Therapy of spondylarthropathy in inflammatory bowel disease

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ABSTRACT
Musculoskeletal manifestations represent the most common extra-intestinal complication of inflammatory bowel diseases (IBD) and are usually included in the clinical spectrum of the spondyloarthropathies (SpA). Although control of intestinal inflammation often ameliorates articular symptoms, sometimes arthropathy is independent of the gut disease course and may require the same therapeutic options which apply to primary SpA diseases, but with caution so as not aggravate the IBD. At the moment, salicylates (sulphasalazine and mesalazine) and selective COX-2 inhibitors (which are preferable to traditional NSAIDs although they cannot be assumed to be safe for the gastrointestinal tract) are the first choice treatment. Several immunosuppressive and biological agents including methotrexate, thalidomide and TNFα antagonists have efficacy for both articular and intestinal inflammation and are currently in use for the induction of remission and for maintenance in more severe cases. New combination therapies and novel biologically-driven treatments, targeted to specific pathophysiological processes, might offer less toxicity and the potential for better treatment outcomes.

Introduction
The most common extra-intestinal complications of inflammatory bowel diseases (IBD) – Crohn’s disease (CD) and ulcerative colitis (UC) – involve musculoskeletal manifestations, which are usually included in the clinical spectrum of spondyloarthropathies (SpA). A wide range of prevalences of extra-intestinal manifestations has been reported, depending in part on the criteria used to define spondylarthropathy and on the selection of patients. Palm et al. reported a prevalence of SpA in IBD of 22% (2), while Salvarani et al. reported that at least 33.1% of the patients with IBD experience at least one musculoskeletal manifestation (3).

Although the association of CD with articular manifestations is well known, few scientific publications and clinical trials have addressed this problem. This dearth might be explained by several reasons. First of all, the presence of concomitant gut inflammation has often been considered to be an exclusion criterion for clinical trials of anti-rheumatic drugs, to avoid possible activation or worsening of the intestinal disease. Furthermore, the natural course of the disease is characterized by periods of flares and remission which complicate the interpretation of treatment efficacy. Finally, articular involvement in IBD includes a wide clinical spectrum of manifestations that may require different therapeutic approaches. Two primary patterns of arthritis have been described in IBD: 1) peripheral, often asymmetric, arthritis, and 2) an SpA resembling idiopathic ankylosing spondylitis (AS) in 10% of patients with ulcerative colitis and less commonly in patients with CD (4). This peripheral arthritis recently has been subdivided into three types: type I, peripheral pauciarticular arthritis with < 5 joints involved; type II, peripheral non-symmetric polyarthritis with ≥5 joints involved; and type III, an SpA, sometimes with peripheral joint involvement (5). In addition to axial and peripheral articular symptoms, enthesitis, tenosynovitis, and dactylitis commonly occur, sometimes representing the only extra-intestinal manifestation of IBD (6). Type I arthritis may precede the diagnosis of IBD and, once established, often parallels the activity of the intestinal manifestation. Types II and III arthritis generally do not reflect the activity of the underlying IBD and rarely precede the diagnosis of IBD.

The general treatment
A general rule in managing arthritis complicating IBD can be formulated as
"what is good for the gut is also helpful for the joints" (7). Unfortunately this statement does not always reflect adequate therapeutic management of the joint disease, resulting in significant impairment of the quality of life. Nonetheless, there is consensus that treatment of the IBD should be the prime consideration, since control of intestinal inflammation will often reduce joint inflammation as well. When the course of arthropathy is apparently independent of the course of gut disease, the same therapeutic options which apply to primary SpA diseases may be considered, but used with caution so as not to aggravate the IBD. No preventive measures for SpA associated with CD are available, as with AS, but most patients can be well managed. Better outcomes are associated with an early diagnosis, a compliant patient, and a competent physician. The treatment includes physical measures with an adequate balance of rest and activity, physical therapy, non-steroidal anti-inflammatory drugs, and local (intra-articular or peri-articular) steroid injections. When these treatments do not control joint inflammation adequately or patients are intolerant to such drugs, a second line treatment may be initiated.

If active inflammation is apparent in both the intestine and joints, clearly one should choose a therapy which is effective on both. However, the IBD often may be completely silent over long periods and the only clinically apparent problem and obvious therapeutic concern may be the SpA. Therefore, caution is mandatory in the management of all patients with SpA to be aware of the possibility of IBD, but especially in patients who have a history of IBD.

We present below a brief summary of the second line drugs that appear to have a beneficial effect on both SpA and IBD and thus are used in patients with both of these conditions.

**Non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay in the treatment of spondyloarthropathies, and often are the only treatment with the capacity to control articular pain and stiffness due to axial involvement and enthesis; they are in wide clinical use also in arthropathies associated with IBD. Their use in Crohn’s disease is problematic. It has been convincingly shown that NSAIDs increase gut permeability and may induce colitis in healthy subjects (8) or activate a quiescent IBD (9). The administration of indomethacin to rats induces inflammatory pathology of the small bowel which closely resembles ileal Crohn’s disease and is used as an experimental animal model for IBD (10, 11). Selective cyclooxygenase-2 (COX-2) inhibitors have been developed to avoid gastrointestinal damage associated with traditional NSAIDs. In general, better gastrointestinal tolerability of these drugs is seen primarily in patients with a normal gastrointestinal tract, and possible selective sparing of an abnormal gastrointestinal tract is controversial.

IBD is associated with the increased local production of prostanoids derived through COX-2 (12) and the effect of selective COX-2 inhibitors on these substances at the intestinal level is not substantially different from that of traditional non-selective NSAIDs (12), although the significance and therapeutic implications of these observations are not completely defined. There is evidence that these prostaglandins may be an important component of the mucosal defense in the small intestine and colon (promoting the healing of mucosal injury, protecting against bacterial invasion, and down-regulating the mucosal immune system) (13). Suppression of COX-2 in a setting of gastrointestinal inflammation and ulceration has been shown in experimental models to impair healing and exacerbate inflammation-mediated injury (14). However, COX-2 derived prostaglandins may also contribute to bowel dysfunction during acute inflammation (sustaining inflammatory edema, hyperemia and increased permeability), and some have suggested that inhibitors of COX-2 may have a beneficial effect in gut inflammation (15).

In conclusion, although selective COX-2 inhibitors are probably preferable to traditional NSAIDs in the treatment of musculoskeletal symptoms when an underlying IBD is present, these compounds should be used carefully until they have been tested adequately in IBD. In a patient with established AS who is taking NSAIDs, it may be necessary to distinguish clinically between effects of NSAIDs on the small intestine and the ileitis of AS and CD, especially if intestinal obstruction, anemia, or hypoalbuminemia occurs (16). The distinction between NSAID enteropathy and the ileitis of AS can be important, because SSZ, mesalamine, and misoprostol reduce inflammation, bleeding, and protein loss in NSAID enteropathy (17), while only SSZ is known to benefit spondylarthropathic ileitis.

**Sulphasalazine and mesalazine**

Sulphasalazine (SSZ) was synthesized in the late 1930s and used for the treatment of IBD. Its efficacy in the treatment of UC has been demonstrated both in the treatment of active disease (18) and in the prevention of relapses (19). Efficacy of SSZ in active CD has been reported on the basis of some double-blind controlled trials (20,21) but not confirmed in others (22), and the efficacy of SSZ in preventing recurrences of CD is even more controversial (23).

After a long period of indifference to the possible value of SSZ as an anti-rheumatic drug, studies by Svartz, McConkey, Amos and others in the late 1970s rekindled interest in its effects on rheumatic syndromes. Since arthritis is a major manifestation in SpA and since the gut plays a crucial role in this disease, it seemed logical to use SSZ to treat patients with various SpA. Several reports indicate the efficacy and safety of SSZ in the short-term treatment of AS and other SpA (24). However, controlled trials on the efficacy of SSZ in IBD arthropathy do not exist. Nonetheless, SSZ has become a first choice treatment for entheropathic arthropathies on the basis of theoretical considerations and clinical experience. SSZ appears to have greater efficacy in patients with early disease. While it may be effective in patients with peripheral arthritis, it has no appreciable influence...
on the persistence of axial disease and peripheral enthesopathy (25, 26). SSZ cannot prevent the onset of an IBD in patients affected by SpA (27). 5-aminosalicylic acid (mesalazine) is more effective than SSZ for active CD and for maintenance of remission, including CD of the small intestine, with lower levels of adverse effects (27). Mesalazine has some efficacy in the treatment of SpA (28), which is however much lower than SSZ (29).

Corticosteroids
Corticosteroids should be used systemically only to control bowel disease, and appear to have no therapeutic effect in terms of retarding disease progression or improving axial involvement (30). Despite this general rule, the short-term administration of systemic corticosteroids may be of value to control peripheral arthritis. Intra-articular injections may also be useful, in particular if only a small number of joints are involved.

Methotrexate
Methotrexate (MTX) is a relatively safe, easily managed, and effective second-line drug for patients with various articular and connective tissue diseases. Because of its efficacy and safety, MTX also may be used in combination with other wide range of second line drugs (31). However, most studies of MTX used as a single agent or in combination have been performed in patients with rheumatoid arthritis. Few well-conducted studies have been performed on the efficacy of MTX in AS, and no specific studies exist concerning the possible efficacy of MTX in IBD arthropathies.

A few open prospective studies suggest that MTX (7.5 – 12.5 mg/week) has variable positive effects in the treatment of patients with SpA (32-35). The primary benefit appeared on peripheral joints, rather than on the axial skeleton and enthesis, although Biasi et al. (but not others) reported benefit for enthesitic and axial symptoms (34). Further long-term, placebo-controlled studies to address spinal symptom relief and the suppression of long-term ankylosis in enthesitis would be desirable.

MTX is emerging as an effective treatment for CD, although it is probably undervalued (36) and often considered a second choice drug with respect to azathioprine by gastroenterologists (37). Low-dose methotrexate has been reported to be effective in inducing remission in chronically active CD (37-39), and maintenance MTX provides long-term benefit with steroid sparing benefits and acceptable remission rates for up to 3 years (38,41-43), particularly in younger patients and when given parenterally (43).

Although MTX toxicity from long-term use (e.g. hepatotoxicity) has been a prominent concern of gastrointestinal physicians, side effects are usually only moderate and their consequences can be limited by appropriate monitoring and concomitant use of folic acid (44-46).

Azathioprine
Azathioprine (AZT) is rarely used in the treatment of SpA. An intravenous loading dose of AZT has been used in severe and refractory AS, but this regimen has limited efficacy and considerable toxicity (47). There is anecdotal evidence that AZT is helpful in intractable enthesopathy, although controlled observations are lacking.

AZT is regarded as an effective therapy for both UC and CD, and has been widely used in the treatment of IBD with (48). The efficacy of AZA is sustained over at least five years, with minimal toxicity (48).

Cyclosporine
Cyclosporine A (CyA) has been successfully used in the treatment of psoriatic arthritis (49,50). Intraavenous high dose CyA may be used to attempt to induce remission or significant improvement in acute corticosteroid refractory IBD (51,52). However, the remission can be maintained only for a short period even with subsequent oral CyA (52, 53), which is associated with a high rate of adverse effects (53, 54). Intravenous high dose CyA is effective in inducing remission or significant improvement in steroid-refractory IBD (50,51). However, with subsequent oral CyA the remission can be maintained only for a short while (51, 52) and with an elevated incidence of adverse events (52, 53).

Cyclophosphamide
One report indicates that cyclophosphamide (Cyc) given intravenously in 200 mg doses on alternate days for 3 weeks, followed by a 100 mg oral dose weekly for 3 months, resulted in a reduction in peripheral joint synovitis and spinal pain although no improvement in spinal movement (55). This was accompanied by a significant fall in the sedimentation rate. However, no controlled studies have been yet undertaken.

Cyc has a role in the therapy of IBD only in intractable cases (56) or for the management of severe systemic complications such as vasculitis (57-59) or malignances (60)

Thalidomide
Thalidomide, which was developed as a non-barbiturate sedative agent, was taken off the market in 1961 after it was linked to major birth defects. Gradually, thalidomide was reintroduced for the treatment of a few skin diseases including leprous erythema nodosum, severe mucosal ulcers (e.g., associated with HIV infection or Behcet’s disease), lymphocytic skin infiltrations, cutaneous lupus erythematosus, and chronic graft-versus-host disease. It has now been established that its effect may linked to inhibition of the release of the cytokine tumor necrosis factor-α (TNF-α) from activated inflammatory cells (61, 62).

On the basis of this observation, thalidomide has been used in other TNF-α mediated diseases. Several open-label studies and case reports have described the short-term effectiveness of thalidomide in CD (62) and AS (63, 64). However, minor but dose-limiting side effects were common, and concern about long-term tolerability will limit the use of thalidomide in SpA. Perhaps the identification of a less toxic thalidomide molecule such as CC-3052 17 may enable the safe use of a non-neurotoxic, non-teratogenic, anti-inflammatory agent for the treatment of IBD and SpA (65, 66), as an effective oral alternative to monoclonal anti-TNF-α antibody.
**Biologic treatments**

Recent experience with the TNF-α blocking drugs infliximab (a chimeric monoclonal anti-TNF-α antibody) and etanercept (a recombinant human TNF receptor (p75):Fc fusion protein) has opened up a new approach to the management of CD patients with SpA.

Infliximab is highly effective and well tolerated for both axial and peripheral joint disease in patients with active AS (62-72) and other SpA (70, 73, 74) even at doses lower than those used to date (72). Etanercept has been successfully used in psoriatic arthritis (75,76) and there is evidence of its efficacy in AS (77,78).

Infliximab is is an effective and well tolerated therapy for the management of acute CD (79, 80) and the drug has obtained FDA and European Medicines Evaluation Agency approval. The results of the Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT I) study showed that the maintenance with infliximab in moderate to severe CD prolonged the response and remission of the disease (81,82). Higher response rates are seen with methotrexate as concomitant medication (83). Etanercept appears to have less efficacy in IB and its use is not yet approved in CD, though an open-label trial for the treatment of CD is in progress in Belgium (84). The higher avidity of infliximab binding the transmembrane TNF and the capacity to form stable complexes with soluble and transmembrane TNF in comparison to Etanercept may explain the different efficacy in CD of these two drugs (85).

Two open, short-term studies on SpA associated to CD (86,87) have shown that infliximab induces rapid and substantial improvement of the articular manifestations and remission of the active intestinal disease. Personal observations suggest that infliximab is relatively safe and very effective over up to 2 years in the treatment of SpA associated with active and inactive IB (88). Infliximab controlled peripheral arthritis, axial involvement, and enthesitis independently from the intestinal inflammatory condition and from the basal levels of acute phase reactants. The tolerability profile was excellent in quiescent IB, with an effective prevention of intestinal inflammatory relapses. Thus, infliximab might be considered as a reliable therapeutic option also in those patients affected by an IB without evident gastrointestinal inflammatory activity, no joint swelling and no laboratory signs of systemic inflammation, but characterized by severe axial and periarticular enthesitic pain, and severe articular stiffness.

Although there are some concerns about the immunogenicity of infliximab resulting in the formation of human antichimeric antibodies (HACA) as well as tuberculosis reactivation and lymphoproliferative disorders, the clinical benefit in the treatment of SpA associated with CD is a major therapeutic breakthrough. Further development of new anti-TNF agents with a better tolerability profile such as CDP-571 (humanized anti-TNF ab) may lead to greater tolerability with similar therapeutic advantages (89).

Associations between SpA and IB lead to a hypothesis that interfering with gut inflammation in patients with SpA could yield a potential target for modulating the synovitis in these patients. Thus, besides TNF-alpha blockade, other strategies with potential efficacy on gut inflammation can be envisioned, such as IL-10, IL-11, IL-1 receptor antagonist, ICAM-1 antisense (ISIS 2302), anti-alpha 4 beta 7 integrin antibodies and humanized antibody to alpha4 integrin (Natalizumab) (90-94), although these exciting novel approaches remain unproven at this time. A further logical step in the biologic treatment of the inflammation will be combination therapy for SpA and IB. Combinations of anti TNF-α agents and MTX is efficacious and safe (83,95), while combinations of various anti-cytokine agents is encouraging in experimental animals (96), but has not been extensively studied in patients.

**Other therapeutic options**

Some other specific problems which are shared by IB and SpA worth to be mentioned: Osteoporosis is a common complication of IB (97,98) and in SpA also it is frequently observed, even in the early stages and in mild patterns of disease (99-101). In both diseases, the incidence of fractures is remarkably higher than in general population (101,102).

The pathogenetic mechanism seems to be multifactorial and is not completely understood yet. Corticosteroid therapy, disease activity, systemic inflammation, hormonal and genetic factors, malabsorption and mechanical factors such as decreased mobility and the support provided by extraspinal bone may all be important determinants of bone loss in these conditions (101,103,104).

Bisphosphonates are effective in the prevention and treatment of corticosteroid-induced osteoporosis and are widely used in SpA, but a study of the relative efficacy of different bisphosphonate agents in patients with AS is required (101). Patients with inflammatory bowel disease have been usually excluded from the largest studies on bisphosphonates because of the uncertainty of the potential relationship between the gastrointestinal adverse events of the treatment and the symptoms of the disease. Recently, alendronate has been shown to increase spine bone mineral density in a small group of patients with Crohn’s disease in remission (105).

Intravenous formulations are now available for some bisphosphonates, and may be of interest in patients with inflammatory bowel disease and SpA. Recent studies suggest that cyclical and prolonged intravenous administration of pamidronate, may possess a dose dependent antinflammation activity in patients with AS (106-108).

Studies of the rheumatological complications of IB have focused on peripheral arthritis and spondylitis, and less is known about soft tissue rheumatism, specifically the fibromyalgia syndrome. Fibromyalgia is common in IB, particularly CD. The lower pain threshold in Crohn’s disease may suggest a disease-specific effect (109). Fibromyalgia does not appear to be a major problem in SpA (110) but the possible coexistence of this problem has to be considered, especially in patients with CD, in order to prevent misdiagnosis and ensure correct treatment.
Aortitis, an uncommon complication of both IBD and SpA, has been successfully treated with leukopheresis (111).

Discussion

The choice of appropriate medical treatment for SpA in IBD requires consideration of many variables: the type, activity and disease duration of SpA; the status of intestinal disease; the influence that the IBD may have directly or indirectly on the articular disease; and the risk of exacerbation of gut inflammation. The therapeutic strategy must carefully balance efficacy and potential toxicity in both diseases at that time. Several immunosuppressive and biological agents including MTX, thalidomide and TNF antagonists have efficacy for both articular and intestinal inflammation, including induction of remission and for maintenance. A key question is when to start and how long to maintain these aggressive treatments. Up to now immunosuppressive and biological therapies have been reserved for patients with severe and active disease when the anti-inflammatory drugs (NSAIDs or salicylates in SpA and IBD, respectively) had failed.

We believe that current therapies for both IBD and SpA, especially those with axial involvement, are often neither sufficient nor disease-modifying. The current therapeutic end-point in the treatment of CD is the remission of symptoms, but recent data suggest that mucosal inflammation may continue in the absence of symptoms (112), and that such subtle, sub-clinical mucosal inflammation may lead to clinical relapse. Current anti-inflammatory therapy often leaves low-grade mucosal inflammation untreated, allowing for recurrent relapses (112).

In SpA recent histological and magnetic resonance imaging studies indicate the presence of synovitis and subchondral bone marrow changes, which may explain the widespread joint destruction more than does enthesis alone (35). Furthermore, enthesis lesions adjacent to synovial joints occur frequently and may be intimately linked to peripheral joint synovitis. Although there is no firm evidence at this time that second line agents have efficacy in axial disease, these observations raise the possibility that the early and prolonged suppression of synovitis through more aggressive immunosuppressive treatment might be of value in the spine (113). At the same time, this therapy could offer mucosal healing and reduction of IBD relapses. Moreover, the consequent normalisation of intestinal permeability might contribute to maintain SpA quiescence. However, safety is a key issue if the aggressive and prolonged use of immunosuppressants/immunomodulatory agents is to become more widespread. Novel biologically-driven therapies targeted to specific pathophysiological processes might offer lower toxicity and the potential for better treatment outcomes.

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