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Inflammatory bowel disease and immune-mediated inflammatory diseases: looking at the less frequent associations

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***Abstract*:** Patients with inflammatory bowel disease (IBD) often have other immune-mediated inflammatory diseases (IMIDs), and the prevalence of any IMID is higher in IBD patients than in the general population. IBD and other IMIDs involve alterations in innate and adaptive immune responses. Their co-occurrence depends on shared immune and inflammatory processes, pathogenic mechanisms, and genetic and environmental risk factors, including drugs, especially tumor necrosis factor inhibitors. The more common IMIDs associated with IBD have been widely described, so this review focuses on the less frequent associations. The IMIDs discussed here are skin disorders (psoriasis, atopic dermatitis, vitiligo, epidermolysis bullosa acquisita, cutaneous polyarteritis nodosa, and hidradenitis suppurativa), hepato-pancreatic diseases (autoimmune hepatitis, granulomatous hepatitis, and autoimmune pancreatitis), endocrine diseases (autoimmune thyroid diseases, and type 1 diabetes mellitus), multiple sclerosis, and respiratory diseases (asthma, bronchiectasis, and interstitial pneumonia). The early detection of IMIDs in IBD patients is important to prevent their deleterious clinical course and limit their psychological impact. Care for IBD patients with IMIDs should be multispecialist, with a single therapeutic strategy instead of treating each disease separately.

Keywords: atopic dermatitis, Crohn's disease, hidradenitis suppurativa, immune-mediated inflammatory disease, inflammatory bowel disease, multiple sclerosis, psoriasis, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is a group of chronic illnesses in which alterations of the innate and adaptive immune responses play a crucial role in starting and perpetuating intestinal inflammation.[1] IBD includes mainly Crohn's disease (CD) and ulcerative colitis (UC). These diseases present not only gastrointestinal symptoms, but also signs that refer to other body districts and, in severe cases, to systemic implication. The involvement of organs other than those of the gastrointestinal tract is called 'extraintestinal manifestations'. These extraintestinal manifestations occur in varying percentages in IBD patients, and often a single patient has more than one such manifestation.[2] Some extraintestinal manifestations of IBD are related to intestinal inflammation, while others are independent of disease course.

Extraintestinal manifestations of IBD were defined at the sixth scientific workshop of the European Crohn's and Colitis Organisation as any 'inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD'.[3] Extraintestinal manifestations more commonly involve the joints (peripheral and axial spondyloarthropathies), skin (erythema nodosum, pyoderma gangrenosum),

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Table 1. Common genetic background between IBD and other IMID.

IMID	Susceptibility genes shared with IBD
Atopic dermatitis	C11Orf30
Type 1 diabetes mellitus	PTPN2, ORMDL3, HERC2, TNFAIP3, IL-10, IL-26, IL-27
Vitiligo	IL-2RA, PTPN22, CCR6, ZMIZ
Psoriasis	IL-23R, IL-12B, CDKAL1, PTPN22
Multiple sclerosis	PTGER4, STAT3, IL-2RA, IL-7R, FCGR2A

IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease.

eyes (uveitis, episcleritis, iridocyclitis), and hepatobiliary tract [primary sclerosing cholangitis (PSC)].[2]

IBD has also been associated with other pathologies, including treatment-related conditions and complications of IBD itself. Moreover, some pathologies are more common in IBD patients, but no pathological link with IBD has been established yet. Thus, they were termed by Hedin *et al.*[3] as 'associated conditions with uncertain mechanism'. Almost all these IBD-associated conditions with uncertain mechanism (and several extraintestinal manifestations) are types of immune-mediated inflammatory disease (IMID). IMID is a heterogeneous group of apparently unrelated conditions involving common inflammatory pathways and pathogenic mechanisms. According to a non-exhaustive listing, IMID encompasses over 100 different conditions, including IBD.[4] Patients with one IMID are more likely to develop another, and various IMIDs may occur within the same family,[5,6] supporting the concept that the diseases are somehow related. The risk of having multiple IMIDs is higher for certain IMIDs. For example, IBD or ankylosing spondylitis patients are more prone to having an additional IMID than rheumatoid arthritis patients are.[7] Furthermore, some IMIDs tend to pair more frequently. For instance, rheumatoid arthritis and psoriasis appear to confer a pronounced risk for IBD and vice versa.[8,9]

About a quarter of IBD patients have a concomitant IMID, while in the general population the total prevalence of these diseases is only about 5–7%.[10–12] In IBD patients, IMIDs mostly affect women and people with CD.[12] It has been estimated that the incidence rate in IBD patients is almost twice that in IBD-free patients.[13] IBD patients with concomitant IMIDs seem to have a more aggressive disease phenotype,[10,13,14] with higher rates of surgery and treatment with anti-tumor necrosis factor (TNF) agents and, in UC, a more frequent pancolonic extent of the disease.[13,14] As observed in a Danish cohort,[14] when the diagnosis of IMID preceded that of IBD, which happened in nearly 80% of cases, the clinical evolution was worse.

Common pathogenetic mechanisms

In recent decades, there has been a progressive increase in the incidence of IMIDs in the general population; this increase is probably a consequence of the progressive globalization and acquisition of Western habits, diet, and lifestyle in new geographic areas.[15] Environmental factors are thought to influence the development of IMID by triggering abnormal immune responses (both innate and cell mediated).[16–18] As shown in Table 1, genetic predisposition for IMID has also been hypothesized.[19–22] Particularly, dermatological immune-mediated disorders seem to be the ones with the wider shared genetic background with IBD: C11Orf30 for atopic dermatitis; IL-2RA, PTPN22 CCR6, and ZMIZ for vitiligo; and IL-23R, IL-12B, CDKAL1, and PTPN22 for psoriasis.[22] Nevertheless, IBD shares their genetics not only with dermatological IMIDs, but also with autoimmune endocrine disorders such as type 1 diabetes mellitus (T1DM); indeed, by means of genome-wide studies, PTPN2, ORMDL3, HERC2, and genes coding for some interleukins (including IL-10, IL-26, and IL-27) have recently been associated to both IBD and T1DM.[23] Interestingly, PTGER4, STAT3, IL-2RA, IL-7R, and FCGR2A have been demonstrated to pose at risk of both IBD and multiple sclerosis (MS).[22]

However, genetics is just one of the parts of the puzzle in which cytokine dysregulation plays a key role. Indeed, we know that TNF-alpha is over expressed in the majority of IMID, while IL-10 is deficient in some other, such as IBD.[24,25] These molecules are produced by T cells, including T helper type 1 (Th1) that usually are pro-inflammatory and Th2 that usually extinguish flogistic process; indeed, the modulation of these has recently become a possible therapeutical target.[26] Also, B cells are of growing interest as their loss of tolerance and their inappropriate cytokine production may have a pivotal role in IMID pathogenesis.[27] This is why there currently are several

Table 2. Conditions associated with IBD with uncertain mechanism, IMID associated with IBD, and their mutual prevalence [modified by Hedin *et al.*[3]]

IMID	IMID prevalence in IBD	IBD prevalence in IMID
Vitiligo	–	2.2%
Psoriasis	3.6% in CD; 2.8% in UC	6.7%
Atopic dermatitis/eczema	–	27% in CD
Epidermolysis bullosa acquisita	–	25%
Cutaneous polyarteritis nodosa	–	–
Hidradenitis suppurativa	17.3% in CD; 8.5% in UC	–
Autoimmune hepatitis	4.5–16% in UC	–
Granulomatous hepatitis	1%	–
Autoimmune pancreatitis	0.4%	17–30%
Type 1 diabetes mellitus	HR 1.68 (95% CI, 1.41–2.00) in CD	–
Autoimmune thyroid diseases	–	–
Multiple sclerosis	0.2%	0.6%
Asthma	7%	–
Bronchiectasis/interstitial pneumonia	–	–

CD, Crohn's disease; HR, hazard ratio; IMID, immune-mediated inflammatory disease; UC, ulcerative colitis.

preliminary studies on the use of anti-CD-20 antibody for some IMID treatment (first of all rheumatoid arthritis), most of which with promising results.[28]

Aim of the review

The aim of this narrative review is to describe those conditions identified by Hedin *et al.*[3] as 'associated conditions with uncertain mechanism' that *de facto* belong in the vast majority to IMID (Table 2), and their association with IBD. We will focus on the rarest of these conditions, here grouped as skin diseases, hepato-pancreatic diseases, endocrine diseases, MS, and respiratory diseases. The main focus of the present paper is to summarize the epidemiological link between IBD and other IMIDs, to enforce clinician awareness on possible coexistence between IBD and other IMID.

Skin diseases

Psoriasis. Psoriasis is a chronic, painful, disfiguring, and disabling disease for which there is no cure. Psoriasis has a great negative impact on patients' quality of life. It affects the skin and nails, and is associated with inflammatory arthritis (psoriatic arthritis), which carries a risk of joint deformation and disability. Skin lesions can be localized or generalized, are usually bilateral, and are characterized by erythematous scaly patches, papules, and plaques that are often itchy and sometimes painful.[29] The disease mostly affects people between the ages of 50 and 70 years, and its prevalence varies from <1% in East Asia to around 10% in Northern Europe.[29–31]

The association between psoriasis and IBD was first reported in 1968.[32] Its prevalence in IBD patients has been found to be increasing, possibly due to the introduction of anti-TNF drugs that can induce psoriasis as a 'paradoxical reaction'.[32–35] Moreover, IBD patients may be at increased risk of psoriasis: a large case–control study found that the prevalence of IBD was higher in psoriasis patients than in age- and sex-matched controls [odds ratio (OR), 2.49 for CD and 1.64 for UC].[36] A recent meta-analysis showed that

the prevalence of psoriasis was 3.6% in CD and 2.8% in UC, and that the prevalence of psoriasis was 6.7% in IBD patients treated with anti-TNF agents and 3.1% in those not treated with biologics.[37]

In a Danish nationwide cohort study, a family history of psoriasis was found in almost one-quarter of IBD patients with psoriasis.[38] The risk of IBD development in patients with psoriasis was higher in females than in males and in people younger than 30 years.[38] As for phenotype, a mild form of psoriasis is more frequent than the plaque-type form.[39,40] The clinical course of CD in patients with concomitant psoriasis was reported to be more severe than in those without.[3] Interestingly, as the severity of psoriasis increases, so does the risk of IBD development (both CD and UC).[37]

It has been hypothesized that genetics is crucially involved in the pathogenesis of psoriasis, and potentially shared with some IBD genetic background.[41,42] In addition, changes in the intestinal microbiota, in particular lower levels of *Faecalibacterium prausnitzi*, have been suggested to be involved in psoriasis.[43]

The subsequent practical implication of the association and of the common pathogenesis of these two immunomediated diseases is the need of common therapy and shared follow-up between gastroenterologist and dermatologist. Given their shared inflammatory pathway, with a strong involvement of IL-23 and TNF signaling, nowadays a growing number of IBD advanced therapies are effective also for psoriasis treatment, first of all anti-TNF agents[44] and anti-p40 subunit of IL-12 and IL-23 blocking ustekinumab.[45] Hopefully, in the near future also, anti-IL-23 agents, already successfully used for psoriasis,[46] will be available for IBD treatment as well, as soon as the results of phase II and III trials will confirm their efficacy in IBD.[47] On the other hand, both dermatologist and gastroenterologist should be aware of the fact that one other class of biologic therapy, anti-IL-17, currently used for psoriasis, may induce or worsen IBD course.[48]

Atopic dermatitis. Atopic dermatitis, also known as eczema, is 'a chronic inflammatory skin disease posing a significant burden on healthcare resources and patients' quality of life'.[49] It has a wide spectrum of presentations and symptoms, including pruritus. It usually presents with patches of skin that are red or brownish, and dry, scaly, and itchy. The cheeks are typically affected in children, while in young adults and older people the disease mostly affects the knees and elbows (often in the folds of the joints), the backs of the hands, and the scalp.[49,50] The prevalence of atopic dermatitis is about 20% in children and 3% in adults.[49]

The link between atopic dermatitis and IBD (both CD and UC) is bidirectional.[22,51–55] One study found that the prevalence of atopic dermatitis was 27% in CD patients.[56] This same study reported that patients with atopic dermatitis had a lower risk of developing IBD if they were undergoing systemic steroid therapy but a higher risk if exposed to topical steroid therapy. A recent meta-analysis showed a higher prevalence of atopic dermatitis in IBD patients than in general population (OR = 1.39) and a higher prevalence of IBD in atopic dermatitis patients than in general population (OR = 1.35).[57]

A common pathogenetic background has been postulated for atopic dermatitis and IBD. A common genetic basis may impair the same inflammatory pathway involving Th cell.[40,44] Altered barrier functions and altered microbiota may trigger inflammatory processes.[41,42]

Despite the possible common pathogenetic pathway, at the moment the only pharmacological class that can be used in both IBD (UC) and atopic dermatitis are anti-JAK, particularly tofacitinib.[58] Subsequently, the treatment of patients with both these disease is still challenging and in need of new shared therapeutical options.

Vitiligo. Vitiligo is a skin disorder characterized by depigmentation, caused by a melanocyte dysfunction and their subsequent destruction on a multifactorial basis. Markers of active, progressive disease are 'Koebner's phenomenon' (vitiligo after minor mechanical trauma), trichrome lesions, inflammatory lesions, and confetti-like depigmentation. The estimated prevalence varies from 0.5% to 2% in the general population.[59–62]

An association between IBD and vitiligo has been known for a long time.[62] A retrospective study reported that, in patients with vitiligo, the prevalence of any autoimmune disease was 23% while that of IBD was 2.2%.[63] In a successive cross-sectional study, these rates were 20% and 0.9%.[64]

As said before, this high frequency of IBD among vitiligo probands suggests that the two diseases share some genetic susceptibility factors.[63,64]

Epidermolysis bullosa acquisita. Epidermolysis bullosa acquisita (EBA) is an acquired, chronic, heterogeneous bullous disease of the skin and mucous membranes.[65] It is characterized by subepidermal blisters and immunoglobulin (Ig)G autoantibodies directed against type VII collagen of the skin epidermal junctions.[66] In the classic form, EBA lesions mostly affect areas subjected to repeated minor trauma, such as elbows, knees, buttocks. In the inflammatory form, bullae are within inflammatory plaques and may be in the flexures, where they resemble bullous pemphigoid, and on mucosae, presenting also blisters, erosions, and scarring.[65,67] In about a fifth of patients, EBA is associated with another IMID.[65,66]

This dermatological disease is a very rare condition, with an estimated prevalence of 0.2 per million people.[68] More than a quarter of EBA patients also have IBD; frequently, they are males and have CD.[69] Typical localizations of EBA in CD patients are esophageal, peristomal, cutaneous, and corneal.[54,56,58,70] This clinical entity can be treated with colchicines, Igs, and anti-TNF agents while steroids should be avoided.[65,67] Clinicians should be able to detect it as soon as possible, to provide an effective treatment.

Although a shared therapy for IBD and this rare dermatological condition has still not been formalized, some cases of EBA responding to ustekinumab have been reported, suggesting the possible use of this therapy for the management of these difficult patients.[71]

Cutaneous polyarteritis nodosa. Cutaneous polyarteritis nodosa (CPAN) is a rare, limited form of polyarteritis nodosa, which causes necrosis of the arteries and complications such as hypertension, coronary artery disease, kidney failure, and gastrointestinal vascular disease.[72,73] CPAN affects the skin and sometimes the muscles and joints; it is often associated with systemic comorbidities.[73,74] Several cases of CPAN with IBD, mostly CD, have been reported, often with ulcerative skin manifestations.[75–77] CPAN may evolve to the systemic form, polyarteritis nodosa.[78] For this reason, a prompt diagnosis in IBD patients is crucial.

Hidradenitis suppurativa. Hidradenitis suppurativa (HS), also called 'acne inversa', is a chronic inflammatory skin disease with recurrent manifestations. It involves the follicular epithelium, often secondary to bacterial infection of skin areas subject to repetitive mechanical stress, in genetically susceptible individuals.[79,80] HS typically presents with inflammatory nodules, abscesses, comedones, fistulous tracts, and scars. It can also generate large, painful abscesses with purulent secretions. HS is most commonly seen in intertriginous skin, armpits, perineum, and sub-mammalian or inguinal folds.[79,80] As the disease progresses, it becomes disabling. Complications are painful and include local scarring, limited mobility of the limbs, and stenosis or fistulas in the anus and urethra as a result of chronic inflammation.[79,81] Systemic complications include fever and septicemia; occasionally, the disease develops into squamous cell carcinoma.[81]

The incidence rate of HS in IBD patients was reported to be nine-fold higher than that in the general population.[82] According to a pooled analysis of four studies, the prevalence of HS was 17.3% in CD and 8.5% in UC patients.[83] A meta-analysis of case–control and cross-sectional studies found significant associations between HS and both CD (OR = 2.12) and UC (OR = 1.51).[84]

Despite the clear bidirectional epidemiological association between the two diseases, the pathogenic mechanisms are not yet clear. IBD and HS are both multifactorial conditions caused by an abnormal immune response to microorganisms and intestinal dysbiosis, and for both there is a possible genetic predisposition.[42,85] Moreover, both diseases have been associated with smoking.[86]

Nevertheless, one of the rare but still challenging localization of HS is perianal disease, which may be difficult to differentiate from perianal CD, often leading to challenging therapeutic choices.[87]

As for psoriasis, HS does not only share genetic background and pathogenetic pattern with IBD, but they also have possible common therapies, including anti-TNF agents.[88]

Hepato-pancreatic diseases

Abnormal liver and pancreatic test results are observed in about one-third of IBD patients.[89]

The abnormal results may be attributable to therapy or be an expression of underlying disease. Therefore, they deserve an accurate diagnostic workup including laboratory tests for autoantibodies and Igs, diagnostic imaging, and tissue biopsy, to permit an early diagnosis and appropriate management.[2]

Autoimmune hepatitis. Autoimmune hepatitis (AIH) is defined as a 'non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression'.[90] The diagnosis of AIH is based on a score that considers the coexistence of some serological markers and requires a liver biopsy for histological characterization for confirmation.[90,91] Type 1 and type 2 AIH are distinguished according to the presence of specific autoantibodies. Anti-neutrophil cytoplasmic antibodies are frequently found in type 1 AIH; these antibodies are also associated with both IBD and PSC.[91]

AIH patients may also exhibit features of primary biliary cholangitis or PSC. Distinctive clinical, histologic, and serologic features for these overlap syndromes are lacking.[92–94] The most common overlap syndrome in IBD patients is AIH with PSC.[89,95–97]

Many reports about the relationship between IBD and AIH have been published since the 1980s, mainly as an overlap syndrome with PSC in adults or with autoimmune sclerosing cholangitis in children.[89,93,94,98] Over time, there have also been numerous reports of cases of AIH associated with IBD without concomitant PSC.[96,99–101] The prevalence of IBD, mainly UC, in AIH patients has been estimated at 4.5%[97] and 16%.[102] The prevalence of AIH in UC patients has been estimated to be around 0.3%.[96,103]

The impact of AIH on IBD clinical course is not clearly defined. Some authors suggested that IBD patients with concomitant AIH have a more refractory form of disease and a higher need for proctocolectomy in UC.[95,100,104] AIH has been reported in some IBD patients treated with infliximab.[100] On the other hand, IBD course may be improved through liver transplantation in patients with PSC in an overlap syndrome.[105]

In addition to that, recently, azathioprine has been proposed as an effective first-line therapy for AIH,[106] and this should be kept in mind by clinicians when managing patients with both IBD and AIH.

Granulomatous hepatitis. Granulomatous hepatitis is a liver disease characterized by the presence of granulomas with various etiologies: inflammatory, autoimmune, infectious, and drug induced. The clinical spectrum is variable, ranging from completely asymptomatic to abdominal pain, fever, and lymphadenopathy with signs of liver dysfunction.[107,108] Granulomatous hepatitis has been observed in around 1% of IBD patients, mainly in CD patients.[109] An association with mesalamine and methotrexate has been suggested.[110,111]

Autoimmune pancreatitis. Autoimmune pancreatitis (AIP) presents in two forms, AIP-1 and AIP-2, that differ in symptoms (fluctuating asymptomatic jaundice *versus* more manifest symptoms, mainly gastrointestinal), high serum IgG4 (observed in up to 40% of cases with AIP-1, but in <10% of cases of AIP-2), and presence of extrapancreatic manifestations (more frequent in AIP-2).[112] AIP-1 is histologically defined as lymphoplasmacytic sclerosing pancreatitis, while AIP-2 is also called idiopathic duct-centric pancreatitis or AIP with granulocyte epithelial lesions.[113,114] These two forms of pancreatitis are diagnosed on the basis of International Consensus Diagnostic Criteria.[112] To this end, the diagnostic workup includes an analysis of the pancreatic parenchyma through computed tomography or magnetic resonance, examination of pancreatic duct morphology through endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography, serology (IgG4 concentration), histological characterization, and assessment of other organ involvement and response to steroid therapy.

An association between pancreatic damage and IBD was first reported in 1950 and 1961.[115,116] AIP is rare in the IBD population[117,118] but more frequent than in the general population (prevalence, around 0.4% *versus* 0.1%).[114,119–121] On the contrary, IBD appears to be present at 17%[122] and in around 30% of AIP patients, especially with AIP-2.[105] The association of AIP with UC has been reported to be stronger than with CD.[117,119] A French multicenter study found that IBD patients with AIP have higher rates of colectomy than IBD patients without AIP.[123] On the

contrary, a recent study showed that in AIP-2 patients, the concomitant UC is characterized by a mild course and a low rate of colectomy.[122]

It has been hypothesized that the etiopathogenic link between IBD and AIP resides in the abnormal immune response of epithelial colonic and pancreatic cells to shared antigenic structures, leading to a cross-reaction with endogenous antigens.[124,125] The similar histological features of AIP and UC are further evidence of a common pathogenesis.[117]

Endocrine diseases

Autoimmune thyroid diseases. Hashimoto thyroiditis and Graves' disease are the main forms of autoimmune thyroid diseases.[126] They are associated with autoantibodies directed against thyroid structures, which cause hypothyroidism and thyrotoxicosis.[127,128]

The first report of an association between IBD and autoimmune thyroid diseases was published in 1962.[129] Since then, numerous case reports and retrospective studies have suggested the existence of an epidemiological link between these clinical conditions, even in association with other autoimmune diseases.[130–134] Other reports showed that female IBD patients have a higher risk of Graves' disease than the general population, while the risk of developing Hashimoto thyroiditis was not higher in the IBD population.[135]

Type 1 diabetes mellitus. T1DM is an autoimmune disorder caused by the destruction of pancreatic beta cells that typically begins in childhood.[136] Both genetic factors and environmental factors play important roles in the development of T1DM.[137,138]

T1DM and IBD share an immune-mediated pathogenesis with genetic variants predisposing to alterations of the immune system.[23] Several studies reported an association between these two diseases. A study from Korea reported a higher risk of T1DM in CD patients than in non-IBD controls.[139] A study from Israel found a higher risk of T1DM in UC patients than in non-IBD controls.[134] However, a recent meta-analysis found no significant association between IBD and T1DM, but suggested that IBD patients from certain geographical areas may have a higher risk of developing T1DM than controls.[140]

Neurological diseases

Multiple sclerosis. MS and its ophthalmic manifestation, optic neuritis, are multifactorial demyelinating diseases of the central nervous system caused by an attack on oligodendrocytes by the immune system.[141] Destruction of oligodendrocytes progressively leads to a deficit in myelin production. The clinical picture is extremely variable. Diagnostic criteria include clinical signs and typical features at magnetic resonance imaging; additional diagnostic tests include evoked potential evaluation and spinal fluid sampling for the assay of specific oligoclonal bands.[142]

The first report of an association between IBD and MS was published in 1982[143] and successively confirmed by several studies (reviewed in Kosmidou *et al.*[144]). According to a recent meta-analysis of 17 studies, the prevalence of MS in IBD patients is 0.2% while the prevalence of IBD in MS patients is 0.6%.[145] The same meta-analysis showed that IBD patients have a significantly higher prevalence of MS than controls [relative risk (RR), 1.91] and that MS patients have a significantly higher prevalence of IBD than controls (RR = 1.53).[145] The association was reported to be higher for women, with no significant difference between CD and UC patients.[8,146–148]

Immunologic studies have demonstrated that Th17 cells are involved in both MS and IBD (reviewed in Maddur *et al.*[149]). These cells produce IL-17 and IL-22, which promote inflammation. High levels of IL-17 were detected in both MS patients and IBD patients,[150,151] supporting a pathogenic role of Th17 cells. In MS, the activation of Th17 cells is thought to promote central nervous system inflammation and degeneration.

In clinical practice, the management of patients with both demyelinating diseases and IBD can be challenging, because anti-TNF agents are known to worsen or even induce demyelination and should be avoided in these patients.[148,152,153] On the other hand, the only advanced therapy that may have a role in both diseases is the class of the sphingosine-1 receptor modulator, which are still on study for IBD.[154] Thus, to date, given the harmless nature of vedolizumab on demyelinating diseases, a possible option is to treat IBD with this drug and MS with a separate target therapy, if needed.[155]

Another particular clinical picture is that of the so-called 'radiologically isolated MS', that is

considered to be the prodromic stage of evolving MS by most of the authors. In this case, a strict follow-up of the patient by both gastroenterologist and neurologist is mandatory, as theoretically anti-TNF therapy may have a deleterious effect, as for MS.[156,157]

Respiratory diseases

Asthma. Asthma is a chronic respiratory disease characterized by recurrent attacks of breathlessness and wheezing, with variable clinical severity and temporal frequency.[158] Symptoms often worsen during physical activity and sleeping. Asthma has a multifactor etiology related to allergy toward several agents.[159]

According to a study from the United States, asthma was the most common IMID associated with CD and UC.[8] However, a population-based case–control study found that the risk of IBD in people with asthma was similar to that in non-asthmatic individuals.[160] Subsequently, a study from Spain reported that prevalence of asthma in the IBD population was around 7%, similar to that in the general population.[161]

Bronchiectasis. Predisposing factors for the onset of bronchiectasis include IBD, rheumatological diseases, pulmonary disease, and systemic causes (e.g. primary ciliary dyskinesia, allergic bronchopulmonary conditions, and alpha-1-antitrypsin deficiency).[162] Data on a potential association between IBD and bronchiectasis come from one case series and one case report.[163,164] Some authors suggested a potential causative role of surgery[165] and mesalamine.[166]

Interstitial pneumonia. The prevalence of interstitial pneumonia in the IBD population is unknown. A recent retrospective study identified 31 patients with interstitial pneumonia at 14 European IBD centers.[167] In most of these cases, the respiratory symptoms were related to IBD therapy. Drugs associated with interstitial pneumonia in IBD patients include mesalamine (in a single case report[168]), methotrexate,[169] and the anti-TNF agent adalimumab.[170]

Discussion

Numerous IMIDs have been observed in patients with IBD. IMIDs often have a chronic, progressively worsening course, requiring specific therapies and interventions. They also cause psychological distress and significant morbidity and have a negative impact on patients' quality of life. Therefore, a prompt, correct diagnosis is necessary to reduce their heavy healthcare and economic burdens. An early diagnosis is even more important when the risk of developing an IMID is higher, such as in IBD patients.

This review looked at the less frequent, less understood associations between IBD and IMIDs, as suggested by Hedin *et al.*[3] IBD patients have an ascertained increased risk of developing some IMIDs, namely psoriasis, atopic dermatitis, HS, AIP, and MS. For IBD patients with psoriasis or atopic dermatitis, the clinical course of IBD is worse. For the other IMIDs discussed here, information on the risk in IBD patients is lacking because of the rarity of such diseases, the lack of adequately powered studies, and possibly the absence of a real association with IBD.

An early diagnosis is pivotal for reducing the progressively deleterious course of both IBD and the associated IMID. Therefore, medical specialists, including gastroenterologists, should be able to recognize the signs and symptoms of IMIDs that require specialist evaluations.

However, the previously described IMIDs are rare disease and, although more prevalent in the IBD population, a formal screening program for each patient at the time of IBD diagnosis would probably not be cost-effective, even though active anamnestic screening should be encouraged. In addition, clinicians should keep in mind that, due to different genetical and environmental background, different IMID have different geographic distribution, as previously discussed for T1DM.[140]

On the other hand, all clinicians dealing with IBD should be familiar with the onset of IMIDs as side effects of some therapies (e.g. anti-TNF agents can induce psoriasis and MS). This knowledge will help reduce the number of unnecessary specialist evaluations. Recently, a consensus between gastroenterologists and rheumatologists identified several signs and symptoms ('red flags') for the prompt, correct mutual referral for specialist examinations, to facilitate an early diagnosis of coexisting IBD and spondylarthropathy.[171]

Further collaborations between different disciplines are needed and should be encouraged.

Patients who have several concomitant IMIDs need multispecialist care. Their clinicians should define a single therapeutic strategy considering the overall characteristics and needs of each patient; each IMID should not be treated separately. This multidisciplinary approach can help avoid diagnostic delays, choose the correct therapies (type and duration), prevent complications, and improve both clinical outcomes and quality of life. However, the insufficient knowledge of the epidemiology of the IMIDs reviewed here limits our ability to recognize the patterns of co-occurrence of these diseases, to assess a patient's overall disease burden, and to provide an effective treatment. Further large, high-quality studies are needed to better clarify the associations between IBD and these rare IMIDs, mainly for those where robust evidence is still lacking.

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Author contribution(s)
Cristina Bezzio: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

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Simone Saibeni: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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