**Title Characters: 160 (Title Character Limit 250)**

**Body Characters excluding title, authors, affiliations, conflicts: 2242 + 500 (fixed character count for each Table is 250) = Total characters 2742.**

**(Body Character Limit 2750 characters excluding title, authors, affiliations, conflicts)**

**Do TNF Inhibitors (TNFi) Alter the Natural History of** **Ankylosing Spondylitis (AS) by Impacting the Incidence and Prevalence of Comorbidities and Extra-Articular Manifestations (EAMs)?**

Atul Deodhar, Kevin L. Winthrop, Benjamin Chan, Sarah A. R. Siegel, Lisa Pisenti\*, Jeffery Stark\*, Robert Y. Suruki\*, Rhonda L. Bohn\*, Huifeng Yun\*\*, Lang Chen\*\*, and Jeffrey R. Curtis\*\*

Oregon Health & Science University, Portland, OR; \*UCB Biosciences, Raleigh, NC; \*\*University of Alabama at Birmingham, Birmingham, AL

**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 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 12-month periods (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; comparisons made using the mid-p exact test (α=0.05).

**Results:** Out of nearly 40 million beneficiaries, 63,052 patients were included. Table 1 shows the prevalence of comorbidities and EAMs of AS, by treatment exposures, stratified by data source. Comorbidities were more common in Medicare AS patients compared to MPCD or MarketScan. Table 2 shows the incidence rates of outcomes by treatment exposures, stratified by data source. Despite the possibility of sicker patients receiving TNFi treatment, their crude incidence of certain cardiac, pulmonary and neurologic comorbidities were lower compared to those treated with NSAIDs or DMARDs alone, though they had higher incidence of some EAMs.

**Conclusion**: This largest investigation of the prevalence & incidence of comorbidities & EAMs of AS within the US suggests TNFi to be disease modifying. In the absence of control for confounding, these findings are considered preliminary.

**Table 1:** Prevalence of physician-diagnosed comorbidities and EAMs during 12 months (per 100 treatment exposures), stratified by data source.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **MPCD** | | | **MarketScan** | | | **Medicare** | | |
| **TNFi** | **DMARDS** | **NSAIDS/ No Exposure** | **TNFi** | **DMARDS** | **NSAIDS/ No Exposure** | **TNFi** | **DMARDS** | **NSAIDS/ No Exposure** |
| **Demographics** |  |  |  |  |  |  |  |  |  |
| N | 1,107 | 421 | 2,356 | 4,797 | 1,799 | 9,340 | 4,866 | 4,231 | 21,877 |
| Age, mean (years) | 41 | 42 | 49 | 43 | 46 | 47 | 55 | 61 | 65 |
| % Female | 38.1 | 44.4 | 39.9 | 46.7 | 54.0 | 44.4 | 44.6 | 55.1 | 41.8 |
| **Specific manifestation** |  |  |  |  |  |  |  |  |  |
| Aortic Insufficiency | 1.80 | 1.04 | 1.54 | 0.52 | 0.64 | 0.73 | 2.48 | 3.39 | 4.52 |
| Conduction Block | 0.23 | 0.00 | 0.66 | 0.50 | 0.93 | 0.88 | 2.16 | 2.81 | 4.53 |
| Myocardial infarction | 0.00 | 0.00 | 0.04 | 0.16 | 0.10 | 0.58 | 0.27 | 0.60 | 1.03 |
| Crohn’s Disease | 5.79 | 3.74 | 3.12 | 3.70 | 2.69 | 1.91 | 8.37 | 6.41 | 4.03 |
| Ulcerative Colitis | 2.89 | 2.49 | 1.62 | 2.18 | 1.52 | 1.11 | 4.17 | 3.81 | 2.29 |
| Amyloidosis | 0.00 | 0.00 | 0.04 | 0.00 | 0.00 | 0.01 | 0.10 | 0.02 | 0.09 |
| IgA nephropathy | 0.31 | 0.21 | 0.12 | 0.05 | 0.10 | 0.02 | 0.19 | 0.25 | 0.23 |
| Nephrotic syndrome | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.02 | 0.19 | 0.25 | 0.18 |
| Apical Pulmonary fibrosis | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.06 | 0.03 |
| Interstitial lung disease | 0.00 | 0.00 | 0.00 | 0.07 | 0.05 | 0.06 | 0.07 | 0.29 | 0.07 |
| Restrictive lung disease | 0.70 | 0.42 | 1.20 | 0.67 | 0.83 | 1.04 | 6.54 | 9.40 | 9.67 |
| Cauda Equina syndrome | 0.00 | 0.00 | 0.08 | 0.00 | 0.10 | 0.03 | 0.13 | 0.02 | 0.20 |
| Spinal Cord compression | 0.16 | 0.00 | 0.35 | 0.09 | 0.24 | 0.22 | 0.51 | 0.69 | 1.22 |
| Psoriasis | 4.14 | 1.25 | 1.81 | 0.85 | 0.88 | 0.50 | 5.04 | 3.50 | 1.77 |
| Psoriatic arthritis | 6.41 | 5.41 | 2.24 | 2.23 | 2.10 | 0.61 | 10.96 | 8.51 | 3.19 |
| Uveitis | 7.19 | 5.82 | 5.17 | 1.85 | 1.52 | 1.58 | 7.98 | 5.31 | 4.13 |
| Hematologic cancer | 0.31 | 0.21 | 0.39 | 0.16 | 0.59 | 0.46 | 0.79 | 2.02 | 2.08 |
| Non-melanoma skin cancer | 0.00 | 0.00 | 0.00 | 0.21 | 0.15 | 0.20 | 0.94 | 0.94 | 1.50 |
| Solid cancer | 2.11 | 1.46 | 3.47 | 0.76 | 2.89 | 2.52 | 6.61 | 8.95 | 12.10 |
| Hospitalized infection | 0.08 | 0.00 | 0.19 | 2.91 | 3.47 | 5.60 | 7.19 | 11.23 | 15.40 |
| Opportunistic infection | 1.33 | 1.04 | 0.81 | 0.74 | 0.78 | 0.55 | 3.31 | 3.14 | 2.12 |
| Clinical vertebral fracture |  |  |  |  |  |  |  |  |  |
| Non-vertebral osteoporotic fracture |  |  |  |  |  |  |  |  |  |

**Table 2:** Crude incidence rates of physician-diagnosed comorbidities and EAMs per 100 patient-years by treatment exposures: 1) TNFi vs. NSAIDs/No treatment, 2) TNFi vs. DMARDs, stratified by data source. Only significant data are shown.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **MPCD** | | | **MarketScan** | | | **Medicare** | | |
|  | **TNFi** | **NSAIDs/No Treatment or DMARDs** | **p Value** | **TNFi** | **NSAIDs/No Treatment or DMARDs** | **p Value** | **TNFi** | **NSAIDs/No Treatment or DMARDs** | **p Value** |
| **Comparison of TNFi vs NSAIDs/No Treatment** | | | | | | | | | |
| Aortic Insufficiency | 1.3 | 1.6 | NS | 0.6 | 0.8 | NS | 1.9 | 3.4 | <0.001 |
| Conduction Block | 0.3 | 0.6 | NS | 0.5 | 0.9 | 0.002 | 2 | 3.8 | <0.001 |
| Myocardial Infarction | 0 | 0 | NS | 0.2 | 0.6 | <0.001 | 0.4 | 0.9 | <0.001 |
| Restrictive Lung Disease | 0.9 | 1.5 | NS | 0.6 | 0.9 | 0.017 | 5.3 | 7.8 | <0.001 |
| Spinal Cord Compression | 0.1 | 0.3 | NS | 0.1 | 0.1 | NS | 0.4 | 0.7 | <0.001 |
| Psoriasis | 3.4 | 1.5 | <0.001 | 0.8 | 0.4 | <0.001 | 2.5 | 1.1 | <0.001 |
| Crohn’s Disease | 4.6 | 2.6 | <0.001 | 2.8 | 1.4 | <0.001 | 3.6 | 2.3 | <0.001 |
| Ulcerative Colitis | 2.5 | 1.3 | 0.006 | 1.5 | 0.8 | <0.001 | 2.2 | 1.5 | <0.001 |
| Uveitis | 4.4 | 3.9 | NS | 0.9 | 0.8 | NS | 4.1 | 2.5 | <0.001 |
| Hematologic Cancer | 0.2 | 0.4 | NS | 0.2 | 0.5 | 0.005 | 0.6 | 1.3 | <0.001 |
| Non Melanoma Skin Cancer | 0 | 0 | NS | 0.3 | 0.2 | NS | 1 | 1.6 | <0.001 |
| Solid Cancer | 1.8 | 3.7 | <0.001 | 0.9 | 2.7 | <0.001 | 4 | 8 | <0.001 |
| Hospitalized infection | 0.1 | 0.2 | NS | 2.6 | 5.4 | <0.001 | 7.1 | 12.7 | <0.001 |
| Opportunistic infection | 0.9 | 0.5 | NS | 0.3 | 0.3 | NS | 1.8 | 1.7 | NS |
| Clinical vertebral fracture |  |  |  |  |  |  |  |  |  |
| Non-vertebral osteoporotic fracture |  |  |  |  |  |  |  |  |  |
| **Comparison of TNFi vs DMARDs** | | | | | | | | | |
| Aortic Insufficiency | 1.3 | 0.5 | NS | 0.6 | 0.5 | NS | 1.9 | 2.5 | 0.003 |
| Conduction Block | 0.3 | 0 | NS | 0.5 | 0.5 | NS | 2 | 2.6 | 0.004 |
| Myocardial Infarction | 0 | 0 | NS | 0.2 | 0.2 | NS | 0.4 | 0.7 | 0.002 |
| Restrictive Lung Disease | 0.9 | 0 | 0.029 | 0.6 | 0.6 | NS | 5.3 | 6.9 | <0.001 |
| Psoriasis | 3.4 | 1 | 0.005 | 0.8 | 0.6 | NS | 2.5 | 2 | 0.011 |
| Ulcerative Colitis | 2.5 | 0.7 | 0.018 | 1.5 | 1.4 | NS | 2.2 | 2.2 | NS |
| Uveitis | 4.4 | 5.2 | NS | 0.9 | 1.2 | NS | 4.1 | 3.1 | <0.001 |
| Hematologic Cancer | 0.2 | 0.2 | NS | 0.2 | 0.4 | NS | 0.6 | 1.3 | <0.001 |
| Non Melanoma Skin Cancer | 0 | 0 | NS | 0.3 | 0.3 | NS | 1 | 1.3 | 0.037 |
| Solid Cancer | 1.8 | 1.9 | NS | 0.9 | 2.7 | <0.001 | 4 | 6.5 | <0.001 |
| Hospitalized infection | 0.1 | 0 | NS | 2.6 | 3.3 | NS | 7.1 | 9.2 | <0.001 |
| Opportunistic infection | 0.9 | 1.2 | NS | 0.3 | 0.7 | 0.044 | 1.8 | 2.1 | NS |
| Clinical vertebral fracture |  |  |  |  |  |  |  |  |  |
| Non-vertebral osteoporotic fracture |  |  |  |  |  |  |  |  |  |

**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