Do TNF Inhibitors Alter the Natural History of Ankylosing Spondylitis by Impacting the Incidence and Prevalence of Comorbidities and Extra-Articular Manifestations?

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Objective

- To evaluate the incidence and prevalence of ankylosing spondylitis (AS)-related comorbidities and extra-articular manifestations (EAMs) in AS patients in the US.

Background

- Tumor necrosis factor inhibitors (TNFi) have been shown to be efficacious in the treatment of AS, leading to reduction in signs and symptoms of disease, improvement in physical function and quality of life in AS patients.
- However, the impact of TNFi use on the incidence and prevalence of AS-related comorbidities and EAMs is not known.

Methods

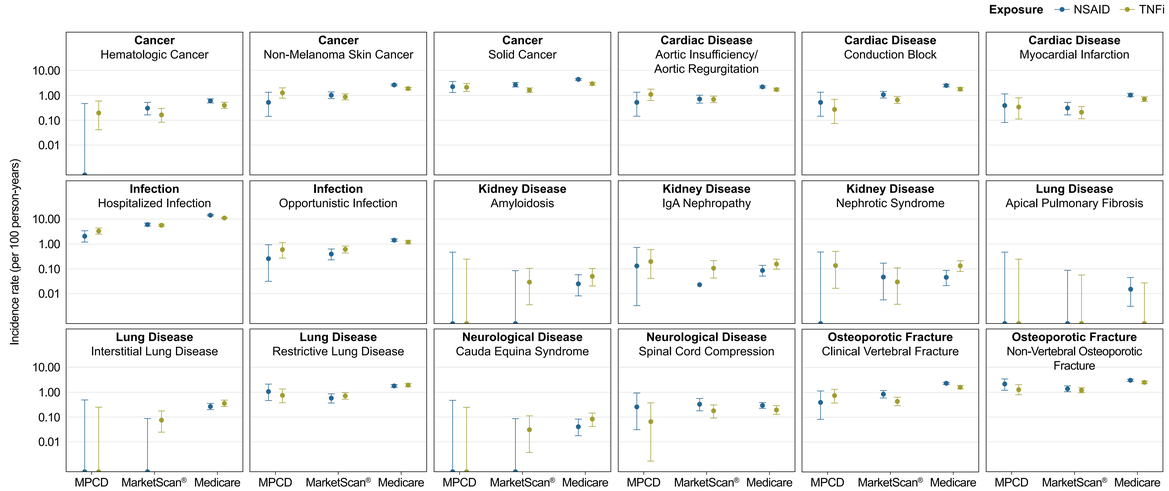
- We conducted a retrospective cohort study using 3 commercial insurance claims databases (Multi-Payer Claims Database [MPCD; 2007–2010], Truven MarketScan® [2010–2014], and the US Medicare Fee-for-Service Claims data [2006–2014]) to evaluate EAMs (uveitis, psoriasis, inflammatory bowel disease) and comorbidities (cardiac, renal, pulmonary, neurologic) in AS patients. Samples of the general population in MPCD and US Medicare were used as controls.
- All patients were required to have a diagnosis made by a rheumatologist (made at the index date), 6-months baseline data prior to index date, and drug-specific exposures after AS diagnosis.
- Three mutually-exclusive hierarchical exposure groups were examined:
  1. TNFi
  2. Conventional disease modifying anti-rheumatic drugs (DMARDs)
  3. No therapy or prescription of non-steroidal anti-inflammatory drugs (NSAIDs)
- Prevalence of comorbidities was ascertained during the 12-month period defined as 6 months pre- and post-index date.
- Incidence of comorbidities and EAMs was ascertained during the period between treatment initiation and the earliest of death, loss of medical coverage, end of study, first outcome occurrence, treatment discontinuation, or initiation of therapy at a higher level in exposure hierarchy.
- As DMARDs are not indicated for the treatment of AS, comparison data between DMARDs and TNFi are not shown.

Table 1. Crude prevalence of comorbidities and EAMs during 12 months (6 months pre- and post-index date) in AS and control populations

Specific Manifestation	AS			Control	
	MarketScan® n=11,982	MPCD n=3,000	Medicare n=22,584	MPCD n=1,139,225	Medicare n=1,844,703
Age, mean (years)	46.3	46.6	63.5	50.1	68.9
Female, %	45.8	39.8	43.5	55.8	61.3
Comorbidities, % (95% CI)					
Hematologic cancer	0.6 (0.4–0.7)	0.5 (0.3–0.8)	1.6 (1.4–1.7)	0.6 (0.6–0.6)	1.2 (1.2–1.2)
Non-melanoma skin cancer	0.6 (0.5–0.8)	0.0 (0.0–0.0)	1.9 (1.7–2.0)	0.0 (0.0–0.0)	0.7 (0.7–0.8)
Solid cancer	3.5 (3.2–3.8)	4.0 (3.3–4.7)	9.8 (9.4–10.2)	3.9 (3.8–3.9)	8.8 (8.8–8.9)
Aortic insufficiency/aortic regurgitation	1.3 (1.1–1.5)	1.9 (1.5–2.4)	4.9 (4.6–5.2)	0.9 (0.9–0.9)	2.7 (2.6–2.7)
Conduction block	1.3 (1.1–1.5)	0.6 (0.4–1.0)	4.5 (4.2–4.8)	0.7 (0.7–0.7)	2.3 (2.2–2.3)
Myocardial infarction	0.6 (0.5–0.7)	0.5 (0.3–0.8)	1.8 (1.6–2.0)	0.2 (0.2–0.2)	1.0 (1.0–1.0)
Hospitalized infection	6.9 (6.5–7.4)	5.2 (4.4–6.0)	19.4 (18.9–19.9)	2.2 (2.2–2.3)	8.9 (8.8–8.9)
Opportunistic infection	1.0 (0.9–1.2)	1.1 (0.7–1.5)	2.4 (2.2–2.7)	0.4 (0.4–0.4)	0.9 (0.8–0.9)
Amyloidosis	0.0 (0.0–0.1)	0.0 (0.0–0.2)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
IgA nephropathy	0.1 (0.1–0.2)	0.1 (0.0–0.3)	0.2 (0.2–0.3)	0.1 (0.1–0.1)	0.1 (0.1–0.1)
Nephrotic syndrome	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.2 (0.1–0.2)	0.0 (0.0–0.0)	0.1 (0.1–0.1)
Apical pulmonary fibrosis	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Interstitial lung disease	0.1 (0.1–0.2)	0.1 (0.0–0.2)	0.7 (0.6–0.8)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Restrictive lung disease	1.4 (1.2–1.6)	1.3 (0.9–1.7)	3.2 (3.0–3.4)	0.7 (0.6–0.7)	1.3 (1.2–1.3)
Cauda equina syndrome	0.1 (0.0–0.1)	0.1 (0.0–0.3)	0.2 (0.2–0.3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Spinal cord compression	0.2 (0.2–0.3)	0.2 (0.1–0.4)	0.9 (0.7–1.0)	0.0 (0.0–0.0)	0.1 (0.1–0.1)
Clinical vertebral fracture	2.2 (2.0–2.5)	2.4 (1.9–3.0)	7.3 (7.0–7.7)	0.5 (0.4–0.5)	1.1 (1.1–1.1)
Non-vertebral osteoporotic fracture	1.9 (1.6–2.1)	2.9 (2.4–3.6)	4.5 (4.2–4.8)	1.2 (1.2–1.2)	2.5 (2.5–2.6)
EAMs, % (95% CI)					
Crohn's disease	3.6 (3.3–3.9)	4.3 (3.6–5.0)	4.8 (4.5–5.1)	2.2 (2.1–2.2)	0.3 (0.3–0.4)
Ulcerative colitis	2.6 (2.3–2.9)	2.5 (2.0–3.1)	2.7 (2.5–2.9)	2.0 (2.0–2.0)	0.4 (0.4–0.4)
Psoriasis	2.7 (2.4–3.0)	2.5 (2.0–3.1)	3.8 (3.5–4.0)	4.6 (4.6–4.7)	1.0 (1.0–1.0)
Psoriatic arthritis	4.1 (3.7–4.4)	3.7 (3.0–4.4)	5.0 (4.7–5.3)	1.0 (1.0–1.1)	0.2 (0.2–0.2)
Uveitis	7.6 (7.1–8.1)	7.0 (6.2–8.0)	4.0 (3.8–4.3)	0.2 (0.2–0.2)	0.2 (0.2–0.2)

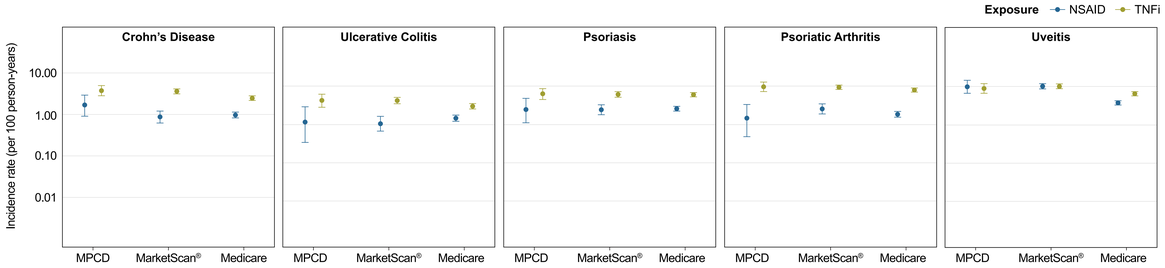
CI: confidence interval; IgA: immunoglobulin A.

Figure 1. Crude Incidence of comorbidities in AS patients treated with NSAIDs and TNFi



IgA: Immunoglobulin A.

Figure 2. Crude incidence of EAMs in AS patients treated with NSAIDs and TNFi



Results

- Out of approximately 40 million beneficiaries, 37,566 patients met drug-specific exposure criteria.
- **Table 1** shows the prevalence of comorbidities and EAMs in AS patients stratified by data source.
- Comorbidities were more common in Medicare AS patients compared with MPCD or MarketScan®. This may be due to the higher average age of the Medicare cohort, which is likely to be accompanied by a higher rate of comorbidities.
- Despite the possibility of patients with more severe disease receiving TNFi treatment,[1] their crude incidence of certain cardiac, pulmonary and neurologic comorbidities was similar to, or lower than, those treated with NSAIDs **(Figure 1)**, although they had a higher incidence of some EAMs **(Figure 2)**.

Conclusions

- To our knowledge, this was the largest investigation of incidence and prevalence of AS comorbidities and EAMs within the US.
- These preliminary findings suggest that TNFi have an impact on the broader disease spectrum of AS.
- In order to establish more conclusively whether TNFi alter the natural history of AS, additional research is necessary to account for potential confounders, such as analysis of propensity score-matched patients.

References

1. Ward M. *et al.* Arthritis Rheumatol 2016;68(2):282-98

Author Contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: AD, KW, RB, BC, RS, LP, JS, SS, HY, LC, JC; Drafting of the publication, or revising it critically for important intellectual content: AD, KW, RB, BC, RS, LP, JS, SS, HY, LC, JC; Final approval of the publication: AD, KW, RB, BC, RS, LP, JS, SS, HY, LC, JC.

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