Association of Anti-Inflammatory Therapy Use With the Incidence of Parkinson's Disease: A Person-Time Analysis Among Patients With Autoimmune Diseases

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CONCLUSIONS

1. Among individuals with autoimmune conditions and anti-inflammatory treatment, specifically anti-tumor necrosis factor (TNF) and anti-interleukin (IL)-17, a lower Parkinson's disease (PD) incidence rate was observed in comparison to those not treated (unadjusted and adjusted)
2. Person-time incidence rates indicate a potential treatment-response relationship
3. Lowering the levels of systemic inflammation may be associated with a reduced risk of PD

INTRODUCTION

- Autoimmune diseases such as rheumatoid arthritis (RA), ulcerative colitis (UC), Crohn's disease (CD), psoriasis (PS), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are characterized by an immune response to self-antigens causing tissue damage.[1]
- Previous studies have linked the development of PD with autoimmune disorders, suggesting shared pathophysiology.[2] Further, seminal scientific publications suggest that reducing inflammatory processes can be a potential target for intervention in PD.[3,4]
- To date, relatively little information is available regarding the potential benefit of anti-TNFs, such as adalimumab, and anti-IL-17 drugs, such as secukinumab and ixekizumab, on the development of PD.

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OBJECTIVE and METHODS

Objective

- To assess the comparative incidence of PD among patients with autoimmune diseases who are exposed to anti-TNF/anti-IL-17 drugs vs those without exposure.

Study Population and Data Source

- This was a retrospective cohort study utilizing closed claims data from the Komodo Health database (2014-2022).
- All eligible patients had at least 1 inpatient claim or at least 2 outpatient claims for RA, UC, CD, AS, or Ps/PsA identified by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes and were ≥18 years of age.
- The index diagnosis date was determined based on the first observable and confirmed diagnosis, assigning patients to the respective disease cohort, with a baseline period of 6 months and a variable follow-up duration.
- Individuals presenting with PD (identified by any diagnosis or prescription claim) any time prior to the index diagnosis date in the 6-month baseline period were excluded.
  - PD events were identified by 1 inpatient or ≥2 outpatient diagnosis claims, or 1 outpatient diagnosis claim and ≥1 prescription claim associated with PD therapy identified by diagnostic codes.
- Among patients with a confirmed autoimmune diagnosis, those with anti-TNF or anti-IL-17 treatment were identified. The index treatment date was defined as the start date of anti-TNF/anti-IL-17 and could occur on the index diagnosis date or within the 12 months thereafter.
- Patients not presenting any prescription claim for anti-TNF or anti-IL-17 treatment within the timeframe of the study were categorized as individuals not treated with anti-TNF/anti-IL-17.

Study Outcomes and Methods

- Charlson Comorbidity Index (CCI) scores using the Quan-enhanced CCI[5] were derived based on the presence of ICD-9 or ICD-10 codes in the 6-month baseline period.
- Binary indicators for the presence of comedications common to autoimmune diseases were generated and each comedication was identified by the presence of National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) codes, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Person-time (in years) with anti-TNF and/or anti-IL-17 treatment (exposure time) was defined as the start date of anti-TNF and/or anti-IL-17 therapy until the end of enrollment or PD index date, whichever was earliest. Person-time (in years) for individuals who had never used an anti-TNF/anti-IL-17 (non-exposure time) included the index diagnosis date until the index treatment date, end of enrollment, or PD index date, whichever came first.
- Descriptive statistics were reported to describe unadjusted PD events across each study group
- Poisson regression models were utilized to assess the association between treatment with anti-TNF and/or anti-IL-17 therapies and the incidence of PD.
  - Poisson regression facilitates adjustment for differences in individual-specific times at risk (time between index diagnosis date and exposure/non-exposure to treatment/end of observation period) due to inclusion of these times as offset in the model. Poisson regression is also the preferred method to evaluate data with rare events.[6] The model allowed for the adjustment of potential confounding factors, including age, gender, baseline CCI, treatment exposure, and post-index date use of other DMARDs, csDMARDs, corticosteroids, and NSAIDs.
  - By incorporating these covariates into the Poisson regression model, it accounted for both confounding effects and time-varying factors such as age and exposure to treatment. The resulting estimated incidence rate ratios (IRRs) with their corresponding 95% confidence intervals (CIs) characterized the relative incidence of PD in patients treated with anti-TNF and/or anti-IL-17 therapies compared to those not receiving these treatments.

RESULTS

Study Population and Demographic Characteristics

- Overall, 2,105,677 patients with confirmed diagnosis of RA, UC, CD, AS, or Ps/PsA were identified, of whom 114,082 received anti-TNF/anti-IL-17 treatment, while 1,991,595 remained untreated in the timeframe of 2015 to 2022. The breakdown by disease category is depicted in **Table 1**.

Table 1. Patient Attrition

	n	%
Patients with 1 inpatient or ≥2 outpatient claims at least 30 days apart but within 12 months for RA, UC, CD, AS, or Ps/PsA between Jan 1, 2015, and Dec 31, 2022	3,969,339	100
Patients excluded	1,863,662	47
Final sample	2,105,677	53

	Overall n (%)	Anti-TNF/ anti-IL-17 n (%)	Anti-TNF only n (%)	Anti-IL-17 only n (%)	Not treated with anti-TNF/anti-IL-17 (n, %)
Overall	2,105,677 (100)	114,082 (100)	106,314 (100)	5,672 (100)	1,991,595 (100)
RA	810,790 (39)	41,728 (37)	41,357 (39)	198 (3)	769,062 (39)
UC	285,467 (14)	11,911 (10)	11,908 (11)	2 (0)	273,556 (14)
CD	188,292 (9)	17,266 (15)	17,263 (16)	2 (0)	171,026 (9)
AS	48,743 (2)	7,014 (6)	6,376 (6)	275 (5)	41,729 (2)
Ps/PsA	675,626 (32)	29,714 (26)	23,332 (22)	4,993 (88)	645,912 (32)
≥1 autoimmune disease	96,759 (5)	6,449 (6)	6,078 (6)	202 (4)	90,310 (5)

- In all study groups that received treatment, the average age at the time of initial diagnosis was 47 years. For the collective group that did not receive anti-TNF/anti-IL-17 treatment, the average age was 54 years (notably higher). The median age across all groups was 48 years and was 56 years in the untreated study group. The largest proportion of patients across all study groups fell within the age range of 45 to 64 years. Furthermore, females constituted a majority in every study group.

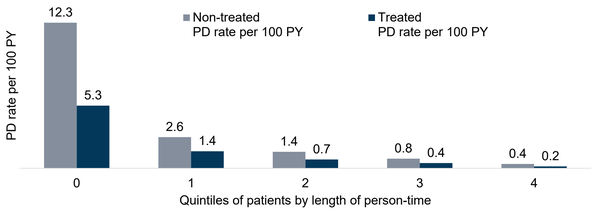
PD incidence (unadjusted)

- The PD incidence rate was 0.661 per 100 person-years (PY) in the exposed cohort compared to 0.949 per 100 PY in the unexposed cohort. The calculated unadjusted IRR comparing the exposed to the unexposed was 0.696 (95% CI: 0.669, 0.724).
- To explore a potential treatment-response relationship, quintiles were created dividing the range of person-time to allow for an equal (or close to equal) number of patients within each of the 5 quintiles. This resulted in a decrease of the PD incidence rate across the quintiles as the duration of follow-up time increased. Overall, the analysis of person-time incidence rates revealed a potential treatment-response relationship, with an incidence rate of 5.295 (95% CI: 4.937, 5.673) in the lowest person-time quintile and 0.158 per 100 PY (95% CI: 0.139, 0.179) in the highest person-time quintile. (**Figure 1**)

PD incidence (adjusted)

- The results of the multivariate Poisson models comparing cohorts exposed to anti-TNF or anti-IL-17 treatment with those lacking exposure revealed a significantly lower risk of PD (adjusted IRR: 0.77 [95% CI: 0.74-0.80]; *P*<0.0001) (**Table 2**).

Figure 1. PD Events as a Function of Quintiles of Follow-up Time



- When comparing anti-TNF treatment only to non-exposure to anti-TNF/anti-IL-17 treatment (**Table 2**), the results were similar (adjusted IRR: 0.77 [95% CI: 0.74-0.81]; *P*<0.0001). Patients exposed to anti-TNF/anti-IL-17 treatment only also demonstrated a significantly lower risk of PD compared to those who were not exposed (adjusted IRR: 0.64 [95% CI: 0.52-0.80]; *P*<0.0001) (**Figure 2**).
- These results suggest that both types of treatments (anti-TNF and anti-IL-17) may have some level of protective effect against PD.

Table 2. Summary of PD Incidence Among Anti-TNF/Anti-IL-17 Treated vs No Exposure

Variable	PD event	Person-years	Multivariate Poisson model[a]	
			Adjusted IRR per 100 person-years (95% CI)	*P*-value
Anti-TNF/anti-IL-17 treatment				
Yes	2,597	393,114.3	0.77 (0.74-0.80)	<0.0001
No	50,562	5,328,307.40	1 (Ref)	
Anti-TNF only treatment				
Yes	2,471	371,667.4	0.77 (0.74-0.81)	<0.0001
No	50,562	5,328,307.40	1 (Ref)	
Anti-IL-17 only treatment				
Yes	81	15,598.3	0.64 (0.52-0.80)	<0.0001
No	50,562	5,328,307.40	1 (Ref)	

[a] **The model allowed for the adjustment of age, gender, baseline CCI, treatment exposure, other DMARDs used post-index, csDMARDs used post-index, corticosteroids used post-index, and NSAIDs used post-index.**

Figure 2. Adjusted IRR per 100 PY