Treatment of arthralgias and spondyloarthropathy associated with inflammatory bowel disease

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Joint involvement is the most frequent extraintestinal manifestation of inflammatory bowel diseases (IBDs). Arthralgias are common and spondyloarthropathy may affect peripheral joints and the axial skeleton, as well as the tendons. The broad spectrum of joint manifestations requires a therapeutic concept that takes the potential influence of agents on the underlying bowel disease into consideration. This review will focus on the current therapeutic approach to the different manifestations of IBD-related joint disease and will outline baseline treatment, the use of conventional agents and biologicals. TNF antagonists have dramatically changed the care of patients. In particular, TNF antagonists have emerged as the most effective treatment for ankylosing spondylitis, which has often been refractory to therapy in the past. For patients who fail to respond to TNF antagonists, several novel agents will provide more treatment choices in the future. Recent insights into disease mechanisms of IBD have revealed attractive potential therapeutic targets, such as the interference with immune dysregulation, the gut barrier and the intestinal microbial flora.

Joint involvement in inflammatory bowel disease

Joint involvement is the most frequent extraintestinal manifestation of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC). Arthralgias and spondyloarthropathy (spondylarthropathy, spondyloarthritis) are associated with considerable functional impairment, as well as disability [1–3].

IBD-related joint manifestations belong to the group of spondyloarthropathies that share several features, such as peripheral arthritis, axial involvement and enthesitis, and show a genetic linkage with HLA-B27 [4,5]. However, the clinical spectrum of musculoskeletal manifestations in IBD is broader [6] than that defined by spondyloarthropathy criteria [4]. Articular manifestations are observed in 39% of patients with IBD [1]. Arthralgias are common and may either be related to bowel inflammation or be non-inflammatory. In particular, Palm *et al.* reported arthralgias that are not associated with bowel inflammation in 16% of patients and described a greater prevalence in CD than in UC [3]. Two types of peripheral arthritis are distinguished, an acute self-limiting pauciarticular and a persistent polyarticular arthritis: type 1 occurs in 6% of CD patients and 3.6% of UC patients, while type 2 occurs in 4% and 2.5% of CD and UC patients, respectively [7]. Axial involvement may vary from chronic inflammatory back pain, symptomatic or asymptomatic sacroiliitis to ankylosing spondylitis. Between 3.7 and 10% of patients with IBD fulfill the criteria for ankylosing spondylitis [1,8]. Clinical characteristics of peripheral arthritides and axial involvement in IBD are shown in **Table 1**. Enthesitis occurs in 7% of patients and affects primarily the lower limbs, most often the heels, and may be the only musculoskeletal manifestation [1,9].

Arthralgias and pauciarticular arthritis, which are closely associated with bowel inflammation, can be expected to respond to treatment of the underlying IBD. Non-inflammatory arthralgias, polyarticular arthritis, axial involvement and enthesitis usually require additional therapy. Conventional therapy includes analgesics, glucocorticoids, DMARDs and immunosuppressive agents. Antagonists directed against one of the most important proinflammatory cytokines, TNF-α, have dramatically changed the care of patients with IBD and spondyloarthropathies [10,11].

Current treatment of IBD-related joint involvement is still based almost entirely on extrapolation from that for other forms of arthritis [12]. Although spondyloarthropathies share clinical manifestations, and some medications that have been shown to improve one disease have similar efficacy in the others, consideration of the unique features of the different entities appears beneficial in guiding therapy [13]. Several drugs are known to have adverse influences on IBD and the use of therapeutic agents depends on the activity of bowel inflammation. Therefore, an individualized therapeutic strategy in IBD-related joint manifestations may improve the outcome of patients.

Keywords: ankylosing spondylitis, arthritis, Crohn's disease, inflammatory bowel disease, sacroiliitis, spondyloarthritis, spondyloarthropathy, therapy, ulcerative colitis

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Table 1. Clinical features of peripheral arthritis and axial involvement in inflammatory bowel diseases.

Clinical feature	Peripheral arthritis		Axial involvement	
	Pauciarticular (≤ 5 joints)	***Polyarticular (>5 joints)***	***Sacroiliitis***	***Ankylosing spondylitis***
Involvement	Large joints, asymmetric	Small/large joints, symmetric	Uni-/bilateral, may be asymptomatic	All parts of the spine
Onset	With/after onset of IBD	With/after onset of IBD	Before/with onset of IBD	Before/with onset of IBD
Clinical course	Self-limiting	Persistent	Persistent	Persistent
Related to IBD activity	Yes	No	No	No
Structural damage	No	No	Yes	Yes
HLA-B27 linkage	Yes	No	Not as close as in idiopathic ankylosing spondylitis	Not as close as in idiopathic ankylosing spondylitis

IBD: Inflammatory bowel disease.
Summarized from [1,2,7,8].

Increasing evidence supports the concept that inflammation results from an increased immune response to the intestinal microbial flora in IBD [14] and in spondyloarthropathy [2,15]. Identical T-cell expansions discovered in the intestinal mucosa, synovium and blood have suggested that impairment of the inflamed gut barrier enables homing of lymphocytes from the gut to the joint tissue [15]. Activated mucosal epithelial cells, macrophages and dendritic cells lead to the secretion of proinflammatory cytokines, such as TNF, and to lymphocyte dysregulation and a T-helper cell type 1 response [14]. Agents that interfere with the pathophysiologic pathways related to both the gut and the joint are of particular interest to the therapy of IBD-associated spondyloarthropathy.

This review outlines the current approach to the treatment of IBD-related joint involvement. Advances are summarized and new strategies are discussed that may be relevant to improve future treatment of IBD-related arthropathies.

Baseline therapy for arthralgias & spondyloarthropathy in IBD

Baseline therapy includes analgesics, local corticosteroids and physiotherapy. **Table 2** shows current treatment options for patients with IBD-related joint involvement.

Relief of pain may be obtained from non-opioid analgesics such as paracetamol [2]. Metamizole (dipyrone) is still frequently used in several countries, although it can rarely induce the potentially lethal side effect, granulocytopenia [16]. We add an opioid analgesic, such as tramadol, or an antidepressant in patients with severe arthralgias. Gastroenterologists are reluctant to use conventional NSAIDs or COX-2-inhibitors because of concerns of reactivation of IBD. However, data on these agents are inconsistent. It has been suggested from careful analysis of several studies that the risk may be less than generally claimed and paracetamol might not be safer than NSAIDs [2]. Data from Bonner *et al.* [17] and Sandborn *et al.* [18] indicate that the risk of IBD reactivation might depend on the dosage of NSAIDs and COX-2-inhibitors as well as on the duration of treatment. El Miedany *et al.* report no increased exacerbation of IBD with the highly selective COX-2-inhibitor, etoricoxib, over 3 months [19]. Therefore, it might be justified to use small doses of NSAIDs and COX-2-inhibitors over short periods of time in patients with IBD.

Injection of corticosteroids into severely inflamed peripheral joints may be helpful; injections into the sacroiliac joints have been shown to be effective for several months [20]. Local steroid injection may also be tried to improve enthesitis [21]. The long-term use of systemic corticosteroids for arthritis should be avoided since IBD patients are at an increased risk of osteoporosis [22]. Moreover, IBD patients are predisposed to corticosteroid-induced osteonecrosis [23].

Physiotherapy and exercise may provide relief of pain and help to prevent disability. Intensive physiotherapy is particularly important for patients with ankylosing spondylitis to maintain flexibility and posture [24]. However, whether and to what extent physiotherapy is beneficial is likely to depend on the degree of spinal inflammation, function and damage [25].

Table 2. Current treatment options for joint involvement in inflammatory bowel disease.

	Baseline therapy	DMARDs	TNF antagonists
Arthralgias and chronic back pain	Analgesics Physiotherapy		
Pauciarticular arthritis	Analgesics Glucocorticoids* Physiotherapy	Sulfasalazine‡ Mesalazine‡	
Polyarticular arthritis	Analgesics Glucocorticoids* Physiotherapy	Sulfasalazine Mesalazine Methotrexate Leflunomide	Infliximab Adalimumab Etanercept§
Sacroiliitis, ankylosing spondylitis	Analgesics Glucocorticoids* Physiotherapy	Sulfasalazine in early disease	Infliximab Adalimumab Etanercept§
Enthesitis	Analgesics Glucocorticoids* Physiotherapy	Sulfasalazine	Infliximab Adalimumab Etanercept§

Local injection is preferred.

‡*If not controlled by treatment of inflammatory bowel disease.*

§*No effect on bowel inflammation.*

DMARDs & immunosuppressive agents

DMARDs are primarily used in patients with IBD-related polyarticular arthritis (**Table 2**). Sulfasalazine has been shown to be beneficial in the treatment of peripheral arthritis in the spondyloarthropathies [26,27] and is usually the drug of first choice for IBD-related arthritis [2,12]. Data on mesalazine in IBD-related peripheral arthritis are limited to two open trials demonstrating improvement [28,29]. Many rheumatologists use methotrexate for IBD-related peripheral arthritis, although data are scarce [2]. Leflunomide has been shown to improve peripheral arthritis in patients with spondyloarthropathies, particularly psoriatic arthritis [30,31]. We suggest that leflunomide might be considered as an alternative treatment in IBD-related peripheral arthritis for patients who cannot tolerate other DMARDs.

Overall, the use of DMARDs for the treatment of axial disease in patients with spondyloarthropathies has been disappointing [25]. Mesalazine, methotrexate and leflunomide have not demonstrated convincing efficacy for treatment of axial disease [31–33]. Sulfasalazine has been effective in patients with early axial symptoms and improves morning stiffness [34,35]. Therefore, sulfasalazine might be used in patients with early axial disease. Studies on other DMARDs have not been performed in early spondyloarthropathies.

Azathioprine and cyclosporine are used in patients with active and severe IBD [12]. The influences of these immunosuppressive agents on IBD-related spondyloarthropathy have not been analyzed. Few data are available on the treatment of other spondyloarthropathies. Efficacy of cyclosporine has been suggested in a randomized controlled trial in psoriatic arthritis [36].

TNF-α antagonists

TNF-blocking agents are used in active spondyloarthropathy not responding to conventional therapy. The efficacy of the three currently available TNF antagonists etanercept, infliximab and adalimumab, in peripheral as well as axial arthritis in spondyloarthropathies, has been well established.

The majority of data have been obtained in ankylosing spondylitis and psoriatic arthritis [11]. Data from several studies suggest that TNF antagonists retard or arrest disease progression in ankylosing spondylitis, at least in the short term [37]. However, virtually all patients with ankylosing spondylitis have a disease flare upon discontinuation [38,39]. Efficacy of infliximab in patients with IBD-related ankylosing spondylitis has been suggested from a double-blind, placebo-controlled multicenter study that included different subgroups of patients with spondyloarthropathies [40]. In addition, several open studies have reported efficacy of infliximab [41–44] and etanercept [45] in CD-related spondyloarthropathy. In IBD, infliximab [46–49] and adalimumab [50–52], but not etanercept [45,53],

have been shown to improve bowel symptoms, and to induce and maintain remission. Therefore, infliximab or adalimumab might be preferred in active IBD, whereas etanercept might be considered in inactive IBD when patients are not responding to conventional therapy of associated spondyloarthropathy. Recent studies indicate efficacy of a pegylated Fab anti-TNF fragment, certolizumab pegol, in CD [54]. It is expected that data on the effects of this agent on IBD-related spondyloarthropathy will soon be available.

The Assessments in Ankylosing Spondylitis International Working Group has published a consensus statement for the treatment of ankylosing spondylitis with TNF antagonists, recommending an adequate trial of NSAIDs as a prerequisite [55]. A significant number of patients do not show a sufficient response to TNF antagonists. Data from a study of patients with ankylosing spondylitis by Rudwaleit *et al.* indicate that the greatest benefit from TNF blockade is achieved in active disease as measured by elevated C-reactive protein and radiologic progression [56].

In addition to ankylosing spondylitis, IBD-related arthritis and enthesitis may both respond to infliximab [41,42]. TNF antagonists are effective for treating enthesitis associated with all forms of spondyloarthropathy [57–61]. Thus, TNF antagonists should also be considered in patients with IBD-related polyarthritis and enthesitis not responding to baseline therapy and DMARDs.

Proteins for therapeutic use have the potential to induce antidrug antibodies. Problems with infliximab treatment arise from the formation of antibodies against the chimeric monoclonal antibody, which may lead to infusion reactions and loss of response [62]. A recent study in patients with rheumatoid arthritis (RA) shows that immune responses that are associated with nonresponse to therapy may also occur with the use of the fully human monoclonal antibody adalimumab [63].

Another potential side effect of TNF inhibition is an increased risk of infections. The risk of induction of autoimmunity may be lower with the newer TNF antagonists. A major concern has been that TNF inhibition might cause an increase in the rate of malignancies. At present, accumulated data from the use of infliximab do not provide evidence for a clear increase over the background incidence of malignancies in general. For other TNF antagonists, the exposure of patients with IBD has been found to be too limited to draw any conclusion [62].

Potential therapeutic targets for IBD-related spondyloarthropathy

For patients who fail to respond to TNF antagonists, agents that are effective in IBD and other arthritides (**Table 3**) might be of particular interest. Novel treatments focus on the interference with dysregulated lymphocytes, altered cytokine secretion and cellular adhesion.

The interaction between molecules on T lymphocytes and antigen-presenting cells is regarded as an interesting therapeutic target in IBD [64]. Abatacept, a fusion molecule of CTLA-4 and immunoglobulin (CTLA-4Ig), is a T-cell costimulator modulator that interacts

Table 3. Potential targets for future treatment of inflammatory bowel disease-related joint involvement.

Target (agent)	Published clinical data in inflammatory bowel disease or joint diseases
Cytokines & cytokine receptors	
IL-2 receptor/CD25 (basiliximab)	Ulcerative colitis [73]
IL-6 receptor (tocilizumab)	Crohn's disease [75] and rheumatoid arthritis [76,77]
IL-12	Crohn's disease [74]
T cells	
CD28/B7 interaction (abatacept)	Rheumatoid arthritis [65]*
CD3 (visilizumab)	Ulcerative colitis [71] and psoriatic arthritis [72]
B cells	
CD20 (rituximab)	Rheumatoid arthritis [66]*
Cellular adhesion	
Integrin (natalizumab)	Crohn's disease [78–81]

Selected from several studies.

with the binding of CD28 to B7. Abatacept has demonstrated efficacy in RA patients not responding to anti-TNF agents [65], and has already been approved for the treatment of RA in several countries. Since development of UC has been reported in one RA patient during CTLA-4Ig therapy [66], effects of this treatment on IBD patients have to be monitored closely. In RA patients who fail to respond to TNF antagonists, the B-cell depleting anti-CD20-antibody rituximab is effective [67] and has been US and EU approved. Data from animal models suggest that the effects of rituximab reach far beyond its influence on antibody production [68]. In particular, B cells have a role in antigen presentation and exert profound regulatory effects on dendritic cells, the most effective antigen-presenting cells [69]. An open trial using rituximab in ankylosing spondylitis will start soon [101]. At present, it is not known whether B-cell depleting or modulating therapies might have a role in IBD.

In IBD, agents directed against activated T cells, the IL-12-driven T-helper cell type 1 response, IL-18 and IL-23 are promising [64,70]. Early studies using visilizumab, an anti-CD3 antibody, have been performed in UC [71] and in psoriatic arthritis [72]. An anti-CD25 antibody has been used in UC [73] and an anti-IL-12p40 antibody in CD [74], revealing promising results. Efficacy of a humanized anti-IL-6 receptor antibody, tocilizumab, has been demonstrated in CD [75] and RA [76,77].

Data from several randomized controlled trials employing the first agent that targeted cellular adhesion, the anti-α4 integrin antibody natalizumab, suggest efficacy for induction of a clinical response and remission in CD [78–81]. Since JC virus-related leukoencephalopathy after natalizumab treatment has been observed in three patients, it has been suggested to weight the clinical benefit of natalizumab against its potential risks [82]. Results from a Phase II study of natalizumab in RA are expected [102].

The barrier dysfunction or the microbial flora are other potential therapeutic targets [14]. Data from IBD animal models suggest that angiogenesis inhibition might improve mucosal healing and restore barrier function in IBD [83]. Increasing data indicate that probiotics may prevent inflammatory processes [14]. A pilot study suggests that patients with arthralgias related to the activity of IBD benefit from the probiotic mixture VSL3 [84].

Conclusion

In patients with IBD, joint disease is a major problem that often requires therapy in addition to treatment of the underlying bowel disease. Current therapy is still based almost entirely on extrapolation from that for other forms of arthritis. Analgesics, corticosteroids and physiotherapy remain important in the treatment of IBD-related joint involvement despite the availability of new agents. DMARDs may be effective in patients with polyarticular arthritis. A trial of sulfasalazine appears justified in early axial disease. However, the use of DMARDs is generally disappointing in ankylosing spondylitis. Treatment with TNF antagonists is a standard care in ankylosing spondylitis refractory to conventional treatment and is of particular importance to IBD patients who cannot tolerate NSAIDs or COX-2-inhibitors. Continuous anti-TNF therapy is required to maintain treatment response and not all patients show sufficient improvement. For patients who fail to respond to TNF antagonists, novel non-TNF biologicals and strategies might provide alternative treatment choices in the future.

Future perspective

Prospective trials focusing on the effects of drugs on IBD-related joint involvement are needed. Studies should particularly concentrate on joint manifestations that are not improved by treatment of the underlying IBD, such as noninflammatory arthralgias, polyarticular arthritis, axial disease and enthesitis.

New pathways and targets, such as barrier function and the microbial flora in IBD [14], will be actively examined in the future. This will lead to an improved understanding of the role of the intestinal microbial flora in IBD and related arthritis. New agents will result from this exciting area of research and might change the current immunosuppressive paradigm in IBD treatment.

Several specific biologic agents will be approved in the next few years. It will be of increasing importance to recognize which patients benefit most from a particular agent. The application of new technologies, such as gene expression arrays and proteomics, to problems of patients will help investigators to clarify this issue [64]. It is likely that these techniques will also improve the understanding of the different entities in the group of spondyloarthropathies. Our hope is that the detection of predictive measures of both individual treatment responses and prognosis will enable clinicians to develop a more rational therapy.

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Executive summary

Joint involvement in inflammatory bowel disease

- Joint involvement is the most frequent extraintestinal manifestation of inflammatory bowel diseases (IBDs) and affects peripheral joints and the axial skeleton, as well as the tendons.
- Noninflammatory arthralgias, polyarticular arthritis, axial involvement and enthesitis usually require therapy in addition to treatment of the underlying bowel disease. The therapy is based on extrapolation from that for other forms of arthritis.
- A therapeutic approach that takes the potential influence of agents on the underlying bowel disease into consideration is necessary.

Baseline therapy for arthralgias & spondyloarthropathy in inflammatory bowel disease

- Baseline therapy includes analgesics and physiotherapy. In patients with peripheral arthritis or sacroiliitis, injections of corticosteroids are used.
- Data on NSAIDs and COX-2-inhibitors in IBD are inconsistent. The risk of exacerbation of IBD by NSAIDs and COX-2-inhibitors may be less than generally claimed and the use of small doses over short periods of time is justified.

DMARDs & immunosuppressive agents

- In patients with IBD-related polyarticular arthritis, sulfasalazine is usually the drug of first choice. Methotrexate or leflunomide may also be used for treating peripheral joint inflammation.
- Overall, DMARDs have not been proven to be effective for treating ankylosing spondylitis. However, sulfasalazine may improve symptoms in patients with early axial disease.

TNF-α antagonists

- TNF antagonists are effective in active ankylosing spondylitis, enthesitis and polyarticular arthritis not responding to conventional therapy.
- Infliximab or adalimumab are preferred in active IBD, while etanercept may be considered in inactive IBD and associated spondyloarthropathy.

Potential therapeutic targets for IBD-related spondyloarthropathy

- Novel approaches focus on the interference with immune dysregulation, altered cytokine secretion, cellular adhesion, barrier dysfunction and the role of the microbial flora.
- CTLA-4Ig (abatacept), anti-CD20 antibody (rituximab), as well as antibodies directed against the IL-2 receptor, IL-12, the T-cell antigen CD3, the IL-6 receptor and α4 integrin may be of potential therapeutic value in patients with IBD-related joint manifestations.

Future perspective

- Prospective trials focusing on the effects of drugs on IBD-related joint involvement are needed.
- New agents and therapeutic strategies that result from an improved understanding of the pathogenesis might change the current immunosuppressive paradigm in IBD.
- It will be of increasing importance to predict the individual treatment response and prognosis. The application of new technologies, such as gene expression arrays and proteomics, seems promising to achieve this goal.

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