Treatment of arthralgias and spondyloarthropathy associated with inflammatory bowel disease

Joint involvement in inflammatory bowel disease

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.

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, 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 sacroilitis to ankylosing spondylitis. Between 3.7 and 10% of patients with IBD fulfill the criteria for ankylosing spondylitis [1,8].

Keywords: ankylosing spondylitis, arthritis, Crohn’s disease, inflammatory bowel disease, sacroilitis, spondyloarthritis, therapy, ulcerative colitis
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 1. Clinical features of peripheral arthritis and axial involvement in inflammatory bowel diseases.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Peripheral arthritis</th>
<th>Axial involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pauciarticular (&gt;5 joints)</td>
<td>Polyarticular (&gt;5 joints)</td>
</tr>
<tr>
<td>Involvement</td>
<td>Large joints, asymmetric</td>
<td>Small/large joints, symmetric</td>
</tr>
<tr>
<td>Onset</td>
<td>With/after onset of IBD</td>
<td>With/after onset of IBD</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Self-limiting</td>
<td>Persistent</td>
</tr>
<tr>
<td>Related to IBD activity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Structural damage</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HLA-B27 linkage</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**IBD:** Inflammatory bowel disease.

*Summarized from [1,2,7,8].*
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],

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

<table>
<thead>
<tr>
<th>Arthralgias and chronic back pain</th>
<th>Baseline therapy</th>
<th>DMARDs</th>
<th>TNF antagonists</th>
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<tbody>
<tr>
<td></td>
<td>Analgesics</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Physiotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Pauciarticular arthritis</td>
<td>Analgesics</td>
<td>Sulfasalazine</td>
<td>Infliximab</td>
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<td></td>
<td>Glucocorticoids*</td>
<td>Mesalazine</td>
<td>Adalimumab</td>
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<td></td>
<td>Physiotherapy</td>
<td></td>
<td>Etanercept</td>
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<tr>
<td>Polyarticular arthritis</td>
<td>Analgesics</td>
<td>Sulfasalazine</td>
<td>Infliximab</td>
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<td>Glucocorticoids*</td>
<td>Mesalazine</td>
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<td></td>
<td>Physiotherapy</td>
<td></td>
<td>Etanercept</td>
</tr>
<tr>
<td>Sacroiliitis, ankylosing spondylitis</td>
<td>Analgesics</td>
<td>Sulfasalazine</td>
<td>Infliximab</td>
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<tr>
<td></td>
<td>Glucocorticoids*</td>
<td>in early disease</td>
<td>Adalimumab</td>
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<tr>
<td></td>
<td>Physiotherapy</td>
<td></td>
<td>Etanercept</td>
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<tr>
<td>Enthesitis</td>
<td>Analgesics</td>
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<tr>
<td></td>
<td>Glucocorticoids*</td>
<td>Sulfasalazine</td>
<td>Infliximab</td>
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<tr>
<td></td>
<td>Physiotherapy</td>
<td></td>
<td>Adalimumab</td>
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</table>

*Local injection is preferred.
†If not controlled by treatment of inflammatory bowel disease.
§No effect on bowel inflammation.
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 non-response 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].

<table>
<thead>
<tr>
<th>Table 3. Potential targets for future treatment of inflammatory bowel disease-related joint involvement.</th>
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<tr>
<td><strong>Target (agent)</strong></td>
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<tr>
<td><strong>Cytokines &amp; cytokine receptors</strong></td>
</tr>
<tr>
<td>IL-2 receptor/CD25 (basiliximab)</td>
</tr>
<tr>
<td>IL-6 receptor (tocilizumab)</td>
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<tr>
<td>IL-12</td>
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<tr>
<td><strong>T cells</strong></td>
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<tr>
<td>CD28/87 interaction (abatacept)</td>
</tr>
<tr>
<td>CD3 (visilizumab)</td>
</tr>
<tr>
<td><strong>B cells</strong></td>
</tr>
<tr>
<td>CD20 (rituximab)</td>
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<tr>
<td><strong>Cellular adhesion</strong></td>
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<td>Integrin (natalizumab)</td>
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*Selected from several studies.
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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 arthralgies, 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 spondyloarthopathies. 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.

### Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


• Includes a clear review of conventional treatment of IBD-related joint disease.
Extensive review on the state of the art in inflammatory bowel disease – REVIEW

8. First study that characterizes the two types of IBD-related peripheral arthropathy.

14. Important paper that discusses the impact of classification of the spondyloarthropathies on disease assessment and on guiding treatment strategies.
16. Clear view of mechanisms that lead to joint inflammation in IBD.
22. Demonstrates lasting efficacy of intra-articular glucocorticoid therapy in sacroilitis.
37. Provides evidence for the efficacy of early treatment of axial disease.
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• Includes patients with IBD-related ankylosing spondylitis.


• Provides clear guidelines for the use of TNF antagonists in ankylosing spondylitis.


• Demonstrates that treatment response to TNF antagonists may be predicted by clinical measures.


• Clear review of the developments in therapeutic approaches to IBD.


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