Chapter 12
Neurological Complications of Anti-TNF Treatments and Other Neurological Aspects of Inflammatory Bowel Disease

Su-Yin Lim and Cris S. Constantinescu

Abstract Inflammatory bowel diseases (IBD) result from dysregulated immune responses in the bowel. They are characterised by pathology mediated by immune cells with upregulated inflammatory profile. These disorders of immune regulation often coexist with other inflammatory conditions with altered immunoregulatory activities, including multiple sclerosis, rheumatoid arthritis, psoriasis, etc. Treatments targeting the pro-inflammatory cytokine, tumour necrosis factor alpha (TNFα), such as antibodies or soluble receptors, have revolutionised the management of IBD. However, paradoxically, such treatments have been associated with a risk of developing demyelinating disease, often typical multiple sclerosis. This chapter reviews the literature on the known prevalence and risk of demyelination in patients with IBD receiving TNF inhibitors, discusses potential mechanisms and also addresses the immunopathogenic, environmental and genetic commonalities of IBD and central nervous system demyelinating disease.

Keywords Autoimmunity • Biological • Comorbidity • Demyelination • Inflammatory bowel disease • Multiple sclerosis • TNF

S.-Y. Lim, MBBS, MRCP, MD
Department of Clinical Neurology, Leicester General Hospital, Leicester, UK

C.S. Constantinescu, MD, PhD (✉)
Department of Clinical Neuroscience, University of Nottingham, University Hospital, Queen's Medical Centre, Nottingham, UK
e-mail: cris.constantinescu@nottingham.ac.uk

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Introduction: Pathological Basis of TNFα in Inflammatory Bowel Disease and Multiple Sclerosis

The two main forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), share characteristic features of chronic, relapsing inflammation of the gastrointestinal tract, although they demonstrate distinct clinical and pathological features. CD most commonly affects the small intestine and colon, although any part of the GI tract can be affected. It is characterised by discontinuous or 'skip' ulcerated lesions and transmural inflammation. UC involves the colonic mucosa, usually extending to the rectum, characterised by mucosal inflammation, ulcers and crypt abscesses [1].

The exact aetiology of IBD is unknown. The development of IBD is believed to be, in part, due to genetic susceptibility and a dysregulated T-cell-mediated immunological response to enteric bacteria, along with other environmental factors [2]. TNFα has been identified as a crucial mediator in the inflammatory response in IBD, and TNF-inhibitory therapies have been effective in the treatment of both CD and UC where conventional therapy has failed [3].

TNFα is part of a large family of pleiotropic cytokines that induce signalling via two receptors, i.e. TNFRI and TNFRII. Cellular proliferation, survival, differentiation and death are mediated via complex signalling pathways, giving rise to inflammatory and immunomodulatory processes. Dysregulation of TNFα expression and of its signalling have been implicated in the pathogenesis of a variety of disorders including cancer, sepsis and autoimmune-mediated inflammatory disorders such as IBD, multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis and psoriatic arthritis (PsA). TNFα is secreted by macrophages, monocytes, lymphocytes, natural killer cells, microglia, fibroblasts, astrocytes and other immune and nonimmune cells. TNFα is expressed in response to a number of stimuli including infective antigens, tumour cells and a variety of complement and cytokines [4]. Signalling via TNFRI can induce both pro- and anti-apoptotic mechanisms via separate pathways [5], whilst activation of TNFRII is thought to enhance the actions of TNFRI and is involved in remyelination [6] and other pro-inflammatory effects [7, 8].

TNF inhibition (TNFi) is achieved by blocking TNFα activation of their receptors using a monoclonal antibody or soluble receptor. A number of TNFi agents are licensed for use in IBD – infliximab (Remicade, Merck Sharp & Dohme), adalimumab (Humira, Abbott Laboratories), certolizumab pegol (Cimzia, UCB) and golimumab (Simponi, Merck Sharp & Dohme). Infliximab, adalimumab and golimumab are monoclonal antibodies to TNFα, and certolizumab pegol is a PEGylated anti-TNFα antibody fragment.

Infliximab, adalimumab and certolizumab pegol have licensed indications in CD, whereas infliximab, adalimumab and golimumab are licensed in UC. Pivotal studies of infliximab, a chimeric monoclonal antibody to TNFα, demonstrated therapeutic efficacy in inducing and maintaining disease remission in luminal and fistulising CD [9–13] and in UC [14] compared to placebo. Adalimumab, a human monoclonal antibody, has shown comparable efficacy to infliximab in the induction of disease remission and

maintenance of remission in both CD [15–17] and UC [18], including those previously unresponsive to infliximab [19]. The newer agents, certolizumab pegol and golimumab, have both shown effectiveness in inducing and maintaining remission in CD [20] and UC [21], respectively. TNFi therapy reduces hospitalisations and surgical intervention in these patients [22]. Infliximab and adalimumab are currently recommended in the UK by the National Institute for Health and Care Excellence (NICE) for patients with severe, active CD who have not responded to or are intolerant of conventional therapy including immunosuppressive and/or corticosteroid treatment. Infliximab, adalimumab and golimumab are recommended by NICE for the treatment of moderate to severe UC in those who have failed or are unsuitable for conventional treatment.

MS is an immune-mediated inflammatory demyelinating disorder of the CNS, with a UK population prevalence of around 203 per 100,000 [23]. The disease is characterised by the appearance of demyelinating plaques disseminated in time and space. The exact aetiology of MS is uncertain and likely involves an interplay between genetic and environmental factors [24]. The immunopathogenesis of MS is shown to be mediated by autoreactive CD4+ T-cells, CD8+ T-cells, antibodies and components of the innate immune system [25].

MS and TNFα

TNFα is detected in MS lesions [26] and cerebrospinal fluid (CSF) of MS patients [27], showing a correlation with disease progression [28] and relapses [29]. TNFα contributes to oligodendrocyte damage and demyelination by signalling apoptotic pathways [30, 31], enhancing leukocyte transgression into the CNS via upregulation of endothelium-based cellular adhesion molecules at the blood–brain barrier [32] and promoting the expression of MHC I and II on neurons and glial cells which are targeted by MHC-restricted cytotoxic T-cells [33, 34]. In the animal model of MS, experimental autoimmune encephalomyelitis (EAE) administration of TNFα causes disease worsening [35]. Mice genetically engineered to overexpress TNFα developed inflammatory demyelination [36], whilst antagonism of TNFα prevented the onset of EAE [37–39].

Despite the role of TNFα in the pathogenesis of MS and its animal model, TNFα inhibition has been shown to worsen disease activity in MS patients. In an early phase I open-label study, infliximab was administrated to two MS patients with rapidly progressive disease [40]. Both patients showed an increase in contrast-enhancing MRI lesions and a corresponding rise in CSF leukocyte counts and IgG index, denoting increased disease activity. Subsequently, two MS patients with active disease were treated with lenercept, a soluble recombinant TNF receptor fusion protein, in a phase II double-blinded trial [41]. Lenercept had previously demonstrated efficacy in preventing the onset of demyelination in the animal model of MS [42]. The lenercept-treated patients showed a higher relapse rate and more severe clinical relapses compared to the placebo-treated group, leading to the cessation of TNFi use for treatment of MS.

Demyelination Associated with TNFi Therapy

There are an increasing number of reports from trial safety data, postmarketing surveillance and cases in the medical literature of the development of CNS demyelination with TNFi therapy for conditions such as IBD, RA, ankylosing spondylitis (AS), psoriasis, systemic lupus erythematosus (SLE) and vasculitis [43–58].

Deepak et al. [59] evaluated neurological adverse events with TNFi treatment (infliximab, adalimumab, certolizumab pegol and etanercept) reported to the FDA Adverse Event Reporting System (FAERS) between 1st January 2000 and 31st December 2009. 18.1 % of patients had IBD whilst the majority of patients had underlying RA (50.9 %). The most commonly reported neurological adverse event was peripheral neuropathy (38.3 %). Of the peripheral neuropathy cases, 16.6 % are composed of acute inflammatory demyelinating polyneuropathy (AIDP) and 5.1 % were chronic inflammatory demyelinating polyneuropathy (CIDP), whilst the remainder consisted of unclassified peripheral neuropathies, sensory neuropathies, motor neuropathies and sensorimotor neuropathies. CNS demyelination was the second most commonly reported neurological adverse event (19.8 %), in addition to reports of optic neuritis (ON) (13.6 %), transverse myelitis (3.4 %) and 'demyelination' where the site of disease was unspecified (3.4 %). Taking into account the temporal association, relevant reported past adverse events and plausible alternative causative factors, the majority of cases were scored as a 'possible' adverse event (71.4 %), whilst the rest were 'probable'. None met the criteria for 'definite' adverse events.

A number of cohort studies have attempted to determine whether TNFi therapy increases the risk of demyelination in IBD patients [50, 60–63]. The largest and most recent study [62] retrospectively examined a total of 9095 IBD patients (4342 with CD and 4753 with UC) across a region of North America. Median follow-up was 10.5 years. 5 of 3425 (0.15 %) patients who were exposed to TNFi treatment developed a CNS demyelinating disorder confirmed on the basis of clinical, MRI and laboratory assessment. Of these, four had an underlying diagnosis of CD and one had UC. Three of the patients with demyelination developed neurological symptoms during treatment with TNFi, one patient developed asymptomatic demyelinating lesions on MR imaging during treatment, and one patient with a past exposure to TNFi experienced progressive neurological symptoms whilst on azathioprine. Neurological symptoms either improved or resolved in two patients following discontinuation of TNFi, whereas a third patient went on to develop a relapsing–remitting demyelinating disease course. In the unexposed patients, 29 of 5670 were diagnosed with CNS demyelination, ten of which developed the condition after the onset of IBD (0.18 %). In this group, five had CD and five had UC. The relative risk of CNS demyelination with TNFi exposure in this study was 0.83 for IBD (95 % CI 0.28–2.42), 0.89 for CD (95 % CI 0.24–3.31) and 0.49 for UC (95 % CI 0.06–4.22), none of which showed statistical significance. The authors concluded that IBD patients exposed to TNFi did not appear to have a significantly increased risk of CNS demyelination over those who were not exposed to TNFi.

A retrospective cohort study by Andersen et al. [43] compared the risk of demyelinating disorders in 651 Danish IBD patients who were TNFi-treated between 1999 and 2005 to that of the general IBD population, with data gathered from four unrelated retrospective cohort studies of demyelinating diseases in IBD patients [64–67]. From the Danish cohort, four patients treated with TNFi agents were reported to develop neurological symptoms; however, only one was confirmed to have a demyelinating disorder in this case, MS – following investigations. They reported a standardised morbidity ratio of 4.2 for developing MS in the study cohort of TNFi-treated IBD patients, which was comparable to that of the general IBD population, leading the group to conclude that TNFi did not appear to significantly increase the risk of demyelination in this cohort.

In a more recent database study, Katsanos et al. [68] retrospectively reviewed cases of demyelination in patients with IBD including those who were treated with TNFi therapy, identified via MEDLINE and EMBASE. The study included 34 case reports, three case control studies [69–71] and eight cohort studies [50, 60, 61, 63–66] including one prospective study [72]. Cases of CNS demyelination are composed of MS or MS-like syndromes, acute disseminated encephalomyelitis (ADEM) and ON and demyelinating polyneuropathies such as Guillain-Barré syndrome (GBS), CIDP and MMN. The group found comparable and overlapping prevalence rates of demyelinating adverse events in TNFi-treated IBD patients compared to those who were treated with conventional therapy [mean prevalence of 0.65 % (0.2–2.5 %) and 0.48 % (range 0.41–1.2 %), respectively].

Other retrospective database studies of TNFi and demyelination in other chronic inflammatory conditions appear to support these findings. A study on the incidence of demyelination in patients with rheumatic diseases such as RA, AS and PsA treated with TNFi examined data from three pharmacovigilance sources – the Spanish registry of biological therapies in rheumatic diseases (BIOBADASER), the Spanish Pharmacovigilance Database of Adverse Drug Reactions (FEDRA) and major biomedical databases (PubMed, EMBASE and the Cochrane Library) [73]. Of 9256 patients receiving TNFi therapy for a total 21,425 patient-years, 14 patients were reported to have developed a demyelinating disease in the BIOBADASER database, including one case of MS, four of ON and one GBS. The incidence rate of demyelinating disease in this group of patients was estimated at 0.65 per 1000 patient-years (95 % CI 0.39–1.1). Nineteen cases of demyelination were reported in the FEDRA database, with some overlap of cases with BIOBADASER, of which nine had MS and seven had ON. 48 case reports from the major biomedical databases were reviewed, including ten cases of MS and 13 of ON. The authors concluded that the number of demyelination cases reported in the registry did not exceed that of the expected rate in the Spanish general population, and thus a direct link between TNFi and demyelination remains to be established.

From published care reports in the literature, the timing of onset of neurological symptoms from TNFi exposure appears wide ranging and does not always support a clear-cut temporal relationship. Reports of symptom onset varying from a few hours to up to 4 years from TNFi exposure have been described in IBD patients [68], whereas an unrelated case review of patients with inflammatory arthritides

report an interval of between 1 week and 5 months [74]. Demyelination has also been reported in patients on other forms of immunomodulation and DMARDs in the treatment of IBD, such as methotrexate, azathioprine and mercaptopurine [49, 75, 76]. Discontinuation of the TNFi tended to cause improvement or lead to resolution of neurological symptoms [47, 52, 58], whilst re-exposure to TNFi has been associated with symptom recurrence [62, 74]. However, this does not necessarily confirm an association; as MS typically runs a relapsing–remitting clinical course, acute demyelinating events often spontaneously improve or recover without specific treatment, and symptom change may reflect a response to steroid initiation or taper.

There is a lack of a clear explanation for the discordant effect of TNF inhibition in conditions such as IBD and RA compared to MS. A possible hypothesis relates to the lack of penetration by TNFi agents into the CNS via the blood–brain barrier [77] and subsequent failure of TNFα antagonism to take place locally, in contrast to the joints and bowel. In the aforementioned phase I study of infliximab in MS, the monoclonal antibody was not detected in the CSF of patients despite the presence of blood–brain barrier disruption [40]. Another theory is based on the dissemination of a latent or recently acquired infection by TNFi agents, inducing an autoimmune response [78]. A further explanation for the discordant effect of TNFi lies in the heterogeneity of the cytokine TNFα and its disparate effects. TNFα promotes remyelination and oligodendrocyte regeneration via activation of the TNFRII receptor [6], and therefore blockade of this process can cause MS worsening. TNFα-mediated apoptosis is important for the deletion of autoreactive cytotoxic T-cells, thus playing a key role in the regulation of autoimmunity [79]. Selective TNFi inhibition, particularly of the TNFRI receptor or its function, may be key to inhibiting the pro-inflammatory properties of TNFα whilst sparing its neuroprotective and immunoregulatory effects [80].

Imaging Studies in TNFi-Treated Patients

It remains unclear whether TNFi treatment unmasked pre-existing (subclinical) MS or whether it induced the onset of new demyelination in these patients. A contributing factor to this ongoing uncertainty is the lack of prospective imaging studies in this field. An early study by van der Bilj [81] examined quantitative MRI metrics (magnetisation transfer ratio [MTR], apparent diffusion coefficient and spectroscopy) before and up to 7 days after treatment with TNFi in seven patients with inflammatory arthritis (five rheumatoid arthritis and two psoriatic arthritis). Reduction in MTR correlates with demyelination, axonal loss and other inflammatory changes in MS [82]. Results showed a significant decrease in the white and grey matter MTR histogram peak height following treatment, although there were no significant changes to the other MRI metrics. The findings would support a possible diffuse CNS inflammatory process related to TNFi treatment; however, without longer term follow-up, it was not possible to ascertain if the MTR changes were transient or clinically relevant in this study.

Our own subsequent imaging study (Lim SY, et al; manuscript in preparation) quantitatively examined white matter lesions and the normal-appearing white matter (NAWM) in a cohort of 15 patients who were receiving TNFi treatment for either RA or AS and compared the findings with 11 healthy controls and seven RRMS controls, obtaining MTR and T1 relaxation times (T1RT). Like MTR, the latter has been shown to correlate with demyelination and axonal loss in MS [82]. Incidental white matter lesions were a common finding in the RA and AS patients, as well as the healthy controls. We demonstrated that white matter lesions and the normal-appearing white matter MTR and T1RT of TNFi-treated patients did not differ to that of healthy controls whilst being significantly abnormal in the RRMS patients. The findings do not support the presence of clinically asymptomatic CNS demyelination in our treatment cohort.

A recent study by Kaltsonoudis [83] prospectively followed 75 patients with RA and spondyloarthropathies treated with TNFi therapy for a mean study period of 18 months. Neurological assessment, MRI and neurophysiological testing were performed in all the patients prior to commencement of TNFi treatment. A total of 38 patients were treated with infliximab, 19 with adalimumab and 18 with etanercept. A proportion of patients remained on concomitant steroids and/or other immunomodulatory agents. Three patients reportedly developed neurological complications – the first patient developed CNS demyelination with corresponding periventricular white matter lesions, a peripheral facial nerve palsy and peroneal mononeuropathy. The second patient developed a unilateral optic neuritis, whilst the third developed a sensory-predominant peripheral neuropathy. Symptom onset ranged from 6 to 25 months from initiation of therapy. In all three cases, TNFi therapy was discontinued. The second and third patients experienced a re-emergence of symptoms shortly following re-initiation of treatment, and TNFi was permanently discontinued thereafter. Incidentally, the study also identified two patients with asymptomatic white matter lesions on MR imaging, described as a radiologically isolated syndrome, prior to commencement of TNFi therapy. This highlighted an important consideration of performing baseline imaging in those being considered for TNFi treatment.

Association Between TNFi and Other Immune Disorders

TNFi therapy has also been associated with the development of other immune disorders. The induction of clinically asymptomatic ANA and anti-dsDNA autoantibodies have been observed in 53 and 35 % of CD patients treated with infliximab, respectively [84], and cases of infliximab-induced lupus have been described [61]. Induction of anti-cardiolipin antibodies has been associated with TNFi therapy [85] which may be associated with clinical features of antiphospholipid syndrome in a significant proportion of patients [86]. Vasculitis and, in particular, cutaneous vasculitis have also been reported in association with TNFi agents [87, 88]. Other autoimmune inflammatory disorders reported in association with TNFi treatment include sarcoidosis, autoimmune hepatitis, psoriasis and myositis, amongst others [61, 87, 88]. However, like the reported associations between TNFi and demyelinating disorders,

a cause and effect association between TNFi and paradoxical induction of autoimmune diseases cannot be made conclusively, given the overall lack of controlled studies and the presence of underlying autoimmune spectrum disorders for which these patients are receiving TNFi therapy in the first place.

Association Between MS and IBD

The concomitance of MS and other immune-mediated disorders has long been recognised [69, 70, 89–97] including the finding of a higher incidence of MS amongst IBD patients prior to the use of TNFi agents [64–67, 98, 99].

IBD in MS

A prospective study [100] of 658 MS patients showed significantly increased rates of IBD, with five patients identified as having UC (0.8 %) and two with CD (0.3 %). The odds ratio for UC and CD in the MS cohort were found to be 3.15 (91 % CI 7.64–1.30) and 3.17 (95 % CI 9.95–1.01), respectively. The study also demonstrated significantly increased rates of asthma, type 1 diabetes, pernicious anaemia, autoimmune thyroid disease, uveitis and seronegative spondyloarthropathies compared to the general population. A North American study of over 5000 MS patients reported the prevalence of IBD in this cohort of 0.79 % and an odds ratio of 1.7 (95 % CI 1.2–2.5) compared to the control population [69]. The study also reported an increased risk of other immune-mediated conditions in MS patients, including uveitis, Guillain-Barre syndrome and bullous pemphigoid.

A recent systematic review and meta-analysis of autoimmune diseases in MS patients and their families [101] derived a significant odds ratio of 1.37 (95 % CI 1.12–1.69) for CD in patients with MS based on four population-based studies [100, 102–104]. They also derived an odds ratio 2.26 for UC in MS (95 % CI 1.23–4.14) from six population-base studies [76, 100, 102–105]. The overall odds ratio for IBD in MS was 1.56 (95 % CI 1.28–1.90). The relatives of patients with MS however did not appear at significant risk of IBD.

MS in IBD

A retrospective cohort study [65] of 7988 CD cases and 12185 UC cases obtained from the UK-based General Practice Research Database demonstrated a higher incidence of demyelinating disease (optic neuritis, demyelination and/or MS) in CD and UC compared to matched controls, although only the UC group showed statistical significance (incidence rate ratio 2.63; 95 % CI 1.29–5.15). The group also

conducted a cross-sectional study in the same cohort of patients, finding a significantly higher prevalence of CD (OR 1.54; 95 % CI 1.03–2.32) and UC (OR 1.75; 95 % CI 1.28–2.39) in comparison to matched controls. Echoing the findings from the retrospective cohort study above, Bernstein et al. [64] also found a significantly increased likelihood of MS in UC patients compared to controls (prevalence rate of at least 1.81; 95 % CI 1.35–2.42) amongst a cohort of 8072 IBD sufferers in Canada. In another study from North America, Kimura et al. [66] found a prevalence of MS amongst 474 newly diagnosed IBD patients between 1950 and 1995 at 3.7 times higher than that expected for the population.

The nature of the association between IBD and peripheral neuropathy, particularly demyelinating neuropathy, is less clear, probably reflecting the variations in the clinical definition of neuropathy and its wide-ranging aetiology. In a prospective study of 31 CD and 51 UC patients followed up for a period of 1 year [72], at least 13.4 % of patients were diagnosed with a cryptogenic large-fibre or small-fibre neuropathy based on clinical and/or neurophysiological assessment, including a single case of demyelinating neuropathy at the diagnosis of CD, leading the authors to conclude that IBD may be a cause of neuropathy either due to immune mechanisms or possible undiagnosed nutritional deficiencies. On the other hand, Bernstein et al. [64] reported a relatively low prevalence of peripheral neuropathy in IBD of 0.10 % in CD and 0.18 % in UC. A subsequent retrospective cohort study of 772 IBD patients [106] extending from 1940 to 2004 identified only nine cases of peripheral neuropathy, comprising either a chronic large-fibre sensory-predominant polyneuropathy or an immune radiculoplexus neuropathy, giving a relatively low cumulative incidence of 2.4 % over 30 years.

The observed co-occurrence of IBD and MS/demyelination in patients pre-dating the use of biological therapy has led to putative genetic and immunopathological associations between the two conditions. Both MS and IBD affect relatively young populations [107, 108]. They share a similar pathogenesis of dysregulated T-helper 1 (Th1) cell function, and recent studies have implicated Th17 cells, a subset of helper T-cells, in the pathogenesis of autoimmune inflammatory diseases such as MS and IBD [109]. The incidence of IBD appears to be highest amongst populations with highest rates of MS [107] and, like MS, follow a latitudinal pattern of geographical distribution [110]. Genomic variations in the major histocompatibility complex (MHC) region are known to confer susceptibility to or protection from autoimmunity including MS and IBD [111, 112]. Genome-wide association studies have identified a number of other shared gene loci conferring susceptibility to IBD as well as MS, for example, the IL2RA (alpha-subunit of IL-2 receptor) on chromosome 10p15 [113]. The hypothesis of genetic susceptibility to autoimmunity is further supported by a clustering study [90] which identified a higher than expected prevalence of IBD in patients with familial MS and their first degree relatives, noting a common variant of the CTLA4 (cytotoxic T-lymphocyte-antigen 4) gene in the families involved.

It is being increasingly postulated that the gut microflora plays an important role in the pathogenesis of systemic inflammatory diseases including MS and IBD [2, 114]. Alteration of gut flora via oral administration of antibiotics ameliorates inflammatory activity in the mouse model of MS, experimental autoimmune

encephalomyelitis (EAE) [115]. Similarly, microbe-directed treatments including faecal transplantation have shown potential in the treatment of IBD, although further study and clinical trials are warranted [116].

Vitamin D has been identified as an important modulator in the adaptive and innate immune response [117]. Vitamin D promotes T regulatory cell function [118] and regulates MHC class II gene expression [119] in MS, and its deficiency is regarded as an environmental risk factor in the development of MS [120]. Vitamin D stimulates the expression of the NOD2/CARD15/IBD1 gene, a susceptibility gene for CD [121], and its deficiency correlates with a higher risk of CD [122].

Extra-intestinal manifestations of IBD are commonly reported, potentially arising from intestinal dysfunction (e.g. nutritional deficiencies), complications from immunotherapy or other autoimmune diseases not directly linked to IBD, for example, systemic vasculitis, polymyositis and Sjogren's syndrome [123]. Neurological conditions reported in IBD patients include peripheral neuropathies, myelopathy, myopathy, myasthenia gravis and cerebrovascular disease [124, 125].

Conclusion

Despite a clear acknowledgement of the risk of demyelination with TNFi therapy, a causal association remains unconfirmed. IBD and MS share similar immunopathogenic characteristics, and the likelihood of co-occurrence may confound the risks associated with TNFi. The risk of CNS demyelination in IBD patients is estimated at over three times that of the general population [100]. However, the concerns about developing a demyelinating disorder with TNFi therapy are fully justified. It is essential that patients are counselled on the risk of demyelination prior to commencement of treatment with TNFi agents and that treatment is avoided in those with suspected or a known diagnosis or of MS.

References

1. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol. 2003;3(7):521–33.
2. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427–34.
3. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med. 2013;369(8):754–62.
4. Rossard TP. Tumor necrosis factor, vol. xii. New York: Nova Biomedical Books; 2009. p. 246.
5. Hehlgans T, Pfeffer K. The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: players, rules and the games. Immunology. 2005;115(1):1–20.
6. Arnett HA, et al. TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. Nat Neurosci. 2001;4(11):1116–22.
7. Tartaglia LA, Pennica D, Goeddel DV. Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor. J Biol Chem. 1993;268(25):18542–8.

8. Weiss T, et al. Enhancement of TNF receptor p60-mediated cytotoxicity by TNF receptor p80: requirement of the TNF receptor-associated factor-2 binding site. J Immunol. 1997;158(5):2398–404.
9. Hanauer SB, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541–9.
10. Present DH, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398–405.
11. Rutgeerts P, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology. 1999;117(4):761–9.
12. Sands BE, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004;350(9):876–85.
13. Targan SR, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997;337(15):1029–35.
14. Rutgeerts P, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
15. Colombel JF, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52–65.
16. Hanauer SB, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323–33; quiz 591.
17. Sandborn WJ, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232–9.
18. Sandborn WJ, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257–65.e1–3.
19. Afif W, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis. 2009;15(9):1302–7.
20. Schreiber S. Crohn's disease--infliximab, adalimumab and certolizumab-pegol: clinical value of anti-TNF-alpha treatment. Dtsch Med Wochenschr. 2007;132(34–35):1770–4.
21. Sandborn WJ, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96–109.e1.
22. Lichtenstein GR, et al. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology. 2005;128(4):862–9.
23. Mackenzie IS, et al. Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2013;85(1):76–84.
24. Ebers GC. Environmental factors and multiple sclerosis. Lancet Neurol. 2008;7(3):268–77.
25. Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol. 2005; 23:683–747.
26. Selmaj K, et al. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. J Clin Invest. 1991;87(3):949–54.
27. Hauser SL, et al. Cytokine accumulations in CSF of multiple sclerosis patients: frequent detection of interleukin-1 and tumor necrosis factor but not interleukin-6. Neurology. 1990;40(11):1735–9.
28. Sharief MK, Hentges R. Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis. N Engl J Med. 1991;325(7):467–72.
29. Beck J, et al. Increased production of interferon gamma and tumor necrosis factor precedes clinical manifestation in multiple sclerosis: do cytokines trigger off exacerbations? Acta Neurol Scand. 1988;78(4):318–23.
30. Selmaj K, et al. Cytokine cytotoxicity against oligodendrocytes. Apoptosis induced by lymphotoxin. J Immunol. 1991;147(5):1522–9.
31. Selmaj KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. Ann Neurol. 1988;23(4):339–46.

32. Carlos TM, et al. Vascular cell adhesion molecule-1 mediates lymphocyte adherence to cytokine-activated cultured human endothelial cells. Blood. 1990;76(5):965–70.
33. Lavi E, et al. Tumor necrosis factor induces expression of MHC class I antigens on mouse astrocytes. J Neuroimmunol. 1988;18(3):245–53.
34. Benveniste EN, Sparacio SM, Bethea JR. Tumor necrosis factor-alpha enhances interferon-gamma-mediated class II antigen expression on astrocytes. J Neuroimmunol. 1989; 25(2–3):209–19.
35. Kuroda Y, Shimamoto Y. Human tumor necrosis factor-alpha augments experimental allergic encephalomyelitis in rats. J Neuroimmunol. 1991;34(2–3):159–64.
36. Probert L, et al. Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor alpha. Proc Natl Acad Sci U S A. 1995;92(24):11294–8.
37. Baker D, et al. Control of established experimental allergic encephalomyelitis by inhibition of tumor necrosis factor (TNF) activity within the central nervous system using monoclonal antibodies and TNF receptor-immunoglobulin fusion proteins. Eur J Immunol. 1994; 24(9):2040–8.
38. Ruddle NH, et al. An antibody to lymphotoxin and tumor necrosis factor prevents transfer of experimental allergic encephalomyelitis. J Exp Med. 1990;172(4):1193–200.
39. Selmaj K, Raine CS, Cross AH. Anti-tumor necrosis factor therapy abrogates autoimmune demyelination. Ann Neurol. 1991;30(5):694–700.
40. van Oosten BW, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology. 1996;47(6):1531–4.
41. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and the University of British Columbia MS/ MRI Analysis Group. Neurology. 1999;53(3):457–65.
42. Klinkert WE, et al. TNF-alpha receptor fusion protein prevents experimental auto-immune encephalomyelitis and demyelination in Lewis rats: an overview. J Neuroimmunol. 1997;72(2):163–8.
43. Andersen NN, et al. Occurrence of demyelinating diseases after anti-TNFalpha treatment of inflammatory bowel disease: a Danish Crohn Colitis Database study. J Crohns Colitis. 2008;2(4):304–9.
44. Bouchra A, Benbouazza K, Hajjaj-Hassouni N. Guillain-Barre in a patient with ankylosing spondylitis secondary to ulcerative colitis on infliximab therapy. Clin Rheumatol. 2009;28 Suppl 1:S53–5.
45. Dubcenco E, et al. Neurological symptoms suggestive of demyelination in Crohn's disease after infliximab therapy. Eur J Gastroenterol Hepatol. 2006;18(5):565–6.
46. Enayati PJ, Papadakis KA. Association of anti-tumor necrosis factor therapy with the development of multiple sclerosis. J Clin Gastroenterol. 2005;39(4):303–6.
47. Felekis T, et al. Reversible bilateral optic neuritis after Infliximab discontinuation in a patient with Crohn's disease. J Crohns Colitis. 2009;3(3):212–4.
48. Freeman HJ, Flak B. Demyelination-like syndrome in Crohn's disease after infliximab therapy. Can J Gastroenterol. 2005;19(5):313–6.
49. Gondim FA, et al. Peripheral neuropathy in patients with inflammatory bowel disease. Brain. 2005;128(Pt 4):867–79.
50. Lees CW, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. Aliment Pharmacol Ther. 2009;29(3):286–97.
51. Lozeron P, et al. Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy. Arch Neurol. 2009;66(4):490–7.
52. Mejico LJ. Infliximab-associated retrobulbar optic neuritis. Arch Ophthalmol. 2004;122 (5):793–4.
53. Nozaki K, et al. Neurological deficits during treatment with tumor necrosis factor-alpha antagonists. Am J Med Sci. 2011;342(5):352–5.

54. Ohyagi M, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in a patient with Crohn's disease. Intern Med. 2013;52(1):125–8.
55. Ouakaa-Kchaou A, et al. Retrobulbar optic neuritis associated with infliximab in a patient with Crohn's disease. J Crohns Colitis. 2009;3(2):131–3.
56. Shin IS, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum. 2006;54(5):1429–34.
57. Solomon AJ, et al. Inflammatory neurological disease in patients treated with tumor necrosis factor alpha inhibitors. Mult Scler. 2011;17(12):1472–87.
58. Weinshenker BG, Sandborn WJ. Demyelination during anti-tumor necrosis factor alpha therapy with infliximab for Crohn's disease. Inflamm Bowel Dis. 2004;10(1):28–31.
59. Deepak P, et al. Neurological events with tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration Adverse Event Reporting System. Aliment Pharmacol Ther. 2013;38(4):388–96.
60. Caspersen S, et al. Infliximab for inflammatory bowel disease in Denmark 1999–2005: clinical outcome and follow-up evaluation of malignancy and mortality. Clin Gastroenterol Hepatol. 2008;6(11):1212–7; quiz 1176.
61. Colombel JF, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology. 2004;126(1):19–31.
62. De Felice KM, et al. Idiopathic inflammatory demyelinating disease of the central nervous system in patients with inflammatory bowel disease: retrospective analysis of 9095 patients. Aliment Pharmacol Ther. 2015;41(1):99–107.
63. Hamzaoglu H, et al. Safety of infliximab in Crohn's disease: a large single-center experience. Inflamm Bowel Dis. 2010;16(12):2109–16.
64. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology. 2005;129(3):827–36.
65. Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology. 2005;129(3):819–26.
66. Kimura K, et al. Concurrence of inflammatory bowel disease and multiple sclerosis. Mayo Clin Proc. 2000;75(8):802–6.
67. Rang EH, Brooke BN, Hermon-Taylor J. Association of ulcerative colitis with multiple sclerosis. Lancet. 1982;2(8297):555.
68. Katsanos AH, Katsanos KH. Inflammatory bowel disease and demyelination: more than just a coincidence? Expert Rev Clin Immunol. 2014;10(3):363–73.
69. Langer-Gould A, et al. Autoimmune diseases prior to the diagnosis of multiple sclerosis: a population-based case–control study. Mult Scler. 2010;16(7):855–61.
70. Marrie RA, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler. 2013;21(3):263–81.
71. Tremlett HL, et al. Asthma and multiple sclerosis: an inverse association in a case–control general practice population. QJM. 2002;95(11):753–6.
72. Oliveira GR, et al. Peripheral neuropathy and neurological disorders in an unselected Brazilian population-based cohort of IBD patients. Inflamm Bowel Dis. 2008;14(3):389–95.
73. Cruz Fernandez-Espartero M, et al. Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. Semin Arthritis Rheum. 2011;41(3):524–33.
74. Mohan N, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001;44(12):2862–9.
75. Constantinescu CS, Gran B. Multiple sclerosis: autoimmune associations in multiple sclerosis. Nat Rev Neurol. 2010;6(11):591–2.
76. Pokorny CS, Beran RG, Pokorny MJ. Association between ulcerative colitis and multiple sclerosis. Intern Med J. 2007;37(10):721–4.
77. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum. 2001;44(9):1977–83.

78. Prinz JC. Autoimmune-like syndromes during TNF blockade: does infection have a role? Nat Rev Rheumatol. 2011;7(7):429–34.
79. Cope AP. Regulation of autoimmunity by proinflammatory cytokines. Curr Opin Immunol. 1998;10(6):669–76.
80. Kassiotis G, Kollias G. Uncoupling the proinflammatory from the immunosuppressive properties of tumor necrosis factor (TNF) at the p55 TNF receptor level: implications for pathogenesis and therapy of autoimmune demyelination. J Exp Med. 2001;193(4):427–34.
81. van der Bijl AE, et al. Advanced magnetic resonance imaging of the brain in patients treated with TNF-alpha blocking agents. Clin Exp Rheumatol. 2007;25(2):301–4.
82. Mottershead JP, et al. High field MRI correlates of myelin content and axonal density in multiple sclerosis–a post-mortem study of the spinal cord. J Neurol. 2003;250 (11):1293–301.
83. Kaltsonoudis E, et al. Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Res Ther. 2014;16(3):R125.
84. Nancey S, et al. Infliximab treatment does not induce organ-specific or nonorgan-specific autoantibodies other than antinuclear and anti-double-stranded DNA autoantibodies in Crohn's disease. Inflamm Bowel Dis. 2005;11(11):986–91.
85. Jonsdottir T, et al. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004;63 (9):1075–8.
86. Ramos-Casals M, et al. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev. 2010;9(3):188–93.
87. Miehsler W, et al. A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohns Colitis. 2010;4(3):221–56.
88. Ramos-Casals M, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore). 2007;86(4):242–51.
89. Baker HW, et al. Multiple sclerosis and autoimmune diseases. Aust N Z J Med. 1972;2(3):256–60.
90. Barcellos LF, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol. 2006;5(11):924–31.
91. Broadley SA, et al. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. Brain. 2000;123(Pt 6):1102–11.
92. de Lau LM, et al. Acute CNS white matter lesions in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(4):576–80.
93. Gotkine M, Fellig Y, Abramsky O. Occurrence of CNS demyelinating disease in patients with myasthenia gravis. Neurology. 2006;67(5):881–3.
94. Heinzlef O, et al. Autoimmune diseases in families of French patients with multiple sclerosis. Acta Neurol Scand. 2000;101(1):36–40.
95. Lo R, Feasby TE. Multiple sclerosis and autoimmune diseases. Neurology. 1983;33(1):97–8.
96. Midgard R, et al. Multiple sclerosis and chronic inflammatory diseases. A case–control study. Acta Neurol Scand. 1996;93(5):322–8.
97. Toussirot E, et al. Association of rheumatoid arthritis with multiple sclerosis: report of 14 cases and discussion of its significance. J Rheumatol. 2006;33(5):1027–8.
98. Minuk GY, Lewkonia RM. Possible familial association of multiple sclerosis and inflammatory bowel disease. N Engl J Med. 1986;314(9):586.
99. Sadovnick AD, Paty DW, Yannakoulias G. Concurrence of multiple sclerosis and inflammatory bowel disease. N Engl J Med. 1989;321(11):762–3.
100. Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. Mult Scler. 2004;10(5):575–81.
101. Dobson R, Giovannoni G. Autoimmune disease in people with multiple sclerosis and their relatives: a systematic review and meta-analysis. J Neurol. 2013;260(5):1272–85.

102. Nielsen NM, et al. Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: a nationwide cohort study in Denmark. Mult Scler. 2008;14(6):823–9.
103. Ramagopalan SV, et al. Autoimmune disease in families with multiple sclerosis: a population-based study. Lancet Neurol. 2007;6(7):604–10.
104. Roshanisefat H, et al. Shared genetic factors may not explain the raised risk of comorbid inflammatory diseases in multiple sclerosis. Mult Scler. 2012;18(10):1430–6.
105. De Keyser J. Autoimmunity in multiple sclerosis. Neurology. 1988;38(3):371–4.
106. Figueroa JJ, et al. Peripheral neuropathy incidence in inflammatory bowel disease: a population-based study. Neurology. 2013;80(18):1693–7.
107. Green C, et al. A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. Am J Epidemiol. 2006;164(7):615–23; discussion 624–8.
108. Ramagopalan SV, Sadovnick AD. Epidemiology of multiple sclerosis. Neurol Clin. 2011;29(2):207–17.
109. Maddur MS, et al. Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. Am J Pathol. 2012;181(1):8–18.
110. Khalili H, et al. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012;61(12):1686–92.
111. Fernando MM, et al. Defining the role of the MHC in autoimmunity: a review and pooled analysis. PLoS Genet. 2008;4(4), e1000024.
112. Lettre G, Rioux JD. Autoimmune diseases: insights from genome-wide association studies. Hum Mol Genet. 2008;17(R2):R116–21.
113. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterology. 2011;140(6):1704–12.
114. Kamada N, et al. Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol. 2013;13(5):321–35.
115. Ochoa-Reparaz J, et al. Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. J Immunol. 2009;183(10):6041–50.
116. Hansen JJ, Sartor RB. Therapeutic manipulation of the microbiome in IBD: current results and future approaches. Curr Treat Options Gastroenterol. 2015;13(1):105–20.
117. Aranow C. Vitamin D and the immune system. J Invest Med. 2011;59(6):881–6.
118. Smolders J, et al. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. PLoS One. 2009;4(8), e6635.
119. Ramagopalan SV, et al. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. PLoS Genet. 2009;5(2), e1000369.
120. Munger KL, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004;62(1):60–5.
121. Wang TT, et al. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. J Biol Chem. 2010;285(4):2227–31.
122. Ananthakrishnan AN, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012;142(3):482–9.
123. Danese S, et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol. 2005;11(46):7227–36.
124. Lossos A, et al. Neurologic aspects of inflammatory bowel disease. Neurology. 1995;45(3 Pt 1):416–21.
125. Moris G. Inflammatory bowel disease: an increased risk factor for neurologic complications. World J Gastroenterol. 2014;20(5):1228–37.