Full title of manuscript: Relation of NSAID, DMARD and TNF-inhibitors for Ankylosing Spondylitis and Psoriatic Arthritis to Risk of Total Hip and Knee Arthroplasty

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ABSTRACT

Objective: Ankylosing spondylitis and psoriatic arthritis (AS/PsA) often affect the hip and/or knee. If effective, treatments might reduce risk of total hip or total knee arthroplasty (THA/TKA). We evaluated risk of THA/TKA related to use of medical therapies in AS/PsA.

Methods: We conducted a nested case-control study using 1994-2018 data from the OptumLabs® Data Warehouse, which includes de-identified medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage enrollees. Among those with AS/PsA, THA/TKA cases were matched up to 4 controls by sex, age, AS/PsA diagnosis, diagnosis year, insurance type, obesity and prior THA/TKA. We assessed AS/PsA treatment 6 months prior to THA/TKA, including disease-modifying anti-rheumatic drug (DMARD) and tumor necrosis factor inhibitor (TNFi), alone or in combination, stratified by NSAID use. We evaluated the relation of treatment to risk of THA/TKA using conditional logistical regression with adjustment for confounders.

Results: Among 16,748 adults with AS, there were 444 THA/TKA cases, and 1,613 matched controls. Among 34,512 adults with PsA, there were 1,003 cases and 3,793 controls. Adjusted odds ratios for treatment category and THA/TKA ranged from 0.60 to 1.92, however none was statistically significant. Results were similarly null in several sensitivity analyses.

Conclusions: Odds of THA/TKA were not reduced with any combinations of NSAIDs, DMARDs, or TNFi among persons with AS or PsA. Given current utilization patterns in this population of US adults with AS and PSA, these medical therapies did not appear to be associated with less end stage peripheral joint damage.

Introduction

Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are subtypes of spondyloarthritis with similar genetics and shared clinical features including peripheral arthritis (1-3). While peripheral arthritis may be ameliorated by medical therapy, some patients experience on-going inflammation and joint destruction even on treatment. Alternatively, therapies may be initiated after irreversible damage has already taken place. Either situation may result in the need for arthroplasty.

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are the most common joint replacement procedures and their frequency is on the rise (4, 5). THA and TKA may be complicated by infection, and, if hardware loosens or wears out, may require surgical revision (4). Moreover, peripheral joint involvement in spondyloarthritis portends a poorer prognosis than those with axial disease alone (2). Therefore, it is essential to optimize medical management to prevent end stage peripheral joint arthritis and improve overall prognosis.

There is a paucity of literature surrounding the use of certain medical therapies for joint replacement surgery among adults with AS and PsA. NSAIDs and DMARDs can reduce joint inflammation and therefore lower the risk of end stage joint damage requiring an arthroplasty. NSAIDs may have an effect on bone metabolism and preserve bone mineral density, which is relevant to osteoarthritis (OA) pathology (6, 7). Tumor necrosis factor inhibitors (TNFi) have been shown to reduce radiographic progression and improve clinical manifestations of AS and PsA (1, 3, 8-11). TNFi inhibiting radiographic progression indicates

these medical therapies have effects on bone mineralization and it is not known if these effects on bone extend beyond the spine.

A recent study showed that TNFi were associated with a reduced rate of THA in older adults with rheumatoid arthritis compared to those on conventional synthetic disease modifying antirheumatic drugs (DMARDs) (12). While there are no studies to date assessing the effect of medications on joint replacements in spondyloarthritis, a Norwegian study found that THA rates in 1988-2010 decreased over time among individuals with AS compared to those with OA (13). Authors speculated this reduced rate was due to the introduction of TNFi medications slowing peripheral arthritis. However, in another Norwegian study, a PsA diagnosis after 1999 was not associated with lower risk of orthopedic surgery relative to diagnosis in an earlier year, suggesting no effect of TNFi uptake (14). Studies in the United Kingdom and the United States (US) found increasing rates of THA among AS patients over time (15, 16). Furthermore, a Danish cohort study from 1996-2012 found that patients with PsA were still twice as likely to require a joint replacement compared to the general population, highlighting the need for better treatment to prevent end stage joint damage (17). These discrepancies in the literature highlight the need for additional study.

There are no published studies to date assessing the effects of NSAIDs, DMARDs or TNFi on joint replacement risk in AS or PsA. These are important to include because NSAIDs are still first line therapy for patients with AS, and both AS and PsA subjects are prescribed DMARDs. Evaluating these classes of medications, in addition to TNFi, is helpful because the findings

could support future guidelines on medical therapies for these patients. We therefore assessed whether specific medical treatments were associated with risk of THA or TKA in AS and PsA, using one of the largest samples to date of adults in the US.

Materials and Methods

We conducted a nested case-control study using data from the OptumLabs® Data Warehouse, which includes de-identified medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage enrollees. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the US. Members in the database had full insurance coverage for physician, hospital, and prescription drug services (18). A nested case control study design was selected to maximize power given the relatively low number of outcomes (knee and hip replacements).

Study sample

Cases were defined as subjects with AS or PsA with THA or TKA, and controls were defined as subjects with AS or PsA without such procedures. ICD 9 and 10 codes were used to identify adults with AS and PsA aged 18 years or older from 01/01/1994 to 12/31/2018. These codes (see Supplemental Table 1) have been validated in AS and PsA in prior studies (19, 20). Subjects were required to have medical and pharmacy coverage at least 6 months prior to AS or PsA diagnosis and were eligible for inclusion on the date of their second AS or PsA diagnosis claim. If a subject had both AS and PsA diagnoses, we categorized them by the first diagnosis listed.

THA/TKAs were defined by ICD 9/10 procedure codes and current procedural terminology (CPT) codes, and the date of first THA/TKA during the study period was defined as the index date. We made the assumption that subjects were undergoing THA/TKA for end stage joint damage due to their AS or PsA. We did not include arthroplasty revisions in this outcome. We did not exclude subjects who had had a single hip/knee replacement to allow for THA/TKA on both left and right sides within each subject. Additional exclusion criteria were: history of two THAs or two TKAs prior to AS/PsA diagnosis; and a diagnosis of inflammatory bowel disease any time prior to AS/PsA diagnosis. Subjects with inflammatory bowel disease were excluded because they may have different treatment patterns than AS and PsA subjects. We excluded hip and knee fractures 30 days prior to the outcome because this is the time frame that we would expect that any THA or TKA would be related to the fracture. As part of our internal validation study, we reviewed 100 random subject profiles and all claims listed 6 months prior to study entry to 6 months after exit of the study. We obtained claim records with the codes of interest from the OLDW via SAS; the data was then exported to Excel for review. We were able to confirm appropriate identification of diseases of interest (AS or PsA), exposures (NSAID, DMARD, and/or TNFi) and outcomes (THA or TKA).

Study design

The outcome of interest was THA or TKA as defined by procedure codes. THA or TKA cases were each matched to up to 4 controls by sex, age (+/- 3 years), spondyloarthritis subtype (AS/PsA), AS/PsA diagnosis year (+/-1), insurance type (commercial or Medicare Advantage), obesity (defined as BMI $\geq$30 kg/m^2), and any prior hip or knee replacement prior to study entry.

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Subjects were matched using risk-set sampling. Thus, subjects could be included as controls before they became a case. We assessed AS/PsA treatment in the 6-month period prior to THA or TKA. We assessed for use of DMARD or TNFi stratified by NSAID use. This is because those taking NSAIDs in the 6 months prior to arthroplasty may have done so due to pain from end stage joint disease, rather than as a treatment for their AS or PsA (confounding by indication). Medical therapies were identified according to records of filled prescriptions. DMARDs included apremilast, auranofin, azathioprine, baricitinib, chloroquine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenol, sulfasalazine, thiomalate, and tofacitinib. While still a subject of controversy, we included apremilast and tofacitinib in this DMARD category, because they are oral small molecules, and the low frequency of use did not allow us to analyze them separately. Janus kinase inhibitors and non-TNFi biologics were not included in this study as there were an insufficient number of subjects on these medications.

Statistical analysis

We evaluated the relation of each type of treatment (DMARD, TNFi stratified by NSAID use) to risk of THA or TKA using conditional logistical regression. The outcome of THA or TKA was binary (yes/no) and was defined as the first THA/TKA code during follow up. Arthroplasty codes excluded revisions. After matching subjects by age, sex, disease, diagnosis year and insurance type, we then performed adjustment for potential confounders. These included age (after matching +/- 3 years for more precision as some subjects were not perfect matches) and history of chronic kidney disease, diabetes, liver disease, peptic ulcer disease, psoriasis (for subjects with PsA only), and rheumatoid arthritis. We also adjusted for a record of erythrocyte

sedimentation rate (ESR) or c-reactive protein (CRP) testing having been performed within 1 year prior to AS/PsA diagnosis as well as at least 1 rheumatology visit in the year prior to AS/PsA diagnosis (versus no visits). These variables were used as surrogates for disease activity. Among the strata of NSAID users, NSAID use alone was the referent group, and for NSAID non-users, the absence of any medication of interest was the referent group. Controls were not excluded on the basis of comorbidities. As a way to assess for effect modification by how much risk a subject would incur with a knee/hip arthroplasty surgery, we considered variables that may deem a subject a poor candidate for joint replacement: BMI $\geq$40 kg/m^2, history of joint infection, any high-risk cancer, end stage renal disease (ESRD) requiring dialysis, and severe pulmonary disease requiring supplemental oxygen. We looked at the prevalence of these across cases and controls to identify any patterns for descriptive purposes, but did not incorporate these variables into the analysis.

Sensitivity analyses

To assess the robustness of our primary results, we performed several sensitivity analyses for AS and PsA individually: models assessing age stratification (<55 versus $\geq$55 years), THA and TKA separately, history of joint replacement prior to the study period (yes/no), 14 month exposure assessment (rather than our standard 6 month period), and 2 or more prescriptions during the exposure assessment (instead of 1). Lastly, we performed a conditional logistic regression model analysis considering each drug category as a binary variable and assessed the effect of each category after adjustment for other confounders.

Ethical approval

Since this study involved analysis of pre-existing, de-identified data, it was exempt from

Institutional Review Board approval.

Results

Among 16,748 adults with AS meeting eligibility criteria, we identified 444 cases of THA or TKA.

There were 1,613 matched controls with AS for these cases. For cases, the mean age was 58.4

(SD +/- 11.9) years, and 206 (46.4%) were female (see Table 1). Cases had an increased

prevalence of peptic ulcer disease (29.1%) versus controls (24.7%). Other characteristics among

AS cases and controls include the prevalence of chronic kidney disease (3.4% versus 3.8%),

diabetes (20.7% versus 20.7%), liver disease (3.2% versus 4.2%), psoriasis (20.0% versus 20.6%),

rheumatoid arthritis diagnosis (24.5% versus 19.1%), body mass index $\geq$ 30 kg/m^2 (15.8% versus

12.3%), rheumatology visit in the year prior to diagnosis (53.8% versus 51.5%) and ESR/CRP

ordered in the year prior to diagnosis (57.4% versus 57.3%). Very few subjects (less than 11

cases and less than 11 controls) had a joint replacement prior to entering the study. We were

unable to report these numbers as low frequencies were not permitted to be published per

OptumLabs data policy.

Among 34,512 adults with PsA meeting eligibility criteria, we identified 1,003 cases with

THA/TKA. There were 3,793 matched controls with PsA for these cases. For cases, the mean age

was 59.7 (SD +/- 9.8) years, and 592 (59.0%) were female. The remaining characteristics

appeared similar across cases and controls including chronic kidney disease (3.3% versus 3.9%),

diabetes (22.7% versus 23.7%), prior joint replacement (3.3% versus 1.3%), liver disease (6.7% versus 6.0%), peptic ulcer disease (24.6% versus 23.9%), psoriasis (74.8% versus 76.4%), rheumatoid arthritis diagnosis (22.7% versus 22.4%), body mass index $\geq$ 30 kg/m^2 (19.7% versus 18.9%), rheumatology visit in the year prior to diagnosis (67.1% versus 66.3%) and ESR/CRP ordered in the year prior to diagnosis (65.0% versus 65.6%).

History of joint infection, high risk cancer, ESRD and severe pulmonary disease occurred in 2.5% or fewer of cases and controls. These low frequencies were not permitted to be published per OptumLabs data policy; however, frequencies were similar between cases and controls for each condition.

Among those with AS, the unadjusted odds of THA/TKA was higher for those on TNFi only (OR 1.71 CI 95% 1.02-2.88) and for those on DMARD/TNFi combination therapy (OR 2.12 CI 95% 1.07-4.23) (see Table 2); however once adjusted for confounders, these associations were no longer statistically significant (adjusted OR 1.58 CI 95% 0.88-2.82 and adjusted OR 1.92 CI 95% 0.91-4.08 respectively). Among PsA, those on NSAIDs and DMARDs had lower unadjusted odds of THA/TKA (OR 0.77 95% CI 0.61-0.98) which also lost significance when adjusted for confounders (adjusted OR 0.78 95% CI 0.61-1.00).

Sensitivity analyses

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No combination of medical therapies showed a significant association with THA/TKA once adjusted for confounding factors as highlighted in Tables 3 and 4. Table 3 includes the adjusted OR for TNFi use in these analyses. These include: age <55 versus ≥55, THA and TKA separately, prior joint replacement (yes/no), and 14 month exposure assessment. Table 4 shows the analysis performed with 2 or more prescriptions during the exposure assessment period. The median number of prescriptions for each drug category with interquartile ranges are listed in Supplemental Table 3. Table 5 reveals each drug category as a binary variable. TNFi use among AS was associated with an increased odds of THA/TKA at 1.83 (1.11-3.00). All other results were null.

Discussion

In this large, US-based study of adults with AS and PsA, we did not find any protective effect of DMARDs or TNFi for THA/TKA. These null findings were confirmed in several sensitivity analyses assessing subgroups based on spondyloarthritis subtype, joint (hip versus knee), and age. The only instance TNFi was associated with a higher risk of arthroplasty was during the binary analysis and this is likely due to confounding by indication. In all other scenarios of TNFi use, the OR was not significantly different from 1 and this could be an indication of effect, as one would expect those using TNFi to be the most severely affected and thus have a higher risk of joint replacement surgery compared to those on DMARDs. Subjects with AS on DMARD/TNFi therapies and no NSAID use had an adjusted OR 1.92 95% CI 0.91-4.08 for THA/TKA, while those on DMARD/TNFi with NSAID use had an adjusted OR 0.60 95% CI 0.32-1.14. Because the confidence intervals for both estimates included 1.0, we cannot conclude there is any increased

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or decreased risk with either treatment category. While subjects with PsA had similar findings, the adjusted ORs were closer to 1 and remained statistically insignificant. Nonetheless, while a statistically significant association of TNFi and lower rates of THA was previously shown in rheumatoid arthritis, our findings do not support such an association in AS or PsA (12).

There are several potential explanations for our findings. These findings may suggest that TNFi have a protective effect on the axial skeleton (21) but not on peripheral joints. It is also possible that TNFi do not prevent need for THA/TKA because they are given too late in the disease course, when irreversible damage from inflammatory peripheral arthritis has already taken place. This is a particular concern in axial spondyloarthritis, in which the diagnosis remains delayed by 5-10 years from symptom onset (22, 23). Lastly, they may suggest residual confounding by indication despite our attempts to adjust for disease severity and comorbidities (see below).

Per most recent guidelines by both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), NSAIDs are the first line of treatment for axial spondyloarthritis followed by TNFi (24, 25). TNFi have been shown to improve disease activity in AS and PsA, making it plausible that this class of medications could reduce the rates of THA and TKA, but this was not observed in our study (1, 2). In the most recent guidelines, TNFi were recommended as an option for first line therapy in PsA (24-26). DMARDs are also conditionally recommended for treatment of PsA in some scenarios, but are not recommended for those with axial spondyloarthritis alone due to lack of efficacy (24, 25).

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There were a substantial number of adults in our study on DMARDs, either alone or in combination with other therapies. The most common DMARDs used by subjects in this study were methotrexate (58.3%), sulfasalazine (11.5%) and hydroxychloroquine (11.0%) (See Supplemental Table 2). Some subjects may have used DMARDs specifically to treat peripheral arthritis symptoms, but others may have used them due to their lower cost, safety profile, contraindications to other therapies, or intolerance of other medications.

As shown in Table 1, 20% of subjects had a diagnosis of RA in addition to AS or PsA. Patients with PsA are often mistaken to have RA initially, which may be why they have both diagnoses in their claims. Additionally, as suggested here, those with an RA diagnosis in their claims history would be more likely to have peripheral arthritis and therefore may be more likely to receive a THA or TKA.

Limitations

There are limitations to this study. First, this is an observational study, and while we attempted to control for confounding through matching and adjustment for potential confounders, residual confounding remains possible. Subjects with more severe AS or PsA would be more likely to be prescribed TNFi and their severe disease would put them at risk for THA/TKA. However, this confounding by indication would result in an increase OR for TNFi, whereas we found no significant increase. Alternatively, a healthy user effect may explain our results, in that only the healthiest AS/PsA patients may have been prescribed TNFi, thereby reducing the

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observed effect of TNFi on THA/TKA. Because we used filled prescriptions to capture

medication use, those taking NSAIDs over the counter would not be captured. Methotrexate,

sulfasalazine and hydroxychloroquine use in these patients could have been prescribed for

conditions other than peripheral arthritis, such as treating psoriatic dermatitis. While the most

recent guidelines do not recommend use of methotrexate, sulfasalazine or hydroxychloroquine

in axial disease, earlier versions of treatment guidelines did not recommend against

methotrexate and sulfasalazine (25). Therefore, there was a period of time in which these

medications were used with the thought that they may prevent anti-drug antibody formation

among biologic users. We only had 6 months of follow up for some subjects and we were

unable to capture a large enough sample to perform analysis over a longer period of time.

While we adjusted for rheumatology appointments and inflammatory marker testing as a proxy

for disease severity, results of standard disease activity instruments were not available. Data

on AS/PsA duration was also not available. Another limitation is that we cannot fully exclude

the possibility of misclassification of the cases or outcomes, however, our internal validation

confirmed the exposure and outcome in all 100 subjects and procedure codes have high validity

in administrative data (27). Lastly, some of our subjects could have undergone THA or TKA for

OA rather than their primary inflammatory arthritis, as diagnostic codes do not distinguish

between AS/PsA and OA manifestations of the hip and knee. This is likely not a large issue as

the mean age of cases is relatively younger than those who typically receive arthroplasty for

OA.

Strengths of this study include its large sample size, inclusion of adults of all ages, and our

ability to ascertain patients' medication use through prescription fill records. While previous

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studies have evaluated THA and TKA among subjects with AS, those studies did not ascertain medication use. Furthermore, previous studies were primarily in older adults with Medicare, whereas our study included both commercial and Medicare Advantage beneficiaries, and our analysis stratified by age showed consistent results (28). Additionally our findings were consistent across a series of other sensitivity analyses.

Conclusions

In this large sample of US adults with AS and PsA, no combination of NSAIDs, DMARDs or TNFi therapy was associated with fewer THAs or TKAs. Further study should investigate strategies to mitigate end stage peripheral arthritis in AS and PsA.

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Figure 1. Selection Criteria

Subjects with at least 2 AS (42,583) or 2 PsA claims (83,233) (n = 125,816)

Excluded: without 6 months of coverage prior to AS (23,359) or PsA diagnosis (46,638) (n = 55,819)

Excluded: not 18 years or older on index date (2,260) or missing sex (12) (n = 53,547)

Excluded: inflammatory bowel disease diagnosis 6 months prior to AS (1,129) or PsA (979) diagnosis (n = 51,439)

Excluded: with hip fracture (111) or knee fracture (17) within 30 days prior to study end (n = 51,311)

Excluded: with 2 THAs or 2 TKAs prior to AS (18) or PsA (33) diagnosis (n = 51,260)

1,447 THA/TKA cases and 5,406 matched controls

Table 1. Characteristics of Cases and Controls

	AS		PsA	
	THR/TKR Cases	Controls	THR/TKR Cases	Controls
Subjects, n	444	1,613	1,003	3,793
Female, n (%)	206 (46.4%)	740 (45.9%)	592 (59.0%)	2,250 (59.3%)
Age, mean (SD)	58.4 (11.9)	58.2 (12.0)	59.7 (9.8)	59.4 (9.8)
Chronic kidney disease, n (%)	15 (3.4%)	62 (3.8%)	33 (3.3%)	147 (3.9%)
Diabetes, n (%)	92 (20.7%)	334 (20.7%)	228 (22.7%)	899 (23.7%)
Prior joint replacement, n (%)	<11	<11	33 (3.3%)	49 (1.3%)
Liver disease, n (%)	14 (3.2%)	68 (4.2%)	67 (6.7%)	227 (6.0%)
Peptic ulcer disease, n (%)	129 (29.1%)	399 (24.7%)	247 (24.6%)	908 (23.9%)
Psoriasis, n (%)	89 (20.0%)	333 (20.6%)	750 (74.8%)	2,896 (76.4%)
Rheumatoid arthritis, n (%)	109 (24.5%)	308 (19.1%)	228 (22.7%)	848 (22.4%)
Body mass index >= 30 kg/m2), n (%)	70 (15.8%)	198 (12.3%)	198 (19.7%)	715 (18.9%)
Rheumatology visit in year prior to diagnosis	239 (53.8%)	830 (51.5%)	673 (67.1%)	2,516 (66.3%)
ESR/CRP ordered in year prior to diagnosis	255 (57.4%)	924 (57.3%)	652 (65.0%)	2,488 (65.6%)

SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein

Table 2. Primary Outcome: Odds of SMARD and/or TNFi Use Stratified by NSAID Use Within 6 Months of THA or TKA Among Adults with AS or PsA

			Cases	Controls	Conditional Logistic OR (95% CI)	Fully Adjusted OR[+] (95% CI)
A S	NSAID use	NSAID use only (referent)	152	527	1.0	1.0
		SMARD use	31	131	0.82 (0.53, 1.27)	0.75 (0.47, 1.20)
		TNFi use	33	105	1.15 (0.73, 1.81)	1.14 (0.71, 1.82)
		SMARD/TNFi use	14	78	0.65 (0.36, 1.20)	0.60 (0.32, 1.14)
	No NSAID use	No medication (referent)	152	584	1.0	1.0
		SMARD use	22	92	0.98 (0.59, 1.62)	0.76 (0.44, 1.31)
		TNFi use	26	69	1.71 (1.02, 2.88)	1.58 (0.88, 2.82)
		SMARD/TNFi use	14	27	2.12 (1.07, 4.23)	1.92 (0.91, 4.08)
P s A	NSAID use	NSAID use only (referent)	225	759	1.0	1.0
		SMARD use	145	640	0.77 (0.61, 0.98)	0.78 (0.61, 1.00)
		TNFi use	83	304	0.96 (0.71, 1.29)	1.00 (0.74, 1.36)
		SMARD/TNFi use	72	252	0.97 (0.71, 1.33)	1.03 (0.75, 1.43)
	No NSAID use	No medication (referent)	247	914	1.0	1.0
		SMARD use	114	468	0.90 (0.70, 1.16)	0.88 (0.68, 1.15)
		TNFi use	60	283	0.78 (0.57, 1.08)	0.77 (0.55, 1.08)
		SMARD/TNFi use	57	173	1.24 (0.89, 1.74)	1.20 (0.84, 1.71)

OR: odds ratio; NSAID: nonsteroidal anti-inflammatory drug; TNFi: tumor necrosis factor inhibitor; SMARD: symptom modifying anti-rheumatic drug

[+]Adjusted for age, chronic kidney disease, diabetes, liver disease, peptic ulcer disease, psoriasis (PsA subjects only), rheumatoid arthritis, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and rheumatology visit prior to study eligibility.

Table 3. Secondary Outcome: Adjusted Odds* of TNFi Use Among Adults with AS or PsA
Stratified by NSAID Use Within 6 Months of THA or TKA

	AS		PsA	
	NSAID use	No NSAID use	NSAID use	No NSAID use
All subjects	1.14 (0.71-1.82)	1.58 (0.88-2.82)	1.00 (0.74-1.36)	0.77 (0.55-1.08)
Age <55 years	0.83 (0.42-1.64)	1.36 (0.60-3.07)	0.95 (0.62-1.44)	0.73 (0.48-1.13)
Age ≥55 years	1.56 (0.79-3.08)	1.75 (0.66-4.65)	1.04 (0.65-1.66)	0.90 (0.52-1.55)
THA only	1.41 (0.74-2.71)	0.57 (0.22-1.48)	0.91 (0.54-1.54)	0.57 (0.31-1.05)
TKA only	0.99 (0.48-2.04)	3.18 (1.41-7.17)	1.05 (0.72-1.54)	0.87 (0.59-1.30)
No prior THA/TKA	1.13 (0.71-1.82)	1.58 (0.88-2.82)	1.01 (0.74-1.38)	0.80 (0.57-1.12)
14 month window	1.13 (0.71-1.80)	1.52 (0.73-3.19)	0.97 (0.72-1.30)	0.71 (0.47-1.07)

THA: total hip replacement; TKA: total knee replacement

*Adjusted for age, chronic kidney disease, diabetes, liver disease, peptic ulcer disease, psoriasis
(PsA subjects only), rheumatoid arthritis, erythrocyte sedimentation rate (ESR), c-reactive
protein (CRP) and rheumatology visit prior to study eligibility.

Table 4. Secondary Outcome: Adjusted Odds* of Two or More Prescriptions Among Adults with AS or PsA Stratified by NSAID Use Within 6 Months of THA or TKA

Number of prescriptions per drug category	AS		PsA	
	NSAID use	No NSAID use	NSAID use	No NSAID use
2+ NSAID/0 TNFi/0 DMARD	1.0	1.0	1.0	1.0
2+ NSAID/0 TNFi/2+ DMARD	0.81 (0.46-1.40)	0.81 (0.45-1.46)	0.79 (0.59-1.06)	0.80 (0.60-1.06)
2+ NSAID/2+ TNFi/0 DMARD	1.08 (0.62-1.88)	1.16 (0.62-2.18)	0.99 (0.69-1.44)	0.76 (0.54-1.08)
2+ NSAID/2+ TNFi/2+ DMARD	0.52 (0.23-1.19)	2.14 (0.95-4.83)	1.02 (0.69-1.53)	1.30 (0.88-1.92)

*Adjusted for age, chronic kidney disease, diabetes, liver disease, peptic ulcer disease, psoriasis (PsA subjects only), rheumatoid arthritis, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and rheumatology visit prior to study eligibility.

Table 5. Secondary Outcome: Adjusted Odds* of Each Drug Exposure Category as Binary Variables Among Adults with AS or PsA Stratified by NSAID Use Within 6 Months of THA or TKA

Drug category	AS		PsA	
	NSAID use	No NSAID use	NSAID use	No NSAID use
DMARD use	0.68 (0.46-1.01)	0.87 (0.54-1.38)	0.85 (0.69-1.04)	1.03 (0.82-1.29)
TNFi use	1.02 (0.69-1.51)	**1.83 (1.11-3.00)**	1.14 (0.90-1.43)	0.98 (0.76-1.26)

*Adjusted for age, chronic kidney disease, diabetes, liver disease, peptic ulcer disease, psoriasis (PsA subjects only), rheumatoid arthritis, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and rheumatology visit prior to study eligibility.

Correction

Relation of NSAIDs, DMARDs, and TNF Inhibitors for Ankylosing Spondylitis and Psoriatic Arthritis to Risk of Total Hip and Knee Arthroplasty

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