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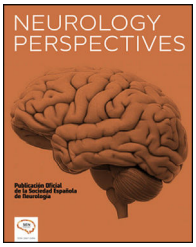

REVIEW

Inflammatory bowel disease and multiple sclerosis

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Abstract
Introduction: Inflammatory bowel disease (IBD), which mainly includes Crohn's disease and ulcerative colitis, is characterised by chronic inflammation in the gastrointestinal tract, triggered and perpetuated by an altered immune response. An association has been established between this condition and other autoimmune diseases, including multiple sclerosis (MS). The prevalence of MS in patients with IBD is 0.2%; the association between the 2 conditions is attributed to shared genetic and environmental pathogenic mechanisms.
Development: In patients presenting with both diseases, several considerations should be taken into account when selecting the most appropriate treatment. Regarding MS treatment, interferons have been associated with worsening of IBD symptoms, whereas such monoclonal antibodies as rituximab and ocrelizumab may cause gastrointestinal toxicity, and alemtuzumab is not recommended due to increased risk of autoimmune complications. Natalizumab and sphingosine 1-phosphate modulators, such as ozanimod, constitute safer and more effective options for patients with IBD.
Regarding treatments for IBD, TNF-α antagonists are contraindicated in patients with MS due to the associated risk of central nervous system demyelination. Vedolizumab and ustekinumab are the recommended alternatives in these cases.
Conclusions: Though weak, the association between IBD and MS should be acknowledged; preferably, management of these patients should include medications that treat both conditions simultaneously.

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PALABRAS CLAVE
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Enfermedad inflamatoria intestinal y esclerosis múltiple

Resumen
Introducción: La enfermedad inflamatoria intestinal (EII), que incluye principalmente la enfermedad de Crohn y la colitis ulcerosa, se caracteriza por producir una inflamación crónica en el tracto gastrointestinal, que se inicia y perpetua por alteraciones en la respuesta inmunitaria. Existe una asociación entre esta patología y otras enfermedades autoinmunes, entre ellas la esclerosis múltiple (EM). La prevalencia de EM en pacientes con EII es del 0,2%, atribuyendo esta relación a diferentes mecanismos patogénicos comunes, tanto genéticos como ambientales.
Desarrollo: En pacientes con coexistencia de ambas entidades deben tenerse en cuenta diferentes consideraciones en la elección del tratamiento. En relación a los fármacos empleados en la EM el uso de interferones se ha asociado con empeoramiento de síntomas en la EII, anticuerpos monoclonales como rituximab u ocrelizumab podrían causar toxicidad gastrointestinal y alemtuzumab no se recomienda por el riesgo de inducir fenómenos de autoinmunidad. Natalizumab y fármacos moduladores del receptor de esfingosina 1 fosfato como ozanimod, serían opciones de tratamiento más seguras y eficaces en pacientes con EII. Con respecto a los tratamientos empleados en la EII los antagonistas del factor de necrosis tumoral alfa están contraindicados en pacientes con EM, por su asociación con la aparición de lesiones desmielinizantes del sistema nervioso central. En este caso son recomendables fármacos como vedolizumab y ustekinumab.
Conclusiones: Aunque la asociación entre ambas patologías es baja, es importante conocerla, siendo preferible elegir un tratamiento que permita una terapia común para ambas patologías.

Inflammatory bowel disease (IBD) encompasses a group of chronic diseases of the digestive system, with the most relevant being Crohn's disease (CD) and ulcerative colitis (UC).[1]

CD and UC are heterogeneous diseases of unknown aetiology that present in the form of relapses. Alterations in the innate and adaptive immune response play a crucial role in triggering and perpetuating gastrointestinal tract inflammation.[1] These conditions differ in terms of the location of inflammation in the gastrointestinal tract: in CD, inflammation is segmental and transmural, affecting the whole digestive system, whereas in UC, it is continuous, affects the mucosa and submucosa, and is restricted to the colon and rectum.[2]

This study reviews the association between IBD and multiple sclerosis (MS), the shared pathogenic mechanisms, and the effect of disease-modifying therapies on these entities.

Epidemiological association

The prevalence of IBD in the general population is approximately 0.3%–0.5%, and a quarter of patients with a diagnosis of IBD have another autoimmune disorder; this is particularly true in the case of women and patients with CD, compared to those with UC. Patients with IBD and concomitant autoimmune diseases are reported to present poorer clinical prognosis and outcomes, more aggressive phenotypes, and higher rates of surgery.[1]

MS is one of the autoimmune diseases reported in association with IBD. The association between the 2 conditions is bidirectional: the risk of IBD is higher among patients with MS than in the general population, and vice versa.[3–6] A recent meta-analysis of 17 studies reports an MS prevalence rate of 0.2% in patients with IBD, whereas the prevalence of IBD in patients with MS is 0.6%.[3] Other studies report IBD prevalence rates at the time of MS diagnosis ranging from 0.1% to 1.6%.[3,7] Regarding MS in the context of IBD, no differences have been observed between patients with CD and those with UC.[7,8] Notably, patients with IBD have been reported to display higher rates of white matter hyperintensities on routine MRI studies. Although the aetiology of these lesions is unknown, ischaemia and/or vasculitis have been proposed as potential causes.[9]

Shared pathogenic mechanisms

The association between MS and IBD is thought to be linked to overlapping autoimmune pathogenic mechanisms and common environmental and genetic risk factors.

Environmental factors associated with both conditions include smoking, vitamin D deficiency, and exposure to cold weather.[3,7] Regarding genetic susceptibility, genome-wide association studies of MS and IBD (UC and CD) have identified different risk variants for each condition, including certain shared loci, such as *IL7R* and *IL2RA*.[10] Furthermore, 3 single-nucleotide polymorphisms have been identified in both MS and IBD: rs13428812, rs116555563, and rs9977672.[11] These

findings suggest a shared genetic predisposition for both conditions, although the extent of this overlap remains poorly understood.[10]

Molecular immunological studies have recently shown that Th17 cells, which produce IL-17 and IL-22 and promote tissue inflammation, are involved in the pathogenesis of both entities. This hypothesis is supported by the fact that both MS and IBD are associated with high IL-17 levels, which points to an immunological link between the 2 diseases.[1,7]

Lastly, with regard to the potential immunological overlap, we should consider the well-known interaction between the digestive and nervous systems. Gastrointestinal inflammation plays a major role in the pathophysiology of IBD, leading to increased intestinal barrier permeability and transmucosal passage of harmful or immunogenic antigens, which further perpetuates neuroimmune dysregulation.[5] For instance, an association has been described between the severity of experimental autoimmune encephalomyelitis (EAE; an animal model of MS) and the degree of alteration in intestinal permeability.[3] Furthermore, recent studies have shown that the gut microbiota, which plays a key role in maintaining the homeostasis of the intestinal barrier (a structure that is crucial to the regulation of neuroinflammation, according to different animal studies,[3] and that has been found to be altered in IBD), may also play a role in MS pathophysiology. In fact, alterations in the gut microbiome have been described in patients with MS.[9]

Treatment considerations

In clinical practice, the presence of autoimmune comorbidities in both IBD and MS has an impact on treatment decision-making, as some drugs may exacerbate pre-existing autoimmune disorders or trigger their onset.[6] Therefore, selection of an appropriate treatment is essential in patients with overlapping autoimmune diseases.

Therapeutic considerations in multiple sclerosis

In the case of MS, several commonly used disease-modifying drugs may exacerbate IBD.

Interferons are immunostimulants that may unmask silent autoimmune processes or induce the appearance of other such processes. In MS, it has been suggested that interferons have an indirect protective effect by reinforcing the blood–brain barrier and preventing the passage of inflammatory cells or cytokines, whereas in other Th17-mediated diseases, these drugs present proinflammatory effects.[11] Therefore, their use in patients with MS and overlapping autoimmune diseases is not recommended. More specifically, treatment with interferon β-1a has been associated with worsening of IBD symptoms.[3]

Among the **anti-CD20 monoclonal antibodies** used in MS (ocrelizumab, ofatumumab, and rituximab), only rituximab has been specifically evaluated for the treatment of IBD, in patients with UC.[12] A placebo-controlled trial of rituximab[13] including patients with UC refractory to corticosteroid therapy demonstrated a short-term response, which was not sustained, without significant effects on remission rates. Furthermore, it should be borne in mind that these drugs may alter gastrointestinal homeostasis, increasing the risk of IBD.[6,12] Evidence of this association is reported in case series, suggesting that treatment with rituximab and ocrelizumab may not only exacerbate existing IBD but also

Table 1 Proposed diagnostic criteria for CD20-induced colitis.

Proposed diagnostic criteria for de novo CD20-induced inflammatory bowel disease.		
Major criteria	**Minor criteria**	**Absence of other possible aetiologies**
Exposure to an **anti-CD20 drug** in the past year	Elevation of acute inflammation biomarkers in laboratory tests (CRP, ESR, lymphocytosis)	Normal neutrophil count
Compatible symptoms that may include fever, abdominal pain, watery or mucoid-bloody diarrhoea	Compatible endoscopic findings: mucosal erythema with oedema and patchy ulcers/erosions with predominant involvement of the ileum and proximal colon. Tendency to spare stomach and duodenum	Absence of infectious causes: CMV, *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, *C. difficile*
CD20+ cell depletion in gastrointestinal biopsy	Chronic active inflammation with cryptitis, goblet cell reduction, and superficial ulcers with areas of spared mucosa	Absence of other comorbidities that could explain the pathology
Lymphoplasmacytic infiltrate (CD3+ T cells and CD79+ plasma cells) in the lamina propria	Good response to glucocorticoid therapy	Absence of other drugs/toxic substances that could explain the pathology
Clinical/endoscopic **recovery after drug withdrawal** and CD20+ cell recovery in intestinal mucosa		

CMV: cytomegalovirus; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.
Source: Quesada-Simó A, Garrido-Marín A, Nos P, Gil-Perotín S. Impact of anti-CD20 therapies on the immune homeostasis of gastrointestinal mucosa and their relationship with de novo intestinal bowel disease in multiple sclerosis: a review. Front Pharmacol. 2023 May 30;14:1186016.

induce direct gastrointestinal toxicity in the form of de novo CD or UC.[12]

Among the reported cases, rituximab is the drug most frequently associated with IBD, although it should be noted that it is widely used for the treatment of multiple diseases. This effect was described in an Icelandic cohort of patients treated with rituximab between 2001 and 2018 (27% of whom had a diagnosis of MS), who displayed an increased risk of IBD compared to the general population (hazard ratio of 6.6).[14] The authors of the study suggest a protective role of CD20 B cells in the gastrointestinal tract, whose depletion leads to the development of IBD. CD20 B cells have 3 main functions in gut-associated lymphoid tissue: regulating CD4 T cells, promoting apoptotic cell clearance in the gastrointestinal tract, and controlling the amount of circulating autoantigens that may contribute to autoimmunity.[14] CD20 B cell depletion in the intestinal mucosa has also been observed in biopsied tissue from patients treated with ocrelizumab. In both cases, this finding seems to be reversible upon discontinuation of the drug, with a median recovery time of 72 weeks for ocrelizumab.[12]

Table 1 presents the recently proposed criteria for the diagnosis of anti-CD20–induced colitis; however, other causes must be ruled out, and this entity should be considered a diagnosis of exclusion.[12] This diagnostic possibility must be considered in order to discontinue the drug and replace it with a therapy with a dual effect to treat both conditions.[12]

Alemtuzumab, a humanised anti-CD52 monoclonal antibody that induces rapid depletion of B and T cells, is also not recommended in patients with concomitant autoimmune processes.[6] The increased risk of autoimmune complications in patients treated with this drug seems to be linked to a B/T cell imbalance during immune reconstitution.[6] Furthermore, in relation to IBD, alemtuzumab may alter the gut microbiome, leading to harmful effects for the integrity of the intestinal barrier.[3]

In the light of this, these patients should avoid the above-mentioned drugs. Natalizumab and sphingosine 1-phosphate modulators constitute safer options.

Natalizumab is an anti–integrin α4 monoclonal antibody that inhibits the adhesion and migration of leukocytes across the blood–brain barrier and the intestinal barrier, where integrin α4 plays an essential role in leukocyte recruitment to the intestinal tissue in IBD.[6] A recent systematic review[15] found that natalizumab, dosed at 300 mg or 3 mg/kg every 4 weeks, effectively induces and maintains remission in patients with moderate-to-severe CD. Treatment benefits were evident both in the short (first infusion) and the long term (after $\geq$3 infusions), with a trend toward greater clinical benefit with additional infusions of natalizumab. None of the studies included in the review reported rare adverse events, such as progressive multifocal leukoencephalopathy (PML). Due to its association with PML and the availability of other treatment alternatives for CD, natalizumab is not currently recommended as the first option. However, it may be considered in selected cases, after careful evaluation of the potential risk of PML.[15]

Sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, ozanimod, and ponesimod) prevent the release of lymphocytes from lymphoid organs by binding to the sphingosine 1-phosphate receptor, thereby decreasing the number of circulating lymphocytes and preventing their migration to the CNS or intestinal tissue. These drugs have been found to be potentially useful in animal models of IBD, although their efficacy is still being explored in clinical trials.[6,12] Ozanimod is the only drug from this group that has been approved for the treatment of UC, with recent clinical

Table 2 Disease-modifying drugs for multiple sclerosis used in inflammatory bowel disease.

	Multiple sclerosis	Inflammatory bowel disease
Interferon β-1a	Indicated in active MS (relapsing–remitting and secondary progressive forms) and clinically isolated syndrome	May worsen symptoms of IBD
Natalizumab	Indicated in highly active RRMS	Effective for inducing and maintaining remission in moderate-to-severe CD Approved for CD by the FDA, but not the EMA
Sphingosine 1-phosphate receptor modulators	- **Fingolimod**: indicated in highly active RRMS - **Siponimod**: indicated in SPMS with active disease - **Ozanimod**: indicated in active RRMS - **Ponesimod**: indicated in active RRMS	- **Ozanimod** is the only drug approved for IBD. It has been proven to be safe and efficacious in moderate-to-severe UC.
Anti-CD20 monoclonal antibodies	- **Ocrelizumab:** indicated in active RRMS and early PPMS - **Ofatumumab:** indicated in active RRMS - **Rituximab:** off-label use for RRMS	Rituximab and ocrelizumab may exacerbate IBD and/or cause direct gastrointestinal toxicity (CD20-induced colitis). Rituximab has not been shown to be more effective than placebo for IBD.
Alemtuzumab	Indicated in highly active RRMS	Not recommended in IBD due to the risk of autoimmunity May alter gut microbiome

CD: Crohn disease; EMA: European Medicines Agency; FDA: Food and Drug Administration; IBD: inflammatory bowel disease; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; UC: ulcerative colitis.

trials[16] demonstrating its safety and efficacy in these patients; it may also represent a treatment option in patients with concomitant active MS. Several placebo-controlled clinical trials of ozanimod in patients with CD are currently underway.[17]

Table 2 summarises the available evidence on disease-modifying treatments for MS with data on IBD.

Treatment considerations in inflammatory bowel disease

One key characteristic of IBD is intestinal perfusion disruption, which involves several cytokines, including tumour necrosis factor-α (TNF-α).[5] As a result, **TNF-α inhibitors** (a class of IgG1 monoclonal antibodies) have emerged as effective treatments for IBD.

These drugs are known to induce or worsen demyelinating processes and are contraindicated in MS: several cases have been reported of demyelinating inflammatory lesions in the central nervous system (CNS) of patients treated with anti–TNF-α agents (infliximab, adalimumab, etanercept). The literature includes reports of optic neuritis and transverse myelitis, as well as MS and neuromyelitis optica spectrum disorder[7,18]; onset of the CNS inflammatory event was reported within 12 months of treatment in up to 90% of cases.[18]

More specifically, the association between MS and anti–TNF-α agents was first described in a randomised, placebo-controlled clinical trial of lenercept in patients with MS; the trial had to be terminated prematurely due to an increase in relapses and radiological activity in the treatment group.[19] A recent study[5] reported a 43% higher incidence of MS in patients with IBD treated with anti–TNF-α agents compared to those not exposed to these drugs (0.099 vs 0.061 cases per 1000 person-years, respectively); however, the difference was not statistically significant. Furthermore, these agents are suspected to accelerate progression to MS in patients with radiologically isolated syndrome (RIS).[3]

In the Spanish registry of biological agents in autoimmune diseases (BIOGEAS), CNS demyelinating events were the most frequently reported immunological processes, with the main trigger factor being treatment with anti–TNF-α agents. In most cases, neurological improvement is described after discontinuation of the drug.[5]

Several mechanisms have been proposed to explain the paradoxical development of CNS inflammatory events following exposure to anti–TNF-α drugs, considering the critical role this cytokine plays in immune regulation and immune cell proliferation.[7,18] Firstly, immune dysregulation would result from inhibition of the apoptosis of autoreactive T cells, which could migrate to the CNS, triggering demyelination. Secondly, TNF-α inhibition may lead to paradoxical overexpression of the cytokine in other tissues; since TNF-α inhibitors cannot cross the blood–brain barrier, this would lead to an increase in TNF-α levels in the CNS. Thirdly, it has been suggested that autoimmune processes may occur as a result of TNF-α–mediated inhibition in regulatory T cell survival and proliferation. However, despite these hypotheses, it is yet to be determined whether this association indicates de novo inflammation or exacerbation of already aberrant inflammatory pathways in patients with autoimmune diseases.[18]

The immunosuppressants vedolizumab and ustekinumab, commonly used in IBD, have not been associated with CNS demyelinating events. Therefore, they are considered safe options in patients with MS and may be used to treat IBD in patients receiving medications for MS.

Vedolizumab, a humanised monoclonal antibody that binds to α4b7 integrin, prevents lymphocyte migration to the intestinal mucosa. It is an effective treatment for patients with moderate-to-severe CD and UC who do not respond to or tolerate TNF-α inhibitors.[20] Despite the limited evidence available, cases have been reported of concomitant use of vedolizumab with such anti-CD20 monoclonal antibodies as ocrelizumab in patients with MS, with no safety concerns.[12,21] As mentioned previously, if a patient receiving anti-CD20 monoclonal antibodies presents colitis, the first step in the diagnostic process is to rule out CD20-induced colitis. Once differential diagnosis is performed, and diagnosis of IBD is established, both biological agents may be used in combination in patients with concomitant MS.[12,20] However, further research is needed to optimise drug selection and better understand their long-term safety and efficacy.

It should be noted that vedolizumab may be less effective for the treatment of extraintestinal manifestations, such as erythema nodosum or episcleritis. Lastly, vedolizumab requires close monitoring due to the risk of PML.[12]

Table 3 Disease-modifying drugs for inflammatory bowel disease used in multiple sclerosis.

	Inflammatory bowel disease	Multiple sclerosis
TNF-α inhibitors	- Indicated in active moderate-to-severe CD with lack of response to conventional therapy: **infliximab**, **adalimumab** - Indicated in active moderate-to-severe UC with lack of response to conventional therapy: **infliximab**, **adalimumab**, **golimumab**	Association with inflammatory, demyelinating events involving the CNS
Vedolizumab	Indicated in active moderate-to-severe CD/UC showing poor response, loss of response, or intolerance to conventional therapy or TNF-α inhibitors	Safe in MS. Described in combination with **ocrelizumab**
Ustekinumab	Indicated in active moderate-to-severe CD/UC showing poor response, loss of response, or intolerance to conventional therapy or TNF-α inhibitors	Safe in MS. Described in combination with **ocrelizumab**

CD: Crohn disease; CNS: central nervous system; MS: multiple sclerosis; UC: ulcerative colitis.

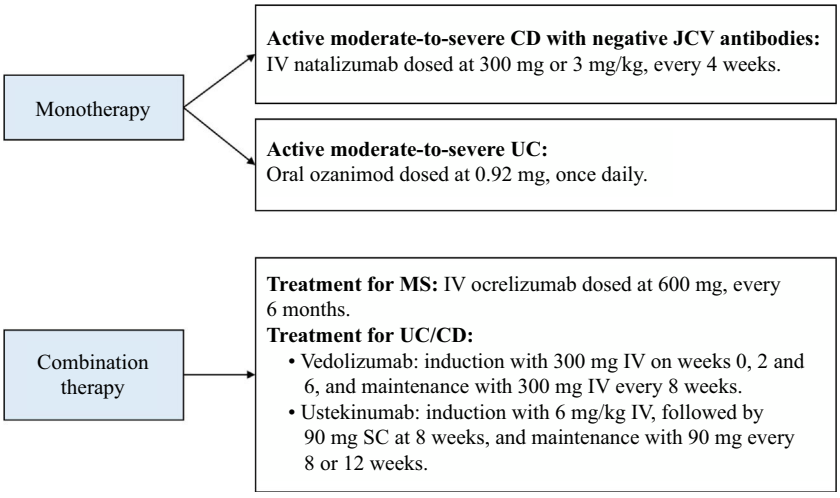

Figure 1 Proposed therapeutic algorithm for patients with inflammatory bowel disease and multiple sclerosis. CD: Crohn disease; IV: intravenous; JCV: John Cunningham virus; MS: multiple sclerosis; SC: subcutaneous; UC: ulcerative colitis.

Ustekinumab is an anti–IL-12/23 monoclonal antibody indicated for IBD, which has been found to be safe in patients with MS, according to evidence from clinical cases. It may be used in combination with ocrelizumab.[12,22] As with vedolizumab, CD20-induced colitis must be ruled out in patients receiving ocrelizumab. IL-12 and IL-23 contribute to the pathogenesis of the early stages of MS by promoting T cell differentiation and entry into the CNS. However, ustekinumab has not shown effectiveness over placebo in the treatment of MS in a phase 2 clinical trial,[23] although it does constitute a safe treatment option for IBD in these patients.

Table 3 summarises the currently available evidence on disease-modifying treatments for IBD in MS.

Therapeutic algorithm

In clinical practice, patients with multiple autoimmune diseases require multidisciplinary management, for which early diagnosis is essential.[1] Although the association between MS and IBD is not frequently reported, it does exist and must therefore be taken into consideration, especially when considering treatment selection.

Current recommendations suggest selecting a treatment with dual effects for both conditions, whenever possible.[1,12] However, the available evidence is limited, and no treatment guidelines have been published, which underscores the need for larger studies to better define the association pattern and establish treatment recommendations.

Two medications may be used to treat both conditions: natalizumab and ozanimod. Natalizumab is recommended for patients with CD who present high inflammatory activity and lack anti-JCV antibodies, whereas ozanimod is recommended for patients with moderate-to-severe UC.[12]

Another possible approach, though less frequently recommended, is the combined use of specific treatments for MS and IBD, such as ocrelizumab with vedolizumab or ustekinumab, which can be used in both CD and UC with moderate-to-severe activity. Given the potential association between anti-CD20 monoclonal antibodies and gastrointestinal toxicity, this alternative is less indicated.

The proposed therapeutic algorithm is presented in Fig. 1.

Patient informed consent

No patient data are reported.

Ethical considerations

Not applicable.

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None.

Conflicts of interest

None.

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