Letters

RESEARCH LETTER

Risk of Demyelinating Diseases in the Central Nervous System in Patients With Inflammatory Bowel Disease Treated With Tumor Necrosis Factor Inhibitors

An association between usage of tumor necrosis factor inhibitors (anti-TNF) in patients with inflammatory bowel disease (IBD) and other immune-mediated diseases and demyelinating diseases in the central nervous system has been suggested by case reports.[1,2] However, it remains uncertain whether these cases are directly related to anti-TNF therapy because there is evidence of an underlying association between demyelinating disease and IBD.[3] In a nationwide population-based cohort, we compared rates of central demyelinating diseases among patients with IBD exposed and unexposed to anti-TNF.

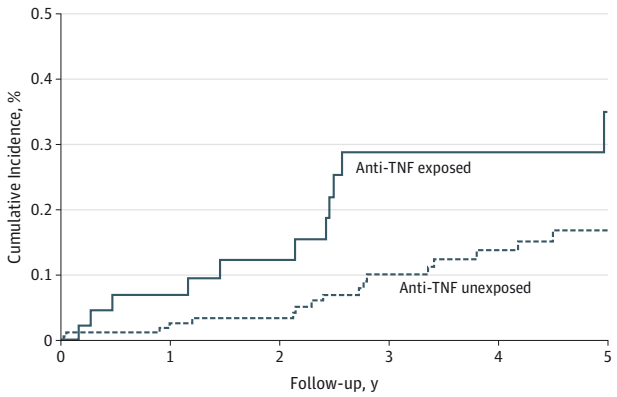
Methods | The general study design and data sources used have been described in detail elsewhere.[4,5] Briefly, using the Danish Civil Registration System, we identified a source population of 4 million people living in Denmark from January 1, 1999, to December 31, 2012. Unique personal identifiers permitted linkage to data from health registries on IBD diagnoses, anti-TNF exposure, and outcomes. After the date of first anti-TNF dose, the patient was categorized as ever exposed. The outcome was defined as a diagnosis of a central demyelinating disease, including multiple sclerosis, optic neuritis, transverse myelitis, and other central demyelinating diseases. Patients with a history of central demyelinating disease and those with use of anti-TNF prior to 1999 or prior to IBD diagnosis were excluded. The study was approved by the Danish Data Protection Agency. Ethics approval is not required for registry-based research in Denmark.

Patients exposed to anti-TNF and those unexposed were matched in a ratio of up to 1:4 on sex, age (5-year interval), and disease duration (<1, 1-4, 5-9, 10-19, and ≥20 years). The cumulative incidences of central demyelinating disease were analyzed using a competing risk model (Aalen-Johansen method). The hazard ratio (HR) was estimated using Cox regression with time since anti-TNF treatment initiation as underlying timescale. Patients were followed from cohort entry (date of first anti-TNF dose for the exposed patients, which was also set as entry date for the corresponding unexposed matches) until first diagnosis of a central demyelinating disease, 5 years of follow-up, emigration, death, or the end of the study (December 31, 2012), whichever event occurred first. No violation of the proportional hazards model assumption was detected. Analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc).

Results | From the source population, 54 843 patients with IBD were identified. Among these, 4504 were exposed to anti-TNF and matched to 16 429 unexposed patients, yielding a study cohort of 20 933 patients. Anti-TNF–exposed patients in the matched cohort had a mean (SD) age of 39.4 (14.7) years, 56% were female, and the mean disease duration was 4.0 years (interquartile range [IQR], 1.1-9.0).

A total of 11 central demyelinating events were observed in exposed patients (2 cases of multiple sclerosis; 5, optic neuritis; 4, other central demyelinating diseases; corresponding to 7.5 events per 10 000 person-years [95% CI, 4.1-13.5]). In un-

Figure. Cumulative Incidences of Central Demyelinating Diseases in Matched Anti–Tumor Necrosis Factor (TNF) Exposed and Unexposed Patients With Inflammatory Bowel Disease Through 5 Years of Follow-up



No. at risk						
Anti-TNF exposed	4504	3862	3245	2608	2023	1538
Anti-TNF unexposed	16429	13633	11199	8790	6717	5063

exposed patients, there were 17 central demyelinating events (5 cases of multiple sclerosis; 6, optic neuritis; 1, tranverse myelitis; 5, other central demyelinating diseases; resulting in 3.3 events per 10 000 person-years [95% CI, 2.1-5.4]).

The HR for central demyelinating disease comparing anti-TNF–exposed and unexposed patients was 2.19 (95% CI, 1.02-4.71) with an absolute risk difference of 3.9 per 10 000 person-years (95% CI, 0.1-12.2). The **Figure** presents cumulative incidences of demyelinating events.

To test for impact of control sampling (because the number of unexposed patients by far exceeded those exposed, our analysis might be sensitive to which patients were selected as controls), we ran the analysis 10 000 times with a new random selection of controls in each analysis. The median HR of the 10 000 analyses was 1.95 (IQR, 1.70-2.25), thus confirming that the observed 2-fold increased risk was not due to control selection.

Discussion | This population-based cohort study suggests a possible 2-fold increased relative risk but a low absolute risk of central demyelinating diseases associated with anti-TNF exposure in patients with IBD. While these preliminary findings could be due to a chance or unmeasured confounding and need confirmation in other studies, they do represent the first analytical data of this potential association. If true, the observed association could either be attributed to the unmasking of a latent demyelinating disease[6] or to the emergence of a de novo demyelinating disease.[1]

The rarity of demyelinating diseases limited the statistical power and capacity to adjust for or match on potential confounder variables. Thus, the estimates should be interpreted with caution because confounding cannot be excluded.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Andersen.
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