Inflamm. res. 49 (2000) 047–054
1023-3830/00/020047-08 $ 1.50+0.20/0



Inflammation Research

Review

# Opportunities for immune modulation in the spondyloarthropathies with special reference to gut inflammation

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Received 4 February 1999; returned for revision 27 April 1999; accepted by M. J. Parnham 6 October 1999

**Abstract.** The spondyloarthropathies (SpA) are a related group of disorders, characterized primarily by spondylitis, pauci-articular arthritis and enthesitis. The presence of subclinical gut inflammation in patients with SpA ranges from 25 to 75%, depending upon the type of SpA. Several data suggest that the association between gut inflammation and synovitis reflects an etiopathogenetic relationship, and that strategies which interfere with the gut inflammation may also modulate the synovitis. Here we review some standard as well as experimental drugs used in the treatment of patients with inflammatory bowel disease and discuss what is known about their effect on SpA-related locomotor manifestations. For the more experimental drugs, such as cytokines, anti-cytokines and anti-adhesion compounds, clinical trials in patients with SpA are still very scarce.

**Key words:** Spondyloarthropathy – Reactive arthritis – Immune modulation – Crohn's disease – Inflammatory bowel disease

The spondyloarthropathies (SpA) are a related group of disorders, with common clinical, biological, genetic and therapeutic characteristics [1].

Spondylitis, pauci-articular arthritis and enthesitis are clinical hallmarks of this group of diseases. The spondylitis typically affects the insertion of the collateral ligaments with syndesmophyte formation, the zygo-apophysial joints and the sacroiliacal joints (Fig. 1). Peripheral arthritis is asymmetrical and mainly affects the lower limbs. The synovitis may be self-limiting or chronic with joint destruction. Enthesitis, mostly localised at the Achilles tendon, fascia plantaris and patella tendon is a hallmark of this disease entity (Fig. 2). Dactylitis (Fig. 3), involving different small joints on one finger or toe, is mostly associated with psoriatic arthritis or inflammatory bowel disease. Clinical manifestations of SpA often occur together with infections. Different micro-organisms may be involved. Enterogenic reactive arthritis can be initiated by Shigella flexneri, Salmonella tiphymurium, Yersinia enterocolitica or Campylobacter jejuni. Arthritis has been reported as well in association with endemic diarrhea without identified pathogens. Urogenital reactive arthritis is associated with urethritis, in which case Chlamydia trachomatis and Ureoplasma urealyticum are the most frequently identified pathogens. The genetic predisposition in the SpA is illustrated by the frequent familial clustering of these diseases and is mainly linked with HLA-B27. Ankylosing spondylitis and reactive arthritis are classical prototypes of the SpA. Other diseases include psoriatic arthritis, arthritis in patients with inflammatory bowel diseases and late onset pauciarticular juvenile chronic arthritis.

The actual standard treatment for SpA is the combination of non-steroidal anti-inflammatory drugs (NSAID) with sulfasalazine and intensive physical training. In cases of persistent monoarthritis, intra-articular injection of corticosteroids is mandatory. NSAID are considered the cornerstone of drug therapy of SpA. In the AMOR classification criteria for SpA [2], the clinical response to administration of NSAID is an important criterion. Usually, the response to NSAID, especially to NSAID with potent anti-inflammatory effects such as phenylbutazone, piroxicam, indomethacin and others, is rapid for both the peripheral arthritis as for the axial disease. Arrest of NSAID intake, however, causes a relapse of the disease. Some authors propose continuous intake of NSAID at a low dosage and some papers suggest that this continuous intake could prevent disease progression, although this has never been proven in a controlled study. With regard to the numerous and important side-effects of

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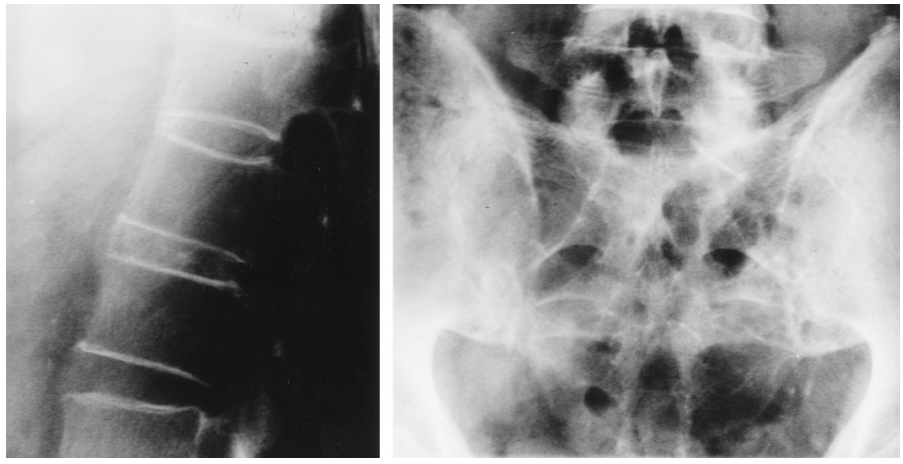

**Fig. 1.** Lateral radiograph of the lumbar spine with typical syndesmophytes in a patient with ankylosing spondylitis (Left). Bilateral sacroiliitis with fusion of the sacroiliacal joints (Right).

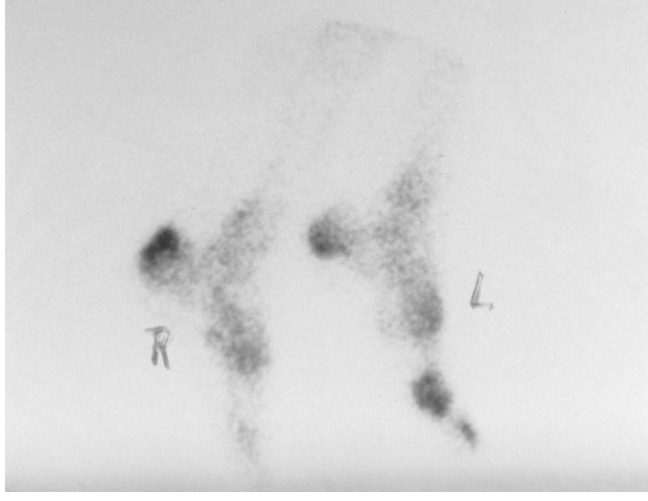


**Fig. 2.** Technetium-methylene diphosphonate scintigram shows increased uptake of the tracer at the insertion of the Achilles tendon of the right foot and the insertion of the plantar fascia of the left foot, corresponding to enthesiopathies.

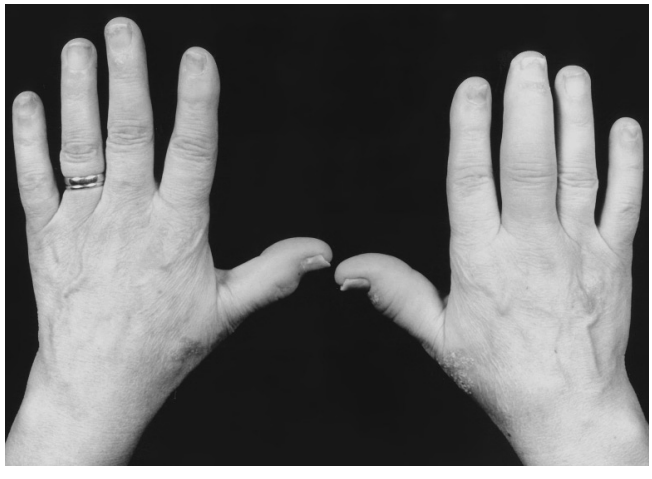

**Fig. 3.** Dactylitis or "sausage digit" of the third digit of the right hand in a patient with psoriatic arthritis.

NSAID, continuous treatment is not always possible. In cases of incomplete response to NSAID, NSAID side-effects or when treatment fails, the intake of sulfasalazine is recommended as a basic treatment.

NSAID may cause colitis. Histologically, this inflammation is mild and non-specific [3]. In the large intestine, NSAID may provoke relapse of quiescent IBD [4], especially in ulcerative colitis. Perforation and bleeding of the small intestine attributable to NSAID has been described [5] and these agents can induce subclinical intestinal abnormalities manifested by an increased intestinal loss of protein and blood [3]. Even bowel ulcerations [6] and intestinal strictures have been described with prolonged use of NSAID. The intestinal blood loss induced by these drugs can be reduced by sulfasalazine intake [7]. These, although relatively infrequent, lesions are different from the subclinical inflammation found in SpA. NSAID-induced enteropathy is localized in proximal and mid-small intestine and never evident in terminal ileum [8] while inflammatory gut lesions in SpA are found in terminal ileum and colon. Moreover, the inflammatory gut lesions in SpA were frequently demonstrated in patients who never took NSAID.

Over recent years, there has been a specific focus of interest on the relation between subclinical gut inflammation in patients with SpA and joint inflammation. The progress that has been made in this field over the last decade, is summarized in [9]. The presence of subclinical gut inflammation in patients with SpA has been confirmed by different groups and ranges from 25 to 75%, depending upon the type of SpA [10]. A fraction of these patients (undifferentiated SpA with histological evidence of chronic inflammation) go on to develop clinically overt Crohn's disease at 5-year's follow-up [11, 12].

The mechanisms underlying the immunological link between the gut and the joint in patients with SpA remain largely unknown. Some of the hypotheses that have been proposed include increased gut permeability for arthritogenic factors, in cases of gut inflammation; activation of immune cells in the gut and recirculation of these cells to the joints; or an altered immune surveillance and potential for persistence of infection in association with immune activation in the

bowel [13]. We recently reviewed the immunopathology of enteropathic arthritis in more detail [14].

Several pieces of data suggest that the association between gut inflammation and synovitis reflects an etiopathogenetic relationship. Indeed, a temporal association between flares of inflammatory bowel disease (IBD) and arthritis have been reported [15] and the severity of arthritis is correlated with the severity and colonic extent of inflammatory bowel disease [16]. Arthritis is more common in Crohn's disease patients with colonic involvement than in those with isolated small bowel lesions, although involvement of the ileum alone can be associated with peripheral arthritis [17]. In repeat ileocolonoscopy studies the remission of joint inflammation in SpA was always associated with disappearance of gut inflammation, whereas persistence of locomotor inflammation was mostly associated with persistence of gut inflammation [11].

This leads us to put forward the working hypothesis that interfering with the gut inflammation in patients with SpA yields a potential target for modulating the synovitis in these patients. We will therefore review some of the standard and experimental drugs currently applied for gut inflammation and discuss their established or potential use in the treatment of patients with SpA. With regard to the new and experimental biological compounds, a selection is made of some compounds (cytokines, anti-cytokines, anti-adhesion compounds) with interesting perspectives in IBD and SpA.

## Sulfasalazine

Sulfasalazine is a drug classically prescribed for patients with ulcerative colitis and Crohn's disease. It's precise mechanism of action is unknown.

The efficacy of the drug in Crohn's disease has been well documented. However, the drug has not been shown to be of benefit as a prophylactic agent in this disease, since it showed no benefit over placebo in preventing postoperative recurrences of Crohn's disease [18]. In ulcerative colitis, sulfasalazine is effective in the treatment of colitis, as well as being useful as prophylaxis for ulcerative colitis in remission [17, 19–21].

A daily dose of 2 g has become the standard maintenance dose.

Recently, two large double-blind multicenter studies performed in Europe and in the USA in patients with ankylosing spondylitis, reactive arthritis and psoriatic arthritis confirmed the overall beneficial effect of the drug with improvement in both clinical and laboratory markers [22–25]. The most pronounced effects were seen in patients with psoriatic arthritis. Overall, the beneficial effect was seen mainly in peripheral arthritis and tendinitis.

## Aminosalicylates

5-ASA is the component of sulfasalazine that is held responsible for the anti-inflammatory action of sulfasalazine in IBD [26]. 5-ASA interferes with different immunological pathways, possibly related to the pathogenesis of gut inflammation: it inhibits the synthesis of cyclo-oxygenase and lipoxygenase; it is capable of blocking chemoattraction of neutrophils; it may serve as a scavenger of oxygen-derived free radicals; and it has been shown to abrogate T cell proliferation [27].

Several studies have confirmed the efficacy of 5-ASA enemas in patients with distal ulcerative colitis in doses ranging from 2 to 4 g/d [28, 29], and have proven the usefulness of this compound in maintaining remission [30]. Similar results have been obtained with oral controlled release forms.

Aminosalicylates were found to be of little benefit for patients with spondylitis. Taggart et al compared the efficacy of sulfasalazine, 5-ASA (coated with acrylic resin S) and sulfapyridine in 90 patients with active ankylosing spondylitis in a 26-week randomized, observer-blinded study [31]. Patients and observers reported a favorable outcome after treatment with sulfasalazine and sulphapyridine more often than with 5-ASA treatment.

The effect on peripheral arthritis and enthesitis has not properly been studied. There are 2 interesting case reports, suggesting a beneficial effect of the compound on these manifestations. Thomson et al [32] reported a patient with longstanding active Reiter's disease and Crohn-like lesions on ileocolonoscopy. Coated 5-ASA therapy was installed with remission of synovitis and enthesitis after 4 months of therapy. After interruption of the therapy, the synovitis reappeared. Mesalamine was reinstalled with good clinical result, as well as resolution of the small bowel changes. Zwillich and Ritchlin [33] reported on another patient with longstanding and active Reiter's syndrome, in whom olsalazine therapy was prescribed. This resulted in improved control of joint pain, tender joint score and enthesis count at 3 months. The therapy was interrupted because of diarrhea (a frequent side effect of olsalazine) with a consecutive flare of rheumatic symptoms. These case reports suggest that 5-ASA compounds, through their action on the gut, modulate peripheral joint symptoms in patients with reactive arthritis. However, the observations need further confirmation in an appropriate trial.

## Antibiotics

A causal relationship between IBD and infection remains plausible [34] and antibiotics have a well established role in the management of this disease. Not only are they applied in the treatment of secondary abscess formation, but also in pouchitis. Specific antimicrobial agents like metronidazole, which has an anti-microbial spectrum particularly against gut anaerobes, have also found a place in the primary treatment of the disease, especially in cases of perineal disease [35]. The latter compound may also have immunomodulatory effects, independently by its antimicrobial action.

The relation between infection and SpA is better defined [36, 37]. However, the role of antibiotics in the treatment of patients with reactive arthritis is still controversial [38, 39]. Best evidence for the use of antibiotics and prevention of reactive arthritis is in the case of chlamydia infection. The use of antibiotics in other forms of acute or chronic reactive arthritis is not settled yet.

## Corticosteroids

Corticosteroids are effective drugs for inducing remission in active inflammatory bowel disease. Prednisolone and methylprednisolone are the most commonly used conventional steroids. More recently, new corticosteroid analogues with high topical antiinflammatory activity but low systemic activity have been made available. Two studies have shown that conventional oral steroids are more effective than placebo in the treatment of active Crohn's disease [18, 40]. Corticosteroid therapy is hampered by side effects, especially in the case of prolonged use. In this respect, much interest has been given to topical acting oral steroids, such as budesonide. Formulations have been developped to deliver the active drug to the ileal and ileocecal area [41]. Multiple therapeutic trials with these newer agents in Crohn's disease have been undertaken. They suggest a promising effect in mild to moderate flares of disease [42].

No controlled trials have been carried out with corticosteroids in patients with SpA. Also, for any effect of conventional systemic corticosteroids, it would be impossible to discriminate between a systemic action or a gut-related immune modulation of the drugs. Oral topical corticosteroids may provide an opportunity to test the challenging hypothesis that immune intervention in the gut, with remission of gut inflammation, would also affect joint inflammation.

## Conventional immunosuppressive drugs: Methotrexate, azathioprine and cyclosporin

Low dose *methotrexate* has become a first choice disease modifying drug for patients with rheumatoid arthritis (RA). Its role in IBD and SpA is less well known. Neither is the mode of action relevant to its clinical effect in arthritis well defined. Doses of up to 25 mg per week are used for patients with Crohn's disease and ulcerative colitis [43, 44]. A short-term effect has been reported. However, there is a significant relapse rate after 1 year follow-up. Randomized controlled trials are necessary to define the clear role of this agent in IBD.

In spite of the extensive experience with methotrexate in RA, no controlled data are available for patients with SpA. Ostendorf et al reported an open trial of methotrexate in a small group of patients with severe highly inflammatory ankylosing spondylitis: no patients responded significantly to the drug [45]. A control group of patients with psoriatic arthritis, included in the same study, did respond clinically and biologically.

*Azathioprine* has been used in the transplantation setting as well as in patients with different types of autoimmune diseases. The drug has been found to be effective in the management of refractory ulcerative colitis and Crohn's disease with cortico-steroid sparing effect [43]. The unproven, but feared effect of inducing neoplasia discourages widespread use of this drug. No controlled data are available on its effect on SpA.

The action of *cyclosporin* is lymphocyte specific. It acts particularly on T cell function and proliferation, mostly through inhibition of IL-2. Its clinical role in organ transplantation is well established. It has also been used in a variety of autoimmune disorders, including RA. Cyclosporin has a well documented effect in ulcerative colitis. However, relapses are frequent upon stopping therapy and low dose therapy has no proven effect in maintaining remission. The addition of low-dose cyclosporin to conventional treatment for Crohn's disease does not improve symptoms or reduce requirements for other forms of therapy [46]. Its role in the therapy of IBD at present is limited to cases that are refractory to conventional immunosuppression. Of advantage is the fact that it can be effective within days.

The place of the drug in the treatment of patients with SpA is unexplored.

## Cytokines and anti-cytokines

A dynamic balance between pro- and anti-inflammatory cytokines is essential for maintaining immune homeostasis, not only in the gut mucosa but also at a systemic level and at the site of so-called tertiary lymphoid tissues and organs (sites exhibiting – under normal circumstances – selective lymphocyte recirculation as part of the normal immune surveillance program; however, in inflammatory conditions, immune cell extravasation at these sites may increase dramatically).

The gut inflammation in Crohn's disease is mainly dependent upon Th1 cytokines. Data on cytokine profiles in SpA are scarce. No in situ data are available on cytokine expression in the gut in this situation. Preliminary data suggest that the joint inflammation would be more dependent upon Th2 cytokines [47, 48].

Biological compounds, such as cytokines, anti-cytokines as well as compounds interfering with recirculation (see below) are experimental drugs. They have been applied in research protocols for selected groups of patients with IBD. Since some of these interventions interact specifically with gut inflammation, it is tempting to speculate upon their effect in patients with SpA. Pilot observations are therefore awaited.

### *Anti-TNF-alpha*

TNF-alpha is produced predominantly in monocytes, macrophages and activated T cells. It acts on a broad spectrum of target cells. TNF-alpha induces macrophages to produce IL-1, IL-8 and IL-12. Endothelium responds to TNF-alpha with enhanced expression of adhesion molecules, thus leading to increased cell infiltration. Fibroblasts constitute another TNF-alpha target, responding with IL-6 secretion which itself induces an acute phase response, as well as increased synthesis of metalloproteinases and decreased production of matrix molecules. In addition, TNF-alpha alters the epithelial permeability thus compromising the gut barrier function. Several data suggest an imbalance between pro- and anti-inflammatory cytokines in the gut mucosa in patients with Crohn's disease [49, 50]. Increased serum levels and stool concentrations of TNF-alpha and an elevated number of TNF-alpha secreting mucosal cells in patients with Crohn's disease strongly suggest TNF-alpha as a key mediator of inflammation in this disease, and thus an interesting target molecule.

cA2 is a humanized chimeric IgG1 anti-TNF-alpha monoclonal antibodies (Mab), capable of neutralizing the soluble cytokine as well as binding to membrane bound cytokine [51]. The latter action alters the function of TNF-alpha-producing cells or may even lead to cell lysis through complement activation. Several clinical trials with the cA2 Mab in patients with Crohn's disease have been reported. Two open-label trials in patients with active Crohn's disease refractory to steroid treatment, reported clinical remission with endoscopic evidence of healing of mucosal ulcers after a single intravenous dose [52,53]. The first multicenter, randomized, double-blind, placebo-controlled trial included patients with moderate to severe Crohn's disease [54]. The treatment produced a rapid and profound benefit for all response variables measured. This was accompanied by a rapid reduction in C-reactive protein (CRP) levels. Clinical improvement was also directly associated with endoscopic improvement. Patients retreated with the Mab remained in stable condition, in contrast to patients receiving retreatment with placebo, showing gradual loss of clinical response over several months [55]. Finally, a placebo-controlled study in 12 centers in the US and Europe in patients with fistulizing Crohn's disease demonstrated a significant reduction in the number of open fistulae and complete remission in a significant number of patients [56]. A dose regimen of 5 mg/kg produced a high degree of benefit lasting at least 3 months.

The effect of anti-TNF-alpha Mab on spondylitis, synovitis or enthesiopathy in patients treated with this compound for IBD, has not been evaluated properly. Nor has the effect of the compound been tested in patients with other types of SpA.

### *IL-10*

The pathogenesis of inflammatory bowel diseases may be associated with a decreased production of cytokines suppressing macrophage and T cell functions, like IL-4 and IL-10. Several data indicate that IL-10 is required to maintain immune homeostasis in the gut. Especially interesting is the observation that IL-10 deficient mice develop enteritis [57] and that IL-10 supplementation is effective in treating this inflammation. In addition, IL-10 is efficacious in the treatment of gut inflammation in another model of bowel inflammation, namely rabbit immune complex induced colitis (induction of colitis by rectal instillation of formalin followed by intravenous infusion of heat-aggregated rabbit immunoglobulin) [58].

Van Deventer et al conducted a randomized, double-blind, placebo-controlled dose-escalating study including 45 patients with active Crohn's disease refractory to steroid therapy [59]. Recombinant human IL-10 was administered by daily intravenous bolus injection for 7 consecutive days. 81% of IL-10 treated patients experienced a clinical response or remission, versus 46% in the placebo group.

Data on the level and the role of IL-10 in patients with SpA are scarce. Chaudepierre et al reported IL-10 plasma levels to be correlated with disease activity in patients with SpA, in particular with duration of morning stiffnes, pain on visual analogue score (VAS) and CRP levels [60]. Simon et al. observed that synovial fluid derived T cell clones from patients with chlamydial reactive arthritis express IL-10 mRNA [61]. IL-10 was also shown to be produced by psoriatic synovium [62]. It is not possible at this time to define the role of IL-10 in the development of SpA. One may consider a feedback response aimed at controlling inflammation. Another interpretation might be that IL-10, given its immunosuppressive role, favors the persistence of bacterial antigens, which could provoke or perpetuate inflammation. Therefore, we need key observations on the effect of this cytokine on locomotor manifestations in patients with inflammatory bowel disease as well as other types of SpA.

### *IL-11*

IL-11 has multiple effects on megacaryocyte, myeloid and erythrocyte progenitors. Recent data indicate that IL-11 may play a role in the immune response and inflammation [63]. In particular, it stimulates B cells and immunoglobulin production. It also down-regulates lipopolysaccharide induced TNF-alpha production in macrophages.

A pilot trial (randomized, placebo-controlled) with IL-11 was performed in patients with active Crohn's disease [64]. There was a trend towards a better outcome in patients treated with IL-11 versus placebo, although statistical significance was not reached.

## Anti-adhesion compounds

The process of lymphocyte trafficking is mainly regulated by receptors that belong to a group of molecules referred to as adhesion molecules. They constitute the molecular basis for cell-cell as well as cell-matrix interactions. Engagement of these surface receptors may also regulate important functional activities of the cell. Adhesion molecules can be divided, according to their molecular structure, into three broad families: the integrins, the selectins and the immunoglobulin superfamily members [65]. Biological compounds have been made available recently, that specifically interact with lymphocyte recirculation [66].

### *ICAM-1 antisense oligonucleotide*

Intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin superfamily, expressed as a transmembrane glycoprotein on vascular endothelium and a subset of leukocytes. Its expression can be upregulated in response to inflammatory mediators. The ligands with which it can interact include beta2-integrins and leukocyte function associated antigen-1 (LFA-1). ICAM-1 and LFA-1 are involved in recruitment and activation of inflammatory cells. In the context of Crohn's disease, they have been found to be up-regulated on mucosal endothelium and lamina propria mononuclear cells [67, 68].

ISIS 2302 is a 20-base phosphorothionate oligodeoxynucleotide designed to specifically hybridize to a sequence in the 3′ untranslated region of the human ICAM-1 message [69]. The oligodeoxynucleotide-RNA heterodimer so formed serves as a substrate for the ubiquitous nuclease RNase-H, with subsequent cleavage and reduction in cellular specific

message content and consequent reduction in ICAM-1 expression. Twenty patients with active, steroid-treated Crohn's disease were randomized to receive intravenous infusions of ISIS 2302 or placebo in a double-blind study [70]. 47% of the ISIS 2302 treated and 20% of the placebo treated patients went into remission. These findings were associated with decreased intestinal mucosa ICAM-1 expression as well as increases in beta7 positive CD3 peripheral blood lymphocytes. No data are available about the effect of this compound in SpA.

*Anti-$\alpha4\beta7$*

The $\alpha4\beta7$ integrin is expressed on lymphocytes with gut tropism. Its ligands include vascular cellular adhesion molecule-1 (VCAM-1) and fibronectin, both of which are upregulated upon inflammation. More recently, it was shown that $\alpha4\beta7$ also binds to the mucosal vascular addressin MadCAM-1, expressed selectively on high endothelial venules in mucosal lymphoid tissue and gut lamina propria. The anti-$\alpha4\beta7$ Mab Act-1, which does not inhibit adhesion to VCAM-1, does inhibit adhesion to MadCAM-1, suggesting that the $\alpha4\beta7$ binding site for VCAM-1 and MadCAM-1 are not identical [71].

$\alpha4\beta7$ positive lymphocytes constitute an interesting cell population in patients with chronic autoimmune arthritis, since they are also represented among the synovial membrane lymphoid infiltrates. In addition, our group demonstrated that $\beta7$ integrin expression was increased among synovial membrane T cell lines derived from patients with SpA, compared to RA [72]. Also, there is evidence that $\beta7$ cells in SpA synovium are mainly derived from mucosal sites. In contrast, the phenotype of $\beta7$ cells in RA synovium reflects more an active recruitment from the peripheral circulation. Thus, a gut-synovium recirculation of T lymphocytes may contribute to the pathogenesis of arthritis in patients with subclinical or clinical gut inflammation in the context of spondyloarthropathy.

The cotton-top tamarin (CTT) is a primate that experiences a spontaneous chronic colitis marked by periodic flares of acute inflammation when in captivity or exposed to temperatures lower than its natural habitat. Podolsky et al. (1993) described the effect of anti-$\alpha4$ Mabs on the intensity of acute flares of CTT colitis in a placebo controlled way [73]. Significant attenuation of acute colitis when compared to both pretreatment activity index and placebo control group was observed. A more recent study reported on the effect of anti-$\alpha4\beta7$ on the colitis in the same animal model [74]. Treatment with the anti-$\alpha4\beta7$ Mab ameliorated inflammatory activity and rapidly improved stool consistency when administered to animals with chronic colitis. Furthermore, antibody therapy reduced the mucosal density of $\alpha4\beta7$ positive cells. Together, these studies suggest that the $\alpha4\beta7$ integrin represents a disease-specific target for the treatment of inflammatory bowel disease. Human trials with the Act-1 Mab in patients with IBD are in progress but have not been concluded yet. The selective enrichment of $\alpha4\beta7$ lymphocytes among synovial infiltrates in arthritis patients and their supposed mucosal origin in SpA arthritis, should encourage research on anti-$\alpha4\beta7$ compounds in SpA as well.

In conclusion, this overview should make it clear that at present, there are indeed compounds available that specifically interact with the immune alterations and inflammation in the gut. Since spondyloarthropathy and gut inflammation are intimately associated – clinically as well as pathogenetically – the efficacy of these compounds, not only on gut inflammation in patients with IBD, but also on articular manifestations in patients with SpA, should be explored, especially since therapeutic options in this frequent rheumatic condition are still limited.

*Acknowledgements.* This work was supported by a concerted action grant GOA 96001 of the University of Gent, Belgium.

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