Medication Effectiveness with the Use of Tumor Necrosis Factor Inhibitors Among Texas Medicaid Patients Diagnosed with Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Adalimumab (Humira [ADA]), etanercept (Enbrel [ETN]), and infliximab (Remicade [IFX]) are tumor necrosis factor (TNF) inhibitors indicated for the treatment of a variety of disorders. While their effectiveness has not been directly compared in a clinical trial, results from the majority of the indirect treatment comparisons suggest comparable efficacy and safety profiles. However, these TNF inhibitor agents differ in administration method and dosing flexibility, which may result in differences in medication use profiles (e.g., adherence, persistence, discontinuation, dose escalation, and switching to a new biologic rheumatoid arthritis drug) and effectiveness in clinical practice.

OBJECTIVE: To estimate the effectiveness of ADA, ETN, and IFX in patients with rheumatoid arthritis (RA) using a validated, claims-based algorithm designed for large retrospective databases.

METHODS: Adult (aged 18-63 years) patients diagnosed with RA, and receiving ADA, ETN, or IFX, and insured by Texas Medicaid were included. The index date was the date of the first prescription claim for ADA or ETN or infusion record for IFX with no claim or infusion record of a biologic drug in the preceding 6 months (i.e., biologic naïve). The study time frame was from July 2003 to August 2011, and prescription and medical claims for each subject were analyzed over an 18-month period (6 months pre- and 12 months post-index). Based on a RA medication effectiveness algorithm (Curtis et al. 2011), a RA medication was classified as effective if each of the following 6 criteria were met: (1) high medication adherence (i.e., medication possession ratio [MPR] $\geq 80\%$, defined as the sum of days' supply for all fills or infusions divided by the number of days in the study period); (2) no switching to (or addition of) new biologic RA drugs; (3) no addition of new nonbiologic RA drugs; (4) no increase in dose or frequency of administration of the RA medication currently evaluated; (5) no more than 1 glucocorticoid (GC) joint injection; and (6) no increase in dose of a concurrent oral GC. Propensity score (PS) matching was employed, and paired tests (i.e., McNemar's) and multivariate conditional logistic regression analysis were used to compare groups. Demographic (i.e., age, gender, race) and clinical (i.e., use of nonbiologic disease-modifying antirheumatic drugs [DMARDs], pain medication use, GC medication use, RA-related and non-RA-related health care visits [i.e., ambulatory and inpatient visits], number of nonstudy RA medications, and comorbidity index) characteristics, including total health care utilization cost at baseline, served as study covariates.

RESULTS: After PS matching, 822 patients ($n=274$ per group) were included. The majority of the sample (69.2%) was between 45-63 years,

female (88%), and Hispanic (53.7%). Results for each TNF inhibitor differed significantly for 2 of the 6 effectiveness criteria (i.e., medication adherence and dose escalation). A significantly higher proportion of patients on IFX were adherent compared with patients on ETN or ADA (38.3% vs. 16.4% and 21.2%, $P<0.0001$ for both). Adherence rates between ETN and ADA were not significantly different. A significantly higher ($P<0.0001$) proportion of patients on ETN had no dose escalation compared with patients on ADA or IFX (98.2% vs. 88.7% and 80.3%, $P<0.0001$). Dose escalation rate was also significantly lower ($P=0.0106$) for ADA compared with IFX. The multivariate conditional logistic regression analysis indicated no significant difference in overall effectiveness using the claims-based algorithm among the 3 TNF inhibitors nor any significant relationship between effectiveness and the study covariates.

CONCLUSION: The study results suggest that when using a medication effectiveness algorithm, IFX, ETN, and ADA have comparable effectiveness in patients with RA. Patient adherence to therapy may be higher if given IFX, and patients who receive ETN are less likely to have a dose escalation.

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What is already known about this subject

- Clinical trials that directly compare the efficacy of adalimumab (ADA), etanercept (ETN), and infliximab (IFX) are lacking.
- Results from the majority of the indirect treatment comparison studies suggest comparable efficacy and safety profiles.
- Differences in the method of administration and flexibility of dosing of these agents may result in differences in medication use profiles (e.g., adherence, persistence, discontinuation, dose escalation, and switching to a new biologic rheumatoid arthritis [RA] drug) and effectiveness in real-life clinical settings.

What this study adds

- The present study estimated the effectiveness of ADA, ETN, and IFX among RA patients using a validated, claims-based algorithm designed for large retrospective databases.
- Study results indicated comparable effectiveness among the study medications.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints.¹ RA is a leading cause of disability and affects about 1% of the adult U.S. population with a higher prevalence, incidence, and lifetime risk in women compared with men.^{2,3} The direct medical cost related to RA management in the United States has been estimated to exceed \$4 billion annually.⁴ RA negatively impacts patients' health-related quality of life, causing significant joint pain, disability, and limited mobility.³ It has also been associated with increased mortality, since it predisposes patients to increased risk for cardiovascular-related diseases, cancer, infections, and mental health conditions.³ Overall, RA contributes to a reduction in lifespan by 5 to 10 years.³ Although the etiology of RA remains unknown, it has been speculated that it may result from an interaction between environmental exposure and genetic factors. Risk factors for RA include age, being of female sex, presence of specific human leukocyte antigen (HLA) class II genotypes (e.g., HLA-DR4, HLA-DRB1 alleles), tobacco use, dietary factors, reproductive hormonal exposures (e.g., oral contraceptives, hormone replacement therapy) as well as exposures to microbial agents (e.g., *Escherichia coli*, proteus species, cytomegalovirus, and Epstein-Barr virus) and their products (heat-shock proteins).³

Current treatment goals focus on slowing or stopping the progression (i.e., inducing remission) of the disease. Among the available treatment options, the tumor necrosis factor (TNF) inhibitors have been shown through randomized clinical trials (RCTs) to significantly improve patients' symptoms as well as inhibit future joint damage.⁵⁻⁹ TNF inhibitors have been recommended for patients who failed to achieve remission or a satisfactory response following treatment with traditional or nonbiologic disease-modifying antirheumatic drugs (DMARDs; e.g., methotrexate). They have been found to be even more effective when used in combination with traditional DMARDs.^{3,6-11} Among the available TNF inhibitors, 3 agents—adalimumab (Humira [ADA]), etanercept (Enbrel [ETN]), and infliximab (Remicade [IFX])—have been extensively studied

and are the most commonly used. While no clinical trial has been conducted to directly compare the 3 agents, results from the majority of the indirect treatment comparison studies suggest that these agents have comparable efficacy and safety profiles.¹²⁻¹⁷ However, the drugs differ in their methods of administration and flexibility of dosing (ADA and ETN administered subcutaneously and IFX administered intravenously),¹⁸⁻²⁰ which may result in differences in medication use profiles (e.g., adherence, persistence, discontinuation, switching, and dose escalation) and effectiveness in real-life clinical settings. In the face of limited health care resources, availability of information on clinical effectiveness will enhance the decision-making process in the management of RA patients.

Prospective data from registries can be used to compare the effectiveness of these agents among RA patients, since they provide detailed information on diagnosis, disease activity, and treatment.²¹ However, many registries have a limited sample size and incomplete information on patient comorbidities and other medications patients might be taking.²¹ Retrospective databases (administrative claims data) typically have larger sample sizes, complete prescription drug data, and greater generalizability,²² but they lack clinical information regarding disease severity and disability status.²³ Curtis et al. (2011) developed an algorithm to serve as proxy for evaluating the clinical effectiveness of RA medications using administrative claims data.²⁴ Based on this algorithm, a RA medication is classified as effective if it requires no increase in its dose or dosing frequency, no switching to (or addition of) new biologic or nonbiologic RA drugs, no more than 1 glucocorticoid (GC) joint injection, no increase in dose of a concurrent oral GC, and has high patient medication adherence. Although this algorithm has been validated, limited information exists in the literature regarding its use.^{24,25} The objective of this study was to estimate the effectiveness of ADA, ETN, and IFX among RA patients using the comparative effectiveness algorithm designed by Curtis et al. for large retrospective databases.²⁴

FIGURE 1 Data Extraction and Subject Identification Period

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TABLE 1 Rheumatoid Arthritis Effectiveness Criteria

Criteria	Details
Adherence (high)	≥80% MPR for patients on ADA or ETN For IFX, patients must have received at least the number of infusions expected between the index and outcome visit dates to conform to a schedule of 0, 2, 6, and 14 weeks and every 8 weeks thereafter
No switching or adding biologics	Between index and last follow-up date (last prescription)
No additions of new nonbiologic DMARDs (MTX, SSZ, LEF, HCQ)	Between index and last follow-up date (last prescription) patients cannot initiate new nonbiologic DMARD unless they received a prescription in the pre-index period
No increase in biologic dose or frequency	No dose escalation of ETN to 50 mg twice weekly or ADA to 40 mg weekly. IFX end dose-IFX start dose < 100 mg, number of infusions must be within 120% of expected based on 0-, 2-, 6-, and 8-week schedule
No more than 1 GC joint injection	No more than 1 GC injection on 1 calendar day between index date + 90 days and last follow-up date (last prescription)
No increase in dose of oral GC	If no oral GC during pre-index period, patients cannot have > 30 days oral GC between index date + 90 days and last follow-up date (last prescription) If patients received oral GC during pre-index period, cumulative GC dose 6 months prior to last follow-up date must be within 120% of the cumulative oral GC dose in the pre-index period
Effectiveness	1 = Yes (met all 6 criteria above); 0 = No (did not meet all of the above criteria)

Adapted from: Curtis JR, Baddley JW, Yang S, et al. Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis.²⁴

ADA = adalimumab; DMARDs = disease-modifying antirheumatic drugs; ETN = etanercept; GC = glucocorticoid; HCQ = hydroxychloroquine; IFX = infliximab; LEF = leflunomide; mg = milligram; MPR = medication possession ratio, which was defined as the sum of days' supply for all fills divided by the number of days in the study period; MTX = methotrexate; SSZ = sulfasalazine.

Methods

Data Source

This was a retrospective study involving de-identified demographic, medical, and prescription claims records of Texas Medicaid patients with RA between the ages of 18 and 63 years on TNF inhibitors (ADA, ETN, and IFX) between July 2003 and August 2011. Subjects were identified during the index period from January 1, 2004, to August 31, 2010. The index date was defined as the date within the identification period (Figure 1) when the patients had their first claim fill or infusion for any of the study TNF inhibitors without any fills or infusion during the prior 6 months (Figure 1). Prescription claims and infusion records for each subject were analyzed over an 18-month study period (i.e., the 6-month pre-index and 12-month post-index periods).

Information extracted from the Texas Medicaid medical and prescription claims files included the following: de-identified unique patient identification numbers, gender, race/ethnicity, enrollment dates, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes, Healthcare Common Procedure Coding System (HCPCS) codes, dates and costs of medical and prescription services, medication quantity, medication days of supply, National Drug Code (NDC), Generic Sequencing Number (GCN), and American Hospital Formulary Service (AHFS) number. The study protocol and data use were approved by The University of Texas at Austin Institutional Review Board and by the Texas Health and Human Services Commission.

Inclusion and Exclusion Criteria

Texas Medicaid recipients who met the following eligibility criteria were included in the study: (a) adults between the ages of 18 and 63 years at the index date; (b) continuously enrolled with Texas Medicaid for at least 6 months before and 12 months after the index date; (c) have a diagnosis for RA in the 6-month pre-index period (ICD-9-CM code 714.0x) based on the medical claims record; (d) have no claim nor received an infusion for a biologic agent (i.e., abatacept [Orencia], adalimumab [Humira], anakinra [Kineret], certolizumab pegol [Cimza], etanercept [Enbrel], golimumab [Simponi], infliximab [Remicade], rituximab [Rituxan], and tocilizumab [Actemra]) indicated for RA within the 6-month pre-index period; and (e) have at least 1 claim or infusion for any of the study TNF inhibitors (ADA, ETN, and IFX) indicated for the treatment of RA.

Subjects with diagnosis for psoriasis (ICD-9-CM 696.1x); psoriatic arthritis (ICD-9-CM 696.0x); ankylosing spondylitis (ICD-9-CM 720.0x); ulcerative colitis (ICD-9-CM 556.0, 556.1, 556.2, 556.3, 556.5, 556.6, 556.8, or 556.9); Crohn's disease (ICD-9-CM 555.0x, 555.1x, 555.2x, 555.9x, 565.1x, or 569.81); juvenile idiopathic arthritis (ICD-9-CM 714.3x); non-Hodgkin's lymphoma (ICD-9-CM 200.xx or 202.xx); or chronic lymphocytic leukemia (ICD-9-CM 204.1x) were excluded, since the TNF inhibitors or other biologics used to treat RA are also used to treat these indications. The age range was limited to a maximum of 63 years to minimize the chance of including patients with dual eligibility status (i.e., Medicaid and Medicare).

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FIGURE 2 Patient Attrition in the Texas Medicaid Database

^aJuly 1, 2003, to August 31, 2011.

^bJanuary 1, 2004, to August 31, 2010.

ADA = adalimumab; AS = ankylosing spondylitis; CLL = chronic lymphocytic leukemia; Crohn's = Crohn's disease; ETN = etanercept; HCPCS = Healthcare Common Procedure Coding System; IFX = infliximab; JIA = juvenile idiopathic arthritis; NHL = non-Hodgkin's lymphoma; PsA = psoriatic arthritis; PsO = plaque psoriasis; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumor necrosis factor; UC = ulcerative colitis.

Study End Point Assessment

The primary end point was RA medication effectiveness, and this was determined by the Curtis et al. algorithm.²⁴ Based on the algorithm, a RA medication was classified as effective in a particular patient if all the of following criteria were met:

- (1) high medication adherence (i.e., medication possession ratio (MPR) $\geq 80\%$, calculated as the sum of days' supply for all fills or infusions divided by the number of days in the study period);
- (2) no switching to (or addition of) new biologic RA drugs;
- (3) no addition of new nonbiologic drugs;
- (4) no increase

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TABLE 2 Comparison of Baseline Characteristics by Type of TNF Inhibitor (Unmatched Population)

	ETN (N = 578)	ADA (N = 401)	IFX (N = 563)	P Value
Age, mean ($\pm$ SD) ^a	49.7 ($\pm$ 10.0)	50.3 ($\pm$ 10.0)	50.8 ($\pm$ 9.3)	0.1761
Female (%) ^b	89.6	89.0	87.6	0.5345
Race/ethnicity (%) ^b				0.8320
Hispanics	53.5	53.6	54.7	
Caucasians	26.6	26.9	28.1	
African Americans	10.4	11.5	10.1	
Others	9.5	8.0	7.1	
DMARD utilization (%) ^b	73.4	75.1	62.0	<0.0001
Glucocorticoid utilization (%) ^b	49.7	52.9	29.0	<0.0001
Pain medication (%) ^b	81.5	78.6	56.7	<0.0001
Total number of nonstudy RA-related medications, mean ($\pm$ SD) ^a	2.7 ($\pm$ 1.4) ^c	2.5 ($\pm$ 1.3) ^c	1.9 ($\pm$ 1.5)	<0.0001
Charlson Comorbidity Index ^d				
Median	1.0 ^e	1.0 ^e	1.0	0.0045
Mean ($\pm$ SD)	1.2 ($\pm$ 0.5)	1.2 ($\pm$ 0.5)	1.3 ($\pm$ 0.6)	
Specialty of prescribing physician (%) ^{b,f}				<0.0001
Rheumatologist	46.0	46.6	32.3	
General/family practice	8.7	9.0	11.6	
Others	45.3	44.5	39.1	
Missing	0.0	0.0	17.1	
RA-related health care utilization ^{d,g-i}				<0.0001
Median	3.0	3.0	5.0	
Mean ($\pm$ SD)	4.0 ($\pm$ 4.0)	4.1 ($\pm$ 2.9)	6.5 ($\pm$ 5.3)	
Non-RA-related health care utilization ^{d,e,i}				<0.0001
Median	0.0 ^e	0.0 ^e	1.0	
Mean ($\pm$ SD)	0.7 ($\pm$ 1.3)	0.8 ($\pm$ 1.2)	1.4 ($\pm$ 1.9)	
Pre-index total health care utilization costs (\$) ^{d,e,j}				0.0308
Median	1,583 ^e	1,432 ^e	1,229	
Mean ($\pm$ SD)	2,433 ($\pm$ 2,790)	2,153 ($\pm$ 2,900)	1,854 ($\pm$ 2,620)	

^aANOVA.

^bChi-square test.

^cPairwise comparison test (i.e., Duncan); like letters were not significantly different.

^dKruskal Wallis test.

^ePairwise comparison test (i.e., Wilcoxon test with type 1 error correction using Bonferroni); like letters were not significantly different.

^fThis variable was dropped in further analysis due to missing data on > 10% of IFX patients.

^gPairwise comparison test (i.e., Wilcoxon test with type 1 error correction using Bonferroni) showed significant difference among each of the 3 groups.

^hVisits associated with ICD-9-CM code 714.0x.

ⁱAmbulatory and inpatient visits.

^jTotal direct medical and medication costs in the pre-index period adjusted to 2011 U.S. dollars.

ADA = adalimumab; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IFX = infliximab; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumor necrosis factor.

in dose or frequency of administration of the RA medication currently evaluated; (5) no more than 1 GC joint injection; and (6) no increase in dose of a concurrent oral GC. The description and implementation of each criterion is presented in Table 1.

Study Covariates

The covariates controlled for in the multivariate analysis included demographic factors (age, gender, race/ethnicity); pre-index use of other RA-related medications (i.e., nonsteroidal anti-inflammatory drugs, cyclooxygenase-2-inhibitors, narcotic analgesics, tramadol, corticosteroids, and nonbiologic DMARDs); total number of nonstudy RA-related medications

at index; Charlson Comorbidity Index score (Dartmouth-Manitoba); pre-index RA, non-RA-related outpatient visits; and total pre-index health care utilization cost. Total pre-index health care utilization costs were the direct costs (i.e., medical and medication costs combined). Texas Medicaid paid claims in the pre-index period for users of each of the study TNF inhibitors were adjusted to 2011 U.S. dollars (using the medical Consumer Price Index from the U.S. Bureau of Labor Statistics).

Statistical Analyses

All statistical analyses were performed using SAS for Windows, version 9.2 (SAS Institute, Cary, NC). All statistical analyses

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TABLE 3 Comparison of Baseline Characteristics by Type of TNF Inhibitor:
Propensity-Score (Caliper) 3-Way Matched^a

	ETN N = 274	ADA N = 274	P Value	ETN N = 274	IFX N = 274	P Value	ADA N = 274	IFX N = 274	P Value
Age, mean (±SD) ^b	49.1 (±9.8)	48.9 (±9.9)	0.7638	49.1 (±9.8)	48.7 (±9.6)	0.6619	48.9 (±9.9)	48.7 (±9.6)	0.8710
Females (%) ^c	88.3	88.3	1.0000	88.3	87.2	0.7982	88.3	87.2	0.7914
Hispanics (%) ^c	54.0	52.6	0.7910	54.0	54.4	1.0000	52.6	54.4	0.7327
DMARD utilization (%) ^c	71.5	69.0	0.5341	71.5	75.9	0.2299	69.0	75.9	0.0558
Glucocorticoid utilization (%) ^c	43.8	45.3	0.7275	43.8	43.1	0.9022	45.3	43.1	0.5560
Pain medication (%) ^c	75.6	77.7	0.4885	75.6	80.3	0.1112	77.7	80.3	0.3916
Total number of nonstudy RA-related medications, mean (±SD) ^b	2.4 (±1.3)	2.4 (±1.3)	1.0000	2.4 (±1.3)	2.5 (±1.3)	0.3297	2.4 (±1.3)	2.5 (±1.3)	0.3174
Charlson Comorbidity Index, mean (±SD) ^d	1.2 (±0.5)	1.2 (±0.5)	0.3679	1.2 (±0.5)	1.2 (±0.5)	0.5508	1.2 (±0.5)	1.2 (±0.5)	0.7994
RA-related health care resource utilization, ^{d,f} median	3.0	3.0	0.5188	3.0	4.0	0.0313	3.0	4.0	0.0430
RA-related health care resource utilization, mean (SD)	4.1 (±3.3)	4.1 (±2.7)		4.1 (±3.3)	4.5 (±2.8)		4.1 (±2.7)	4.5 (±2.8)	
Non-RA-related health care resource utilization, ^{d,f} median	0.0	0.0	0.9650	0.0	0.0	0.1679	0.0	0.0	0.2472
Non-RA-related health care resource utilization, mean (±SD)	0.8 (±1.3)	0.8 (±1.2)		0.8 (±1.3)	0.9 (±1.3)		0.8 (±1.2)	0.9 (±1.3)	
Pre-index total health care resource utilization cost (\$), ^{d,g} median	1,477	1,376	0.7230	1,477	1,651	0.2383	1,376	1,651	0.0747
Pre-index total health care resource utilization cost, mean (±SD)	2,097 (±1,955)	1,988 (±1,890)		2,097 (±1,955)	2,210 (±2,152)		1,988 (±1,890)	2,210 (±2,152)	

Source of macros: Rassen JA, Doherty M, Huang W, Schneeweiss S. *Pharmacoepidemiology toolbox*.⁵¹

Article reference: Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S. Matching by propensity score in cohort studies with three treatment groups.²⁷

^aCaliper set at 0.05; Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior P value set at 0.0167 (0.05/n, where n=3, which is the number of comparisons).

^bFor the matched analysis, differences between matched pairs were evaluated using paired t test.

^cFor the matched analysis, differences between matched pairs were evaluated using McNemar's test.

^dFor the matched analysis, differences between matched pairs were evaluated using signed rank test.

^eVisits associated with ICD-9-CM code 714.0x.

^fAmbulatory and inpatient visits.

^gTotal direct medical and medication costs in the pre-index period adjusted to 2011 U.S. dollars.

ADA=adalimumab; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; IFX=infliximab; RA=rheumatoid arthritis; SD=standard deviation; TNF=tumor necrosis factor.

were two-tailed, and the significance level was set a priori at $P < 0.05$. Power to detect significant differences was set at 80%. Frequencies, skewness, kurtosis, and normality tests were computed to check for data abnormalities and normality distribution. Due to baseline differences in the covariates among the groups, a propensity score technique was used.²⁶ Propensity scores (PS) were generated using multinomial logistic regression, and the study groups were matched using a 3-way match (nearest neighbor) with caliper set at 0.05.²⁷ To determine if balance was achieved among the matched groups, differences between matched pairs were evaluated on each of the study covariates using the paired t-test or signed-rank test for continuous data and the McNemar's test for binary data.²⁶ Bonferroni correction was used to control for type 1 error due to multiple comparisons. Descriptive statistics (mean, standard deviation, and frequency) were used to summarize baseline sociodemographics, clinical characteristics, and health care utilization cost patterns. Based on the type (categorical or

continuous) and the distribution of data, appropriate statistical tests, which accounted for the matched nature of the final study sample, were conducted (e.g., McNemar's test for unadjusted pairwise comparison and conditional logistic regression for multivariate analysis).

Results

A total of 1,542 patients met the study criteria (Figure 2). At baseline, the 3 study groups presented with comparable demographic characteristics (i.e., age, gender, and race). However, at baseline, the ADA and ETN study groups differed in clinical characteristics from the IFX group, necessitating the need for a matching procedure to be conducted (Table 2). After PS matching, a final sample size of 822 patients ($n = 274$ per group) was obtained (Table 3), and there were no significant differences in clinical or demographic characteristics among the 3 study medications. At baseline, the majority of the matched sample (69.2%) was between 45–63 years, female (88%), and Hispanic (53.7%).

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TABLE 4 Baseline Summary Statistics for Matched Sample

Demographic & Clinical Characteristics	N	%	Demographic & Clinical Characteristics	N	%
Age groups			Types of oral glucocorticoids^b		
18-34	77	9.4	Dexamethasone	1	0.1
35-44	176	21.4	Hydrocortisone	0	0.0
45-54	292	35.5	Methylprednisolone	48	5.8
55-63	277	33.7	Prednisolone	0	0.0
Total	822	100.0	Prednisone	301	36.6
Race/ethnicity			Cortisone	0	0.0
Caucasians	226	27.5	Types of glucocorticoid injections^b		
African Americans	84	10.2	Corticotrophin	0	0.0
Hispanics	441	53.7	Dexamethasone	7	0.9
Others	71	8.6	Hydrocortisone	0	0.0
Total	822	100.0	Methylprednisolone	25	3.0
Gender			Prednisolone	0	0.0
Female	723	88.0	Triamcinolone	28	3.4
Male	99	12.0	Pain medications		
Total	822	100.0	Yes	640	77.9
Index TNF inhibitor			No	182	22.1
Etanercept	274	33.3	Total	822	100.0
Adalimumab	274	33.3	Types of pain medications^b		
Infliximab	274	33.3	NSAIDs	212	25.8
Total	822	99.9^a	COXIBs	161	19.6
Pre-index DMARD utilization			Narcotic analgesics	437	53.2
Yes	593	72.1	Tramadol	138	16.8
No	229	27.9	Total number of nonstudy RA-related medications		
Total	822	100.0	0	41	5.0
Types of DMARD utilization^b			1	157	19.1
Methotrexate	478	58.2	2	242	29.4
Leflunomide	75	9.1	3	218	26.5
Sulfasalazine	79	9.6	≥4	164	20.0
Hydroxychloroquine	145	17.6	Total	822	100.0
Other DMARDs ^c	6	0.7	Charlson Comorbidity Index score		
Pre-index glucocorticoid utilization			1-2	798	97.1
Yes	362	44.0	≥3	24	2.9
No	460	56.0	Total	822	100.0
Total	822	100.0	Health care resource utilization (# of visits)		
			RA-related ambulatory and inpatient care ^d	3,489	84.1
			Non-RA-related ambulatory and inpatient care	660	15.9
			Total visits	4,149	100.0

^aDoes not add up to 100.0% due to rounding error.

^bGroups are not mutually exclusive because subjects may have used more than 1 medication.

^cExamples of other DMARDs: azathioprine, chloroquine, cyclophosphamide, cyclosporine, minocycline, and sodium aurothiomalate (gold).

^dVisits associated with ICD-9-CM code 714.0x.

COXIB=Cox-2 inhibitors; DMARD=disease-modifying antirheumatic drug; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; NSAIDs=nonsteroidal anti-inflammatory drugs; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

Over 70% (72.1%) of the sample used nonbiologic DMARDs in the pre-index period, with methotrexate (58.2%) being the most commonly prescribed nonbiologic DMARD. Forty-four percent of the matched sample received GCs in the pre-index period, and 77.9% of the sample used pain medications with narcotic analgesics (53.2%) being the most commonly prescribed (53.2%). The majority of the sample patients were on at least 2 nonstudy RA-related medications (75.9%) and had a Charlson Comorbidity Index (CCI) score ranging from 1-2 (97.1%) in the

pre-index period. The CCI score often reflects the severity of the disease as well as the overall health status of the patient. Higher CCI scores indicate higher disease severity. Of the 4,149 total pre-index clinical visits, the majority (84.1%) were for RA-related ambulatory and inpatient care (Table 4).

The index TNF inhibitor therapy was classified as effective using the claims-based algorithm in 15.7% of the study sample (12.4%, 14.6%, and 20.1%, for ETN, ADA, and IFX, respectively). Overall, 74.7% of the sample had a low adherence to the

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TABLE 5 McNemar's Test Comparing Each Criterion of the Medication Effectiveness Algorithm Among TNF Inhibitors (Unadjusted Analysis)^a

Curtis Algorithm Criteria	ETN (n = 274)	ADA (n = 274)	Statistic	P Value
Adherence (MPR ≥ 80) (%)	16.4	21.2	2.1392	0.1766
No switching (%)	89.4	86.5	1.0323	0.3742
No additions of new nonbiologic DMARDs (%)	82.5	79.6	0.7619	0.4452
No increase in biologic dose or frequency (%)	98.2	88.7	19.8824	<0.0001 ^b
No more than 1 GC joint injection (%)	99.3	98.9	0.2000	1.0000
No increase in dose of oral GC (%)	89.8	83.6	5.0702	0.0331
Effectiveness (%)	12.4	14.6	0.6667	0.4966
Curtis Algorithm Criteria	ETN (n = 274)	IFX (n = 274)	Statistic	P Value
Adherence (%)	16.4	38.3	30.5085	<0.0001 ^b
No switching (%)	89.4	88.3	0.1636	0.7877
No additions of new nonbiologic DMARDs (%)	82.5	82.1	0.0141	1.0000
No increase in biologic dose or frequency (%)	98.2	80.3	40.6949	<0.0001 ^b
No more than 1 GC joint injection (%)	99.3	97.1	3.6000	0.1094
No increase in dose of oral GC (%)	89.8	88.3	0.2963	0.6835
Effectiveness (%)	12.4	20.1	5.8800	0.0203
Curtis Algorithm Criteria	ADA (n = 274)	IFX (n = 274)	Statistic	P Value
Adherence (%)	21.2	38.3	17.9593	<0.0001 ^b
No switching (%)	86.5	88.3	0.4098	0.6089
No additions of new nonbiologic DMARDs (%)	79.6	82.1	0.6049	0.5052
No increase in biologic dose or frequency (%)	88.7	80.3	7.0533	0.0106 ^b
No more than 1 GC joint injection (%)	98.9	97.1	2.2727	0.2266
No increase in dose of oral GC (%)	83.6	88.3	2.6825	0.1299
Effectiveness (%)	14.6	20.1	2.5862	0.1329

Adapted from: Curtis JR, Baddley JW, Yang S, et al. Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis.²⁴

^aADA and IFX were individually compared with ETN. Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior P value set at 0.0167 (0.05/n, where n = 3, which is the number of comparisons).

^bSignificant at P < 0.0167.

ADA = adalimumab; ETN = etanercept; DMARDs = disease-modifying antirheumatic drugs; GC = glucocorticoid; IFX = infliximab; MPR = medication possession ratio; TNF = tumor necrosis factor.

index drug; 11.0% had a dose escalation; 11.9% had a switch from the index TNF inhibitor therapy to another biologic agent; 18.6% had an addition of a new nonbiologic DMARD; 12.8% had an increase in concurrent oral glucocorticoid dose; and 1.6% had more than 1 GC joint injection (Table 5). The 3 treatment groups (ADA, ETN, and IFX) differed significantly for 2 of the 6 effectiveness criteria (medication adherence and dose escalation). A significantly higher proportion of patients on IFX were adherent compared with patients on ETN or ADA (38.3% vs. 16.4% and 21.2%, $P < 0.0001$ for both). Adherence rates between ETN and ADA were not significantly different. A significantly higher proportion ($P < 0.0001$) of patients on ETN had no dose escalation compared with patients on ADA or IFX (98.2% vs. 88.7% and 80.3%, $P < 0.0001$). Dose escalation rate was also significantly lower ($P = 0.0106$) for ADA compared with IFX. The multivariate conditional logistic regression analysis indicated no significant difference in overall effectiveness using the claims-based algorithm among the 3 TNF inhibitors nor any significant relationship between effectiveness and the study covariates (Table 6).

Discussion

This study estimated the effectiveness of ADA, ETN, and IFX among Texas Medicaid patients with RA using the Curtis et al. (2011)²⁴ comparative effectiveness algorithm and found the algorithm-defined effectiveness to be comparable among the 3 TNF inhibitors. Demographic (age and gender distribution) and clinical characteristics of the final matched study sample were found to be consistent with those reported by other studies of patients with RA that were conducted using retrospective database analysis.^{2,4,28-42} However, in contrast to other studies where the majority of participants were white, the present study had a majority Hispanic population (53.7%).^{31,32,36,37} This was expected, since Hispanics have been reported to account for a significant proportion ($\approx 40\%$) of the Texas population.⁴³

The 2 main components of the effectiveness algorithm's criteria for which significant differences were found were dose escalation and adherence. Based on the study result, a significantly lower level of dose escalation was observed with ETN (1.8%) compared with the use of ADA (11.3%) and IFX (19.7%). This result was not unexpected, since dose increases are described in the U.S. prescribing information for patients

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TABLE 6 Conditional Logistic Regression Analysis Comparing Likelihood of RA Medication Effectiveness Among TNF Inhibitors (N=822)^a

	Odds Ratio	95% CI		Wald X ²	P Value ^b
Medication type					
Adalimumab vs. etanercept	1.139	0.684	1.898	0.2510	0.6164
Infliximab vs. etanercept	1.628	1.000	2.649	3.8399	0.0500
Adalimumab vs. infliximab	0.700	0.439	1.117	2.2411	0.1344
Covariates					
Age	1.005	0.973	1.039	0.1099	0.7403
Male ^c	1.422	0.628	3.220	0.7110	0.3991
Nonwhites ^{c,d}	0.822	0.338	2.000	0.1868	0.6656
Pre-index DMARD nonuse ^c	1.029	0.167	6.337	0.0009	0.9755
Pre-index pain medications nonuse ^c	1.436	0.103	20.108	0.0721	0.7882
Pre-index glucocorticoids nonuse ^c	1.249	0.143	10.934	0.0404	0.8408
Pre-index RA-related visits	1.033	0.624	1.711	0.0159	0.8998
Pre-index non-RA-related visits	0.840	0.377	1.872	0.1825	0.6692
Total number of nonstudy RA-related medications	1.136	0.509	2.537	0.0966	0.7559
Pre-index total utilization cost	1.000	1.000	1.000	0.5580	0.4551
Charlson Comorbidity Index	0.709	0.315	1.594	0.6936	0.4049

^aModel Fit Statistics: likelihood ratio = 15.0572, *df* = 13, *P* = 0.3038; Score = 14.9098, *df* = 13, *P* = 0.3130; Wald = 13.5507, *df* = 13, *P* = 0.4062.

^bSignificant at *P* < 0.05.

^cReference categories: females, whites, DMARD users, glucocorticoid users, and pain medication users.

^dRace was dichotomized into 2 groups (whites and others) due to small cell sizes.

CI = confidence interval; DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

on ADA or IFX in situations of suboptimal treatment response but not for patients on ETN.^{18-20,44-47} Dose escalation patterns obtained in the present study were similar to those reported across a number of dose escalation studies with the proportion of patients having a dose escalation being consistently and significantly lower for ETN compared with ADA and IFX.^{28,29,34,35,37,39,40,42,48} Across all methods used to define dose escalation, the proportions ranged from 0.4% to 10.3%, 8.3% to 33.6%, and 16.4% to 60% for ETN, ADA, and IFX, respectively.^{28,29,34,35,37,39,40,42,48}

Overall, the proportion of adherent patients in the study sample was low (≈25%) with significantly higher adherence shown with the use of IFX and comparable adherence observed between ETN and ADA. The direction of study results was comparable with those of earlier studies regardless of the method used for estimating adherence.^{2,31,33,36} Differences in adherence may be a function of the route and frequency of administration.⁴ IFX is administered intravenously at the physician's office by a health care provider, while ETN and ADA are administered subcutaneously by the patient. IFX is infused at week 0, 2, and 6 and every 8 weeks thereafter, while ETN is given once weekly and ADA is administered once every other week.¹⁸⁻²⁰ The patients on IFX may have adhered better because of appointment reminder messages that may have been sent by the clinic. However, the reasons responsible for the overall low level of adherence values is difficult to ascertain because other important information that impacts adherence (e.g., incidence of adverse events, lack of treatment response, and increased disability) were lacking in the administrative claims data used for this analysis.

Adherence seen in this study was lower than has been reported in previous adherence studies that also used administrative claims data (commercial or Medicaid).^{2,30,31,36} This may be because of the high Hispanic population (53.7%) in the study sample. Being of an ethnic minority has been associated with poor medication adherence.⁴⁹ In addition, the study subjects were of low socioeconomic status (income and education), and subjects may have lacked adequate knowledge/understanding of their disease and its treatment. Other possible factors may include poor prior medication-taking behaviors and beliefs about medications.⁴⁹ Clinicians caring for Medicaid patients need to be aware of these factors and should endeavor to work with each patient to identify patient-specific factors responsible for poor TNF-inhibitor therapy adherence.⁵⁰ Reducing the impact of these factors and improving adherence should be included as a major part of the treatment plan for each RA patient.

Limitations

The present study is unique as it estimated effectiveness of ADA, ETN, and IFX among Medicaid RA patients using the 2011 Curtis et al.²⁴ comparative effectiveness algorithm. However, the study has limitations that need to be considered when interpreting the study results. Administrative claims data are developed for the purpose of reimbursement rather than research. The presence of a claim for a TNF-inhibitor therapy (i.e., ETN or ADA) in the prescription claims data does not necessarily mean that the patient used the medication. However, for IFX, in the absence of fraudulent claims, the presence of an HCPCS J-code 1745 in the medical claims data indicates that it was infused.

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The nonrandomized distribution of the study groups and presence of baseline differences in clinical characteristics could introduce bias (i.e., selection bias) in the study results. Although PS matching and multivariate analyses were used to control for selection/channeling bias and confounding on known variables, there is the possibility that the study groups may still differ in unknown or unmeasured parameters that were not available in the dataset (e.g., disease activity and disability). In addition, the use of PS matching resulted in a significant decrease in the study sample size, causing a decrease in power. This may have been responsible for the inability to detect significant differences among study groups on some of the components of the effectiveness algorithm.

Due to the absence of unit of service information in the medical claims, cost information associated with HCPCS J-code 1745 was used as a proxy in assessing dose escalation for IFX. This may have either overestimated or underestimated dose escalation rates in this study group. The present study only analyzed 12 months of post-index data for biologic-naïve patients. Study outcomes may differ if patients were followed for a longer time period, since RA is a chronic and progressive disease condition. Finally, the study sample had an over-representation of women, minorities (Hispanics), and people of lower socioeconomic status compared with the general U.S. population and thus cannot be generalized to other populations.

Conclusion

The study results suggest that when using a medication effectiveness algorithm, IFX, ETN, and ADA have comparable effectiveness in patients with RA. Patient adherence to therapy may be higher if given IFX, and patients who receive ETN are less likely to have a dose escalation.

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DISCLOSURES

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Oladapo and Barner collaborated on the conception of the project, study design, data analysis, and writing of the manuscript. Lawson, Novak, Rascati, Richards, and Harrison critically reviewed the study design, data analysis, results interpretation and contributed in the development and editing of the manuscript.

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