

Rheumatic Manifestations Associated with Inflammatory Bowel Diseases

Marta Podswiadek¹, Renata D'Incà², Giacomo Carlo Sturniolo², Francesca Oliviero¹ and Leonardo Punzi^{*,1}

¹Rheumatology Unit and ²Gastroenterology Unit, University of Padova, Italy

Abstract: Rheumatic manifestations, in particular joint complaints, are frequent features in inflammatory bowel disease (IBD), with a prevalence varying from 10 to 35%. Their spectrum is almost wide, involving bone, tendons, entheses and joints. Joint manifestations may be seen as arthralgia and/or inflammatory arthropathies. These latter may in turn be found in three principal forms: the peripheral, the axial or spondylitis and that overlapping between these two varieties. Peripheral arthritis may be classified in oligoarticular (type I) and polyarticular (type II) forms. Oligoarthritis is the most frequent. Usually asymmetric, involving large joints of lower limbs, it is transient, commonly associated with IBD flares, and may disappear after few weeks, although in 10% of cases it may evolve to chronic arthritis. Type II arthritis is polyarticular and symmetric, involving hands and feet but also large joints. The prevalence is about 2-4% of IBD patients, its course is independent from IBD flares and usually evolves in chronic disease. Peripheral arthritis is classically non-deforming, non erosive, and seronegative for the rheumatoid factor. Axial involvement is equally frequent in both CD and UC and varies in different studies from 10 to 30% for sacroiliitis and from 3 to 10% for ankylosing spondylitis. Its course is independent from IBD state, the extension of IBD involvement and the occurrence of flares. The treatment of rheumatic manifestations in IBD is frequently problematic, due to the possibility of frequent side effects. Among drugs used for IBD, corticosteroids, also effective in joint complaints, may have osteopenic effects; sulfasalazine, sometimes able to control peripheral arthritis, is ineffective for the axial involvement. A potential gut toxicity is associated with the use of NSAIDs, which in some patients may induce asymptomatic lesions causing small gut bleeding and loss of proteins. Local injections with steroid may be used for tendonitis, monoarthritis or isolated sacroiliac inflammation. In patients with peripheral arthritis, especially when involving several joints and/or refractory to other therapies, disease modifying drugs for rheumatoid arthritis (DMARDs) should be used. Among these, methotrexate is also useful for CD while it seems ineffective in UC. Cyclosporin, administered alone or in association, may contain flares of steroid refractory UC. Azathioprine is commonly used to induce and maintain remission in refractory CD while its role on arthritis is marginal. Amino-bisphosphonates seem effective for both axial and peripheral involvements and probably, it may represent a good option for the future in the management of enteropathic arthritis, because of their anti-osteopenic effect. Finally, the most promising opportunities derive from the recently introduced biologic agents, in particular anti-tumour necrosis factor (TNF) α . Infliximab, a chimeric anti-TNF α monoclonal IgG1 antibody, has largely demonstrated its efficacy in refractory CD and in all rheumatic manifestations. Other biologic agents are proposed, including the human anti-TNF monoclonal antibody adalimumab, antibodies to integrins (anti- $\alpha 4\beta 7$), anti-ICAM-1 (intracellular adhesion molecule 1) and IL-10. Concerning the surgical options, the colectomy may be protective on type I peripheral arthritis but is not influential on the course of axial disease, while the surgery on small intestine usually do not prevent the appearance of peripheral arthritis. In the case of destructive arthritis, like coxitis, joint prosthesis may be necessary.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, enteroarthritis, arthritis, rheumatic manifestations, anti-TNF therapy.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of unknown etiology characterised by the involvement of all digestive tube and by the association with some common features, such as familial history, intermittent course, good responsiveness to steroids and high prevalence of extraintestinal manifestations [1, 2]. The total prevalence of the IBD, which include Crohn's disease (CD) and ulcerative colitis (UC), is between 90 and 150 cases/100.000 inhabitants [2, 3]. CD is a granulomatous disease, it also called terminal ileitis or regional enteritis, which may involve all alimentary tract and when localised at colonic

mucous, is called Crohn's colitis. UC, which is double more frequent than CD, has continuous and not segmental involvement and is localised quite exclusively at "large gut" [2, 3].

The pathogenesis of these affections is unknown. The most frequent hypothesised agents are microorganisms [1-4]. However, their role in human is still not well defined, although it is possible to obtain an infective experimental model of acute distal ileitis [5]. A possible mechanism may be a crescent and inappropriate activation of gut mucous immune system by normal intestinal flora. The abnormal response may be facilitated by a dysfunction of epithelial barrier, leading to an augmented gut permeability that in turn permits the antigen absorption and consecutive immune stimulation [5, 6]. The intestinal barrier integrity or the reparative processes may be genetically imperfect [6]. These factors interact with the cells of immune system, in particular

*Address correspondence to this author at the Rheumatology Unit, University of Padova, Via Giustiniani 2, 35128 Padova, Italy; Tel: +39 49 8212190; Fax: +39 49.8212191; E-mail: punzireu@unipd.it

dendritic cells and lymphocytes inducing the adaptative immune response [3]. The immune cells activation stimulates the inflammation reaction with an acute phase response and the production of cytokines, prostaglandins, leukotrienes, all agents know hoe to mediate the inflammatory process but they can also cause the tissue injury [7]. It has also reported that some environmental factors, such as smoking [2] and zinc deficiency [4], may influence the course of IBD.

The higher prevalence in homozygous twins has stimulated several studies on genetic deregulation of immune system in IBD [8-10]. The most studied were the major histocompatibility classes I and II, revealing associations with HLA-DR2 for the UC, HLA-B8/DR3 for UC and sclerosing cholangitis, and HLA-A2, DR1 and DQw5 for extraintestinal complications in CD [10]. Recently, a CARD15/NOD2 mutation frequently associated with different granulomatous diseases was detected in some patients with CD, thus confirming the genetic predisposition to this disease [11]. CARD 15 was also found in sarcoidosis and in the rare familial granulomatous disease called Blau syndrome [12-14]. Such diseases are recently classified as "autoinflammatory" syndromes to underline their genetic predisposition in facilitating stimulation and persistence of inflammatory reactions. In CD, this mutation was found in only 25% of patients, prevalently young male with ileal localisation of CD. Thus, CARD15 mutation has been proposed as a marker of exclusive ileal involvement of CD [11].

Extraintestinal manifestations in IBD occur rather commonly, since their presence is estimated in up to 30% of pa-

tients [3]. These manifestations may be various in frequency and severity, and may involve several organs or tissues (Table 1). The most commonly encountered are rheumatic manifestations (RM) [3]. However, despite this frequency, few studies have until now investigated their prevalence and characteristics [15-19] (Table 2). Main aim of the present paper is to offer a comprehensive review on the large and various spectrum of RM associated with IBD.

RHEUMATIC MANIFESTATIONS

Clinical Aspects

The prevalence of RM in IBD patients varies from 10 to 35% depending on the diagnostic criteria used and on the modality of patient selection [15-19]. Although the spectrum of these complaints is almost wide, involving bone, tendons, entheses and joints, this latter involvement is the most classic (Table 3) [15-19]. Joint manifestations may be seen as arthralgia and arthritis. Arthralgia may involve few or, more frequently, several joints and so called polyarthralgia. It is rather common in IBD patients, as demonstrated by a recent epidemiological study from Northern Italy [20]. In this study we found that CD is more prone to develop an articular disease, since its prevalence was 12.8%, compared to 7.2% in UC.

The most frequently encountered RM are inflammatory arthropathies, which in turn may have different types of presentation and evolution. In an attempt of schematisation, they may be subdivided in two groups, those predominantly

Table 1. Main Extraintestinal Manifestations in Patients with Inflammatory Bowel Diseases

Organ Involved	Type of Manifestation	Prevalence (%)
Skin	Erythema nodosum	10-25
	Pyoderma gangrenosum	<1
	Necrotizing vasculitis	<1
	Enteropathic acrodermatitis (due to zinc deficiency)	<1
	Purpura (due to vitamin C and K deficiency)	<1
Eye	Anterior uveitis	3-11
	Episcleritis	<1
	Corneal ulcerations	<1
Liver	Sclerosing cholangitis	<1
	Cholangiocarcinoma	<1
	Autoimmune hepatitis	<1
Kidney	Nephrolithiasis	3-6
	IgA nephropathy	<1
Bone and Joint	Peripheral arthritis	4-20
	Axial involvement (spondylitis)	3-10
	Osteoporosis/osteomalacia	20-35
Other	Aseptic necrosis	<1
	Amyloidosis	<1

Table 2. Percentage of Spondyloarthropathy (SpA) and Ankylosing Spondylitis (AS) in Patients with IBD, in Different Prospective Studies

Author (Ref.)	Diagnostic Criteria	Number of Patients	Number of Patients Affected With SpA (%)	Number of Patients With Crohn Disease	Number of Patients With Ulcerative Colitis
De Vlam <i>et al.</i> 2000 (15)	ESSG for SpA NY modified for AS	103	36 (35) 10 (10)	25 7	11 3
Queiro <i>et al.</i> 2000 (16)	ESSG for SpA NY modified for AS	62	42 (67.7) 2 (3.2)	19 1	23 1
Salvarani <i>et al.</i> 2001 (17)	ESSG for SpA NY modified for AS	160	29 (18.1) 5 (3.1)	11 3	18 2
Palm <i>et al.</i> 2001 (IBSEN study) (18)	ESSG (only synovitis considered)	521	62 (12)	24	38
Personal series (unpublished)	ESSG for SpA NY modified for AS	651	56 (8.6) 9 (1.4)	32 5	24 4

ESSG=European Spondyloarthropathy Study Group criteria; NY= New York criteria.

affecting spine and therefore spondylitis, and those predominantly affecting peripheral joints, and therefore peripheral arthritis. It is useful to specify that in some cases this distinction may be hard, due to difficulties to establish the aspect which is prevalent and mainly, to exactly detect spondylitis when symptoms are mild or confusedly reported.

Table 3. Clinical Findings in 651 Patients with IBD and Current Articular Symptoms

	Ulcerative Colitis	Crohn's Disease
Patients with current articular symptoms	28 (7.2%)	34(12.8%)
Mean age (yrs)	42±12	40±12
M/F	15/13	18/16
Mean disease duration (yrs)	9.2 ± 6.7	10.1 ± 6.9
Disease localisation and extension		
Proctitis	2	-
Left sided colitis	9	-
Extensive colitis	17	-
Ileitis	-	14
Ileocolitis	-	10
Colitis	-	10
Rheumatological diagnosis		
Axial arthropathy	12 (3.1%)	20 (7.5%)
Peripheral arthropathy		
Oligoarticular	8 (2.1%)	2 (0.7%)
Polyarticular	7 (1.8%)	7 (2.6%)
Mean number of small joints involved	5.6± 4.3	9.9± 8.2
Fibromyalgia/arthralgia	1 (0.2)	3 (1.1%)
Tendinitis	1 (0.2)	1 (0.4%)

IBD patients presenting inflammatory low back pain or peripheral synovitis in lower limbs, may be classified and

diagnosed as spondyloarthropathies (SpA) according to the European Spondyloarthropathy Study Group (ESSG) criteria [21]. The term of SpA was introduced many years before by Moll and Wright, in keeping with their classic proposition to classify in a same family “a group of similar and strongly correlated conditions rather than a single disease with different clinical manifestations”. This group included ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis and also enteropathic arthritis or arthritis associated with IBD [22].

As observed in other forms of SpA, arthritis of IBD may have different clinical patterns that vary from tendonitis or enthesitis to peripheral arthritis or a true AS [15]. Uveitis, another frequent extra-intestinal manifestations of IBD, may also accompany this form [18].

Clinical presentation of arthritis associated with IBD has a wide spectrum of symptoms and signs which may be transient and mild, but sometimes persistent and vary disabling. However, this arthritis is classically non-deforming and non erosive, thus some reported cases of erosive arthritis associated with CD [23] should be carefully evaluated, due to possibility of an association of IBD with psoriatic arthritis or rheumatoid arthritis, especially in genetically predisposed individuals [24].

Three principal forms of arthritis may be found in IBD patients: the peripheral, the axial and that overlapping between these two forms. The prevalence of peripheral arthritis in IBD may vary from 5 to 20% [25], usually more frequent in CD [20, 26]. An epidemiological study performed in 651 IBD patients of Venetian area, past articular symptoms were referred as axial in 19%, peripheral in 45% and both peripheral and axial in 36% of the interviewed patients. The majority of the patients (86.6%) had to take extra self-administered drugs in order to control articular symptoms, 20% non-steroidal anti-inflammatory drugs (NSAIDs), 15% steroids and 65% analgesics. Fifty one patients (43%) referred symptoms starting before than the diagnosis of inflammatory bowel disease was made: in 63% of them the main complaint was back pain. Concomitant active intestinal disease was present in 60% of the patients with oligoarticular symptoms and 50% of the patients with polyarticular or axial symp-

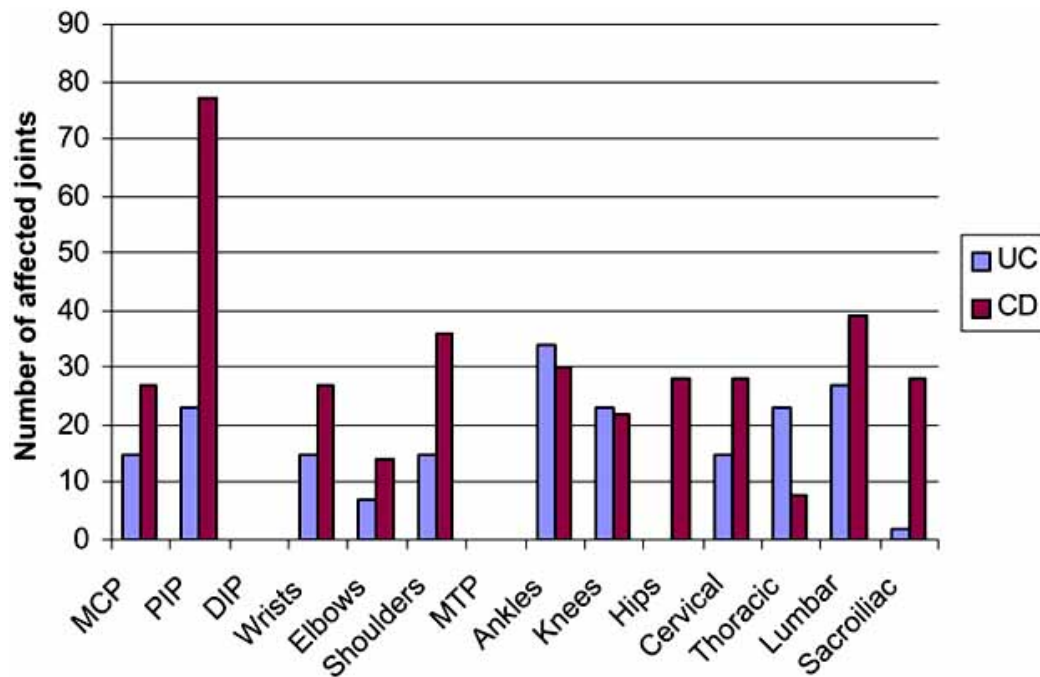


Fig. (1). Distribution of joint involvement in inflammatory bowel diseases. Comparison between Crohn's disease (CD) and ulcerative colitis (UC). MCP=metacarpophalangeal, PIP=proximal interphalangeal, DIP=distal interphalangeal, MTP=metatarsophalangeal.

toms. Sixty two patients (9.5%) referring current articular symptoms were evaluated by a rheumatologist and subsequently classified as follows: 32 (52%) with axial arthropathy, 24 (39%) with peripheral arthropathy, of which 14 (23%) were polyarticular and 10 (16%) oligoarticular (Fig. 1). Other RM included 4 cases with fibromyalgia, 2 with localised tendinitis and 1 with arthralgia. Among patients included in the axial group, 9 satisfied criteria for AS (27): 7 were men, 5 had CD and 4 UC (Table 3). While oligoarticular involvement was more frequent in UC than in CD, axial arthropathy was more frequent in CD than in UC (Table 3). Peripheral arthropathy in CD was exclusively seen in patients with ileal or ileocolonic localisation. Male gender was not associated with higher frequency of axial arthropathy, except for the subgroup with AS, where 7/9 patients (77%) were males. Symmetrical polyarthritis was found in 9 patients (14.5%). Oligoarthritis involved mainly the joints of the lower limbs, which were affected in 9 patients while upper limbs in just one.

A retrospective study performed by the Oxford Inflammatory Bowel Disease Clinic on 1459 IBD patients regarding their joint complaints (26), showed that the prevalence of peripheral arthritis was 6% for UC and 10% for CD, while in another study performed in Gent [15] the prevalence was 10% for both UC and CD (Table 2). The most common arthropathy was oligoarticular, asymmetric and transient, with frequent Achilles tendon involvement, plantar fasciitis and rarely dactylitis (25). In the Oxford study, Orchard *et al.* proposed to classify arthritis associated with IBD in oligoarticular (type I) and polyarticular (type II) [26]. The first one is sometimes migratory, involves large joints of lower limbs and is associated with IBD flares. It is usually self-limiting but commonly recurs, sometimes in concomitance with uveitis or erythema nodosum. However, in 10% of cases it evolves in chronic arthritis [28]. In some patients, type I ar-

thropathy may be associated with axial disease and, in about 2% of subjects with CD, with a destructive coxitis [29]. Type II arthritis, which may precede IBD symptoms, is polyarticular and symmetric, usually evolves in chronic disease, and involves not only mainly hands and feet but also large joints. Its prevalence is about 2-4% of IBD patients and its course is independent of IBD flares. Type I arthritis may be underestimated due to its transient character and the good response to steroids used for IBD flares. In fact, when questioned, 29% of patients declared to have had joint effusion [15]. Peripheral enteropathic arthritis is classically non-deforming, non erosive, and seronegative for the rheumatoid factor. Its occurrence probably depends on genetic predisposition, since some studies performed in UC patients revealed the high prevalence of the rare HLA antigen DR103 in patients with pancolonic severe involvement and frequent extraintestinal complaints [30], including type I arthritis, as confirmed by the Oxford's group [31].

Axial involvement (type III) is equally frequent in both CD and UC and varies in different studies from 10 to 30% for sacroiliitis and from 3 to 10% for AS (Table 2). Although there is an almost equal sex distribution in both, it seems that females have an earlier beginning and a poorer prognosis [32, 33]. The AS variety may occur at any age with the peak of onset at 18-40 years (34). The course of type III is independent of IBD state, extension of IBD involvement and occurrence of flares. In a study by De Vlam it was reported that 30% of IBD patients were suffering from inflammatory low back pain and 33% have limited lumbar mobility (Schoeber's test inferior to 3 cm) [15]. About one third of IBD subjects had II grade sacroiliitis and 18% of them were completely asymptomatic, with low back pain absent and a good lumbar mobility. The most important symptoms are: inflammatory low back pain [26], unilateral or alternate buttock pain with extension to the posterior surface of thigh



Fig. (2). 28 old patient with Crohn's disease and ankylosing spondylitis. The picture shows bilateral 4th grade sacroiliitis and involvement of the left hip.

“sciatica like”; anterior chest pain; cervical pain; dorsal pain. Sometimes patients with axial involvement are quite asymptomatic and are diagnosed because of a limitation of spine mobility [35]. We recently investigated the prevalence of radiographic sacroiliitis in IBD patients affected with inflammatory low back pain [36]. Among 50 symptomatic patients 19 (38%) had radiologically relevant sacroiliitis (at least grade 2) and 14 (28%) had AS according to New York modified criteria [27]. The axial involvement frequently precedes the diagnosis of IBD. Type III may remain purely axial or may be associated with type I peripheral arthritis, similarly to AS with peripheral arthritis (Figs. 2, 3). This behaviour is not observed in patients after total colectomy that rarely present type I peripheral arthritis. The prevalence of peripheral enthesopathy is lower in IBD patients than in other forms of SpA. Other rare RM include clubbing, periostitis, and granulomatous disease of bone and joints.

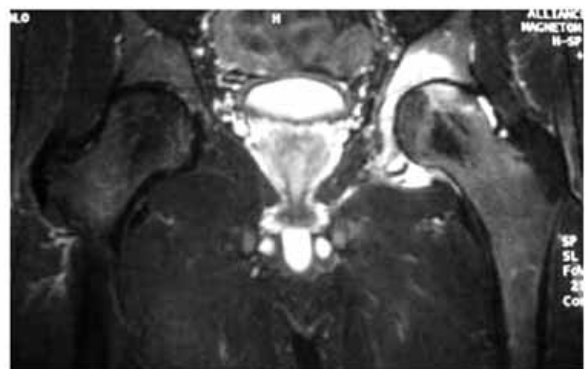
Laboratory and Genetic Aspects

There is no laboratory marker for diagnosis or prognosis of arthritis associated with IBD (Table 4). Rheumatoid factor and antibodies anticyclic citrullinated peptide (anti-CCP) are usually absent [37]. Antinuclear and anti-neutrophil cytoplasmic antibodies (ANCA), are sometimes found in IBD, particularly in UC, reflecting an increased risk for vasculitis. The most frequently found are p-ANCA or atypical ANCA, in particular anti-cathepsin G. Their significance for the intestinal disease is still a matter of debate, although most recent studies seem to exclude a role of these substances in the evolution, extent, and extraintestinal manifestations of IBD [38, 39].

Due to inflammatory character of both IBD and arthritis, a reliable marker of inflammation may be useful in clinical



(a)



(b)

Fig. (3). MRI imaging of the same patient of Fig. 2. Note severe bone edema of the left hip with slightly augmented synovial film in T1 (a) and T2 (b).

Table 4. Main Laboratory Findings in Inflammatory Bowel Diseases with or without Arthritis

Finding	CD	CD With A	UC	UC With A
ESR elevation	+++	+++	+	++
CRP elevation	+++	+++	+	++
Rheumatoid factor	-	-	-	-
Anti-CCP	-	-	-	-
ANA	-	-	-	-
ANCA	-	-	-	+
ASCA	+	+	-	-
HCgp-39	+	+++	+	+++
Synovial fluid	-	Slightly/moderate inflammatory	-	Slightly inflammatory
HLA	DR4, DR7, B5	B35, B44, B27, DR*0103	DR2, DR*0103	B35, B44, B27, DR*0103

CD=Crohn's disease; UC=Ulcerative colitis; A=arthritis.

assessment of their activity. However, the major indices of acute phase reaction, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be increased in active IBD, with or without arthritis. Thus, in these patients, an appropriate interpretation of the elevation of acute phase response is difficult. For this reason, we need marker which may specifically reflects the activity of joint or bowel disease. Since to our knowledge, no such marker was available for the bowel district, we proposed as new possible marker of articular involvement in IBD the HCgp-39, also called YKL-40, a substance produced by many cell types including articular synoviocytes and mainly, activated chondrocytes [40]. The levels of HCgp-39 were thus determined in IBD patients with arthritis found higher than in IBD patients without joint complaints. Furthermore, HCgp-39 values were not influenced by gut disease activity [41].

The HLA associations were studied in patients with IBD, both in presence or absence of arthritis. HLA-B35 and HLA-DR103 haplotypes were found in 32% and 33% of patients with type I arthritis, respectively, while 62% of type II had a HLA-B44 association [31] (Table 4). In the axial involvement, the HLA-B27 antigen is not so frequent than in classical form of AS, although the phenotype B27, B44 seems to predispose to the association between CD and AS [42]. The low prevalence of HLA-B27 in IBD associated spondylitis, varying from 12 to 33%, is confirmed by other studies [15, 43]. However, it is possible that this association is lower because of the frequent asymptomatic misdiagnosed sacroiliitis. Anyway, isolated sacroiliitis in IBD seems not associated with an increased prevalence of HLA-B27 phenotype [44]. In our data, the frequency of B27 in type III was only slightly higher than in controls ($p=ns$) but all B27 positive subjects had AS. In the group of AS associated with IBD the prevalence of B27 was 30% [43].

BONE INVOLVEMENT

Osteopenia and osteoporosis were found in CD independently of steroids intake (45). Associations with bone mineral density (BMD) and age, BMI and serum magnesium were found in patients affected with IBD [45]. Lifetime steroid use was a weaker predictor of bone loss. Those with ongoing steroid use had lower spine BMD. Disease activity,

systemic inflammation, hormonal, nutritional and genetic factors may be all involved in the pathogenesis of bone loss in CD. Between genetic factors non carriage of the 240-base pair allele of the IL-6 were associated with increased bone loss [46]. During a 2-year follow-up period, the BMD measured by dual X-ray absorptiometry (DXA) showed significant bone loss in 22% of CD and 27% of UC patients. CRP was significantly higher in CD with bone loss but there was no relationship between corticosteroids intake and bone loss in CD [47].

Vitamin D deficiency was also studied in CD, but without differences in bone mineral density (BMD). Sunlight exposure, nutrition and smoking seems to be predictors of 25-OHD deficiency [48]. In another interesting study, a total of 293 patients with IBD were screened with DXA of the lumbar spine (L1-L4) and proximal right femur [49]. In 156 patients with lumbar osteopenia or osteoporosis (T score <-1), X-ray examinations of the thoracic and lumbar spine were performed. In 34 (21.8%; 18 female) of these, 63 osteoporotic vertebral fractures were found. The fractures were clinically evident and associated with severe back pain in only four patients. Since approximately one third of patients with fractures were younger than 30 years and pain was relevant only in 12% of patients with fractures, these aspects deserve further clinical attention. The bone turnover in CD patients in clinical remission is characterised by suppressed bone formation and normal bone resorption [50]. The serum levels of bone specific alkaline phosphatase and osteocalcin, markers of bone formation, are decreased in CD patients compared to controls, while collagen type I C-terminal crosslinks and deoxypyridinoline, as bone resorption markers were normal. The mean level of vitamin D were low in about 35% of CD patients. This unbalanced bone metabolism seems to be an ongoing process with the bone degradation-formation cycle disequilibrium. These abnormalities and low BMI, malnutrition and malabsorption may lead to progressive bone loss and vertebral fractures.

The management of bone disease should be directed to the prevention of bone loss and the restoration of bone quality in patients with low BMD. Treatment with alendronate improves significantly bone turnover of CD patients when compared to placebo [51]. In addition to hormone replace-

ment therapy, vitamin D, sodium fluoride, and a regular physical activity have to be considered in patients with CD for the management of this frequent and disabling but yet underestimated problem.

GUT INFLAMMATION AND SYNOVITIS

It is well-known that SpA patients have subclinical gut inflammation [25, 52]. Two types of bowel involvement are recognised: acute enterocolitis resembling bacterial one and chronic ileitis indistinguishable from CD [53, 54]. By a colonoscopic study, in 37 of 55 (67%) patients with reactive arthritis and in 30 of 35 (56.6%) with AS, there was histological evidence of inflammatory bowel disease with features either of acute enterocolitis or early CD [54]. Only 18 of 67 (27%) of the patients with histological gut inflammation, however, had intestinal symptoms. The initial lesions have been subdivided in acute and chronic types. The acute type is characterised by infiltration of ileal villi and crypts by polymorphonuclear cells. In the lamina propria there is an increased number of granulocytes, lymphocytes and plasma cells, especially in enterogenic reactive arthritis [55]. The chronic type is frequently indistinguishable from classical CD, with alterations of mucosal architecture, irregular villi and the crypt distortion, infiltration of lamina propria by mononuclear cells. These findings are detected prevalently in AS, especially when peripheral joint are involved [55]. Both acute and chronic lesions may appear in SpA, in 29% and 32-44% of cases, respectively [56].

Recent studies revealed that 20% of SpA patients with subclinical gut inflammation in 4 years of follow-up evolved in IBD with clinical symptoms [57]. In a follow-up study on SpA patients, there was a remission of the gut alterations after the disappearance of the joint inflammation [58]. This confirms the strong relationship between gut and joint inflammation. After a long term follow-up on SpA patients with subclinical gut inflammation, about 6% of them developed an IBD 2 to 9 years later [57]. All of these patients initially had features of chronic inflammation [57]. The HLA-Bw62 was found in 30% of patients with chronic ileal lesions, similarly to the CD prevalence [56]. An increased gut permeability was also found in all forms of juvenile chronic arthritis, often without any intestinal symptoms (59). Another study found increased gut permeability and subclinical mucosal inflammation in psoriatic arthritis [60].

Animal models are very useful to study the pathogenesis of CD. A mouse with silenced AU-rich TNF promoter gene region (ARE) has abnormally stable mRNA for TNF and so increased levels of TNF [61]. These mice develop both arthritis and CD-like lesions in the ileum when stimulated with endotoxin [61]. Another model is called senescence-accelerated mouse P1/Yit strain, SAMP1/Yit. In pathogen free environment this strain develops spontaneous changes reminiscent of CD (62). In both animal models, the disease ameliorates after TNF inhibition.

THERAPY

The management of IBD include the control of gut disease relapses and an appropriate maintaining therapy [3, 19]. Corticosteroids commonly used for acute IBD are also effective in most cases with joint complaints for which, especially in peripheral arthritis, low doses are frequently sufficient.

However, even at these low doses, corticosteroids should be used with caution, due to their possible osteopenic effects.

The use of NSAIDs should be avoided because of their potential gut toxicity. Although NSAID enteropathy may be asymptomatic, some patients may experience small gut bleeding and loss of proteins. Large gut ulcers are rarely seen. IBD flares after NSAID administration, especially in CD, are also described. The intestinal mucous damage may be direct on the surface membrane phospholipids which leads to increased gut permeability and an inhibition of cyclo-oxygenase (COX)-1. Conventional NSAIDs and selective COX-2 inhibitors both have been implicated in aggravation of experimental colitis [63]. However, we need controlled randomised trials evaluating the safety of anti-COX2 on gut permeability.

Antibiotics commonly used in flares of CD, in particular ciprofloxacin and metronidazole, are ineffective on joint symptoms and in addition, fluoroquinolone derivatives may induce tendons rupture in susceptible patients.

The 5-ASA, which is considered as the gold standard in maintaining remission of IBD, is not useful for joint complications. In the presence of arthritis, the treatment with mesalazine may be substituted by sulfasalazine 3 to 4g daily, which sometime seems to be able to control peripheral arthritis, even if it is ineffective in axial involvement. The beneficial effect of this drug on peripheral joint inflammation may be linked to the reduction of gut inflammation by 5-ASA moiety but interestingly those with IBD-associated arthritis may benefit after the switch from mesalazine to sulfasalazine, probably due to the effects of sulfapyridine moiety [63].

Analgesics like acetaminophen, taken alone or in association with opioids, may be useful in the management of moderate pain. Local injections of steroids are usually performed for tendonitis, monoarthritis or isolated sacroiliac inflammation, with good results in most cases.

In patients with peripheral arthritis, especially when refractory to other therapies and/or several joints are involved, disease modifying drugs commonly used for rheumatoid arthritis (DMARDs) should be considered [19, 64, 65]. Among these, methotrexate may be also useful for CD while it seems inefficacious in UC. Cyclosporin A, administered alone or in association with methotrexate, seems able to contain flares of steroid refractory UC. Azathioprine is commonly used to induce and maintain the remission in refractory CD but its role on arthritis is marginal. Hydroxychloroquine too has a marginal role, when used in monotherapy for enteropathic arthritis.

Therapy of osteoporosis consists on calcium and vitamin D3 supplementation, especially if low serum levels of vitamin D3 are found. The association of calcium-vitamin D3 is mandatory during corticosteroid therapy, especially in CD patients. Recently, the effect of parenteral aminobisphosphonates in SpA was documented for both axial and peripheral involvements [66] and probably, it may represent a good option for the future in the management of enteropathic arthritis, especially because of their anti-osteoporotic effect. Oral alendronate and risedronate are proposed for the treatment of IBD-related osteoporosis but, due to their low gastrointestinal tolerability, these drugs are poorly accepted by

IBD patients. In these cases parenteral neridronate or pamidronate may be proposed [66, 67]. It should be pointed out that physical activity is also important to maintain the bone structure.

Evidence indicates that a dysregulation of mucosal immunity in the gut of IBD causes an overproduction of inflammatory cytokines into the bowel, thus leading to an uncontrolled intestinal inflammation, has created a recent trend of novel biological therapies which specifically inhibit the molecules involved in the inflammatory cascade. Major targets for such treatment are inflammatory cytokines and their receptors. New promising therapeutic opportunities derive from the recent introduction of biologic agents, in particular anti-tumour necrosis factor (TNF) α . Infliximab, a chimeric anti-TNF α monoclonal IgG1 antibody, neutralising the soluble and membrane bound cytokine is allowed for refractory CD and AS, and it is likely to be beneficial for UC [68-70]. Its effects on fistulas or severe CD are well documented [71]. Furthermore, a significant improvement in articular and axial symptoms was observed in a small group of patients treated for CD [72]. The efficacy of infliximab on AS and psoriatic arthritis is well known. There is some case reports of its effect on pyoderma gangrenosum, uveitis and sclerosing cholangitis, all manifestations which may be found in IBD. The most common regimen of treatment with infliximab is of 5mg/kg e.v. at 0-2-6 and every 6-8 weeks. In patients with both IBD and SpA, other biologic agents are proposed, including the human anti-TNF monoclonal antibody adalimumab. Adalimumab is a human immunoglobulin G1 (IgG(1)) monoclonal antibody targeting TNF. A randomised, double-blind, placebo-controlled, dose-ranging trial was recently performed to evaluate the efficacy of adalimumab induction therapy in patients with CD [73]. Adalimumab was superior to placebo for induction of remission in patients with moderate to severe CD naive to anti-TNF therapy. The primary endpoint was demonstration of a significant difference in the rates of remission at week 4 (defined as a CD Activity Index score <150 points) among the 80 mg/40 mg, 160 mg/80 mg, and placebo groups. The optimal induction dosing regimen for adalimumab in this study was 160 mg at week 0 followed by 80 mg at week 2, without significant side effects.

Antibodies to integrins (anti- α 4 β 7), anti-ICAM-1 (intra-cellular adhesion molecule 1) and IL-10 have been also proposed for the treatment of IBD, but their role in arthritis seem marginal [74].

The colectomy may protect type I peripheral arthritis but is not influent on the course of axial disease. The surgery on small intestine usually do not prevent the appearance of peripheral arthritis. The gut stenosis dewing to bacterial overgrowth often predispose to relapse of peripheral arthritis and give no response to infliximab treatment. In some cases the enteroscopic dilatation may be useful.

In the case of destructive arthritis, like coxitis, the joint prosthesisation may be necessary. Rarely, vertebroplasty in severe spine deformations is performed.

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Received: July 31, 2006

Revised: August 21, 2006

Accepted: August 23, 2006