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**Do TNF Inhibitors Reduce the Incidence and Prevalence of Comorbidities in Ankylosing Spondylitis (AS)?**

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**Background:** Patients with ankylosing spondylitis (AS), a multi-system immune-mediated chronic inflammatory disease, have shown a reduction in signs and symptoms, improvement in physical function and quality of life with the advent of tumor necrosis factor inhibitors (TNFi) treatment. The magnitude of the impact of TNFi on the incidence of AS-related comorbidities and disease manifestations is not known.

**Methods:** We conducted a retrospective cohort study using three 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 extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease) and comorbidities (cardiac, renal, pulmonary, neurologic) in three mutually-exclusive hierarchical exposure groups of AS patients, categorized as (lowest to highest): (1) those managed with either no AS therapy or on prescription non-steroidal anti-inflammatory drugs (NSAIDs), (2) those on conventional disease modifying anti-rheumatic drugs (DMARDs), and (3) those prescribed TNFi. Entry criteria were a rheumatologist’s diagnosis of AS, six-months of baseline data with medical and pharmacy coverage, and administration of drug-specific exposures of interest after AS diagnosis. Prevalent comorbidities were identified from the period between AS cohort entry and treatment exposure. Incident comorbidities were identified from the period between treatment exposure and the earliest of date of death, loss of medical coverage, end of study period, first outcome occurrence, or treatment discontinuation or initiation of therapy at a higher level in exposure hierarchy.

**Results:** Total number of beneficiaries included in the three databases is approximately 40 million. The prevalence of comorbidities and extra-articular manifestations of AS by treatment exposures, stratified by each data source, are shown in Table 1. The incidence rates of outcome of interest by treatment exposures, stratified by each data source, are shown in Table 2.

**Table 1:** Prevalence of comorbidities and extra-articular manifestations per 100 treatment exposures, stratified by data source.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Specific manifestation** | **MPCD** | | | **MarketScan** | | | **Medicare** | | |
| **TNFi** | **DMARDS** | **NSAIDS/**  **No Exposure** | **TNFi** | **DMARDS** | **NSAIDS/ No eExposure** | **TNFi** | **DMARDS** | **NSAIDS/ No Exposure** |
| Aortic Insufficiency | 1.5 | 0.8 | 2.0 | 1.8 | 2.1 | 2.8 | 8.0 | 10.9 | 11.7 |
| Conduction Block | 0.4 | 0.8 | 0.8 | 1.7 | 2.4 | 2.5 | 6.8 | 8.6 | 10.5 |
| Myocardial infarction | 0.3 | NA | 0.5 | 0.5 | 0.5 | 0.5 | 1.7 | 1.9 | 2.4 |
| Crohn’s Disease | 6.1 | 4.2 | 2.9 | 6.4 | 4.8 | 3.3 | 10.4 | 8.8 | 5.8 |
| Ulcerative Colitis | 3.7 | 3.1 | 2.0 | 4.9 | 3.0 | 2.6 | 7.4 | 7.2 | 4.9 |
| Amyloidosis | NA | NA | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 | 0.2 |
| IgA nephropathy | 0.1 | 0.2 | 0.1 | 0.2 | 0.2 | 0.1 | 0.7 | 0.9 | 0.6 |
| Nephrotic syndrome | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | 0.2 | 0.5 | 0.3 |
| Apical Pulmonary fibrosis | NA | NA | 0.0 | 0.0 | NA | 0.0 | 0.0 | 0.1 | 0.0 |
| Interstitial lung disease | 0.2 | NA | 0.0 | 0.1 | 0.2 | 0.1 | 0.3 | 0.5 | 0.2 |
| Restrictive lung disease | 1.0 | 0.6 | 1.6 | 3.9 | 4.4 | 4.7 | 15.5 | 20.1 | 18.0 |
| Cauda Equina syndrome | NA | NA | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.3 | 0.3 |
| Spinal Cord compression | 0.1 | NA | 0.3 | 0.3 | 0.5 | 0.5 | 1.7 | 2.0 | 2.4 |
| Psoriasis | 4.1 | 2.5 | 2.7 | 5.1 | 3.8 | 2.3 | 9.9 | 8.0 | 5.8 |
| Psoriatic arthritis | 6.6 | 4.8 | 2.4 | 8.5 | 6.2 | 2.9 | 13.9 | 10.1 | 5.4 |
| Uveitis | 11.3 | 8.5 | 7.4 | 13.4 | 11.0 | 11.2 | 13.4 | 10.1 | 8.0 |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Specific manifestation** | **MPCD** | | | **MarketScan** | | | **Medicare** | | |
| **TNFi** | **DMARDS** | **NSAIDS/**  **No Exposure** | **TNFi** | **DMARDS** | **NSAIDS/ No eExposure** | **TNFi** | **DMARDS** | **NSAIDS/ No Exposure** |
| Aortic Insufficiency | 1.3 | 0.4 | 0.1 | 0.9 | 0.9 | 0.7 | 4.8 | 5.8 | 3.9 |
| Conduction Block | 0.2 | 0.0 | 0.1 | 0.9 | 1.2 | 0.6 | 3.9 | 4.6 | 3.5 |
| Myocardial infarction | 0.2 | 0.0 | 0.0 | 0.3 | 0.2 | 0.2 | 1.0 | 1.0 | 0.6 |
| Crohn’s Disease | 5.0 | 2.9 | 0.7 | 4.8 | 3.4 | 0.9 | 8.3 | 6.5 | 2.1 |
| Ulcerative Colitis | 2.1 | 1.5 | 0.6 | 3.3 | 1.6 | 0.6 | 5.1 | 4.6 | 1.6 |
| Amyloidosis | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 |
| IgA nephropathy | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.0 | 0.4 | 0.4 | 0.3 |
| Nephrotic syndrome | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 | 0.1 | 0.2 | 0.1 |
| Apical Pulmonary fibrosis | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 |
| Interstitial lung disease | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 | 0.0 | 0.2 | 0.3 | 0.1 |
| Restrictive lung disease | 0.7 | 0.4 | 0.4 | 2.1 | 2.3 | 1.1 | 9.0 | 11.4 | 6.2 |
| Cauda Equina syndrome | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.1 | 0.2 | 0.1 |
| Spinal Cord compression | 0.0 | 0.0 | 0.1 | 0.1 | 0.2 | 0.2 | 1.0 | 1.1 | 0.7 |
| Psoriasis | 2.7 | 1.0 | 0.6 | 3.3 | 2.2 | 0.8 | 7.0 | 5.1 | 2.0 |
| Psoriatic arthritis | 5.2 | 2.9 | 0.5 | 6.5 | 4.0 | 1.1 | 11.4 | 7.7 | 2.3 |
| Uveitis | 6.7 | 5.2 | 2.0 | 8.6 | 5.4 | 3.1 | 9.8 | 6.6 | 3.6 |

**Table 2:** Crude Incidence Rates of comorbidities and disease manifestations per 100 patient-years by treatment exposures (TNFi versus NSAIDs/No treatment, or TNFi versus DMARDs), stratified by data source. Only significant data are shown.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **MPCD Database** | | | **Marketscan Database** | | | **Medicare Database** | | |
|  | **TNFi** | **NSAIDs/No Treatment** | **p Value** | **TNFi** | **NSAIDs/No Treatment** | **p Value** | **TNFi** | **NSAIDs/No Treatmetn** | **p Value** |
| **Comparison of TNFi vs NSAIDs** | | | | | | | | | |
| **Aortic Insufficiency** | 1.3 | 1.9 | NS | 1.2 | 2.1 | 0.000 | 3.2 | 6.0 | 0.000 |
| **Conduction Block** | 0.3 | 0.9 | 0.03 | 1.1 | 2.4 | 0.000 | 2.9 | 5.9 | 0.000 |
| **Myocardial Infarction** | 0.3 | 0.6 | NS | 0.2 | 0.6 | 0.000 | 0.7 | 1.5 | 0.000 |
| **Restrictive Lung Disease** | 0.9 | 2.0 | 0.008 | 1.9 | 3.2 | 0.000 | 5.9 | 8.7 | 0.000 |
| **Spinal Cord Compression** | 0.1 | 0.3 | NS | 0.3 | 0.5 | 0.01 | 0.4 | 0.8 | 0.000 |
| **Psoriasis** | 3.5 | 1.6 | 0.000 | 3.8 | 1.8 | 0.000 | 3.8 | 2.1 | 0.000 |
| **Crohn’s Disease** | 4.7 | 3.0 | 0.006 | 4.8 | 2.6 | 0.000 | 3.9 | 2.5 | 0.000 |
| **Ulcerative Colitis** | 2.5 | 1.6 | 0.05 | 3.1 | 2.1 | 0.000 | 2.4 | 1.8 | 0.000 |
| **Uveitis** | 5.0 | 4.9 | NS | 7.6 | 8.0 | NS | 5.0 | 3.0 | 0.000 |
| **Comparison of TNFi vs DMARDs** | | | | | | | | | |
| **Aortic Insufficiency** | 1.3 | 0.5 | 0.132 | 1.2 | 1.5 | 0.279 | 3.2 | 4.7 | 0.000 |
| **Conduction Block** | 0.3 | 0.0 | 0.286 | 1.1 | 1.4 | 0.473 | 2.9 | 4.2 | 0.000 |
| **Myocardial Infarction** | 0.3 | 0.0 | 0.286 | 0.2 | 0.3 | 0.568 | 0.7 | 1.2 | 0.000 |
| **Restrictive Lung Disease** | 0.9 | 0.0 | 0.029 | 1.9 | 2.4 | 0.190 | 5.9 | 7.7 | 0.000 |
| **Psoriasis** | 3.5 | 1.0 | 0.003 | 3.8 | 3.3 | 0.397 | 3.8 | 3.4 | 0.161 |
| **Ulcerative Colitis** | 2.5 | 0.9 | 0.041 | 3.1 | 3.2 | 0.816 | 2.4 | 2.6 | 0.472 |
| **Uveitis** | 5.0 | 6.5 | 0.228 | 7.6 | 8.6 | 0.200 | 5.0 | 3.8 | 0.000 |

**Conclusion**: This is the largest investigation of the prevalence of comorbidities and extra-articular manifestations of AS within the US, using three insurance claims databases. Patients treated with TNFi have lower crude incidence of certain cardiac, pulmonary and neurologic comorbidities compared to those treated with NSAIDs or DMARDs alone, and higher incidence of some extra-articular manifestations (e.g. psoriasis, uveitis and IBD) where TNFi may be implicated.

**CONFLICTS:**

AD has received research grants from Amgen, Eli Lilly, GSK, Janssen, Novartis, UCB; and has served on the advisory boards of Eli Lilly, Janssen, Novartis, UCB.

RLB is a Contractor for UCB and Owner of Bohn Epidemiology, LLC. There are no conflicts with other clients.

KLW has consulting with UCB, Roche, Lilly, Pfizer, GSK, AbbVie, Galapagos, and BMS; and has research grants with BMS.

HY has research grants from BMS