**Do TNF Inhibitors (TNFi) Impact the Comorbidities and Extra-Articular Manifestations (EAMs), and Thereby Alter the Natural History of** **Ankylosing Spondylitis (AS)?**

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**Background:** TNFi treatment has led to reduction in signs and symptoms, improvement in physical function and quality of life in AS patients. Whether TNFi impact the incidence of AS-related comorbidities & 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 physician-diagnosed comorbidities (cardiac, renal, pulmonary, neurologic) in AS patients diagnosed by a rheumatologist (index date), having 6-months baseline data prior to the index date, and drug-specific exposures after AS diagnosis. Three mutually-exclusive hierarchical exposure groups were examined: (1) no therapy or prescription non-steroidal anti-inflammatory drugs (NSAIDs), (2) conventional disease modifying anti-rheumatic drugs (DMARDs), and (3) TNFi. Prevalence of comorbidities were ascertained in a 12-month period (6 months pre & post index date). Incidence of comorbidities & EAMs were ascertained during the period following 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. Patients with history of prior events (except infections) were excluded from the incidence assessment for that event. To ensure comparability of cohorts, a propensity score model predicting the propensity to be prescribed a TNFi using a multinomial logistic regression model was employed. Hazard ratios comparing TNFi versus DMARDs and no therapy or NSAIDs were estimated using inverse probability treatment weighted Cox proportional hazards models.

**Results:** Out of nearly 40 million beneficiaries, 37,566 patients were included. Prevalence of AS in the MPCD population was 0.26% and in the Medicare population was 1.21%. Table 1 shows the prevalence of comorbidities and EAMs of AS, by treatment exposure, stratified by data source. As expected, comorbidities were more common in Medicare AS patients compared to MPCD or MarketScan in all exposure groups. Table 2 shows the incidence rates of outcomes by treatment exposures, stratified by data source. The propensity score matched incidence of solid cancers, myocardial infarction, conduction block, cord compression and vertebral fractures were lower in TNFi treated patients compared to those treated with NSAIDs or DMARDs alone, though TNFi treated Medicare patients had a higher incidence of EAMs such as psoriasis, uveitis and ulcerative colitis.

**Conclusion**: This is the largest investigation of the prevalence & incidence of comorbidities & EAMs of AS within the US. It suggests that TNFi use is associated with a lower incidence of some comorbidities, but a trend of higher incidence of EAMs. Although some differences in results across data sources may be explained by baseline characteristics (e.g. Medicare patients being older), our results suggest that TNFi are associated with lower prevalence of those comorbidities for which the Medicare population is at greater risk.

**Table 1:** Prevalence of physician-diagnosed comorbidities and EAMs during 12 months (6 months pre and 6 months post index date; per 100 cohort members), stratified by data source.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome categories** | **Specific manifestation** | **AS cohort** | | |
| **MPCD** | **Market Scan** | **Medicare** |
|  | N | 3,000 | 11,982 | 22,584 |
|  | Mean age | 46.6 | 46.3 | 63.5 |
| Cancer | Hematologic Cancer | 0.5 | 0.6 | 1.6 |
| Non Melanoma Skin Cancer | 0.0 | 0.6 | 1.9 |
| Solid Cancer | 4.0 | 3.5 | 9.8 |
| Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 1.9 | 1.3 | 4.9 |
| Conduction Block | 0.6 | 1.3 | 4.5 |
| Myocardial infarction | 0.5 | 0.6 | 1.8 |
| Infection | Hospitalized infection | 5.2 | 6.9 | 19.4 |
| Opportunistic infection | 1.1 | 1.0 | 2.4 |
| Inflammatory bowel disease | Crohn’s Disease | 4.3 | 3.6 | 4.8 |
| Ulcerative Colitis | 2.5 | 2.6 | 2.7 |
| Kidney disease | Amyloidosis | 0.0 | 0.0 | 0.1 |
| IgA nephropathy | 0.1 | 0.1 | 0.2 |
| Nephrotic syndrome | 0.0 | 0.0 | 0.2 |
| Lung disease | Apical Pulmonary fibrosis | 0.0 | 0.0 | 0.0 |
| Interstitial lung disease | 0.1 | 0.1 | 0.7 |
| Restrictive lung disease | 1.3 | 1.4 | 3.2 |
| Neurological Disease | Cauda Equina syndrome | 0.1 | 0.1 | 0.2 |
| Spinal Cord compression | 0.2 | 0.2 | 0.9 |
| Osteoporotic fracture | Clinical vertebral fracture | 2.4 | 2.2 | 7.3 |
| Non-vertebral osteoporotic fracture | 2.9 | 1.9 | 4.5 |
| PsO/PsA | Psoriasis | 2.5 | 2.7 | 3.8 |
| Psoriatic arthritis | 3.7 | 4.1 | 5.0 |
| Uveitis | Uveitis | 7.0 | 7.6 | 4.0 |

**Table 2:** Propensity score weighted hazard ratios of physician-diagnosed outcomes and EAMs by treatment exposures: 1) TNFi vs. NSAIDs/No treatment, 2) TNFi vs. DMARDs, stratified by data source. Unstable hazard ratios due to zero incident events are not shown. Only significant results are shown due to size constraints.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **disease** | **comparison** | **database** | **HazardRatio** | **RobustWaldLower** | **RobustWaldUpper** |
| Non Melanoma Skin Cancer | TNF vs DMARD | Medicare | 1.29 | 1.03 | 1.61 |
| Solid Cancer | TNF vs NSAID or no exposure | Marketscan | 0.72 | 0.56 | 0.93 |
| Solid Cancer | TNF vs NSAID or no exposure | Medicare | 0.80 | 0.70 | 0.92 |
| Conduction Block | TNF vs NSAID or no exposure | Medicare | 0.81 | 0.67 | 0.98 |
| Myocardial infarction | TNF vs NSAID or no exposure | Medicare | 0.62 | 0.47 | 0.80 |
| Hospitalized infection | TNF vs DMARD | Medicare | 0.88 | 0.80 | 0.97 |
| Hospitalized infection | TNF vs NSAID or no exposure | Marketscan | 0.80 | 0.69 | 0.93 |
| Hospitalized infection | TNF vs NSAID or no exposure | Medicare | 0.76 | 0.70 | 0.82 |
| Ulcerative Colitis | TNF vs DMARD | Marketscan | 0.62 | 0.42 | 0.93 |
| Ulcerative Colitis | TNF vs NSAID or no exposure | Medicare | 1.28 | 1.05 | 1.56 |
| Cauda Equina syndrome | TNF vs DMARD | Medicare | 17.50 | 2.10 | 145.90 |
| Spinal Cord compression | TNF vs NSAID or no exposure | Medicare | 0.47 | 0.31 | 0.73 |
| Clinical vertebral fracture | TNF vs NSAID or no exposure | Marketscan | 0.38 | 0.23 | 0.63 |
| Clinical vertebral fracture | TNF vs NSAID or no exposure | Medicare | 0.56 | 0.47 | 0.67 |
| Psoriasis | TNF vs NSAID or no exposure | Marketscan | 1.43 | 1.14 | 1.80 |
| Psoriasis | TNF vs NSAID or no exposure | Medicare | 1.39 | 1.19 | 1.63 |
| Psoriatic arthritis | TNF vs DMARD | Marketscan | 0.54 | 0.42 | 0.70 |
| Psoriatic arthritis | TNF vs NSAID or no exposure | Marketscan | 1.77 | 1.43 | 2.18 |
| Psoriatic arthritis | TNF vs NSAID or no exposure | Medicare | 1.95 | 1.68 | 2.26 |
| Uveitis | TNF vs NSAID or no exposure | MPCD | 0.63 | 0.44 | 0.90 |
| Uveitis | TNF vs NSAID or no exposure | Marketscan | 0.75 | 0.64 | 0.88 |
| Uveitis | TNF vs NSAID or no exposure | Medicare | 1.29 | 1.11 | 1.49 |

**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
* JC has research grants and consulting with UCB, Janssen, Amgen, Roche, Myriad Genetics, Lilly, Novartis, BMS, and Pfizer
* 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
* LP, JS, RYS are employed by UCB Biosciences, the sponsor of this study.
* RLB is a Contractor for UCB and Owner of Bohn Epidemiology, LLC; There are no conflicts with other clients