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Occurrence of demyelinating diseases after anti-TNFα treatment of inflammatory bowel disease: A Danish Crohn Colitis Database study☆

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Abstract

Introduction: It remains uncertain whether patients with inflammatory bowel disease (IBD) are at increased risk of developing demyelinating diseases, primarily multiple sclerosis (MS) and whether the introduction of biologic drugs in the treatment of IBD has altered this risk.
Aim and methods: The aim was to conduct a systematic review of literature on occurrence of demyelinating diseases in IBD patients, to assess a national Danish anti-TNFα treated IBD cohort in order to search for and describe the IBD cases with coexisting demyelinating diseases, and finally to compare the occurrence of MS in the anti-TNFα cohort to the occurrence in the general Danish population.
A systematic MEDLINE literature search was conducted, medical files were scrutinized for identification and description of cohort patients with demyelinating disease, and risk of MS was calculated as a standardized morbidity ratio (SMR) using general population data for comparison.
Results: Four studies on the risk of demyelinating diseases in IBD were identified. One study revealed an observed prevalence of MS at onset of IBD at 3.7 times the expected (95% CI, 0.8–10.8). In the Danish anti-TNFα IBD cohort, 4 out of 651 patients developed demyelinating disorders after anti-TNFα treatment. The SMR for developing MS among Danish IBD patients treated with anti-TNFα was 4.2 (95% CI, 0.1–23.0).
Conclusion: The literature review revealed an up to four-fold increased risk of demyelinating diseases, in particular MS, in IBD patients in general. The risk of developing MS in the anti-TNFα treated Danish cohort did apparently not exceed this risk.
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Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; SMR, standardized morbidity ratio; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; ON, optic neuritis.

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1. Introduction

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD) are chronic intestinal diseases of unknown origin, often categorized as autoimmune diseases.

The aetiology of IBD remains unknown and consequently treatment is based on empirical features with the primary purpose of inducing and maintaining remission. New biological therapies such as the tumor necrosis factor α (TNFα) blocker infliximab (REMICADE) have shown efficacy in severe and fistulizing CD[1,2] as well as in UC.[3] TNFα is a cytokine released by activated monocytes, macrophages, and T-lymphocytes. It is involved in several processes, but plays an important role particularly in inflammation. Several direct side effects of infliximab treatment including an increased risk of infections, lymphomas and demyelinating diseases have been suggested,[4–10] but still a profound experience of the long-term outcome of infliximab treatment remains unknown. In addition to infliximab, the biological drug adalimumab (HUMIRA) has been approved for CD by the American Food and Drug Administration (FDA) in February 2007[11] and subsequently by EMEA (European Agency for the Evaluation of Medicinal Products) in May whereas the approval of certolizumab (CIMZIA) is still awaited. Another biological drug, natalizumab (ANTEGREN) was originally approved for CD but in 2005 the drug was suspended by the Adverse Event Reporting System (AERS) due to three side events reports of progressive multifocal leukoencephalopathy (PML), a usually fatal demyelinating disease caused by the JC virus.[12] A follow-up study with more than 3000 patients treated with natalizumab found no additional cases of PML[13] but The EMEA has finally not approved natalizumab for CD in Europe whereas the decision from FDA is still awaited. Infliximab is currently by far the most utilized biological drug in the treatment of Danish IBD patients and when referring to anti-TNFα in the present study, it primarily refers to infliximab.

Demyelinating diseases are characterized by inflammation and focal destruction of the myelin sheets in the white matter of the central nervous system (CNS), which ultimately can lead to complete block of the nerve signal. The most common demyelinating disease is multiple sclerosis (MS) and others to be mentioned are optic neuritis, which can be a pre-state to MS, progressive multifocal leukoencephalopathy (PML) and Guillain–Barré syndrome.[14]

It has been suggested that patients with IBD have a higher risk of demyelinating diseases than the general population and that treatment with infliximab and other new biological therapies may add further to this potentially increased risk. In a recent study of a population-based national cohort of 651 consecutive Danish IBD patients receiving anti-TNFα treatment during 1999–2005, four cases of possible or certain multiple sclerosis were observed.[15]

The aim of the present study was 1) to conduct a systematic review of literature on occurrence of demyelinating diseases, in particular MS, developed spontaneously or as a consequence of treatment with biological therapies in patients with IBD 2) to assess the national Danish anti-TNFα IBD cohort in order to further describe the four IBD demyelinating diseases cases and 3) to compare the specific occurrence of MS in the anti-TNFα cohort to the occurrence in the general Danish population.

2. Materials and methods

2.1. Literature search

In order to identify all papers – in English or other European languages – regarding occurrence of demyelinating disease in patients with IBD treated or not treated with anti-TNFα drugs, we conducted a systematic MEDLINE search (1966–2006) using the terms 'inflammatory bowel disease AND demyelinating diseases' and 'demyelinating diseases AND TNFα therapy' with the following limitations: only items with abstracts and studies of humans. Lastly, reference lists of all included papers were scrutinized to disclose additional literature on the topic.

2.2. Cases from the Danish anti-TNFα IBD cohort

Medical records of patients with a possible or certain diagnosis of demyelinating disease from the national Danish anti-TNFα database (1999–2005) were scrutinized for additional clinical information.

2.3. Statistics

The standardized morbidity ratio (SMR) for occurrence of MS was calculated as the observed number of cases in the Danish IBD-anti-TNFα cohort divided by the expected number in the general Danish population. The expected number was estimated by use of age- and sex-specific incidence rates of MS in the general population (the Danish Multiple Scleroses Register[16]) and age- and gender specific person-years at risk in the IBD-anti-TNFα cohort (Danish Crohn Colitis Database[14]). Under the assumption of a Poisson distribution of observed cases, a 95% confidence interval (CI) for the SMR was calculated.

3. Results

3.1. Systematic review of demyelinating diseases in IBD

A total of nine papers concerning the association between IBD and demyelinating diseases were identified, two population-based studies,[17,18] two referral-centers studies,[19,20] and five case-reports.[4–9] Of these, four studies concerning the risk of demyelinating disease in IBD patients *not* treated with infliximab or other biological therapies were identified (Table 1). The oldest study from 1982 by Rang et al., reported 10 cases of MS among 2261 female UC patients from the register of the Ileostomy Association in England, followed from 1944 until 1979. The incidence was three times that of the normal population.[19]

Another population-based study, from Olmsted County, Minnesota, found four cases of MS in a population of 474 IBD patients from The Rochester Epidemiology Project Database, diagnosed between 1950 and 1995.[17] The observed prevalence of MS at onset of IBD was 3.7 times the expected (95% confidence interval, 0.8–10.8). The four patients had been treated with either sulfasalazine or prednisone and mercaptopurine.

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