

Rheumatological manifestations in inflammatory bowel disease

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Abstract

Rheumatological manifestations in inflammatory bowel disease (IBD) are frequent and include peripheral arthritis, axial involvement and peripheral enthesitis. Secondary osteoporosis and hypertrophic osteoarthropathy may also occur. Complications of IBD (e.g. septic arthritis) must be distinguished from sterile inflammation. Adverse effects of corticosteroid treatment, such as osteonecrosis, may also affect joints. Axial involvement ranges from low back pain to true ankylosing spondylitis. Human leukocyte antigen B27 is associated with axial involvement of IBD. Peripheral arthritis has been classified into two types. Type I is a pauciarticular, asymmetric usually non destructive arthritis affecting large joints and is usually associated with active bowel disease. Type II is a polyarthritis affecting small joints and tends to run a course independent of the bowel disease. Treatment of joint symptoms in IBD include sulphasalazine, azathioprine, methotrexate and glucocorticoids. Anti-tumor necrosis factor antibodies are effective in treating resistant or complicated Crohn's disease as well as peripheral arthritis and axial involvement.

Keywords peripheral arthritis, sacroiliitis, enthesitis, axial involvement

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Introduction

The idiopathic inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are systemic disorders that may be complicated by extraintestinal manifestations in up to 40% of patients, depending on the study population and definitions used [1-3]. Rheumatological manifestations in IBD are frequent and include peripheral arthritis, axial involvement, peripheral enthesitis, secondary osteoporosis, and secondary hypertrophic osteoarthropathy (HOA) (Table 1). Complications of IBD may also cause joint pain and must be distinguished from sterile inflammation. Bacterial infection of the sacroiliac or peripheral joints may occur due to fistulization or bacteremia. Adverse effects of treatment of IBD may also affect joints such as osteonecrosis due to corticosteroid use. IBD may be associated with relapsing polycondritis and cutaneous vasculitis. A relationship

between the gut and arthritis was postulated in 1929 by Bargen who recognized arthritis as a complication of UC [4]. Hench in 1935 described a peripheral arthritis in patients with IBD and observed the tendency of arthritis to flare with exacerbations of the colitis and to subside with remission of the gut symptoms [5]. The introduction of the concept of spondyloarthropathies (SpA) by Wright and Moll generated further study of the relationship between arthritis and bowel inflammation [6]. IBD belong to SpA, sharing common features with other members of this family of disorders such as the asymmetric pattern of peripheral joint involvement, the occurrence of sacroiliitis (SI) and spondylitis, the peripheral enthesopathy, the absence of rheumatoid factor, the association with human leukocyte antigen (HLA) B27, as well as extra-articular features, including uveitis, carditis, skin and mucous membrane lesions.

Table 1 Rheumatological manifestations in IBD

1. Peripheral arthritis
2. Axial involvement (low back pain, SI, spondylitis, true AS)
3. Enthesitis
4. Secondary HOA
5. Secondary osteoporosis

IBD, inflammatory bowel diseases; SI, sacroiliitis; AS, ankylosing spondylitis; HOA, hypertrophic osteoarthropathy

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Epidemiologic features and genetic markers of rheumatological manifestations in IBD

The prevalence of UC ranges between 50 and 100 per 100,000 of the population. The disease seems to be more frequent in whites. The prevalence of CD has increased during the past few decades to about 75/100,000 of the population. Early epidemiologic studies on IBD-associated arthropathies from the 1960s, 70s and 80s include patients with classic ankylosing spondylitis (AS) or SI together with peripheral arthritis [7-15]. From these studies AS was present in 2-16% of patients mainly in CD. Asymptomatic and symptomatic SI was found in 12 to 20% of patients and peripheral arthritis in 11 to 20%. Association with HLA-B27 ranged from 3.9 to 18.9%. Studies on IBD populations using the European Spondyloarthropathy Study Group criteria [16] or the Amor Diagnostic Criteria for Spondyloarthropathy [17] showed various results [18-32]. More specifically, AS ranged from 1 to 45.1%, SI from 1.9 to 45.7%, peripheral arthritis from 2.8 to 30.6% and enthesopathy from 5.4 to 50% of patients. Most of these studies reported similar findings in CD and UC for peripheral and axial involvement. In addition, most studies agreed that ulcerative proctitis is rarely complicated by joint inflammation and that inflammatory joint disease occurs with increased frequency in CD patients with colitis or with more extensive bowel disease compared to those with ileal involvement. Furthermore, some patients develop one or more manifestations of SpA (e.g. enthesitis or/and dactylitis) without fulfilling the classification criteria.

Arthritis or axial symptoms may precede the gastrointestinal symptoms by lengthy periods of time, and the patients may be regarded as undifferentiated spondyloarthropathy until the IBD declares itself. The study of Mielants and Veys has provided evidence that patients with undifferentiated SpA and even AS may have subclinical bowel inflammation that plays an important role in triggering and perpetuating joint inflammation [33]. A 20-year follow-up study of patients with IBD reported musculoskeletal features in 30% [34]. HLA-B27 positive patients with CD have a high likelihood of progressing to frank AS. Conversely, the frequency of true IBD (UC or CD) in AS is below 4%. However, if the occurrence of subclinical bowel inflammation is considered, the prevalence of gut involvement in a group of patients with SpA increases to 60% [35].

Other studies aimed to clarify the frequency of symptomatic or asymptomatic SI. Steer et al found on computed tomography (CT) examination signs of SI in 31/134 of CD patients [36]. In another study carried out in 50 CD patients symptomatic for back pain, 28% fulfilled the modified New York criteria for AS on x-ray examination [37]. On the other hand, asymptomatic SI may be present in 10 to 50% of patients with IBD [38]. In a comparative study using conventional x-ray and CT, findings compatible with SI were found in 29% of CD patients with only 3% being symptomatic [39]. Magnetic resonance imaging (MRI) is the most sensitive method of detecting SI in IBD patients. In the literature there are also studies which describe musculoskeletal symptoms in IBD patients without

using exact diagnostic criteria for IBD related SpA. Thus, racial differences in the prevalence of the extraintestinal including rheumatologic manifestations have been reported. A large study showed that African Americans with IBD were more likely to develop both uveitis and SI [40]. Another study described an increased incidence of arthritis and uveitis in African American patients with CD [41], although there are different results in the literature [42]. In addition, investigators from Spain reported extraintestinal manifestations almost in half (46%) of 157 patients with CD, while 22% had rheumatologic findings which were more frequent in patients with disease confined to the colon [43]. A study from Ukraine showed that 29.8% of 319 UC patients had joint manifestations. Arthritis correlated with extensive forms of UC and was more frequent in patients with left-sided UC and pancolitis. Arthralgia was a prevalent symptom in patients with distal UC [44]. The joint involvement in UC ranges between 20 and 35% in other studies [45-47]. A study from Japan found that 10.3% of CD patients had arthritis and 1.5% had spondylitis [48]. In a Greek cohort of CD patients 30% had arthritis/arthralgias [49]. Another study from Canada reported a 4% prevalence of AS in IBD hospitalized patients, with male CD patients being more frequently affected than male UC patients [50]. However in a Brazilian study prevalence was 14.4% with no difference between CD and UC [51]. Finally, a study from Kuwait reported arthritis in 8.9% of UC patients while the overall prevalence of rheumatologic complaints was 31% [52].

Such racial differences in the prevalence of rheumatologic manifestations may be attributed to both immunologic and genetic factors. Peripheral arthritis occurring in IBD is not associated with HLA-B27. SI and especially spondylitis, however, are associated with HLA-B27 [40% and 60% respectively], but to a lesser degree than in uncomplicated AS [90%]. CD has been associated with mutation in the NOD2 [CARD15] gene on chromosome 16 [53]. This is of interest in the pathogenesis of CD because NOD2 plays an important role in innate immunity to pathogens and indirectly implicates microbial triggers in IBD. To date, studies have found no significant relationship between CARD15 and SpA. However, CARD15 mutations may be found more commonly among patients with CD complicated by SI [54], although this was not confirmed in a more recent series [55].

Clinical features of rheumatologic manifestations in IBD

Arthritis

Articular complications are the most common extraintestinal manifestations [56]. Arthritis is more likely to occur in patients with large-bowel disease and in patients with complications such as abscesses, pseudomembranous polyposis, perianal disease, massive hemorrhage as well as in patients with erythema nodosum, stomatitis, uveitis and pyoderma gangrenosum. In addition, patients with CD and colonic

involvement are at higher risk of developing synovitis than those with isolated small bowel disease. Men and women are equally affected. Peripheral arthritis has been classified into two types [57]. Type I is a pauciarticular arthritis typically affecting fewer than five large (weight-bearing) joints. It is usually associated with active bowel disease and has an asymmetric pattern; a monoarthritis is not uncommon. Large and small joints are involved, predominantly those of the lower limbs (knees, ankles, and metatarsophalangeal joints). Arthritis of hips and shoulders is less frequent and tends to be associated with SI and spondylitis. Arthritis occurs early in the course of bowel disease. It is generally migratory and transient but recurrent, although it does not result in joint deformities [58, 59]. Five percent of IBD patients develop type I arthropathy. Joint symptoms may occur prior to the onset of bowel disease especially in CD. This can also remain absent, although ileocolonoscopy biopsy specimens taken from the terminal ileum reveal mild to severe inflammatory lesions indicating the presence of subclinical CD in these patients [60]. The timing of the first attack of arthritis seems to be independent of the duration of colitis in UC. In addition, a flare of the gut symptomatology mainly in UC is frequently accompanied by recurrence of peripheral arthritis. Surgical removal of the colon in UC has been reported to have a curative effect on the peripheral joint symptoms [60].

Type I peripheral arthritis is associated with the class II allele HLA-DRB1* O103 [56]. This allele is found in 35% of type I arthritis patients versus 3% of controls. If patients with recurrent arthritis are studied this association is found in 65% [2].

Type II is a polyarthritis mainly affecting the small joints. It rarely precedes the diagnosis of IBD. It tends to run a course independent of the bowel disease. Metacarpophalangeal joints are frequently involved and the differentiation of type II peripheral arthritis and rheumatoid arthritis is important and requires radiographic and immunologic correlation. Approximately half of the patients with IBD have migratory arthritis. Active synovitis may persist for months, and may recur repeatedly. Episodes of exacerbations and remissions may continue for years. Evolution to chronicity may occur together with radiographic erosive lesions [61]. Type II arthropathy affects 3 - 4% of patients with IBD. Type II peripheral arthritis is associated with HLA-B44* in 62% of patients versus 30% of controls [56]. It is also associated with uveitis but not with other extraintestinal manifestations.

Spondylitis and SI

The spectrum of axial involvement ranges from inflammatory lower back pain with or without radiological evidence of SI, to asymptomatic SI and true AS characterized by the classical clinical [pain, spine stiffness] and radiologic features [squaring, syndesmophytes, bamboo spine]. The prevalence of axial involvement in patients with IBD is between 5 and 12% [62], but these percentages could be higher because of the existence of silent axial involvement [63] especially in SI. The male to

female ratio is 3:1, comparable to AS. Axial involvement can precede the bowel disease by many years. The main complaints are inflammatory low back pain, buttock pain and chest pain. Inflammatory back pain is insidious in onset, usually before the age of 45 years, frequently monolateral and intermittent at onset, more intense at rest, associated with morning stiffness but relieved by movement, exacerbated by cough or sneezing, and accompanied by fatigue. The pain is persistent with duration of at least 3 months. The diagnosis of inflammatory back pain is reinforced when there is an improvement with exercise, awakening because of pain and the presence of alternating buttock pain [64]. Thoracic pain results from enthesitis of costovertebral, costosternal, manubriocostal articulations. It exacerbates with cough and deep inspirations and limits respiratory expansion with episodes of variable duration. Dactylitis can be seen in AS. It is characterized by the inflammatory swelling of one or more fingers [sausage fingers] or toes caused by tenosynovitis of the flexor tendons. The limitation of cervical spine mobility is a hallmark of progression of the disease to generalized ankylosis. In the presence of inflammatory back pain, the radiologic evaluation of the sacroiliac joints allows to make the diagnosis of SI [65]. In the absence of radiologic findings, MRI evaluation may lead to diagnosis and, thus, effective early treatment of axial spondyloarthritis [66]. The evidence of bone edema with T1 post-gadolinium and STIR (short tau inversion recovery) techniques is a sign of active inflammation in the sacroiliac joints and/or spine. The axial and spine symptoms are independent of exacerbation of bowel inflammation. Similarly, surgical therapy of UC or CD has no impact on the associated spondylitis. Consequently it has been suggested that peripheral arthritis is a manifestation of IBD, whereas the spondylitis is an associated disease.

Enthesopathy

Enthesopathy is a pathologic alteration at an enthesis (a site of insertion of a tendon or ligament into bones). It manifests radiographically as ossification of entheses. In IBD, enthesopathies can occur at the heel (insertion of the Achilles tendon or the plantar fascia) or at the knee (insertion of the patellar tendon). Inflammation at enthesis may cause erosive lesions which may lead to spur formation.

Osteoporosis

Osteoporosis is a silent condition characterized by reduced bone mass and microarchitectural changes leading to increased bone fragility and susceptibility to fracture. Osteoporosis is a complication of corticosteroid treatment in IBD.

HOA

HOA is a syndrome characterized by excessive proliferation of skin and bone at the distal parts of the extremities. Its

most prominent feature is a bulbous deformity of the tips of the digits, conventionally known as clubbing. In advanced stages, periosteal proliferation of the tubular bones and synovial effusions become evident. UC and CD are two causes of secondary HOA. In patients with IBD the development of clubbing is usually a poor prognostic sign.

Diagnosis of rheumatologic manifestations in IBD

There is no pathognomonic finding to confirm the clinical suspicion of arthritis due to IBD. The diagnosis may be suspected in the proper clinical setting. Laboratory findings are determined by the activity of the IBD. Anemia is common in enteropathic SpA reflecting both the anemia of chronic disease and iron deficiency anemia due to gastrointestinal blood loss. Leukocytosis, a marked thrombocytosis with platelet counts higher than $700,000/\text{mm}^3$ is not uncommon. The erythrocyte sedimentation rate and C-reactive protein as well as other acute-phase reactants are elevated. Rheumatoid factor is absent and antinuclear antibodies are absent in most patients. The synovial fluid is not characteristic: mild to marked inflammatory changes can be found with a white blood cells ranging from $1,500-50,000/\text{mm}^3$. Glucose levels are not reduced. Microbiologic cultures are negative [63]. Synovial membrane biopsies reveal nonspecific abnormalities including, proliferation of synovial lining cells, increased vascularity and infiltration of mononuclear cells [67]. In cases of monoarthritis or oligoarthritis it is important to exclude septic arthritis performing a joint aspiration because its presentation may be atypical in patients with IBD who are receiving antiinflammatory or immunosuppressive treatment.

Radiographic findings

Radiographs of the spine and pelvis may show typical findings of AS and SI. The latter is typically bilateral, although a higher frequency of asymmetric SI and zygapophyseal joint ankylosis has been reported [68]. Peripheral joint involvement is generally not accompanied by radiographic changes, but erosive lesions mainly of the metatarsal joints, have been described. These lesions show some differences to rheumatoid lesions, for example an absence of osteoporosis and the presence of adjacent bone proliferation. Rarely, a destructive granulomatous synovitis may be seen in CD. Entesopathies do not differ radiographically from those seen in other SpA.

Differential diagnosis

In patients with intestinal manifestations and arthritis the diagnosis of IBD excludes other diseases with similar

symptoms: reactive arthritis (formerly Reiter syndrome), Whipple's disease, Adamantiades-Behçet's disease, intestinal bypass, gluten sensitive enteropathy and parasitic infections. Initially the clinical signs of SpA must be recognized and differentiated from those of rheumatoid arthritis and other connective tissue diseases. IBD is included in the differential diagnosis of SpA even when gut symptoms are mild. The presence of spondylitis in an HLA-B27 negative patient increases the risk of IBD. The differential diagnosis of joint pain in a patient with IBD is broad. It includes HOA [67], septic arthritis (common or opportunistic infections), osteonecrosis especially in patients treated with glucocorticoids and experience pain that is out of proportion to the degree of limitation of passive range of motion of the affected joint. Erythema nodosum may be difficult to distinguish from arthritis when lesions occur in a periarticular location. Inability to aspirate synovial fluid from a swollen and painful joint is a clue to the diagnosis.

Pathogenesis of musculoskeletal manifestations of IBD

HLA-B27 is the major risk factor for AS and SpA associated with IBD. HLA-B27 transgenic rats develop a SpA. HLA-B27 is present in >90% of patients with AS while only 5 to 15% of the general population are HLA-B27 positive. Among the HLA class B molecules that determine the antigen binding cleft, HLA-B27 has a unique B pocket that likely influences the peptide repertoire. The subtypes of HLA-B27 (there are more than 30) differ in part only by single amino acids. Only a few HLA-B27 subtypes (e.g. HLA-B*2705, HLA-B*2702 or, HLA-B*2704 and HLA-B*2707) are associated with AS. There are 4 main theories on the pathogenesis of spondyloarthritis related to HLA-B27 (Table 2). The first is the arthritogenic peptide hypothesis. According to this HLA-B27 binds a unique set of antigenic peptides, bacterial or self, and these peptides are presented to CD8⁺ T cells giving rise to an HLA-B27-restricted cytotoxic T-cell response. The second theory is the self-association of the HLA-B27 molecule. A unique property of HLA-B27 is that its heavy chain can form homodimers *in vitro* that are dependent on disulfide binding through their cysteine-67 residues in the alpha-1 domain. These homodimers occur as a result of B27 misfolding within the endoplasmic reticulum. The accumulation of misfolded protein may result in a proinflammatory intracellular stress response. Alternatively, B27 homodimers can migrate to the cell surface where they either become antigenic themselves or present peptide to other inflammatory cells. The third theory refers to the alteration of intracellular handling of microbes due to HLA-B27. The HLA-B27 molecule leads to a less effective elimination of microbes, such as salmonella, in conjunction with an upregulated production of cytokines. The fourth hypothesis represents the recognition of HLA-B27 as an autoantigen. The HLA-B27 itself can be recognized by CD4⁺ T cells when presented by HLA class II (DR, DQ, DP) heterodimers as an autoantigen. This was also part of

Table 2 Major theories on the pathogenesis of SpA related to HLA-B27

1. The arthritogenic peptide theory
2. Self-association of the HLA-B27 molecule
3. Alteration of intracellular handling of microbes due to HLA-B27
4. The role of HLA-B27 as an autoantigen

SpA, spondyloarthropathies; HLA-B27, human leukocyte antigen B27

the molecular mimicry hypothesis, which supports that the homology of peptides from the HLA-B27 molecule shares striking sequence homology with that from bacterial sources [67]. However, non-major histocompatibility complex genetic effects appear to also have significant influence on disease severity [68-70].

The association between axial involvement and HLA-B27 in IBD patients is less conclusive because only 40-60% of patients with CD and AS present positivity for HLA-B27. The altered gut permeability could be a key factor in the development of SpA [71]. In addition, type 1 peripheral arthritis is associated with HLA-DRB1* 0103, B*35 and B*27 [72] while no HLA-B27 nor DR-4 associations were observed for type 2 arthropathy. These data indicate that type 1 and 2 arthropathies are immunogenetically distinct entities and that type 1 is more similar to that of axial SpA. Apart from the genetic predisposition, the role of bacterial antigens seems to be important in the pathogenesis of peripheral arthritis. A number of bacterial agents, including adherent, invasive *E. coli* and anaerobic rods of bacteroides and fusobacterium have been implicated in the etiopathogenesis of CD. Several studies have focused on an important "gut-synovium axis" [73,74]. Furthermore, cross-reactivity between gut bacteria and cartilage has been demonstrated in patients with CD [75].

The role of CARD15 in the process of presentation of intestinal bacteria by antigen-presenting cells remains unclear. CARD15 protein is expressed by monocytes, granulocytes, dendritic cells and epithelial cells. *In vitro* this protein induces the activation of the nuclear factor (NF) κ B pathway after recognition of murrayl dipeptide and may help to protect the gut wall. Genetic mutation of CARD15 may lead to disturbed handling of bacterial products and hence inappropriate elimination. Cytokine production by antigen-presenting cells plays a critical role in directing adaptive immune responses. In addition, interaction between microorganisms and toll-like receptors (TLRS) on mucosal epithelial cells, monocytes, macrophages and dendritic cells induces the secretion of a variety of mediators like cytokines such as tumor necrosis factor (TNF) alpha and interleukin 6 by activation of NF- κ B and triggers lymphocyte activation. Effector T cells need to migrate from inductive to effector sites. Intestinally activated T cells may enter the synovium, either through the presence of cognate antigens at both sites or by homing of lymphocytes primed by adhesion molecules [76,77]. The discovery of identical T-cells expansions in colon mucosa, synovium

and blood support this hypothesis [78]. Thus, TLRs sit at the crossroads of innate and adaptive immunity, where microbial invasion is translated from nonspecific to antigen-specific inflammatory responses.

Treatment of musculoskeletal manifestations in IBD

The aims of therapy in musculoskeletal manifestations of IBD are to reduce inflammation and to prevent disability or deformity. Rest and physical therapy are used as non pharmacologic treatment. In patients with true AS, physical therapy is of great importance to maintain spinal mobility and to prevent deformities of the spine with subsequent respiratory compromise and disability. Breath exercises, spinal exercises and swimming should be preferred. Nonsteroidal antiinflammatory drugs (NSAIDs) are usually prescribed to control peripheral arthritis, back pain and stiffness. Caution is necessary because these drugs may exacerbate IBD, particularly UC [79, 80]. NSAIDs-related adverse events may also mimic a flare of IBD and complicate management. Experience with the cyclooxygenase - 2 (Cox-2) selective inhibitors (such as celecoxib and rofecoxib, the latter is no longer available) in patients with IBD is limited. It is known that Cox-2 activity promotes epithelial proliferation and wound healing. Theoretically, Cox-2 inhibition could have deleterious effects in patients with IBD [81]. On the other hand, selective Cox-2 inhibitors ameliorate the severity of experimental colitis [82]. In a placebo - controlled trial the use of celecoxib in IBD patients for two weeks showed no significant difference in the rate of relapse of IBD [83]. Another study included 45 IBD patients with arthralgias treated with rofecoxib (12.5 mg/daily) ranging from three days to three months [84]. Arthralgia relief was reported by 71% of patients (complete relief in 18% and partial relief in 53%). However, 20% of IBD - 9 patients - versus 3% of control group (patients with dyspepsia) discontinued therapy due to gastrointestinal symptoms, which subsided after treatment was stopped. The rate of discontinuation was similar for those with CD or UC. Cox-2 selective agents may be better tolerated in the short term, but the withdrawal of rofecoxib and valdecoxib because of cardiovascular toxicity has raised concerns about their overall benefit.

Despite concern about the potential for NSAIDs and Cox-2 selective agents to cause worsening bowel inflammation, rheumatologists, have used the above drugs successfully in patients with IBD. However, if symptoms or signs of IBD develop or worsen during the use of NSAIDs or Cox-2 selective treatment it is prudent to temporarily or permanently discontinue their use. Of the available NSAIDs, indomethacin and naproxen, have been used more, but anti-inflammatory doses of any NSAID or Cox-2 selective agent may be effective. Since the peripheral arthritis of IBD is generally nondestructive, therapy is primarily directed at symptomatic relief. NSAIDs or Cox-2 selective agents improve spinal pain and stiffness in AS although radiographic progression to bony

ankylosis may occur.

Sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate and glucocorticoids may be helpful for both bowel and joint inflammation. Intraarticular glucocorticoid injections can be used for flares of peripheral arthritis. Sulfasalazine has been effective in treating peripheral, but not axial arthritis in IBD patients. The initial dose is 500 mg twice daily with an increase in daily dose every two weeks until arthritis symptoms improve or a dose of 1000 mg three times daily is reached. Maintaining the maximum dose for up to 12 weeks is recommended before assessing efficacy.

Azathioprine and 6-mercaptopurine used for IBD may also have beneficial effects on joint disease. However, aminosalicylates (e.g. mesalamine), useful for controlling intestinal inflammation, appear to have no direct anti-inflammatory effect on the synovium [85].

Studies that address the efficacy of methotrexate in the peripheral arthritis of IBD are lacking. Many rheumatologists use methotrexate in patients with IBD and peripheral arthritis and the methotrexate may be preferred to azathioprine, but this is an empirical approach not backed by trial evidence [56]. Oral administered methotrexate is adequately absorbed, even in patients with active IBD. Subcutaneous injection of the drug may reduce gastrointestinal side effects.

Budesonide, a glucocorticoid with first-pass hepatic metabolism and fewer systemic side effects as a result has been used for CD flares, but there are no studies to date addressing the effect of this steroid on enteropathic arthritis.

Anti-TNF agents have had a major impact on the therapeutic approach to IBD and the associated musculoskeletal manifestations. The anti-TNF monoclonal antibodies (infliximab, adalimumab) are effective in IBD particularly CD and they are useful in patients with axial involvement and peripheral arthritis [86-88]. Etanercept can control the arthritis associated with CD while having no effect on the bowel disease itself [89]. Patients with IBD and true AS who have an inadequate response to conventional treatment are candidates for anti-TNF α treatment. Infliximab, adalimumab, etanercept and golimumab (human monoclonal antibody, 50 mg once per month subcutaneously) can be used in patients with AS, although golimumab has not been approved for CD.

Certolizumab pegol is a pegylated humanized antibody, Fab fragment of TNF α monoclonal antibody. Certolizumab binds to and selectively neutralizes human TNF α activity. Since it is not a complete antibody (lacks Fc region) it does not induce complement activation, antibody dependent cell-mediated cytotoxicity or apoptosis. Pegylation of certolizumab allows for delayed elimination and therefore an extended half life. Certolizumab pegol received approval from the United States Food and Drug Administration in 2008 for treatment and maintenance of response in adults with moderate to severe CD who had an inadequate response to conventional therapy. The drug is also approved in Switzerland but it has not been approved by the European Medicines Agency and is therefore not widely available in Europe. The recommended dosing for induction is 400 mg subcutaneously at weeks 0, 2, and 4 and then every four weeks for maintenance of response.

Studies evaluating the efficacy of infliximab, adalimumab and certolizumab have generally shown similar results but no studies have directly compared them. Preliminary data suggest that certolizumab pegol can be effective in patients who responded to infliximab and lost response or became intolerant to it [90-92]. Safety and precautions are similar to all anti-TNF α agents. All patients should have a skin test for tuberculosis prior to initiation of the anti-TNF α therapy and should be evaluated for latent infection.

Conclusions

- Rheumatological manifestations of IBD are frequent and may be present in one third of patients.
- Axial involvement ranges from inflammatory lower back pain to SI or true AS while enthesopathies can also occur.
- HLA-B27 is associated with axial involvement of IBD.
- The role of HLA-B27 in the pathogenesis of axial disease or AS in IBD has been supported by various theories.
- Peripheral arthritis has been classified into two types. Type I is a pauciarticular, asymmetric usually non destructive arthritis affecting large joints and it is usually associated with active bowel disease. Type II is a polyarthritis affecting small joints and tends to run an independent of the bowel disease course.
- Sulfasalazine, azathioprine, methotrexate and glucocorticoids have been used to treat IBD and joint symptoms.
- Anti-TNF α antibodies are effective in patients with resistant or complicated CD as well as for both axial and peripheral arthritis.

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