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<td>Peripheral arthritis</td>
<td>17.9</td>
<td>18.2</td>
<td>17.7</td>
<td>37.4</td>
<td>39.8</td>
<td>40.9</td>
<td>19.6</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>12.6</td>
<td>15.2</td>
<td>11.3</td>
<td>39.4</td>
<td>37.8</td>
<td>43.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>20.0</td>
<td>24.2</td>
<td>17.7</td>
<td>20.9</td>
<td>19.3</td>
<td>12.4</td>
<td>23.2</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>1.1</td>
<td>0</td>
<td>1.6</td>
<td>6.3</td>
<td>8.4</td>
<td>4.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>10.5</td>
<td>6.1</td>
<td>12.9</td>
<td>10.2</td>
<td>9.2</td>
<td>9.8</td>
<td>14.3</td>
</tr>
<tr>
<td>IBD</td>
<td>5.3</td>
<td>3.0</td>
<td>6.5</td>
<td>2.6</td>
<td>2.5</td>
<td>1.8</td>
<td>5.4</td>
</tr>
<tr>
<td>BASDAI, mean (0–10)</td>
<td>4.0</td>
<td>3.8</td>
<td>4.1</td>
<td>4.0</td>
<td>4.0</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>BASFI (0–10), mean</td>
<td>2.9</td>
<td>3.1</td>
<td>2.8</td>
<td>3.1</td>
<td>3.1</td>
<td>2.5</td>
<td>N/A</td>
</tr>
<tr>
<td>BASMI (0–10), mean</td>
<td>1.7</td>
<td>1.9</td>
<td>1.6</td>
<td>2.0</td>
<td>1.9</td>
<td>1.1</td>
<td>N/A</td>
</tr>
<tr>
<td>ASDAS, mean</td>
<td>2.5</td>
<td>2.6</td>
<td>2.4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2.9</td>
</tr>
<tr>
<td>Elevated CRP, %</td>
<td>47.3</td>
<td>54.5</td>
<td>43.1</td>
<td>51.9</td>
<td>49.6</td>
<td>29.8</td>
<td>69.1</td>
</tr>
</tbody>
</table>

*Patients in RCTs were selected for high disease activity

Table 3: baseline characteristics of newly diagnosed SpA patient in the GIANT cohort, compared to other cohorts
About one third of the newly diagnosed patients presents as AS. Mean symptom duration is higher in the AS group (6.3 years) compared to the nr-axSpA group (4.4 years). A higher proportion of male patients is seen in the AS group, similarly to other cohorts[3, 4]. No differences in peripheral and extra-articular manifestations are seen between patients presenting as nr-axSpA and AS. Besides, there are no differences in burden of disease. Higher inflammatory parameters are seen in AS. This is completely in line with findings in other cohorts[3-8].

In this thesis, we wanted to investigate the role of gut inflammation as a risk factor for progressive axial SpA. We aimed to develop a prediction model for the risk on microscopic gut inflammation, based on surrogate markers. We anticipated such model may be useful in the future to identify individuals, who would benefit from an early aggressive therapeutic approach.

In chapter 3, we have assessed the rates and explored predictors of microscopic gut inflammation in a cohort of patients with axial and peripheral SpA. We found an overall prevalence of microscopic gut inflammation in SpA patients of 46.2%. This high prevalence has been known for many years and has been established by several investigators[9-12]. In axial SpA we found, male sex (OR=8.9, p=0.035); high disease activity measured by the BASDAI (OR=2.05, p=0.032); restricted spinal mobility measured by the BASMI (OR=1.94, p=0.009); and younger age (OR=0.85, p=0.013) to be independently associated with gut involvement. No clear association was found for HLA-B27 status, presence of peripheral arthritis, enthesitis, uveitis, psoriasis, intake of NSAIDS and family history of SpA. The prevalence of gut inflammation in non-radiographic axial SpA and ankylosing spondylitis was comparable.

The fact that BASDAI, but not CRP did show a significant association with gut inflammation, was surprising. However, similar results were found in a retrospective logistic regression analysis in the Outcome in AS International Study (OASIS), performed to identify characteristics associated with the presence of any EAM[13]. In this analysis, patient reported disease activity (measured with the BASDAI), with a 2 year time lag, was associated with the development of IBD during follow up. The commonly used laboratory parameters, such as CRP and ESR are acute-phase reactants known to correlate only partially with underlying disease[14]. Ideal markers to be used in the clinical follow-up should mirror disease activity, predict structural damage, be economical, easy to implement, reproducible with high sensitivity and specificity. Phagocyte-specific S100 proteins have been recognized as useful markers of both local and systemic inflammation[15].
They have been found to be associated with autoinflammatory diseases and correlate to disease activity in rheumatic diseases, vasculitis, IBD, lung disease, and infections[16-22]. Most importantly, they allow a patient stratification and prediction of relapse[23]. Possibly, these new biomarkers may contribute to a more accurate evaluation of the disease(discussed below).

A recurring concern about studies involving gut inflammation in SpA patients, is the possible influence of NSAID use. NSAIDs, the first line treatment in the pharmacological management of axial SpA are often considered to be contraindicated in patients with IBD, as it has been suggested that the use of those anti-inflammatory medications can cause the bowel inflammation to flare. A number of retrospective case–control studies and cohort studies have been conducted to clarify the role of NSAIDs in causing flares of IBD, with very contradictory results[24-29]. There are only two randomized controlled double-blinded trials in which patients with quiescent IBD were randomized to receive either a COX-2-selective inhibitor (celecoxib/etoricoxib) or placebo[30, 31]. Remarkably, the investigators found no significant difference in the frequency of disease exacerbation between the COX-2-selective inhibitor and placebo groups supporting the notion that COX-2 inhibitors do not cause IBD flares, at least not in the short term. Although the association between NSAIDs and IBD flares cannot be considered as definitive, practice guidelines prepared by the American College of Gastroenterology have deemed the use of NSAIDs to be a potential exacerbating factor for IBD. Presently, clinical experience would suggest that, avoiding NSAID use, particularly in difficult-to-control IBD patients, would be prudent, while a cautious trial of NSAIDs in well-controlled patients may be tolerated. Considering microscopic gut inflammation, Mielants et al. observed an equal prevalence in patients on NSAIDs, compared to patients not receiving anti-inflammatory drugs[32]. Furthermore, no microscopic gut inflammation was found in RA patients on NSAID treatment[32]. It is not clear whether NSAID use can influence the evolution to overt IBD in patients with microscopic gut inflammation. In the current study, we controlled for intake of NSAIDs in our predictive model. However, no association was found with microscopic gut inflammation in either the univariate or the multivariate analysis.

In a study by Klingberger et al.[33] NSAID-using patients displayed higher levels of fecal calprotectin, but elevated levels were frequently found in patients not on NSAIDs as well. In this study, one could argue that patients with higher disease activity have a higher need for anti-inflammatory medication. Another argument against the influence of NSAIDs on microscopic gut inflammation is the high prevalence of NOD2 polymorphisms found in SpA patients with chronic gut inflammation, similarly to CD patients (chapter 1, section 3.1)[34]. These results confirm the idea that patients with chronic gut inflammation are a distinct subset prone to progressive disease.
In this analysis, the acute and chronic type of gut involvement were pooled, as we presumet that the development of chronic bowel inflammation occurs through a transition phase, in which inflammation evolves from an acute into a chronic state (chapter 1, section 3.2). However, when we performed the same analysis only assessing the chronic group, similar results were found with young age and high BASMI as significantly associated parameters but with high BASDAI and male sex not reaching significance of p<0.05. Though, this is possibly because of lack in power as only 16 out of 49 patients showed chronic gut inflammation in this study.

Chapter 4 addresses the association between gut inflammation and the quantification of bone marrow edema on MRI. In this study, we found that SPARCC-scores were significantly higher in axial SpA patients presenting with chronic gut inflammation (16.9 [3.8-68.3]) compared to axial SpA patients presenting normal gut histology (9.8 [0.0-45.0]; p= 0.045). Our results confirm the link between inflammation and progressive disease. The presence of chronic lesions of the gut is undeniably relevant in clinical practice, as in literature chronic gut inflammation has proven to predispose to AS. Also, transition into CD in up to 20% of patients with AS and chronic microscopic gut inflammation after 5 years was observed, whereas only 6.5% of the overall group of AS patients presented similar transition[35]. Thus, an indirect relationship between inflammation of the SIJs and progressive disease has been highlighted by our results.

A multiple regression analysis confirmed our results, and additionally identified male sex as an independent predictor of higher degrees of BME, not related to HLA-B27 positivity or age. Indeed, this is in line with other authors reporting male sex as a parameter linked to MRI inflammation and progressive disease[3, 5, 36].

Previous reports on a link between HLA-B27 positivity, MRI inflammation of the SIJs and the development of radiographic sacroiliitis have shown contradictory results[3, 5, 37]. It is clear that HLA-B27 positivity determines the age at disease onset, but studies on the effect of MRI inflammation and radiographic progression are inconclusive.

Interestingly, multiple studies searching for parameters predicting the clinical response to TNFα-blockers have identified an association with young age, short symptom duration and high disease activity. Glintborg et al. found CRP >14 mg/l, lower BASFI and younger age at baseline to be associated with clinical response and achievement of a BASDAI <40 mm in the Danish nationwide rheumatological database (DANBIO) among patients with AS receiving their first treatment with a TNFα-blockers (445 (53%) received infliximab, 247 (29%) adalimumab and 150 (18%) etanercept) [38]. Rudwaleit et al. identified a shorter disease duration, younger age, and a lower BASFI to be predictors of a major clinical response in active AS in two placebo controlled, randomised trials conducted in Germany with infliximab (n = 69) and
etanercept (n = 30). Raised CRP and a higher BASDAI may also be valuable predictors, however not significantly associated in this study[39]. Also in another study by Rudwaleit et al.[40], widespread inflammation in the spine as detected by MRI contributed to predicting a BASDAI 50 response in active patients with AS treated with anti-TNF agents. A trend was found for the MRI score of SI joints to be predictive. Lord et al.[41] found that the strongest predictors of improvement in disease activity were raised inflammatory markers at the start of therapy and the higher baseline levels of disease activity, whereas a higher BASFI score was associated with a lesser response. Vastesaeger et al.[42] and Rudwaleit et al.[43] additionally identified HLA-B27 genotype, however it is unclear whether HLA-B27 facilitates early and correct diagnosis or whether the disease biology differs in HLA-B27-positive versus negative AS patients.

These results are in line with ours, and all point in one direction: there is a subgroup of young patients with high disease activity, susceptible to aggressive disease that needs aggressive and early intervention. Our results add yet another independent risk factor: gut inflammation.

**Future perspectives and conclusions**

The current gold standard of assessing gut inflammation in SpA is ileocolonoscopy and histological assessment. This however, has drawbacks as it is an invasive and costly procedure. The growing understanding of the pathogenesis of SpA has identified multiple candidate biomarkers. S100 proteins in stool and antimicrobial antibodies (chapter 1, section 3.2) in serum have earned their place in IBD and consecutively, their place in SpA can be anticipated. The exact role of these markers in SpA demands further research, as does the link with microscopic gut inflammation. As suggested in previous studies[33,44] they could be a marker for microscopic gut inflammation in AS. To prove this hypothesis, ileocolonoscopic studies of a large number of SpA patients are needed. Currently, we are analyzing these markers in our GIANT cohort according to patients’ gut histology. Possibly, the results of this study can be used to consolidate the prediction model for microscopic gut inflammation. Surrogate markers of mucosal inflammation could potentially have practical implications as we anticipate that identification of microscopic gut inflammation in patients with SpA could be of great relevance in therapeutic decision making.
Over the past decade, the role of TNF inhibition (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol) in improving signs and symptoms and overall quality of life has been well documented in various forms of SpA. It also became clear that the monoclonal antibodies neutralizing TNF are considerably more efficacious than etanercept in modulating extra-articular manifestations of SpA, even though a comparable efficacy is noted for both axial and peripheral joint manifestations[45]. This has been incorporated in the ASAS therapeutic recommendations for the management of AS[46]. Nevertheless, there is an urgent need for new mode of action drugs that could be of benefit in patients that have an unsatisfactory clinical response or have severe side effects on TNF blocking agents. The common genetic susceptibility between AS and IBD and the relation between gut and joint in general in SpA is reflected in at least a partial therapeutic overlap between both diseases. There are, therefore, great expectations that a better understanding of the relation between gut and joint inflammation in SpA will broaden our therapeutic options in the near future in SpA.

It is obvious that there is no exclusive treatment approach for all patients with SpA, which is due to the diversity of phenotypes and the differences in severity. We need to evaluate carefully and consider the best pharmacotherapy for each patient individually. We may evolve to a case-by-case approach in which our treatment will be based on the presence or absence of (microscopic) gut inflammation. Given the immunologic link between the SpA and IBD, it is an attractive hypothesis to test whether immunomodulating drugs targeting gut inflammation (apart from SASP and TNF-α blockade) would also be of benefit for patients with SpA. Consistent with this idea, clinical trials with the administration of different medications based on gut biopsies should be performed. Thus, further research on long term outcome and impact of microscopic gut inflammation on therapeutic response is needed. Furthermore, future research will have to identify patients with a relatively benign clinical course of disease who will benefit from a “step-up strategy,” as compared with patients at high risk of disease progression, in whom a “top-down strategy” (opportunity to start early with immunobiological therapy) would provide a positive risk-benefit profile.

Since October 2012, the GIANT cohort has extended to a national multicentric cohort: Be-GIANT. The global objective of this study is to provide accurate data on the epidemiology of early axial and predominant peripheral SpA in Belgium. Following the included patients (aim: 500 patients) in a prospective way will allow to gain insights in the natural evolution of these diseases, when diagnosed early and classified according to the newly developed ASAS-criteria. The study design will allow to describe the demographics and disease characteristics of patients with axial or peripheral SpA, compared to patients in historic cohorts established using conventional classification criteria. These characteristics will be described extensively at baseline,
as well as at years 1, 2 and 5. As a consequence of a systematic clinical follow-up with 6-month intervals, we will be able to determine which patients, newly diagnosed with SpA, are at risk to AS, IBD and/or PsA: as such this will allow us to determine the value of the new ASAS-criteria for SpA in reducing the delay between symptom-onset and diagnosis, and will potentially provide insights in contributing factors to the development of more specific subsets within the SpA concept. Finally, MRI has been proposed as the imaging technique most capable of detecting SpA patients in an early disease stage. Nevertheless further validation of this imaging modality is still needed in large, independent prospective cohorts. The standardized data collection will allow to determine the additional value of the different MRI sequences (T1, STIR) on top of conventional radiography. This may eventually provide a rationale to expose less patients to diagnostic ionizing radiation.
References


Chapter 6
Nederlandstalige samenvatting
Zoals beschreven in hoofdstuk 1, zijn spondylartritiden (SpA) een groep van chronisch inflammatoire aandoeningen met gemeenschappelijke pathofysiologische, klinische, genetische en zelfs therapeutische kenmerken. De ziekte kan zich axiaal manifesteren, met ontstekingen van de sacroiliacale gewrichten en de wervelzuil, alsook perifeer met enthesitis en artritis (typisch asymmetrisch en ter hoogte van de onderste ledematen). Verder kunnen er extra-articulaire manifestaties optreden onder de vorm van uveïtis, psoriasis en inflammatoir darmlijden. De ziekte is vrij prevalent (0.2-1% van de bevolking) en start op jonge leeftijd (typisch voor de leeftijd van 40 jaar). SpA kan leiden tot belangrijke structurele schade en beperkingen met een weerslag op de levenskwaliteit en economische gevolgen voor patiënt en maatschappij.

Echter, het laatste decennium heeft het veld van de reumatologie spectaculaire vorderingen gemaakt; onder andere door de introductie van MRI kan axiale SpA nu in een vroeg stadium worden opgespoord en op therapeutisch vlak heeft de komst van de TNFα-blokkers voor een ware revolutie gezorgd.

De precieze oorzaak en het ontstaansmechanisme van de ziekte blijven onduidelijk. In de jaren ’80 ontdekten de groep van Prof. Mielants en Prof. Veys dat ongeveer de helft van de SpA-patiënten microscopische darminflammatie vertoont. Dit pleit voor een belangrijke rol van darminflammatie in het ontstaan van de aandoening. Opvolgstudies hebben aangetoond dat patiënten met chronisch microscopisch darmlijden bovendien een hoog risico lopen op het ontwikkelen van inflammatoir darmlijden en spondylitis ankylosans (het radiografisch, gevorderd stadium van axiale SpA - SA).

In hoofdstuk 2 wordt het doel van deze thesis verduidelijkt. We wilden een strategie ontwikkelen om patiënten met axiale SpA met een hoog risico op snelle ziekteprogressie, vroeg op te sporen. Hiervoor zijn we uitgegaan van de hypothese dat we het risico op microscopisch darmlijden konden voorspellen, gebaseerd op surrogaat marker. Zo een model zou nuttig kunnen zijn in de toekomst, om risicopatiënten te identificeren die baat hebben bij een vroeg agressieve therapeutische aanpak. In dit opzicht weten we dat etanercept, een TNFα-blocker gebruikt in de behandeling van SpA, geen indicatie heeft in de behandeling van inflammatoir darmlijden, in tegenstelling tot infliximab en adalimumab (en certolizumab en golimumab) die efficiënt zijn bij beide aandoeningen. Etanercept is dan ook mogelijk niet de beste keuze voor behandeling van SpA-patiënten met microscopisch darmlijden, in het bijzonder diegenen met een verhoogd risico op inflammatoir darmlijden. Daar tegenover staat dat patiënten behandeld met etanercept mogelijk minder vatbaar...
zijn voor infectieuze complicaties, in tegenstelling tot patiënten behandeld met monoclonale antilichamen. Verder weten we dat de klinische remissie bij SpA-patiënten behandeld met sulphasalazine significant hoger is bij patiënten met microscopische darminflammatie.

In hoofdstuk 3 wordt een multiparameterisch voorspellend model voorgesteld om het risico op microscopisch darmlijden bij axiale SpA in te schatten. Ondanks verbeterde hygiëne en een veranderde blootstelling aan micro-organismen (hygiëne hypothese) vonden we een even hoge prevalentie van microscopisch darmlijden bij SpA-patiënten in vergelijking met de studies in de jaren ’80. We vonden dat jonge leeftijd (een korte ziekteduur), gevorderde ziekte, mannelijk geslacht en hoge ziekte activiteit onafhankelijk geassocieerd zijn met microscopisch darmlijden bij axiale SpA. Dit model heeft en sensitiviteit van 81.8 % en een specificiteit van 78.3 %. Na validatie zou dit model praktisch geïmplementeerd kunnen worden om risicopatiënten te identificeren.

Hoofdstuk 4 onderzoekt de link tussen de graad van beenmergoedeem op MRI van de sacroiliacale gewrichten en microscopische darminflammatie. Volgens onze eigen ervaring vertonen patiënten met ernstig beenmergoedeem op MRI vaker microscopisch darmlijden en omgekeerd. In deze studie ondergingen 68 consecutieve patiënten, naïef voor TNFα-blokkers, een ileocoloscopie en MRI van de sacroiliacale gewrichten. Het beenmergoedeem was effectief significant uitgebreider in de groep van patiënten met chronisch microscopisch darmlijden. In een multiple lineaire regressie konden we dit bevestigen en bleek ook het mannelijke geslacht onafhankelijk geassocieerd aan graad van beenmergoedeem. Wanneer chronische darminflammatie gelinkt is aan beenmergoedeem van de sacroiliacale gewrichten, waarvan gekend is dat deze patiënten een dubbel zo hoog risico hebben op evolutie naar SA, kunnen deze gegevens voor de clinicus een extra middel zijn om patiënten met een hoog risico op progressie te identificeren. Verder was er een lage tot middelmatige correlatie tussen de graad van beenmergoedeem en C-reactief proteïne \( r=0.39, p=0.002 \) en de Ankylosing Spondylitis Disease Activity Score \( r=0.35, p=0.007 \).

Deze studies verschaffen nieuwe inzichten in de opsporing van vroege axiale SpA en de overlap tussen SpA en inflammatoire darmlijden, in het bijzonder microscopisch darmlijden en mogelijksche functionele consequenties hiervan.
Curriculum vitae

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   - 04/07/2013 ICH-GCP Training Course, Ghent University Hospital, Department of Rheumatology, by Prof. Dr. F. Van den Bosch
   - 15/11/2013 ICH-GCP Investigator training TransCelerate
Scientific publications

* Van Praet L and Jacques P contributed equally to this article.
* Jacques P and Van Praet L contributed equally to this article.

Presentations on scientific meetings

Abstracts selected for oral presentation


Poster presentations and abstracts on scientific meetings

5. Melis L, Venken K, Van Praet L, Elewaut D. Elevated soluble E-cadherin levels in chronically inflamed joints favour TNF production by KLRG1 expressing T cells. Eight International Congress on Spondylarthopathies, Ghent, October 4-6 2012, poster 95

Committees

2012-present

Associate member - Assessment of Spondyloarthritis International Society (ASAS)
Dankwoord

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