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Optic Neuritis Associated or Not with TNF Antagonists in Patients with Inflammatory Bowel Disease

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Abstract

Background and Aims: Acute optic neuritis [ON] is an inflammatory condition affecting the optic nerve. Clinicians should suspect optic neuritis in cases of painful and rapidly progressive loss of central visual field. This condition may be associated with a multitude of diseases, and mostly with multiple sclerosis [MS] where it may present as an initial symptom. The literature reports that optic neuritis and MS occur in patients with inflammatory bowel disease [IBD] before and after the era of anti-tumour necrosis factor-α [TNFα] drugs. At the present moment, there is little consensus for managing this complication, currently treated with corticosteroids and discontinuation of the causative agents.
Methods: We collected cases through a retrospective multicentre European Crohn's and Colitis Organisation CONFER [COllaborative Network For Exceptionally Rare case reports] project. We also performed a comprehensive retrospective search of the available literature on this topic.
Results: We report herein 12 new cases of ON, including 10 under anti-TNF therapy, collected through the CONFER project. We also compare characteristics of ON associated or not with anti-TNFα agents.
Conclusions: The exceptional and current observation of distant family history of MS in 17% of our patients who developed ON, despite the small number and the lack of a control arm, might be an important signal that should be taken into account in our therapeutic strategies in the future.

Keywords: Inflammatory bowel disease; optic neuritis; retrobulbar neuritis; papillitis; anti-TNF; multiple sclerosis

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1. Introduction

Optic neuritis [ON] is a condition associated with primary inflammation of the optic nerve with a normal [retrobulbar] or swollen [anterior/papillitis] retina visible in the ocular fundus. Literature reports an incidence and a prevalence of 5 to 10.4 per 100 000 person-years and 115 per 100-000, respectively.[1,2,3,4] It is the most frequent optic neuropathy encountered in inflammatory bowel disease [IBD].[5] In a cross-sectional study, ON was more prevalent in ulcerative colitis [UC] patients compared with Crohn's disease [CD].[6]

The diagnosis of ON is based on clinical and ophthalmological examination [Table 1].[1,7,8,9] ON can be associated with a variety of conditions and we here report the most common form, related to an acute demyelinating process.[8] Magnetic resonance imaging [MRI] of the orbits and brain [and spinal cord] and visual-evoked potentials are performed both to confirm the demyelinating process and to serve as a prognostic tool.[10,11,12] Intravenous methylprednisolone remains the standard treatment for ON despite its limited benefit over placebo in relation to the speed of recovery of visual acuity [VA], the absence of long-term positive impact on the ophthalmic prognosis,[13,14,15] and its numerous side effects.[13,14,15,16] Intravenous immunoglobulins and plasma exchange have also not shown a significant effect.[17,18,19] Visual recovery is encountered in the majority of patients, traditionally within 4 weeks,[20] but a severe loss of vision persists in less than 5% of patients.[21] The risk of developing MS after an initial episode of ON is estimated to be 8.3–56% over 10–15 years.[11,22] Little information is available on the possible risk to develop ON in patients with IBD. Therefore, we collected a group of IBD patients with ON through the retrospective multicentre European Crohn's and Colitis Organisation [COllaborative Network For Exceptionally Rare Case reports] project.

The primary aim of this study was to extensively describe ON in patients with IBD, associated or not anti-TNFα therapies. The secondary aim was to compare the characteristics of ON separately between those with and without anti-TNF treatments in IBD patients.

2. Materials and Methods

2.1. Study design

This European Crohn's and Colitis Organisation [ECCO] observational multicentre study retrospectively collected cases through the CONFER project. The CONFER project was initiated by ECCO in order to specifically identify and report together rare IBD disease associations, which otherwise are seldom reported due to their exceptional rarity. Once a specific topic was selected by the Steering Committee as a CONFER project, ECCO launched a call to identify similar cases encountered by IBD physicians worldwide. The call to physicians was made through announcements at the ECCO annual congress and in national and international IBD meetings across Europe. Furthermore, the call for similar cases was disseminated by direct emails to all ECCO members and affiliated physicians and on the ECCO website and eNews. Physicians were then prompted to report their case to the CONFER database using pre-determined standardised Case Reporting Forms [CRF]. The authors were also reminded to report their case[s] to their national pharmacovigilance authorities.

2.2. Patients and procedures

Adult IBD patients suffering an optic neuritis were eligible for inclusion in this project. The CRF was divided into two sections. Section 1 included patient and IBD disease characteristics and section 2 described the details of the event.

2.3. Methodology of the literature overview

A comprehensive retrospective search of the available literature using the isolated or combined terms and variants (optic neuritis [retrobulbar], papillitis, optic neuropathy, demyelinating disease, ulcerative colitis, Crohn's disease, anti-TNF and multiple sclerosis]) was performed within Pubmed and Embase, and was restricted to human studies [1959 to 2014]. Studies were included if they were published in English or French and if related to optic neuritis and demyelinating complications with special focus on IBD either on anti-TNF or not. Additionally, references from relevant literature were hand-searched.

Table 1. Clinical features of typical acute demyelinating optic neuritis.

Patient characteristics
Young age [20–50 years]
Sex ratio 3 female: 1 male
Symptoms
Pain [> 90%], exacerbated by eye movements, resolves within 1 week, may precede other visual manifestations
Unilateral in adult patient
Progress over a period of hours to days; usually less than 2 weeks.
Phosphenes or photopsias with eye movement
Uhthoff phenomenon
Typical signs
Impaired visual acuity [90%] [10/10 to no light perception]
Blurred vision
Dyschromatopsia [88%] [red-green axes typically]
Impaired contrast sensitivity [87–99%]
Visual field loss [69%]
Afferent pupillary defect [Marcus Gunn]
Normal optic disc [70% retrobulbar] or swelling [30% papillitis]; evolution to pallor and atrophy; haemorrhages and retinal exudates rare
Normal macula and peripheral retina
Associated lesions
Uveitis or retinal periphlebitis
Outcome
Recovery of visual acuity begins within 2 to 4 weeks and often reaches 20/20

2.4. Ethics

The ECCO CONFER Cases project has been centrally approved by the institutional ethics committee of Sheba Medical Center. All cases included will be anonymous to protect confidentially and respect patients' privacy.

For investigators who are in need of local institutional review board [IRB] approval in their own institution to participate in this retrospective project, the project protocol, CRF, and the central site IRB approval can be downloaded at the ECCO CONFER website at [https://www.ecco-ibd.eu/science/ecco-confer-cases.html].

2.5. Statistical analyses

Demographic and disease specific data will be given descriptively or tabulated. Continuous variables are described as median and interquartile range [IQR]. Fisher's exact test was used to compare the frequencies and Wilcoxon rank sum test with continuity correction was used to compare continuous variables. A value of $P < 0.05$ was considered statistically significant [SPSS v 21.0].

3. Results

3.1. ECCO CONFER series of optic neuritis in IBD patients

Sixteen cases were voluntarily reported to the CONFER group. Four were excluded due to alternative diagnosis or lack of robust ophthalmological and neurological data. None of the remaining 12 cases had been previously reported. Other infectious and systemic causes of visual loss were ruled out by physicians. Screening for tuberculosis was performed in 11 patients according to national guidelines, which ruled out active or latent tuberculosis.

Table 2. Clinical characteristics of inflammatory bowel disease [IBD] patients presenting optic neuritis [*n* = 12].

Male sex, *n* [%]	3 [25]
Tabaco use, *n* [%]	
Current	5 [42]
Former	2 [16]
Never	5 [42]
Medications [other than IBD], *n* [%]	5 [42]
IBD subtype	
UC	2 [17]
CD	7 [58]
IC	3 [25]
Familial history of IBD/MS, *n* [%]	3 [25]/2 [17]
Age at ON diagnosis [years], median [IQR]	40 [31–46]
IBD duration at ON diagnosis [years], median [IQR]	6 [2–14]
Disease activity at ON diagnosis	
Active, *n* [%]	6 [50]
Quiescent, *n* [%]	5 [42]
Unknown, *n* [%]	1 [8]
IBD medications within 6 months before ON, *n* [%]	
Anti-TNF	10 [83]
Infliximab [*n*]	5
Adalimumab [*n*]	5
Certolizumab pegol [*n*]	1[a]
Steroids	7 [59]
5-ASA	5 [42]
AZA/6-MP	4 [33]
MTX	2 [16]
Combotherapy	5 [42]
Infliximab [*n*]	3
Adalimumab [*n*]	2

[a]One patient received two anti-TNFs, consecutively.

5 ASA, 5-aminosalicylic acid; AZA, azathioprine; CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indefinite colitis; MTX, methotrexate; 6-MP, 6-mercaptopurine; MS, multiple sclerosis; ON, optic neuritis; TNF, tumour necrosis factor; UC, ulcerative colitis; IQR, interquartile range.

Clinical characteristics of the patients and IBD disease are shown in Table 2. A family history of IBD was observed for three patients [two CD and one UC among first- and second-degree relatives] and a family history of MS [second- and third-degree relative] in two patients. Ten patients were exposed to anti-TNFα (42% on combotherapy with either a thiopurine or methotrexate [MTX]) within 6 months before onset of ON and nine patients had ongoing treatment at onset. The median duration of exposure to anti-TNF was 25 months [IQR: 4 to 40.5 months]. Clinical data at the onset of ON, ophthalmological and neurological characteristics, MRI findings, treatments, and prognoses are summarised in Tables 3a and3b. Relevant comorbidities or specific medications known to induce optic neuropathy were reported in none of the patients at the onset of ON.

All patients were examined by an ophthalmologist. Abnormal ocular motility was not seen. Abnormal fundoscopic exam associated with papillitis included a swollen aspect of the optic disc [*n* = 4], isolated or concomitantly with retinal exudates [*n* = 1] and parapapillary haemorrhage [n = 1]. Concomitant active uveitis, optic disc atrophy, and impaired venous sheathing appearance sometimes associated with ON ophthalmological findings were absent. Angiography was performed in two patients and was normal. All patients were referred to a neurologist. Three patients were diagnosed concomitant MS based on the ON symptoms, associated demyelinating cerebral lesions on MRI, and abnormal cerebrospinal fluid analysis. All three patients had a normal neurological examination. Abnormal cerebrospinal fluid [CSF] findings included proteinorachia with specific oligoclonal banding of IgG for two patients and unspecified abnormal results for one patient.

Treatment of the ON was based on anti-TNF withdrawal [*n* = 10] and use of corticosteroids [*n* = 9]. Among five patients on prednisone at onset of the ON [median dose of 15 mg [IQR: 8 to 20 mg], three received additional intravenous methylprednisolone pulse therapy. Two patients with MS were treated with weekly interferon β1a for 6 months and 7 weeks, respectively, and one was left untreated. Follow-up data were available in 11 patients. MRI was repeated in seven patients, with a follow-up time available for four of them [median: 6 months, IQR: 4 to 8 months]. A fourth patient, previously treated with IV steroids for ON, was diagnosed with MS 1 year later. Visual outcomes were favourable [partial or total recovery] for all but two patients, both on prednisone at onset of the ON.

3.2. Comparison of ON characteristics in IBD patients with and without anti-TNFα

In the literature we found eight reports of ON in IBD patients without anti-TNFα treatment [Table 4][23,24,25,26]and six associated with anti-TNFα [Table 5], in total 14 that were added to our 12 CONFER cases [26 cases in total].[27,28,29,30,31,32] Both groups of ON, with [*n* = 16] and without [*n* = 10] anti-TNF, from our cohort and from the literature were compared [Table 6]. ON with anti-TNFα treatment was more often observed in CD than UC.

The clinical characteristics of ON, its treatment and outcomes were similar in the two groups. However, concomitant diagnosis of MS was found only in the suspected anti-TNFα induced ON group [*P* = 0.14], thus, despite our limited number of patients, the association of MS and ON was not significant in the anti-TNFα group.

Table 3A. Clinical characteristics of optic neuritis cases associated or not with anti-TNFα in IBD patients [*n* = 12].

Visual field	Superior and temporal defect	Altitudinal defect	Ukn	Altitudinal defect	Ukn	No	No	Temporal defect	Ukn	Altitudinal defect	Central defect	Ukn
Initial VA RAPD/VEP Symptoms	6/10 Positive/PL Blurred vision, pain, dyschromatopsia	Finger count / positive/PL Blurred vision, dyschromatopsia	5/10 ND/ND Blurred vision, discomfort	ND positive/PL Blurred	3/10 ND/ND No	4/10 ND/PL Ukn	5/10 ND/ND Blurred vision, pain, phosphenes	5/10–6/10 ND/PL Blurred vision, pain, phosphenes, dyschromatopsia	4/10 ND/ND Blurred vision	5/10 positive/U Blurred vision	6/10 ND/ND Blurred vision	Ukn ND/PL Blurred vision, pain, phosphenes, diplopia
Time interval since last anti-TNF administration [days]	Ukn	6	No anti-TNFα	Ukn	Ukn	30	44	60	17	No anti-TNFα	90	1
Onset [days]	3	5	7	Ukn	Ukn	14	18	7	1	Few	3	Acute
Ocular involvement	MR	MR	MR	MA	MR	MR	MA	BR	MA	MA	MR	MUkn
Sex/age [years]	M/37	F/46	F/31	F/42	M/41	F/36	F/31	F/47	F/58	M/50	F/29	F/30
Cases	1	2	3	4	5	6	7	8	9	10	11	12

BR, bilateral retrobulbar; F, female; IBD, inflammatory bowel disease; M, male; MA, monocular anterior; MR, monocular retrobulbar; MUkn, monocular unknown; ND, not done; PL, prolonged latency; RAPD, relative afferent pupillary defect; TNF, tuour necrosis factor; Ukn, unknown; VA, visual acuity; VEP, visual evoked potential.

Table 3B. Clinical characteristics of optic neuritis cases associated or not with anti-TNFα in IBD patients [*n* = 12].

Evolution to MS during F-U [months]	No [83]	No [7]	No [385]	No [34]	No [Ukn]	No [15]	No [165]	No [13]	No [56]	No [46]	Y [16]	No [52]
ON recurrence	No	No	No	No	No	No	No	No	No	No	Y	Y
Visual outcome	Complete recovery	Partial recovery	Complete recovery	Partial recovery	Complete recovery	Partial recovery	Complete recovery	Partial recovery	Partial recovery	Stable	Worsening	Complete recovery
Therapy	Pulse MP [3days]	Pulse MP [2 x 3days] / IFN/plasma exchange	No therapy	IFN	Oral prednisone [NS] + Pulse MP[a] [5days]	Oral prednisone [40 mg]	Oral prednisone [30 mg]	Pulse MP[a] [3 and 5 days] / IFN	Oral prednisone [80 mg]	No therapy	Pulse MP[a] [3days]	Pulse MP[a] [5days]
Associated concomitant MS lesions	Y	No	No	Y	No	No	No	Y	No	No	No	No
CSF	Abnl	NL	ND	Abnl	ND	ND	ND	Abnl	ND	ND	ND	NL
MRI spinal	Abnl	NL	NL	ND	ND	NL	NL	Abnl	ND	ND	NL	NL
MRI brain	Abnl	Abnl	NL	Abnl	Abnl	NL	NL	NL	Abnl[b]	NL	NL	NL
MRI orbit	Abnl	Nl	Abnl	ND	Abnl	Nl	Nl	Abnl	ND	NL	NL	NL
Cases	1	2	3	4	5	6	7	8	9	10	11	12

Abnl, abnormal; CSF, cerebrospinal fluid; F-U, follow-up; IBD, inflammatory bowel disease; IFN, interferon; Mo, months; MP, methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; Nl, normal; ND, not done; TNF, tumour necrosis factor; Y, yes.

[a]Oral tapering dose of prednisone.

[b]Not compatible with demyelinating process.

Table 4. Cases of optic neuritis in IBD patients in the absence of anti-TNFα reported in the literature ($n = 8$)

Case Sex/Age	References	Type/Duration/ Activity IBD	IS	Associated MS lesions	Initial VA/ RAPD/VEP	Therapy	Visual outcome	ON recurrence during F-U (mo)
1 F/40	Ernst BB. Ophtalmology 1991	UC/17ys Quiescent	Ukn	No	20/20 positive/ Ukn	No	Total recovery	No (Ukn)
2 F/25	Ernst BB. Ophtalmology 1991	CD/1y Quiescent	Ukn	No	20/25 positive/ Ukn	Pulse MP	Total recovery	No (Ukn)
3 M/U	Felekis T. Inflam Bowel Dis 2009	CD/Ukn Ukn	No	No	Ukn Ukn / Ukn	Pulse MP	Ukn	Ukn
4 F/38	Sedwick LA. Clin Neuro-ophtalmol 1984	UC/Ukn Quiescent	No	No	Ukn Ukn / Ukn	Oral prednisone	Total recovery	No (0.5)
5 F/21	Sedwick LA. Clin Neuro-ophtalmol 1984	UC/12ys Quiescent	No	No	Finger count positive/ Ukn	Oral prednisone	Color desaturation	No (Ukn)
6 F/26	Sedwick LA. Clin Neuro-ophtalmol 1984	UC/9ys Active	No	No	Loss of vision Ukn / Ukn	Oral prednisone	Hands motions	No (1)
7 F/36	Sedwick LA. Clin Neuro-ophtalmol 1984	UC/concomitant Active	No	No	20/30-15/20 Positive/ Ukn	Oral prednisone	Total recovery	No (36)
8 M/45	Van de Scheur MR. J Clin Gastroenterol 2002	CD/1y Quiescent	No	No	Ukn No/PL	Oral prednisone	Stabilization	No (1)

(CD = Crohn's disease; F = female; F-U = follow-up; IBD = inflammatory bowel disease; IS = immunosuppressive therapy; M = male; Mo = months; MP = methylprednisolone; MS = multiple sclerosis; PL = prolonged latency; RAPD = relative afferent pupillary defect; Ukn = unknown; UC = ulcerative colitis; VA = visual acuity; VEP = visual evoked potential; Y(s) = year(s))

Table 5. Cases of optic neuritis associated with anti-TNFα in IBD patients reported in the literature ($n = 6$)

Case Sex/Age	References	Type/Duration/ Activity IBD/ Biologic (duration(m))	IS	Associated MS lesions	Initial VA/ RAPD/VEP	Therapy	Visual outcome	ON recurrence during F-U (mo)
1 M/32	Felekis T. J Crohns and Colitis 2009	CD/4ys quiescent IFX (1.5)	No	Y	6/10–4/10 Positive/Ukn	IFN-β	Total recovery	No (6)
2 M/44	Hejazi R. Gastroenterol Clin et Biol 2008	UC/11ys Quiescent IFX (1.5)	Yes	No	2/10 U/PL	Pulse MP	Total recovery	No (1)
3 F/50	Mejico LJ. Arch Ophthalmol 2004	CD/U U IFX (U)	No	No	Ukn Ukn/Ukn	No	Total recovery	No (U)
4 F/51	Mumoli M. QJ Med 2007	UC/15ys Active IFX (4.25)	Yes	No	20/60 Ukn/Ukn	Pulse MP†	Total recovery	No (1)
5 M/55	Ouakaa-Kchaou A. J Crohns and Colitis 2009	CD/5ys Quiescent IFX (1.5)	Yes	No	1/10 Ukn/Ukn	Pulse MP†	Partial recovery	No (2)
6 F/45	Strong YC. Annals of Internal Medecine 2004	CD/2ys Quiescent IFX (9.5)	Yes	No	20/70 Positive/Ukn	Pulse MP†	Total recovery	No (3)

(CD = Crohn's disease; F = female; F-U = follow-up; IBD = inflammatory bowel disease; IFN = interferon; IFX = infliximab; IS = immunosuppressive therapy; M = male; Mo = months; MP = methylprednisolone; MS = multiple sclerosis; PL = prolonged latency; RAPD = relative afferent pupillary defect; Ukn = unknown; UC = ulcerative colitis; VA = visual acuity; VEP = visual evoked potential; Y = yes; Y(s) = year(s))

† followed by oral tapering dose

Table 6. Comparison of ON with and without anti-TNFα in IBD patients

	ON with anti-TNFα (n = 16)	ON without anti-TNFα (n = 10)	P value
Male, n (%)	5 (31)	3 (30)	1
Median age at ON diagnosis, y (IQR)	43 (35 to 48)	36 (26 to 40)*	0.08
Crohn disease, n (%)	10 (62)	4 (40)	0.42
Ulcerative colitis, n (%)	4 (25)	5 (50)	0.23
Indefinite colitis, n (%)	2 (13)	1 (10)	1
Active IBD at onset of ON, n (%)	6 (43)**	2 (25)**	0.65
Median disease duration, y (IQR)	6 (4.5 to 14)*	5 (0.8 to 12.5)**	0.35
IBD medication within 6 months before ON, n (%)			
Anti-TNFα	16 (100)	0	-
Corticosteroid	6 (37)	2 (20)	0.42
Azathioprine	5 (31)	0	0.12
Methotrexate	2 (12)	0	0.51
Ocular manifestation, n (%)			
Unilateral	14 (87)	7 (78)*	0.61
Median Initial visual acuity (IQR)	0.4 (0.3 to 0.5) ***	0.5 (0.25 to 0.75) ***	0.28
Diagnosis of concomitant MS, n (%)	4 (25)	0	0.14
Treatment			
Oral corticosteroid, n (%)	4 (25)	5 (50)	0.23
IV corticosteroid, n (%)	9 (56)	2 (20)	0.11
Interferon, n (%)	3 (19)	0	0.26
Visual outcomes			
Total recovery, n (%)	9 (56)	5 (55)*	1
Partial recovery, n (%)	6 (37)	2 (20)	0.42
Stable or Worse, n (%)	1 (6)	2 (20)	0.54
Recurrence, n (%)	2 (12)	0	0.51
Evolution to MS during follow up, n (%)	1 (7)**	0****	1

IBD; inflammatory bowel disease; IQR = interquartile range; MS = Multiple sclerosis; N = number; ON = optic neuritis; TNF = tumor necrosis factor; Y = year(s)
* data missing in 1 patient; ** data missing in 2 patients; *** data missing in 3 patients; **** data missing in 4 patients

4. Discussion

The pathophysiological mechanisms of ON during the course of IBD are still poorly understood.[27] The association of anti-TNFα agents and ON has been reported in the past 13 years but strict causative relationship remains inconclusive. In our retrospective series, we found that 83% of the patients with ON were receiving biological therapy, but we cannot answer the question as to whether anti-TNF therapy is associated with a higher risk of ON. A recent retrospective population-based cohort study [*n* = 61 227 inflammatory disease patients] found that ON occurred with similar frequency among those with Disease-Modifying AntiRheumatic Drugs [DMARDs] and those exposed to biologicals.[33]

However, in a Spanish registry on 20 000 patients treated with anti-TNF therapy for rheumatoid arthritis, ON was reported at an incidence of 0.19 per 1000 patient-years (95% confidence interval [CI]: 0.07–0.5].[34] This figure seems slightly higher than the usual incidence reported in the general population.[1,2] The 'association data' come from post-marketing monitoring and specific medical rec ords,[35,36,37,38,39] the Food and Drug Administration [FDA]'s adverse event reporting system,[40] and two Spanish registries[34,41] mainly involving rheumatology patients treated with different anti-TNFα therapies with a possible bias of duplicates of data that obscures its analysis. Last, several authors have published their cases, through case studies[40,42,43] or individual case reports, collecting 30 cases of ON in patients receiving various anti-TNFα therapies (infliximab [IFX] [*n* = 15], adalimuab [ADA] [*n* = 8], and etanercept [*n* = 7]). Biological therapies were prescribed for CD [*n* = 4],[27,29,31,32] UC [*n* = 2],[28,30] rheumatoid polyarthritis [*n* = 9],[42,44,45,46,47,48,49,50,51] psoriatic arthritis [*n* = 4],[47,52,53,54] skin psoriasis [*n* = 4],[55] juvenile idiopathic polyarthritis [*n* = 4],[56,57] ankylosing spondylitis [*n* = 1],[56] and finally recurring uveitis [*n* = 2].[40,58] In conclusion, ON characteristics are globally the same between IBD and non IBD patients.

ON is the initial symptom for MS in around 20% of patients. In this retrospective study, four patients [three in our series and one in the literature] had concomitant MS at the onset of the ON. One extra case of MS occurred 1 year after the diagnosis of ON. Interestingly, all MS/ON diagnoses occurred after anti-TNFα therapy [two IFX, two ADA, and one certolizumab]. The presence of MRI brain-demyelinating lesions under anti-TNFα treatment has already been rep orted.[6,59,60,61,62,63] Several physiopathological hypotheses were proposed to explain this relationship, but none has been widely validated.[32,52,64,65,66,67,68,69] Andersen showed in his Danish IBD cohort a 4-fold higher risk of developing MS while treated by anti-TNF than in the general population.[70] The Spanish registry reported an MS incidence of 0.05 per 1000 patients-years [95% CI: 0.01–0.33], which was somewhat similar to the rate observed in the untreated Spanish population.[34] However, the increasing use of these biological agents and the growing incidence of MS in our Western countries[47,70] make it essential to carefully examine the association between the two to rule out a reporting bias. An association between IBD and MS was also illustrated repeatedly in isolation or within families since its first description in the early 1980s, with a pronounced approximately 4-fold risk of developing them, especially in UC.[6,71,72]

In our series, family history [second- and third-degree relative] of MS was mentioned in two patients [17%] who developed ON and concomitant MS while treated with anti-TNFα; but without a control arm it is impossible to draw any conclusion about the impact of a family history of MS.

Most of our patients had a partial or total improvement of VA, but we observed in two patients no recovery and even worsening of

visual outcome. The visual outcome and risk of relapse are negatively influenced by the severity of the initial VA,[73,74] the association with MS,[11,15] and treatment using oral prednisone.[74] One patient was diagnosed lattterly with MS and the second patient was on steroids at onset. In our series, neurological and imaging follow-up when performed revealed only one new diagnosis of MS.

Interestingly, two patients exhibited cerebral lesions on MRIs [Cases 2 and 5] located in peri- and non-periventricular areas with different sizes and aspects compatible with the demyelinating process. None of the patients expressed neurological symptoms other than ON, and the lumbar puncture results available for Case 2 were normal.

We reported herein the ON characteristics in IBD patients with and without anti-TNFα therapy. We found that the association of ON and anti TNFα therapy was more frequent in CD patients as compared with UC, but the size of our group was too restricted to draw safe conclusions.

5. Conclusion

Optic neuritis, either while under anti-TNFα therapy or not, is a very rare condition, associated or not with multiple sclerosis. Intravenous methylprednisolone therapy, pending stronger new evidence, should mostly likely continue to be the standard treatment of this complication whereas oral prednisone may be associated with worse outcomes. This study cannot answer the question as to whether anti-TNF therapy is associated with higher risk of ON in patients with IBD. In view of the lack of a control arm and the rarity of this complication, we suggest to avoidance of anti-TNF or recommend a strict neurological follow-up in some settings of patients with family history of ON or MS. Definitely, prospective studies are needed. The majority of ON cases in IBD patients have a favourable outcome when symptoms are reported early and anti-TNFα discontinuation is prompt.

Conflict of Interest

PDC has received educational support, consulted on advisory boards and been a speaker at educational symposia sponsored by Shire, Ferring, Janssen, AbbVie and Baxter.

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Author Contributions

All authors have made substantial contributions to all of the following: concept and design of the study, literature search, data collection and analysis, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

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