Exposure to Anti-TNF Medications Does Not Increase the Risk of Cardiac Arrhythmia in Inflammatory Bowel Disease: A Population-Based Cohort Study

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RESEARCH LETTER

Exposure to Anti-TNF Medications Does Not Increase the Risk of Cardiac Arrhythmia in Inflammatory Bowel Disease: A Population-Based Cohort Study

Anti-tumor necrosis factor (anti-TNF) agents are widely used in the management of the inflammatory bowel diseases (IBDs), Crohn's disease (CD), and ulcerative colitis (UC), when disease cannot be controlled by means of anti-inflammatory drugs, immunosuppressive drugs, or systemic corticosteroids.[1–3] Although anti-TNF is generally considered safe, and serious adverse events are either rare or controversial,[4–6] a clinical concern for serious cardiac arrhythmia as a possible adverse event to anti-TNF treatment has been presented in case reports.[7–9] We therefore aimed to perform a nationwide cohort study investigating the risk of cardiac arrhythmia among IBD patients treated with anti-TNF.

Using the Danish National Patient Register, we identified a cohort of all Danish residents diagnosed with IBD between January 1, 1995, and December 31, 2018. Individuals were included if in this time frame, they had at least two registrations with the International Classification of Diseases version 10 code K50 for CD or K51 for UC within a two-year period. Earliest date of study entry was January 1, 2005 from where the exposure, anti-TNF, was reliably registered. We excluded prevalent IBD cases diagnosed before January 1, 1995, individuals with prevalent outcome at or before study entry, and individuals exposed to anti-TNF before study entry. Study outcomes included the International Classification of Diseases-10 and surgery codes of any cardiac arrhythmia, cardiac arrest, and implantation of cardiac pacemaker or cardioverter-defibrillator, and were treated as a combined outcome (see Supplementary Material). Information on major gastrointestinal surgery, comorbidities, anti-TNF treatment, and outcome diagnoses was obtained through the Danish National Patient Register (see Supplementary Material). Information on exposure to oral corticosteroids was obtained through the Danish National Prescription Registry (Anatomical Therapeutic Chemical code H02AB). For a description of additional covariates, see Supplementary Materials. Individuals were followed from study entry until outcome of interest or time of censoring, including death without a cardiac arrhythmia diagnosis, emigration, or end of study, December 31, 2018, whichever occurred first. Exposure to anti-TNF (infliximab, adalimumab, golimumab) was treated as a time-varying covariate, where individuals exposed to anti-TNF were considered exposed from first administration until the end of follow-up. We performed a Cox regression adjusted for sex, age at study entry, Charlson comorbidity index score, age at IBD diagnosis, subtype of IBD, IBD severity score, year of study entry, year of IBD diagnosis, Degree of Urbanization (DEGURBA) of municipality, and socioeconomic index of municipality. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

A total of 44,053 IBD patients (CD, n = 14,660; UC, n = 29,393) were followed for 379,862 person-years (PYs) with a median follow-up of 9.57 years (95% CI, 9.46–9.66). During the follow-up, 8589 patients (19%) were exposed to anti-TNF with a median (interquartile range) observed exposure time of 4.7 (2.2, 8.1) years. Cardiac arrhythmia was observed in 2137 patients during 44,607 unexposed PYs and in 161 patients during 335,256 exposed PYs, with an incidence rate of 637.4/100,000 PY among unexposed individuals and 360.9/100,000 PY among exposed individuals. The median (interquartile range) time from study entry to anti-TNF was 1.8 (0.5, 4.9) years.

In adjusted analyses, the risk of cardiac arrhythmia was not increased among anti-TNF exposed as compared to anti-TNF unexposed individuals (HR, 0.95; 95% CI, 0.80–1.13). Nor was the risk increased among women (HR, 1.00; 95% CI, 0.78–1.27) or men (HR, 0.90; 95% CI, 0.70–1.15) separately (Figure).

In a sensitivity analysis, where patients were only considered exposed during the first 8 weeks after anti-TNF treatment and thus allowed to shift back and forth between the exposed and unexposed group, the risk of cardiac arrhythmia was not statistically significantly increased immediately following anti-TNF exposure either (HR, 1.10; 95% CI, 0.85–1.42).

To the authors' knowledge, this is the first unselected nationwide cohort study to examine cardiac arrhythmia as a possible adverse event to anti-TNF treatment among all IBD patients treated in a given country and followed long-term. Several case reports have suggested an association between anti-TNF and cardiac arrhythmia,[7–9] whereas one placebo-controlled trial[10] examined cardiac arrhythmia as an acute reaction to infliximab infusion in patients with rheumatoid arthritis and found no increase in the infliximab group compared to the placebo group.

The principal strength of this study lies in the unselected cohort of >44,000 IBD patients, facilitated by the Danish registries. With nearly 380,000 PYs of follow-up, even rarely occurring events would be expected to be detected.

Certain possible limitations of this study should be considered. With the registries available, we could not obtain data on certain classical

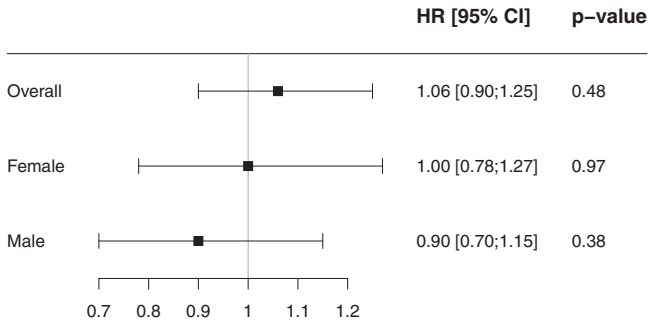

Figure. Risk of arrhythmia in patients with IBD—exposed vs unexposed to anti-TNF. CI, confidence interval; HR, hazard ratio.

cardiovascular risk factors such as body mass index and smoking status, only indirectly through data on comorbidity (eg, diabetes) which were included in the Charlson comorbidity index score. Also, we did not account for any drugs that may alter the risk of arrhythmia (QTc-prolonging drugs or antiarrhythmics), but we have no reason to believe that these drugs associate with likelihood for TNF exposure. Finally, it should be noted that in terms of arrhythmia, our combined outcome may be seen as heterogenous, but power did not allow for more refined categories.

In conclusion, in this nationwide, population-based cohort study of >44,000 patients with IBD, we found no statistically significantly increase in risk of our combined arrhythmia outcome (any arrhythmia, cardiac arrest or implantation of pacemaker or implantable cardioverter-defibrillator) when comparing IBD patients exposed to anti-TNF with patients not exposed. While this study alone may not completely answer the clinical concern in question, the results are indeed reassuring.

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Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.01.019.

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Abbreviations used in this paper: anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; PYs, person-years; UC, ulcerative colitis.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Due to Danish legislation, data will not be made available.

Reporting Guidelines:
STROBE.