Patient characteristics associated with use of TNF vs interleukin inhibitors as first-line biologic treatment for psoriatic arthritis

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What is already known about this subject

- Newer non-tumor necrosis factor (TNF) biologics, such as interleukin (IL)-12/23 or 17 inhibitors are highly effective in the management of psoriatic arthritis (PsA) treatment.
- Treatment persistence comparing TNF inhibitors and IL-12/23 or 17 inhibitors in the real-world setting in the United States is unknown.

What this study adds

- IL-12/23 or 17 inhibitor initiators had a greater comorbidity burden than initiators of TNF inhibitors among PsA patients.
- One-year treatment persistence was similar between initiators of IL-12/23 or 17 inhibitors and TNF inhibitors.
- Medication adherence was higher with TNF inhibitors than with IL-12/23 or 17 inhibitors during the first year of treatment.

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ABSTRACT

BACKGROUND: Previous studies have examined treatment patterns among patients who use tumor necrosis factor (TNF) inhibitors for psoriatic arthritis (PsA). However, little data exist for a comparison between the TNF inhibitor treatment pattern and that of newly available biologics such as

interleukin (IL)-12/23 or 17 inhibitors in the United States.

OBJECTIVES: To (a) examine patient characteristics and their association with initiation of TNF inhibitors vs IL-12/23 or 17 inhibitors among PsA patients and (2) compare treatment persistence of PsA patients who initiated TNF inhibitors vs IL-12/23 or 17 inhibitors as first-line biologic

treatment in a real-world setting in the United States.

METHODS: Using claims data from MarketScan (2013-2017), we identified a cohort of PsA patients who initiated TNF inhibitors or IL-12/23 or 17 inhibitors. The primary outcome was treatment persistence, defined as continuous use of the index drug at 1 year, regardless of refill gaps. The

secondary outcome was treatment persistence with high adherence at 1 year (ie, refill gaps ≤ 30 days). Multivariable logistic regression was used to assess the association between patient characteristics and treatment initiation and persistent use of TNF inhibitors vs IL-12/23 or 17 inhibitors.

RESULTS: We identified 3,180 TNF inhibitor initiators and 214 IL-12/23 or 17 inhibitor initiators. Initiators of IL-12/23 or 17 inhibitors had more comorbidities than TNF inhibitor initiators. The proportion of patients with treatment persistence was 53.0% in TNF inhibitor initiators and 53.7% in IL-12/23 or 17 inhibitor initiators; 37.1% of TNF inhibitor users and 24.8% of IL-12/23 or 17 inhibitor users were treatment persistent with high adherence. There was no difference in 1-year treatment persistence between the 2 groups after adjusting for baseline characteristics (adjusted odds ratio [aOR] for TNF inhibitors vs IL-12/23 or 17 inhibitors: 0.86, 95% CI=0.63-1.15). However, use of TNF inhibitors was associated with a greater treatment persistence with high adherence compared with use of IL-12/23 or 17 inhibitors (aOR=1.61, 95% CI=1.15-2.26).

CONCLUSIONS: PsA patients who initiated an IL 12/23 or 17 inhibitor had a greater comorbidity burden compared with those who initiated TNF inhibitors. Treatment persistence was similar between the 2 groups, whereas medication adherence was higher with TNF inhibitors than with IL 12/23 or 17 inhibitors during the first year of treatment.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis and affects 6%-41% of patients with psoriasis.¹⁻³ Patients with PsA experience heterogeneous and complex symptoms from musculoskeletal system and skin conditions. Symptoms of PsA range from mild to severe with variable clinical manifestations that include peripheral and axial joint involvement, enthesitis, dactylitis, spondylitis, nail disease, and fatigue.^{4,5} PsA is also associated with comorbidities such as cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, Crohn disease, ophthalmic disease, depression, and anxiety.⁶ The complexity of the disease, level of disease severity, and associated comorbidities make the management of PsA challenging.

Recent developments in treatments for systemic inflammatory conditions significantly expanded pharmacotherapeutic options for PsA from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate and biologic DMARDs (bDMARDs). Currently available bDMARDs for PsA treatment include tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol), an interleukin (IL)-12/23 inhibitor (ustekinumab), IL-17 inhibitors (secukinumab and ixekizumab), and abatacept. A Janus kinase inhibitor (tofacitinib) is also available for PsA.

Although clinical trials have proven the efficacy of the newer biologics in PsA patients,⁷ treatment guidelines have some discrepancies in therapy selection and final recommendations because of the heterogeneous nature of PsA manifestations.⁸⁻¹² The European League Against Rheumatism (EULAR) 2019 update and Grading of Recommendations Assessment, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 guidelines generally recommend using any of the approved bDMARDs as the first-line biologic agent after failure of csDMARDs^{9,12}; however, the American College of Rheumatology/National Psoriasis Foundation (ACR/NPF) 2018 guideline conditionally recommended IL-17 inhibitors earlier in patients with contraindications to TNF inhibitors, or with severe psoriasis or nail disease.¹¹

Treatment persistence or medication adherence is the key to treatment success for treatment of chronic diseases such as PsA.¹³ As more biologic treatments become available, it is important to understand their persistence rates in a real-world setting. To date, most studies have focused on the treatment patterns of TNF inhibitors or only 1 of the IL inhibitors,¹⁴⁻²⁰ so little data exist for a comparison between a TNF inhibitor treatment pattern and that of newly available bDMARDs such as IL-12/23 or 17 inhibitors among PsA patients in the United States.

The objectives of this study were to (1) examine patient characteristics and their association with initiation of TNF inhibitors vs IL-12/23 or 17 inhibitors among PsA patients and (2) compare treatment persistence of PsA patients who initiated TNF inhibitors vs IL-12/23 or 17 inhibitors as first-line biologic treatment in a real-world setting in the United States.

Methods

DATA SOURCE

We conducted a cohort study using claims data provided by IBM MarketScan from January 1, 2013, to December 31, 2017. The MarketScan database contains patient demographics and longitudinal information on medical and pharmacy claims drawn from large employers, health plans, and public organizations, generally representing a commercially insured population from all 50 US states. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Brigham and Women's Hospital (IRB protocol number: 2018P001322). Patient-informed consent was not required, since the data were deidentified.

TABLE 1 Baseline Patient Characteristics

	TNF inhibitors ^a n=3,180	IL inhibitors ^b n=214	Absolute SMD ^c
Demographics			
Age, years, mean (SD)	50.4 (11.7)	52.9 (11.6)	0.21
Female, %	57.0	55.6	0.03
Male, %	43.0	44.4	0.03
Cohort entry year, %			
2014	25.4	11.2	0.37
2015	40.2	35.1	0.11
2016	34.4	53.7	0.40
Region, %			
Northeast	13.6	24.3	0.28
South	45.5	43.9	0.03
Midwest	15.3	11.2	0.12
West	25.4	20.1	0.13
Comorbidities, %			
Hypertension	41.0	48.1	0.14
Hyperlipidemia	37.0	46.7	0.20
Diabetes	16.4	24.8	0.21
Obesity	15.9	16.4	0.01
Smoking	9.0	10.8	0.06
Alcohol abuse	1.3	1.4	0.01
Psoriasis	63.2	72.9	0.21
Rheumatoid arthritis	30.1	26.6	0.08
Inflammatory bowel disease	1.6	0.5	0.11
Ischemic heart disease	6.0	10.8	0.17
Heart failure	1.3	6.1	0.26
Malignancy	4.4	12.2	0.28
Chronic renal disease	2.2	5.1	0.15
Chronic liver disease	6.5	12.2	0.19
Pulmonary disease	12.9	16.8	0.11
Viral hepatitis	1.3	1.4	0.01
Hypothyroidism	13.4	16.8	0.10
Depression	16.1	17.8	0.04
Glaucoma	4.6	7.9	0.14
Combined comorbidity score, mean (SD)	0.3 (1.2)	0.9 (1.8)	0.39
Hospitalized infection, %	2.6	4.2	0.09
Medications, %			
Nonbiologic DMARDs	66.5	60.8	0.12
Methotrexate	55.4	34.6	0.43
Leflunomide	5.1	5.1	0.00
Sulfasalazine	10.0	6.5	0.13

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STUDY COHORT AND DESIGN

We identified PsA patients with at least 2 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth Revision (ICD-10-CM) codes for PsA (ICD-9-CM: 696.0; ICD-10-CM: L40.50-L40.59) separated by 7 to 365 days, recorded in any position from inpatient or outpatient claims. We required patients to have 1 new dispensing of a bDMARD for PsA on or after the second PsA diagnosis date. These bDMARDs included TNF inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab) and IL inhibitors (secukinumab, ustekinumab, and ixekizumab), identified by National Drug Code numbers and Healthcare Common Procedure Coding System (HCPCS) codes.

The claims-based algorithm, which combined at least 2 diagnosis codes for PsA and at least 1 dispensing for PsA treatment, had a positive predictive value of 82.4% for identifying patients with PsA.²¹ The index date was defined as the date of the first dispensing of TNF inhibitors or IL-12/23 or 17 inhibitors with no previous use of biologics. Eligible patients were required to be aged at least 18 years on the index date and have a 1-year continuous enrollment before and after the index date (Supplementary Figure 1, available in online article). The first and last cohort entry date was January 1, 2014, and December 31, 2017.

PERSISTENT USE OF INDEX BIOLOGIC AGENT

The primary outcome was treatment persistence, which was defined as continuous use of the index drug at 1 year, regardless of a gap between refills. Patients were considered as persistent users if they were still using the index drug at the 365th day of follow-up (ie, a patient's last refill plus days of supply plus 30 days covers the 365th day

TABLE 1 Baseline Patient Characteristics (continued)

	TNF inhibitors ^a n=3,180	IL inhibitors ^b n=214	Absolute SMD ^c
Azathioprine	0.4	0.0	0.09
Medications, %			
Cyclosporine	1.7	2.3	0.04
Apremilast	5.5	27.1	0.61
Any psoriasis medication	79.5	78.0	0.03
Topical treatment for psoriasis	45.7	49.1	0.07
Systemic psoriasis medications	64.9	60.8	0.09
Systemic conventional medications	64.8	58.9	0.12
Biologic systemic psoriasis medication	0.3	3.7	0.25
UV therapy	2.4	4.7	0.12
Oral steroids at baseline	49.4	41.1	0.17
Cumulative prednisone equivalent dose in mg, median (IQR)	0 (0-495)	0 (0-420)	0.05
Recent use of oral steroids 30 days before and including index date	21.2	17.3	0.10
NSAIDs	55.4	43.0	0.25
Coxibs	8.1	7.5	0.02
Opioids	49.0	47.7	0.03
Antihypertensives	41.0	50.5	0.19
Antidiabetics	14.0	18.2	0.12
Statins	22.5	27.6	0.12
Nonstatin lipid-lowering drugs	5.0	7.5	0.10
Antiplatelets	2.0	3.7	0.11
Anticoagulants	3.2	5.6	0.12
Osteoporosis medications	1.5	4.2	0.16
Antibiotics	56.4	59.8	0.07
Antivirals	6.1	5.6	0.02
Health care utilization			
Number of unique generic prescriptions, median (IQR)	11 (7-16)	11 (7-18)	0.14
ED visit, %	21.2	20.6	0.02
Hospitalizations, %	8.2	11.2	0.10
Number of physician visits, median (IQR)	11 (7-16)	12.5 (8-23)	0.24
Number of rheumatologist visits, median (IQR)	3 (0-4)	2 (0-4)	0.15
Number of dermatologists visits, median (IQR)	0 (0-1)	1 (0-3)	0.47

^aTNF inhibitors included etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab.

^bIL inhibitors included secukinumab, ustekinumab, and ixekizumab.

^cAbsolute SMD > 0.1 considered as significant difference.

Coxibs = selective COX-2 inhibitors; DMARD = disease-modifying antirheumatic drugs; ED = emergency department; IL = interleukin; IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs; SMD = standardized mean difference; TNF = tumor necrosis factor.

of follow-up). Otherwise, patients who were no longer on any study bDMARD on the 365th day of follow-up were defined as the discontinuation group. We allowed for any treatment gaps between adjacent refills. Treatment switching was defined as starting another study bDMARD different from the initial agent during the 365-day follow-up period.

Since the treatment gap may affect the outcome definition, we defined treatment persistence with high adherence at 1 year (ie, refill gaps ≤ 30 days) as the secondary outcome. The 30-day refill gap was applied after accounting for days of supply or dosing interval of each refill. Therefore, the refill gap was defined as the days between the end of last supply or dosing interval and the dispensing date of the next refill. Days of supply for each HCPCS code of the study drugs were assumed, as shown in [Supplementary Table 1](#) (available in online article). For sensitivity analysis, we repeated the analysis with 14-day and 60-day refill gaps.

In addition, we assessed pharmacy claims-based medication adherence using proportion of days covered (PDC), calculated as the number of days covered by the index drug divided by 365 days as a percentage. Generally, patients are considered adherent if they have a PDC of at least 80% in a given interval.^{22,23}

COVARIATE ASSESSMENT

During the 1-year baseline period, we assessed a number of variables that are potentially related to PsA disease activity and severity, including index year; demographics (ie, age, sex, and region); comorbidities (ie, hypertension, hyperlipidemia, diabetes, obesity, smoking, alcohol, psoriasis, rheumatoid arthritis, ischemic heart disease, heart failure, malignancy, chronic renal disease, chronic liver disease/viral hepatitis, pulmonary

disease, hypothyroidism, depression, glaucoma, hospitalized infection, and combined comorbidity score^{24,25}); PsA treatment history (ie, methotrexate, leflunomide, sulfasalazine, cyclosporine, apremilast, topical steroids, topical vitamin D derivative, and topical tacrolimus/pimecrolimus); other medications (ie, oral steroids, nonselective nonsteroidal anti-inflammatory drugs [NSAIDs], selective COX-2 inhibitors, opioids, antihypertensives, antidiabetics, statins, nonstatin lipid-lowering drugs, antibiotics, and antivirals); and the markers of health care utilization (ie, emergency department visits, hospitalizations, number of distinct generic prescriptions, visits to dermatologists, visits to rheumatologists, and visits to primary care providers).

STATISTICAL ANALYSIS

Treatment Initiation. We described baseline characteristics in the 2 groups: TNF inhibitors and IL-12/23 or 17 inhibitors. Standardized mean differences (SMD) were calculated to assess any differences between the 2 groups. SMDs greater than 0.1 were considered as having meaningful differences or imbalance between the groups.²⁶

To examine the association between patient characteristics and initiation of TNF inhibitors or IL-12/23 or 17 inhibitors, we used a multivariable logistic regression model that included all of the baseline variables previously mentioned (Table 1). Adjusted odds ratios (aORs) with 95% CIs were reported for each variable. In addition, we used logistic regression with least absolute shrinkage and selection operator (LASSO) regularization to identify potentially important variables related to initiation of TNF inhibitors vs IL-12/23 or 17 inhibitors.²⁷

Treatment Persistence. We compared the proportions of treatment persistence (primary outcome), treatment persistence with high adherence (secondary outcome), discontinuation, switching, and medication adherence (ie, PDC $\geq$ 80%) during the 1-year follow-up period between TNF inhibitors and IL-12/23 or 17 inhibitor initiators. Furthermore, we performed multivariable logistic regression models to determine the association between the treatment type (TNF inhibitors vs IL-12/23 or 17 inhibitors) and treatment persistence adjusted for baseline characteristics.

In a subgroup analysis, we examined treatment persistence among TNF inhibitor vs ustekinumab initiators, since ustekinumab is a different class of IL inhibitors (IL-12/23 inhibitor) than secukinumab and ixekizumab (IL-17 inhibitors). Because of the limited sample size, we were unable to conduct an analysis separately for TNF inhibitors vs IL-17 inhibitors.

Results

STUDY COHORT

After applying the inclusion and exclusion criteria, we identified 3,394 patients with PsA who initiated a TNF inhibitor (n=3,180) or IL-12/23 or 17 inhibitors (n=214; [Supplementary Figure 2](#), available in online article). The TNF inhibitors group included 1,743 (54.8%) adalimumab, 1,011 (31.8%) etanercept, 256 (8.1%) infliximab, 115 (3.6%) certolizumab, and 55 (1.7%) golimumab initiators. In the IL-12/23 or 17 inhibitor group, 154 (72.0%) used ustekinumab; 56 (26.2%) used secukinumab; and 4 (1.9%) used ixekizumab.

BASELINE CHARACTERISTICS

TNF inhibitor initiators were older than initiators of IL-12/23 or 17 inhibitors (mean age [SD] 50.4 [11.7] years vs 52.9 [11.6] years, respectively). While both groups had a high comorbidity burden, we noted substantial differences in baseline characteristics between the 2 groups (Table 1). Initiators of IL-12/23 or 17 inhibitors had more baseline cardiovascular diseases, including hypertension, hyperlipidemia, ischemic heart disease, and heart failure. Psoriasis and other diseases, such as diabetes, malignancy, chronic renal/liver disease, pulmonary disease, and hospitalized infection, were also more prevalent among IL-12/23 or 17 inhibitor initiators than initiators of TNF inhibitors. However, a greater portion of the TNF inhibitor group had rheumatoid arthritis and inflammatory bowel disease at baseline compared with the IL-12/23 or 17 inhibitor group. The mean (SD) combined comorbidity score was higher for IL-12/23 or 17 inhibitors compared with initiators of TNF inhibitors (0.9 [1.8] vs 0.3 [1.2], respectively).

With regard to PsA treatment history (Table 1), 55.4% of TNF inhibitor initiators used methotrexate at baseline, whereas 34.6% of IL-12/23 or 17 inhibitor initiators used methotrexate. In contrast, apremilast use was more common in the IL-12/23 or 17 inhibitor group (27.1%) than the TNF inhibitor group (5.5%). Use of oral steroids and NSAIDs were more frequent in initiators of TNF inhibitors than in IL-12/23 or 17 inhibitor initiators. However, other medications were more often used among IL-12/23 or 17 inhibitors than initiators of TNF inhibitors, consistent with the relevant comorbidities more commonly noted in IL-12/23 or 17 inhibitor initiators.

Both groups had high health care utilization at baseline (Table 1). The median number of different prescription drugs used in the year before the index date was 11 in both groups, and one-fifth had emergency department visits. Initiators of TNF inhibitors had more rheumatologist visits, whereas IL-12/23 or 17 inhibitor initiators had more dermatologist visits and acute hospitalizations.

TABLE 2 Adjusted OR for Patient Characteristics Associated with Initiation of TNF vs IL Inhibitors Among PsA Patients^{a,b}

Patient characteristics	aOR ^c (95% CI)	aOR (95% CI) for LASSO selected variables
Age	1.00 (0.98-1.01)	–
Female vs male	1.04 (0.75-1.43)	–
Calendar year 2015 vs 2014	0.67 (0.41-1.09)	–
Calendar year 2016 vs 2014	0.36 (0.23-0.58)	–
Region Northeast vs South	0.62 (0.42-0.92)	–
Region Midwest vs South	1.37 (0.84-2.24)	–
Region West vs South	1.32 (0.88-1.97)	–
Combined comorbidity score	0.92 (0.79-1.08)	0.88 (0.78-0.98)
Hypertension	1.29 (0.82-2.03)	–
Hyperlipidemia	0.93 (0.64-1.36)	–
Diabetes	0.85 (0.50-1.44)	–
Obesity	1.07 (0.70-1.63)	–
Smoking	0.84 (0.51-1.39)	–
Alcohol	2.06 (0.53-8.02)	–
Psoriasis	0.68 (0.48-0.98)	0.73 (0.52-1.02)
Rheumatoid arthritis	1.10 (0.77-1.57)	–
Ischemic heart disease	1.05 (0.58-1.88)	–
Heart failure	0.34 (0.14-0.82)	0.36 (0.16-0.81)
Malignancy	0.47 (0.27-0.82)	0.51 (0.30-0.84)
Chronic renal disease	0.72 (0.31-1.67)	–
Liver disease/hepatitis	0.76 (0.46-1.24)	0.83 (0.51-1.33)
Pulmonary disease	1.08 (0.68-1.71)	–
Hypothyroidism	0.86 (0.57-1.31)	–
Depression	0.98 (0.64-1.50)	–
Glaucoma	0.73 (0.40-1.30)	0.71 (0.40-1.26)
Hospitalized infection	1.15 (0.42-3.12)	–
ED visit	1.47 (0.97-2.22)	1.41 (0.96-2.07)
Hospitalization	0.87 (0.46-1.65)	–
Methotrexate	1.91 (1.37-2.67)	1.84 (1.35-2.52)
Leflunomide	1.12 (0.56-2.24)	–
Sulfasalazine	1.51 (0.83-2.73)	1.46 (0.82-2.61)
Cyclosporine	0.90 (0.33-2.46)	–
Apremilast	0.22 (0.15-0.33)	0.22 (0.15-0.31)
Topical steroid	1.36 (0.97-1.92)	–
Topical vitamin D derivative	0.79 (0.50-1.25)	0.81 (0.53-1.26)
Topical tacrolimus/pimecrolimus	0.85 (0.33-2.17)	–
Oral steroids	1.37 (0.99-1.90)	1.34 (0.98-1.82)
NSAIDs	1.40 (1.02-1.92)	1.39 (1.03-1.87)
Coxibs	1.06 (0.60-1.86)	–

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PATIENT CHARACTERISTICS AND TREATMENT INITIATION

Multivariable logistic regression model identified several factors associated with the initiation of TNF inhibitors vs IL-12/23 or 17 inhibitors. After adjusting for all the baseline characteristics, age and sex were not associated with the treatment type (Table 2). However, since IL-12/23 or 17 inhibitors became available later than TNF inhibitors, the odds of initiating IL-12/23 or 17 inhibitors increased with calendar year (aOR for year 2016 vs 2014: 0.36, 95% CI=0.23-0.58; aOR for year 2015 vs 2014: 0.67, 95% CI=0.41-1.09).

We also observed a regional difference: patients from the Northeast were associated with more use of IL inhibitors compared with those from the South (aOR=0.62, 95% CI=0.42-0.92). Comorbidities that showed negative associations with TNF inhibitor initiation were psoriasis, heart failure, and malignancy. Patients with previous use of methotrexate had 2-fold increased odds of initiating a TNF inhibitor over an IL-12/23 or 17 inhibitor (aOR=1.91, 95% CI=1.37-2.67). In contrast, previous use of apremilast was negatively associated with TNF inhibitor initiation (aOR=0.22, 95% CI=0.15-0.33).

These results were consistent in a multivariable logistic regression model with LASSO selected variables. C-statistics were 0.777 for the regular model and 0.767 for the model with LASSO selection.

TREATMENT PERSISTENCE

In the primary analysis, the proportion of patients with treatment persistence (with any refill gaps) was similar between the 2 groups at the 1-year follow-up: 1,685 (53.0%) TNF inhibitor and 115 (53.7%) IL-12/23 or 17 inhibitor initiators. Among TNF inhibitor initiators, 355 (11.2%) switched to a different TNF inhibitor, and 149 (4.7%) switched to an IL-12/23 or 17 inhibitor.

TABLE 2 Adjusted OR for Patient Characteristics Associated with Initiation of TNF vs IL Inhibitors Among PsA Patients^{a,b} (continued)

Patient characteristics	aOR ^c (95% CI)	aOR (95% CI) for LASSO selected variables
Opioids	1.22 (0.85-1.74)	–
Antihypertensives	0.68 (0.45-1.05)	0.75 (0.55-1.03)
Antidiabetics	1.33 (0.75-2.39)	–
Statins	1.01 (0.66-1.53)	–
Nonstatin lipid-lowering drugs	0.67 (0.37-1.23)	0.69 (0.39-1.22)
Antibiotics	1.03 (0.71-1.49)	–
Antiviral	1.23 (0.64-2.36)	–
Number of unique generic prescriptions	0.97 (0.94-1.01)	–
Number of dermatologist visits	0.98 (0.96-1.00)	0.98 (0.96-1.00)
Number of rheumatologist visits	1.04 (0.98-1.11)	1.04 (0.98-1.10)
C-statistics	0.777	0.767

^aTNF inhibitors included etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab.^bIL inhibitors included secukinumab, ustekinumab, and ixekizumab.^cAdjusted simultaneously for all the covariates presented in Table 1.

aOR=adjusted odds ratio; Coxibs=selective COX-2 inhibitors; ED=emergency department; IL=interleukin; LASSO=least absolute shrinkage and selection operator; NSAIDs=nonsteroidal anti-inflammatory drugs; PsA=psoriatic arthritis; TNF=tumor necrosis factor.

Among IL inhibitor initiators, 13 (6.1%) switched to a TNF inhibitor, and 12 (5.6%) switched to another IL-12/23 or 17 inhibitor (Figure 1).

In the secondary analysis, where high adherence to treatment was required with refill gaps of 30 days or less, 1,181 (37.1%) TNF inhibitor users and 53 (24.8%) IL-12/23 or 17 inhibitor users were treatment persistent with high adherence (Figure 1). In other words, among the 53% persistent users in the primary analysis, 15.9% of TNF inhibitor users and 28.9% of IL-12/23 or 17 inhibitor users had a refill gap of more than 30 days but resumed the index treatment with use at the 1-year follow-up.

When different refill gaps were used (14 days and 60 days), the relative results remained similar, where initiators of TNF inhibitors had a higher persistence rate compared with IL inhibitor initiators ([Supplementary](#)

[Figure 3](#), available in online article). During the 1-year follow-up period, 1,368 (43.0%) in the TNF inhibitor group and 60 (28.0%) in the IL-12/23 or 17 inhibitor group had a PDC of at least 80% during the 1-year follow-up period.

Table 3 presents crude and fully adjusted ORs for treatment persistence associated with use of TNF inhibitors vs IL-12/23 or 17 inhibitors. There was no difference in 1-year treatment persistence between the 2 drugs even after adjusting for baseline characteristics (aOR for TNF inhibitors vs IL-12/23 or 17 inhibitors: 0.86, 95% CI=0.63-1.15). However, use of TNF inhibitors was associated with a significantly higher treatment persistence with high adherence compared with IL-12/23 or 17 inhibitors (aOR=1.61, 95% CI=1.15-2.26). Similarly, use of TNF inhibitors was also significantly associated with increased PDC of at

least 80% for 1 year compared with IL-12/23 or 17 inhibitors (aOR=1.78, 95% CI=1.29-2.46).

In the multivariable logistic regressions, we found that obesity, smoking, alcohol, ischemic heart disease, heart failure, and chronic renal disease were associated with a lower treatment persistence; baseline use of methotrexate was associated with a higher treatment persistence ([Supplementary Figure 4](#), available in online article). When we only adjusted for LASSO selected variables, the results remained very similar (data not shown).

The subgroup analysis showed similar associations between patient characteristics and treatment initiation of TNF inhibitors vs ustekinumab as the findings from the main analysis ([Supplementary Table 2](#), available in online article). Seventy-eight (50.6%) ustekinumab users remained on the treatment 1 year after the treatment initiation, and 29 (18.8%) were treatment persistent with high adherence ([Supplementary Table 3](#), available in online article). Treatment persistence was not different between TNF inhibitor and ustekinumab initiators (aOR=1.02, 95% CI=0.72-1.44). Similar to the main analysis, use of TNF inhibitors was associated with a greater treatment persistence with high adherence (aOR=2.32, 95% CI=1.52-3.55) and a PDC of at least 80% (aOR=2.69, 95% CI=1.79-4.04) compared with ustekinumab.

Discussion

In this real-world cohort of 3,394 PsA patients who initiated a TNF inhibitor or an IL-12/23 or 17 inhibitor as a first-line biologic treatment, both groups had high comorbidity burden and health care utilization. IL-12/23 or 17 inhibitor initiators generally had a higher prevalence of comorbidities

FIGURE 1 Treatment Patterns in First Year Following Initiation of TNF or IL Inhibitors for PsA: Primary Analysis Allowing for any Refill Gaps and Secondary Analysis Requiring High Adherence

IL = interleukin; PsA = psoriatic arthritis; TNF = tumor necrosis factor.

and medication use compared with initiators of TNF inhibitors. Treatment persistence was similar between the groups, whereas medication adherence was higher with TNF inhibitor initiators than with IL 12/23 or 17 inhibitor initiators during the first year of treatment.

This study has highlighted the differences in baseline characteristics of PsA patients and their treatment patterns between the 2 most widely used biologic drug classes for PsA—TNF inhibitors and IL-12/23 or 17 inhibitors—in a real-world US setting. During the study period, TNF inhibitors were much more commonly used for PsA as the first-line biologic agent than IL-12/23 or 17 inhibitors. Presence of certain comorbidities, including psoriasis, heart failure, and malignancy, and PsA treatment history (ie, methotrexate, apremilast, and NSAIDs) were positively associated with initial selection of IL-12/23 or 17 inhibitors as the first biologic treatment compared with TNF inhibitors.

These findings are mostly consistent with clinical practice guidelines, including GRAPPA,⁹ EULAR,¹² and the ACR/NPF,¹¹ which generally recommend use of TNF inhibitors over IL-12/23 or 17 inhibitors after the failure of csDMARDs, but IL-12/23 or 17 inhibitors could also be used earlier than TNF inhibitors under certain comorbid conditions, such as preexisting heart failure, which is a contraindication for TNF inhibitors. Our study results are also in line with this recommendation; for example, heart failure was associated with 66% lower odds of initiating TNF inhibitors, and psoriasis patients had 32% lower odds of initiating TNF inhibitors over IL-12/23 or 17 inhibitors. Such associations were not surprising and are a result of the prescribing practice based on indication or contraindication of these medications.

For chronic diseases such as PsA, where remission is the primary goal of treatment, treatment persistence or

TABLE 3 Crude and Fully Adjusted OR (95% CI) for 1-Year Treatment Pattern After Initiation of TNF vs IL inhibitors for PsA^a

Outcome	N (%)	Crude OR (95% CI)	aOR (95% CI)
Treatment persistence			
TNF inhibitors	1,685 (53.0)	0.97 (0.74-1.28)	0.86 (0.63-1.15)
IL inhibitors	115 (53.7)	reference	reference
Treatment persistence with high adherence			
TNF inhibitors	1,181 (37.1)	1.79 (1.30-2.47)	1.61 (1.15-2.26)
IL inhibitors	53 (24.8)	reference	reference
PDC ≥ 80%			
TNF inhibitors	1,368 (43.0)	1.94 (1.43-2.63)	1.78 (1.29-2.46)
IL inhibitors	60 (28.0)	reference	reference

^aAdjusted for all the covariates presented in Table 1.

IL = interleukin; OR = odds ratio; PDC = proportion of days covered;

PsA = psoriatic arthritis; TNF = tumor necrosis factor.

medication adherence is the key to treatment success.¹³ Therefore, it is crucial to understand treatment persistence or adherence and associated factors between different biologic drugs among PsA patients. In this study, we observed an overall persistence rate of 53%, which was similar in TNF inhibitors and IL-12/23 or 17 inhibitors as the first-line biologic drug, allowing for any refill gaps. While our result fell within the range of previously published persistence rates of biologics (40.5%–66%) in PsA from studies based on US claims data,^{14-16,18-20,28} it is important to note that difference in treatment persistence between published studies may be related to variations in its definition. Specifically, assessing treatment persistence in pharmacy claims data is mostly based on certain treatment gaps between the adjacent refills, and these gaps varied among 45 days,^{14,19,28} 60 days,^{15,18} 90 days,^{16,20,28} or 180 days²⁸ in different studies.

In our study, when we only allowed patients to have 30-day refill gaps or less to define the secondary outcome (ie, treatment persistence with high adherence), the proportion of patients with treatment persistence was much lower (37.1% for TNF inhibitors and 24.8% for IL-12/23 or 17 inhibitors). This indicates that some patients (15.9% of the TNF inhibitor group and 28.6% of the IL-12/23 or 17 inhibitor group) discontinued the initial treatment for more than 30 days and then restarted the same medication or had less frequent administrations than expected. A study conducted by Bonafede et al estimated that 47%–56% of persistent users and 17%–29% of restarters among etanercept, adalimumab, or infliximab initiators in PsA patients after at least

45 days of discontinuation during the first year of follow-up.¹⁴ Another study by Zhu et al used a longer treatment gap, which was 90 days, and found that 50.9% continued use and 6.1% restarted the initial TNF inhibitor treatment.¹⁶

Compared with these studies, our study presents relatively lower persistence rates, which might be a result of the shorter treatment gap allowance.²⁸ However, there is no consensus on the optimal treatment gap to study drug persistence rates. The difference in our findings compared with the previous studies might also be a result of the inclusion of more recent data and the availability of newer biologic agents in our study, potentially allowing for more treatment modifications.

We found that initiators of TNF inhibitors had increased odds for treatment persistence with high adherence compared with IL-12/23 or 17 inhibitors initiators. Similarly, a greater proportion of initiators of TNF inhibitors also had PDCs of at least 80% than did initiators of IL-12/23 or 17 inhibitors during their first year of follow-up. In addition, switching to another biologic agent occurred in 16.8% of TNF inhibitor initiators vs 11.7% of IL-12/23 or 17 inhibitor initiators at the 1-year follow-up, which could potentially imply better clinical effectiveness of IL-12/23 or 17 inhibitors as the first-line biologic agent for PsA. Nevertheless, it is unclear whether a higher persistence to TNF inhibitors vs IL-12/23 or 17 inhibitors is related to better tolerance (ie, less side effects), shorter half-lives of medications, or a specific reason for treatment initiation (PsA vs psoriasis).

Our data suggest that IL-12/23 or 17 inhibitors in this study were more frequently indicated for concurrent psoriasis or other skin disease. We observed that the proportion of patients with a baseline psoriasis code was higher in the IL-12/23 or 17 inhibitor group (72.9%) than in the TNF inhibitor group (63.2%), with an SMD of 21%. Also, the concurrent use of methotrexate was lower in the IL-12/23 or 17 inhibitor group (34.6%) than in the TNF inhibitor group (55.4%). This finding may be expected, since biologic monotherapy is more typical for psoriasis than methotrexate-biologic combination therapy.

Previous studies have shown that, for psoriasis, IL-12/23 and IL-17 inhibitors have higher efficacy compared with TNF inhibitors.²⁹⁻³¹ Therefore, if it is true that IL-12/23 or 17 inhibitors was prescribed for psoriasis indication or other skin disease more frequently than TNF inhibitors, then that might explain why patients had missed doses, especially those with long half-lives such as IL-12/23 inhibitors.

Although TNF inhibitor treatment patterns were studied in several previous studies, evidence is sparse for the treatment patterns of newer bDMARDs such as IL-12/23 or 17 inhibitors. A recent study of 292 PsA patients based on Italian prescription drug claims data showed no difference

in the retention rate of TNF inhibitors vs ustekinumab or secukinumab.³² A claims-based cohort study with 1,558 PsA patients found that secukinumab initiators were more adherent than initiators of TNF inhibitors,²⁸ and a study based on a large health care provider database concluded that secukinumab was superior to adalimumab, infliximab, and ustekinumab, only when they were indicated as second-line therapy.³³

In contrast, registry-based studies such as PSOriasis Longitudinal Assessment and Registry (PSOLAR), British Association of Dermatologists Biologic Interventions Register (BADBIR), and a population study using Swedish administrative registries reported a better drug survival of ustekinumab compared with TNF inhibitors among PsA or psoriasis patients.³⁴⁻³⁶ Nevertheless, data in these studies and in our study are limited to further identify specific reasons for treatment discontinuation or switching.

STRENGTHS AND LIMITATIONS

This study has several strengths. First, we used a large US commercial claims database that covers all the states, so the study results are generalizable to the general US population across all regions. Second, we included data from recent calendar years, which enabled us to include ustekinumab and secukinumab initiators in the IL-12/23 or 17 inhibitor group. Third, we performed a comprehensive assessment of patient characteristics including over 46 prespecified variables.

The results of this study, however, should be interpreted in the context of some limitations. First, the study was subject to residual confounding even though we tried to assess a number of baseline characteristics in the study cohort. While the study database provided comprehensive, longitudinal data on patient medical

diagnoses, medication dispensing, and health care utilization, it had no information on PsA disease activity or severity, smoking or other behavioral factors, or socioeconomic status.

Second, we were unable to address physician and patient preferences in the treatment initiation and modifications, which may play an important role in the treatment course, and did not have information on why the initial treatment was initiated (eg, more for joint symptoms or skin lesions). Similarly, we were unable to determine the reasons of discontinuation or continuation with longer refill gaps than indicated intervals. Future research using claims data linked with electronic medical records may be able to explore the reasons for treatment changes.

Third, although we used relatively recent data, we still had very few patients initiating ixekizumab, and we did not have power to compare individual TNF inhibitor and IL-12/23 or 17 inhibitor agents.

Finally, because there is no consensus on an optimal refill gap for treatment of bDMARDs to determine drug persistence using claims data, the challenge still remains to reflect the true persistence rate for patients who had longer treatment intervals than indicated.

Conclusions

In this real-world cohort study using U.S. administrative claims data, PsA patients were more likely started on a TNF inhibitor than on an IL-12/23 or 17 inhibitor as the first-line biologic treatment. PsA patients who initiated IL-12/23 or 17 inhibitors generally had a higher prevalence of comorbidities and health care utilization. Treatment persistence was similar between the 2 groups, whereas medication adherence was higher with TNF inhibitors than with IL-12/23 or 17 inhibitors

during the first year of treatment. Some baseline comorbidities and health care utilization patterns were associated with the initial treatment choice, as well as with 1-year treatment persistence. Our findings provide a new insight into treatment patterns that compares TNF inhibitors vs newer biologic drugs for PsA, IL-12/23 or 17 inhibitors, in a real-world setting.

DISCLOSURES

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