Clinical Review

Spondyloarthritis and Idiopathic Inflammatory Bowel Diseases

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Summary: Spondyloarthritis (SpA) as observed in patients with idiopathic inflammatory bowel diseases is categorized according to the recently developed criteria of the European Spondylarthropathy Group, and belongs to a large complex of rheumatic disorders, encompassing ankylosing spondylitis, Reiter's disease, psoriatic arthritis, and reactive arthritis. It has been recognized for many years that patients with ulcerative colitis or Crohn's disease frequently have arthritic complications. The gastroenterologist should therefore carefully evaluate any symptom of peripheral or axial arthritis, in an attempt to provide an accurate diagnosis, to define a realistic prognosis, and to establish adequate therapy at an early stage. In this review, clinical and etiopathogenic aspects are analyzed, not only of patients with inflammatory bowel diseases and SpA, but also of patients developing arthritic symptoms after gastrointestinal bacterial infections (reactive arthritis). The significance of ileal mucosal inflammation as observed frequently in patients with SpA is discussed; the contribution of immunogenetic factors in the development of SpA, such as HLA-B27, is briefly reviewed. Finally, analysis is made of the different therapeutic options that are available at present. Key Words: Ulcerative colitis—Crohn's disease—Genetics—HLA antigens—HLA-B27—Cytokines—Ankylosing spondylitis—Arthritis—Sacroiliitis—Reactive arthritis—T lymphocyte—Salmonella—Shigella—Campylobacter—Yersinia—Chlamydia—NSAID—Sulfasalazine—Tumor necrosis factor.

The occurrence of joint abnormalities in patients with idiopathic inflammatory bowel diseases (IBD) has been well recognized. In recent years, a large number of important studies and reviews have elucidated the clinical complex of spondyloarthropathy (SpA). SpA has been defined by the European Spondylarthropathy Group as: inflammatory spinal pain or synovitis, together with at least one of the following items: positive family history, psoriasis, IBD, urethritis, cervicitis or acute diarrhea within 1 month before arthritis, alternating buttock pain, enthesopathy or radiologic evidence of sacroiliitis (SI) (1). In daily practice, when evaluating patients with SpA, one may observe peripheral arthritis, axial arthritis [SI or ankylosing spondylitis (AS)], or a combination of peripheral and axial arthritis; extraarticular manifestations (eye, skin). The HLA-B27 status is often present. In this review, some recent data on the arthropathies as occurring in IBD are discussed. In addition, clinical aspects and etiopathogenic mechanisms of reactive arthritis are reviewed, the contribution of immunogenetics is defined, and attention is also given to the evaluation of therapeutic possibilities in patients with IBD and rheumatic complaints.

IDIOPATHIC IBD

Peripheral Arthritis (Synovitis)

There are no major differences between the clinical symptoms of peripheral arthritis in ulcerative colitis (UC) or Crohn's disease (CD) (2,3), as shown in Table 1. Peripheral arthritis in patients with UC or CD usually starts after the onset of bowel symptoms, but in a minority of patients, joint symptoms may precede the onset of IBD symptoms (3–9). The onset
### TABLE 1. Features of peripheral arthritis in patients with ulcerative colitis (UC) and Crohn's disease (CD)

<table>
<thead>
<tr>
<th>Feature</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mono/oligoarticular</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Asymmetric</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mainly large joints</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Migratory character</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lower extremities &gt; upper extremities</td>
<td>10–20%</td>
<td>10%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>20–25%</td>
<td>20–25%</td>
</tr>
<tr>
<td>Frequency of HLA-B27 in patients with peripheral joint involvement</td>
<td>Increase in case of complications</td>
<td>Yes (colon &gt; ileum)</td>
</tr>
<tr>
<td>Relation to localization</td>
<td>Yes</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Relation to other extraintestinal manifestations</td>
<td>Increased frequency</td>
<td>Increased frequency</td>
</tr>
<tr>
<td>Occurs in patients with ileoanal pouch reconstruction</td>
<td>No data available</td>
<td>Possibly</td>
</tr>
<tr>
<td>Relation to pouchitis</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Cartilage/bone destruction</td>
<td>Usual</td>
<td>Rare</td>
</tr>
<tr>
<td>Activity runs parallel to bowel activity</td>
<td>Disappearance after colectomy</td>
<td>No</td>
</tr>
<tr>
<td>Spontaneous disappearance of clinical symptoms</td>
<td>Spontaneous disappearance of clinical symptoms</td>
<td>No data available</td>
</tr>
</tbody>
</table>

is often abrupt, within a few hours or days, with spontaneous pain, erythema, warmth, and effusion; symptoms are typically localized in the joints of the lower limb, knee, or ankle, but also occur in elbows, metacarpophalangeal joints, shoulder, or hip (6,8,10,11) (Fig. 1). A migrating oligoarthritis in UC may persist for several months, slowly disappearing spontaneously, after starting medical therapy for colitis symptoms, or after colectomy (2,5,12). In general, arthropathy seems to be more prevalent in UC patients with chronic intermittent or continuous symptoms (13); arthritis occurs more frequently in patients with extensive colitis than with distal colitis, although not all studies confirm this correlation (14,15). A high incidence of peripheral arthritis occurs in patients with other extraintestinal manifestations (15–17). There is a strong association between peripheral arthritis and colonic localization of the disease (14,15,18). It is not known why other extraintestinal manifestations are associated with arthritis; sharing of certain peptides by colonic epithelium, ciliary processes of the eye, and chondrocytes of the joints may be an attractive possibility (19); however, these data need further confirmation. Studies on the histology of the synovial tissue of patients with IBD are very scarce; they usually show a nonspecific synovitis (20,21). Occasionally, crystal deposits have been shown in the joints of patients with CD (22) or synovial granulomas (23,24). In general, destruction of bone or cartilage is not a feature of peripheral arthritis in patients with IBD, although erosive arthropathies have been described (25,26). A recent prospective Portuguese study of the incidence of extraintestinal manifestations in a large group of patients with IBD (n = 792) showed that peripheral arthritis occurs frequently, twice as often in CD as in UC (20.2 versus 11.0%). The onset of symptoms preceded bowel symptoms in 18.5%, ran synchronously in 43.5%, and occurred later in the disease in 48.0%; recurrent episodes were noticed in 54.3%. The most affected joints were the knee (62.7%) and ankle (54.2%). Significant associations were noticed with skin, eye, and mouth manifestations (15). These data are comparable with those from the large earlier

study from New York (17). In comparing these two studies, it seems that during the last 30 years, a tendency to lowering of arthritic complications has occurred in UC: 26% (17) and 11% (15), respectively. One cannot rule out the possibility that the IBD course in Portugal is milder than that in New York. The recent study from Oporto was a prospective one; all patients attended only one available clinic, whereas the study from New York included many patients with Jewish ancestry. From our personal experience, it seems that fewer patients with incapacitating migrating arthritis are encountered; milder forms of arthralgias or arthritis are observed more commonly. It is possible that a more adequate diagnostic approach to patients with IBD, as well as a change in therapeutic management, have influenced the clinical picture of IBD as well as the natural history of peripheral arthritis. Surgical alternatives are proposed much earlier in the course of the disease than previously. A timely planned proctocolectomy and ileoanal pouch reconstruction in patients with severe or long-standing UC may theoretically prevent potential septic complications and development of extraintestinal manifestations, such as arthritis. Usually, arthritic symptoms disappear after proctocolectomy (14); however, when the rectal stump is retained at surgery and inflammation of the rectal mucosa worsens, recrudescence of peripheral arthritis may occur. In about a quarter of a large group of patients with UC who underwent restorative proctocolectomy, arthritic symptoms started only after the surgical procedure; apparently, colectomized patients with IBD may also develop SpA in a relatively quiescent phase (9). Pouch-related SpA seems to be a new clinical entity: ileal pouch arthritis has been described by several authors in patients with an ileoanal pouch reconstruction (9,13,27), but it is not yet clear whether this complication is particularly associated with clinical pouchitis. Patients with an ileal pouch before ileostomy closure or with pouchitis have an increased 51Cr-EDTA urinary excretion as evidence of increased mucosal permeability; two patients in this study with the highest permeability both had arthritis (28). A positive history of pre- or postoperative extraintestinal symptoms in patients with UC is associated with an increased chance to develop pouchitis, which may be refractory to medical therapy (29,30).

**Axial Arthritis (Spinal Involvement)**

In patients with IBD, both SI and AS occur with increased frequency (31-33); a minority of the patients have clinical signs of peripheral arthritis (34). Clinical features are listed in Table 2. SI may be present in an isolated form without production of clinical symptoms or tendency toward progression (3). Patients with AS and IBD have a more or less equal sex distribution, which is in contrast to the male preponderance in AS (35). From Table 3 it becomes clear that in patients with UC and CD, the prevalence of SI, often asymptomatic, is much higher than that of AS. Features of symptomatic SI are inflammatory back pain and early morning stiffness, usually improving after some exercise. Techniques for the detection of SI are conventional radiography, bone scanning (36), computed tomography (CT) (37), as well as magnetic resonance (MR) imaging. CT scanning is particularly useful for scanning of bone lesions (38,39), whereas MR imaging is more useful for the detection of early inflammation and cartilage abnormalities. It has been shown that contrast-induced enhancement with gadolinium allows the early detection of SpA and is quantifiable. Patients with IBD and low back pain as well as children will benefit from this approach (40). In comparison with the other techniques MR imaging was found to be the most useful method for the detection of SI joint abnormalities (41). Still, with appropriate conventional radiographic techniques, one may assess accurately the advanced stages of SI: bilateral sclerosis, erosions with irregular appearance of the joint space, narrowing, and finally bony fusion (42,43). Occasionally, spondylitis seems difficult to classify in patients with UC, despite the use of recent technology (44). As already mentioned, the onset of SI and AS is not

### TABLE 2. Features of axial arthropathy in patients with ulcerative colitis and Crohn’s disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prevalence</th>
<th>Sex distribution</th>
<th>Present before onset IBD</th>
<th>Sacroilitis asymptomatic</th>
<th>Association between joint and intestinal symptoms</th>
<th>Radiologic features</th>
<th>Joints</th>
<th>Association with eye and skin symptoms</th>
<th>Association with HLA-B27</th>
<th>Treatment</th>
</tr>
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<tr>
<td></td>
<td>1–25%, usually 3–5%</td>
<td>male &gt; female or equal</td>
<td>Often</td>
<td>Often</td>
<td>Usually absent</td>
<td>Indistinguishable from classic AS</td>
<td>SI joints, spine, hips, shoulders</td>
<td>Less evident than in peripheral arthritis</td>
<td>Symptomatic, early physiotherapy</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effect of immunosuppressives or anti-TNF not been studied.</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; AS, ankylosing spondylitis; TNF, tumor necrosis factor.
related to the onset of IBD and usually precedes it (13). There is no association between the severity, or waxing and waning of IBD and axial arthritis, whereas in general surgical interventions do not influence rheumatic complaints caused by SI or AS. Penetration of bacterial or toxic antigens into the sacroiliac joint spaces originating from a diseased bowel wall or inflamed lymphatics may possibly provide an explanation (45,46).

**IMMUNOGENETIC STUDIES**

**Association with HLA-B27 and Other Genes on the Short Arm of Chromosome 6**

Class I HLA antigens are dimeric molecules, composed of a variable transmembrane α chain and an invariant β chain, β2-microglobulin (hβ2m), expressed on the membranes of all nucleated cells and platelets that present intracellular antigens to CD8 lymphocytes (47). HLA-B27 is the most important antigen related to AS and SpA, and most studies have focused their interest on the antigen B27. The original publications on the strong association between HLA-B27 and AS (48,49) have launched an important area of research on the contribution of genetic factors to SpA. Ninety to 95% of AS patients possess the B27 allele (48-50). Six to 9% of the Western European population possesses the antigen B27, which contrasts with 10–16% B27 positives in Northern Scandinavians, 25–40% in the Eskimo population, and 50% in Haida Indians in North America (51,52). Between 1 and 6% of the HLA-B27-positive whites have AS (51,53), with an average of ~2% (54).

Approximately 2% of a large group of healthy blood donors in Berlin fulfilled the diagnostic criteria for SpA, but overall data for SpA prevalence are lacking (55). The risk of acquiring AS in an HLA-B27-positive first-degree relative of B27-positive patients is very much higher, up to ~20% (53). The association between HLA-B27 and other forms of SpA is less evident. Our analysis of a large group of patients with AS-IBD showed HLA-B27 positivity in just over 50% (CD: 52.6%, UC: 66.7%). However, this group was found to be heterogeneous: Patients with classic features of AS were more likely to be HLA-B27 positive (56). These data are in agreement with other studies in which no increased incidence of HLA-B27 was observed in patients with IBD with isolated Convincing support for the pathophysiological role of HLA-B27 has been provided experimentally. Human B27 and hβ2m genes were introduced into inbred rats, which, in contrast to previous similar but negative experiments in transgenic mice (58,59), produced highly successful results. The disease-prone B27/hβ2m transgenic rat strain 21-4H developed a multiorgan system disease, with striking similarities to human AS: Lesions occurred in peripheral and axial joints, gut, male genital tract, nails, skin, and heart (60). Joints were swollen, with erythema and tenderness. Histological examination revealed synovial hyperplasia, inflammatory cell infiltration, pannus formation, and destruction of cartilage and bone structures. The levels of B27 and hβ2m mRNA transcripts in the transgenic tissues paralleled those of other endogenous tissues, suggesting physiological
regulation. The disease susceptibility correlated with gene copy numbers and the quantity of B27 in lymphoid cells (61). Although molecular mechanisms were not clarified, it was established that in the transgenic rat a normal bacterial flora is required for the development of colitis and arthritis, thereby confirming that the gut flora plays a pivotal role in the development of joint disease (62,63). Alternatively, eradication of the intestinal bacterial flora in rat prevented reactivation of arthritis (64). For a detailed overview of the role of animal models in the development of intestinal and bacterial inflammatory reactions, referral is made to two recent reviews (47,65).

At least nine HLA-B27 subtypes have been described, B*2701 to B*2709, which differ by a few amino acid residues. B*2705 has been found in most populations and is detectable in the very large majority of white B27-positive individuals (>90%) (66,67). B*2702 has only been found in whites and is the predominant type in Jews, and B*2704 is the predominant subgroup in Asians (67–69). AS or related SpA has been described in patients with the subtypes B*2701, B*2702, B*2704, B*2705, and B*2707 (52). Up to now, no associations have been found within the group of SpA between AS or AS with acute anterior uveitis and any HLA-B27 subtype (67,70). To the best of our knowledge, no studies have yet been published on HLA-B27 subtyping in patients with IBD, and these results are therefore to be awaited. Classic idiopathic AS seems to be rare in HLA-B27-negative Dutch whites; 8 of 24 B27-negative patients with AS were found to have IBD, in contrast to 6 of 182 B27-positive cases, and the percentage of isolated SI in the B27-negative AS group was higher than in the positive group (45.8 and 24.2%, respectively) (45). Routine determination of HLA-B27 does not seem to be warranted in patients with IBD with rheumatic complaints. In selected patients with IBD with severe or progressive symptoms of axial arthritis, the HLA-B27 status may be determined, but it must be realized that a substantial number of these patients will be B27 negative. Besides HLA-B27, no other definite associations have been found between AS and HLA antigens; only HLA-B60 was found to be associated in a limited number of studies (70,71). The antigen HLA-Bw17 was found significantly more frequently in CD patients with peripheral arthritis (72), but this observation also needs confirmation.

Cytokine-encoding genes also have been shown to be of importance in the immune response. These cytokines encompass both the proinflammatory cytokines, tumor necrosis factor (TNF)-α, TNF-β, and IFN-γ, as well as the immunoregulatory cytokines such as interleukin (IL)-4 and IL-10 and genes of the IL-1 family. There is strong evidence that the cytokine network regulates immune and inflammatory responses, which are implicated in the pathogenesis of IBD. To determine the relevance of TNF in the genetic predisposition to IBD, the diallelic NcoI and AspHII RFLPs in the first intron of TNF-β as well as polymorphisms at positions -308 and -238 in the promoter region of TNF-α at the major histocompatibility complex (MHC) class III region were studied; in the Dutch white population, only five TNF haplotypes have been found (73). In UC, the frequency of haplotype TNF-E (alleles 1, 2, A, and G, respectively) was significantly increased, and the frequency of the haplotype TNF-C (1, 2, G, G) decreased. In contrast, in CD no differences were apparent (74). Stable variations in the production rates of these cytokines by peripheral blood mononuclear cells of healthy individuals and patients with IBD stimulated with T-cell-specific stimulants have been observed (75). Carriers of the haplotype TNF-E produced the highest concentrations of TNF-α, and carriers of the haplotype TNF-C the lowest. Because these haplotypes differ at position -308 in the promoter region of TNF-α, this position may be of relevance for the secretion of TNF-α, and may be used to delineate a subgroup of patients with UC, particularly those who have developed peripheral or axial arthritis.

Studies of the non-HLA-B27 genetic factors that must play an equally important role in the pathogenesis of AS have also addressed these cytokine genes (76). However, no evidence has been found for a contribution of either the NcoI and EcoRI alleles of the TNF-β gene (77), or the polymorphisms at position -308 (78), or at positions -163, -238, and -376 of the TNF-α gene (79). The uncommon allele 2 of a penta-allelic polymorphism in intron 2 of the IL-1 receptor antagonist (IL-1ra) gene was found more frequently in white patients with UC than in healthy controls (80); in this study as well as in a confirmatory study, the association was strongest with the group of patients with total colitis; no association was observed with CD (81). The allele 2 was also observed more frequently in patients with rheumatoid arthritis (82); however, studies on genes of the IL-1 gene family in SpA patients are not yet available. In conclusion, up to now only the antigen HLA-B27 has been of value in the definition and evaluation of SpA (83). It is to be expected that genome wide screening studies as well as linkage studies in nuclear families with af-

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fected sib pairs and extended pedigrees with multiple affected members will reveal new and important genetic factors.

**ENTEROGENIC REACTIVE ARTHRITIS**

"Enterogenic reactive arthritis" (ReA) is a non-infectious asymmetrical oligoarthritis, which, for example, occurs after acute bacterial gastroenteritis, caused by *Yersinia, Salmonella, Shigella*, or *Campylobacter*. Several large outbreaks of food poisoning have been described, causing acute gastroenteritis in otherwise healthy individuals and followed by the occurrence of arthritic complications (84-88). Reactive arthritis after *Salmonella* infections have been reported in between 1-2 and 20% of infected individuals. In a recent series, 6.4% of 423 infected persons developed ReA after infection with *Salmonella typhimurium* (88). The median time in this study necessary for development of arthritis after gastroenteritis was 2 weeks, which is about the average reported in other studies. Usually oligoarthritis develops in one of the larger joints (knee, ankle, shoulder, elbow), often with fever (85). Persistence of arthritic symptoms beyond 3-4 months after onset may indicate that the person involved will continue to have symptoms during following years (88). Development of SI and AS has been described previously after *Yersinia* infection (85,89). Arthritis occurred after *Campylobacter* gastroenteritis in ~5% (86). The relative risk of developing ReA after bacterial gastroenteritis seems many times higher in HLA-B27-positive individuals (8); a firm association has been shown between B27-positive and *Campylobacter, Salmonella, Shigella, Yersinia, Chlamydia*, and *Clostridium*, with a prevalence of 60-80% (90). The presence of HLA-B27 may influence the clinical course of ReA (91), but this is not always the case (86,88). B27 was found less frequently to be positive in enterogenic ReA after *Salmonella* infections (0-33%) (88,92,93) than after *Yersinia, Campylobacter, or Shigella* infections (85,94,95). Although bias may occur in the selection of infected individuals, HLA-B27-positive individuals with more severe disease are more commonly referred for further evaluation (96)—It seems likely that a genuine difference exists with regard to an HLA-B27 association in patients infected with *Salmonella* or *Shigella* (97). Bacterial lipopolysaccharides (LPS) are likely to be of importance for the development of ReA. They persist long after the acute infection has disappeared, and intraarticular antibodies against LPS are detectable thereafter (98-100). However, it remains poorly understood why only a small percentage of patients will develop ReA after an enterogenic infection and why at the same time gastroenteritis may be mild and the ReA severe.

Is it possible that the presence of bacterial antigens indeed contribute to the development of joint abnormalities in patients with SpA? Chlamydiae are likely to be present in synovial fluid; bacterial DNA and RNA have been detected in patients with ReA (101-103). In contrast, yersinial DNA has not yet been isolated. It is not known whether this is due to technical differences or to different behavior of the two bacteria (104). Data on the intraarticular presence of *Salmonella* or *Shigella* in patients with SpA are also lacking (95,104). Bacterial antigens, in particular intracellular antigens, and to a lesser extent capsular antigens, are recognized by CD4+ T cells, as shown for *Yersinia* (105). No common bacterial antigen (immunodominant antigen) has been recognized. The specificity of the CD4+ response is therefore likely to be different (104). Data on a CD8+ T lymphocyte response are scarce; however, intraarticular CD8+ responses have recently been documented for *Salmonella* (106,107) and *Yersinia* (108). Synovial HLA-B27 may play an important role in presenting bacterial (arthritogenic) antigen to CD8+ T lymphocytes, although no common bacterial antigen has yet been isolated. Not only CD8 αβ T-cell receptor-T lymphocyte cell clones seem to be important, but also synovial γδ T lymphocytes (109). It is possible that bacterial peptides within the joint induce a cytotoxic lymphocyte response, cross reacting with structurally similar peptides from normal articular tissue ("the arthritogenic peptide model") (110-113).

Several theories have been formulated to define the role of HLA-B27 in presentation of (bacterial) antigens to CD8+ lymphocytes and the respective role of these CD8+ as well as CD4+ lymphocytes (104). If an effective CD8+ response fails, an immune response mediated by CD4+ lymphocytes may occur. Alterations in antigen processing or transportation may be responsible (114). Ineffective presentation of the responsible antigen by HLA-B27 to CD8+ cells may take place, for example, because of competition of different class I MHC molecules for the same antigen (115). Autoimmunity may also be of importance in the development of SpA: peptides derived from immunodominant intracellular bacterial proteins and presented by HLA-B27 may cross-react with self peptides from the host, being presented to CD8+ T cells (104). Alternatively, HLA-B27-derived peptides presented by class II MHC molecules could become the
target of an autoimmune attack by CD4+ cells (104). IL-4, secreted by Th2 cells, may prevent effective elimination of intraarticular bacterial antigens by interference with IFN-γ (116). The role of the cytokines in the induction and maintenance of inflammatory joint disease therefore needs a detailed analysis. For an update on this topic, referral is made to a summary of the Third International Workshop on ReA (117).

The original observation that AS is linked to infection with *Klebsiella pneumoniae* and that serum antibodies to *Klebsiella* may be of etiopathogenetic importance in AS patients (118,119) has only been validated in part, and the issue has not been settled. Most of the studies in AS have shown raised serum antibody titers against *K. pneumoniae*, the hexamer amino acid sequence of the *Klebsiella* nitrogenase reductase enzyme (120–122) or antibodies against other proteins (pullulanase enzyme system) of *K. pneumoniae* (123). After sulfasalazine (SASP) therapy, *Klebsiella* IgA antibodies were found to be reduced (124,125). Other groups, however, have not been able to confirm differences in antibody titers between patients with AS and controls (126–128); experimental support in transgenic mice has also been lacking (129). Increased levels of *Klebsiella* IgA have been found in CD and UC, but are not different from those in AS (130). This could mean that increased absorption of *Klebsiella* antigens or products from other Enterobacteriaceae (131) and induction of a nonspecific humoral immune response may take place because of increased intestinal permeability of the inflamed distal small intestine, as observed in SpA (132).

**ETIOPATHOGENIC AND CLINICAL SIGNIFICANCE OF INFLAMMATION OF THE DISTAL ILEUM IN PATIENTS WITH SpA**

Several arguments favor an important role of the intestinal mucosa in the development of arthropathies. As already shown herein, transgenic rats develop features of arthritis only in the presence of a normal bacterial flora, and eradication of this flora with antibiotics retards the development of joint inflammation. Patients with IBD with colonic involvement have more chance to develop arthritic complications. IBD relapse with extraintestinal manifestations may be caused by enteric bacterial or viral infections. ReA occurs frequently after acute infectious diarrhea caused by *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*, and during the last few years it has been shown repeatedly that an association exists between joint inflammation and intestinal inflammation in the distal ileum. In addition, the efficacy of SASP, but not of the 5-aminosalicylic acid (5-ASA) moiety, at least in AS, underlines the important role of the bacterial flora (133,134).

The most important contribution toward a better understanding of the interrelationship of gut–joint inflammation comes from the Gent group (Belgium), which has published a large number of important studies on this topic during the last 10 years. In 1985, in 19 of 35 patients with HLA-B27-positive ReA, macroscopic abnormalities of the ileocecal valve and terminal ileum were demonstrated and classified in three stages (stage 0: normal; stage 1: edema of the valve, slight reddening, friability, granularity and nodular aspect of the ileal mucosa; and stage 2: narrowing of the valve and ulcerations, usually accompanied by histological abnormalities) (135). In patients in whom a second ileocolonoscopy was performed, remission of peripheral joint inflammation was associated with disappearance of gut inflammation (136). Histologic abnormalities, as observed in ileal biopsies, with lymphoid hyperplasia and chronic inflammatory reaction were found in more than half of the patients with AS and also in patients with ReA, regardless of the presence of HLA-B27 (137). The gut lesions have been divided in two forms: “acute inflammation” with normal architecture, neutrophilic infiltration, sometimes crypt abscesses and small superficial ulcers; “chronic lesions” were characterized by crypt distortion, villous blunting and fusion, increase of cellular density, basal lymphoid aggregates, and occasionally sarcoid-like granulomas (137,138). About three-quarters of the patients with histological abnormalities had no intestinal complaints (137). In the enterogenic form of ReA, 70% of the biopsies showed “acute lesions,” whereas in AS, “chronic lesions” were observed more frequently. Patients with seronegative SpA were followed during several years, and clinical investigations, including ileocolonoscopy, were repeatedly performed. Forty-nine of 123 patients with seronegative SpA in whom IBD or psoriasis was excluded were reinvestigated after a follow-up of at least 2 years. Nine of the 123 patients (7.3%) developed CD; this observation confirms the existence of subclinical IBD, preceded by peripheral arthritis or AS. The ileal biopsies of these patients with CD usually showed “chronic lesions,” and in retrospect the histologic abnormalities were already present during the first examination. A striking association was observed in patients with SpA between endoscopic abnormalities and persistence of articular...
disease. In case of articular remission, endoscopy of the terminal ileum was nearly always normal (139). Therefore, intestinal and articular inflammatory reactions seem to run in parallel, although ileal inflammation may disappear while SpA continues. Periods of recurrent diarrhea were also found to be a risk factor for persistence of active articular disease. Not only "chronic lesions" of the terminal ileum were important for the development of IBD, but also other risk factors were HLA-B27 negativity in the presence of SI and/or AS. In contrast, uveitis, tendinitis, inflammatory low back pain, or HLA-Bw62 did not seem to be risk factors for IBD (140). Taking into consideration all of the data, gut inflammation of the distal ileum seems to be a principal feature in the majority of patients with seronegative SpA. Disappearance of the inflammatory lesions of the gut are associated with remission of joint activity (138). These data by and large have been confirmed by other groups, although histological findings have varied (141–144). Some questions, however, have not been answered. It is remarkable that relatively little information has been presented on the endoscopic and histologic features of the colon, whereas colonic localization of IBD in general seems to be associated more frequently with ReA. Is the inflammatory reaction of the gut limited to the ileum, or are discrete histologic abnormalities of the colon also present? No data are available on the evolution toward UC, only toward CD; a satisfactory explanation for this discrepancy is lacking. Although 7.3% of the patients with SpA developed CD during follow-up, no details are available on the radiological features of the ileum, the extent of the disease, or the presence of stenotic lesions in the ileum (139). Fortunately, recent scintigraphic studies have provided more information on hidden localization of affected bowel segments in patients with SpA. Abdominal scintigraphic methods have been used to study intestinal uptake of 

\[ \text{\textsuperscript{99m}Tc-HMPAO-labeled leukocytes} \]

in patients with IBD and patients with SpA (145). The terminal ileum was involved more frequently in CD (63.6%) than in SpA (23.5%). In nearly a quarter of the patients with SpA, rectal or sigmoid involvement was also noted. This observation indicates that colonic inflammation may occur more frequently in patients with SpA than was assumed until now.

It is evident from the studies cited herein that the large majority of patients with SpA (>90%) will not develop IBD during long-term follow-up. Theoretically, it cannot be excluded that ileal inflammation is mainly indicative of a "strongly activated" Peyer's patches system, with increased numbers of M cells (132). Early disruption of M cells may indicate disruption of the epithelial lining, allowing increased penetration of bacterial antigens and initiating a sequence of immunological events leading to SpA (132). Specific histological abnormalities have been observed, more suggestive of chronic IBD, as shown by conventional light microscopy as well as by demonstration of strong enterocytic HLA-DR expression, and a specific pattern of immunoglobulin-containing plasma cells in the terminal ileum (137,146,147). The etiopathogenic significance of these observations needs further clarification.

HOW SHOULD PATIENTS WITH BOTH IBD AND PERIPHERAL OR AXIAL ARTHRITIS BE TREATED?

In general, therapeutic options are limited and should—after carefully establishing an accurate diagnosis—be directed toward reducing inflammation and preventing disability and/or deformity. In patients with IBD and peripheral arthritis, the main issue will be to control the clinical activity of UC or CD. As already stated, in UC arthritic complaints will usually diminish rapidly after colectomy. In CD, the remaining length of active bowel is likely to determine the effect of the surgical procedure on joint activity. Rest, physical therapy and oral or rectal prescription of nonsteroidal antiinflammatory drugs (NSAIDs) will usually be sufficient to control peripheral arthritis. Steroids taken orally are rarely required, although a certain number of patients already receive steroids systematically; intraarticular injection of steroids may also provide benefit. In patients with IBD with axial arthropathy intensive physiotherapy is important to relieve pain, as well as to maintain optimal mobility and posture. Guided exercise programs may retard progressive clinical complaints and reduce the consequences of spinal joint fusion (46). Attention should be given to the cervical region of patients with AS, to avoid rare neurological complications (for example, cervical atlantoaxial subluxation). Osteoporosis may aggravate clinical symptoms, and an evaluation of the skeleton by means of DEXA scanning should be considered, particularly in female patients with IBD, who run an additional risk of loss of bone mass. Supplements of calcium as well as vitamin D are therefore strongly advised.

NSAIDs, as mentioned, are used frequently with success to control symptoms, particularly in AS and psoriatic arthritis (8,148,149), but many patients with

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SpA, in particular with chronic symptoms, need other therapeutic options (139). The issue of increased intestinal permeability from the use of NSAIDs has not been settled. Intestinal inflammation itself may increase permeability (150), but few studies have elucidated the effect of NSAIDs on mucosal inflammation in IBD. No differences in the $^{51}$Cr-EDTA resorption test, as a measure of intestinal absorption, were observed between AS patients and relatives, whether they used NSAIDs or not (151). It seems that increased intestinal permeability in patients with SpA occurs independently of NSAID intake; ileocolonoscopy may be of value to establish terminal ileum disease, indicative of SpA or possibly CD (152). Alternatively, it has been noted in patients with SpA that despite continuous intake of NSAIDs, ileal histology remained normal or normalized after previous inflammation (139). With regard to dosing to patients with IBD, no clear guidelines are available, but one should prescribe NSAIDs in a dose that has antiinflammatory activity; such dosing is usually higher than the one used for analgesic purposes. Although not observed frequently, NSAIDs may cause exacerbations of IBD, both in UC as well as in CD (153–155). The clinical relapse of IBD could be the consequence of increased intestinal permeability (152). In conclusion, the use of NSAIDs in the treatment of arthropathies is certainly indicated; however, the effect may be disappointing and new generations might need to be tried (e.g., Cox-2 selective inhibitors). Intraarticular corticosteroid injections have been given in patients with SpA with success, the effect may last several months (39,156). SASP has been studied in more detail during the last few years and is certainly of clinical use in SpA. In one of the first studies, clinical and laboratory parameters improved in patients with AS, with few side effects (157). A meta-analysis of SASP in AS patients showed a beneficial effect on clinical symptoms in the short term (158); this was confirmed in a multicenter, double-blind, placebo-controlled study (159). SASP produced a significantly higher remission rate in patients with SpA, compared with a nontreated group (52 versus 23%) (139). In particular, patients with SpA with inflammation of the terminal ileum needed SASP because of persistence of articular complaints. For several years it has been questioned which component of SASP is responsible for the improvement of the joint inflammation, and although sulphapyridine seems to be the active agent, up to now this question has not been solved completely (133,134). It indeed remains possible that the 5-ASA compo-

definition, its anti-inflammatory action on the intestinal mucosa, reduces the intestinal permeability and thus minimizes the chance for penetration of the responsible antigens. However, it should be borne in mind that the main action of SASP is concentrated within the colon, as a consequence of the azo-bond splitting colonic bacterial flora. Specific studies, specifically addressing the question of whether patients with IBD and with SpA improve after SASP therapy do not—to the best of our knowledge—exist, and one has to apply the same principles of management as in other categories of SpA. It may be possible that use of inhibitory cytokines or anticytokine antibodies may be of value in patients with IBD with therapy resistant SpA (116). In particular, the value of chimeric anti-TNF should be established in patients with IBD with persistent and incapacitating joint activity, as suggested by several authors (160–162).

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REFERENCES


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