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ORIGINAL RESEARCH

Diabetes-Related Complications and Costs in Medicare Beneficiaries with Comorbid Rheumatoid Arthritis and Diabetes Treated with Abatacept Versus Other Targeted DMARDs

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ABSTRACT

Introduction: Targeted DMARD (tDMARD) use in patients with rheumatoid arthritis (RA) and type 2 diabetes mellitus (T2DM) may increase whole-body insulin sensitivity. Evidence comparing the T2DM-related clinical and economic impact of abatacept versus other tDMARDs is limited. This study compared differences in T2DM-related healthcare resource utilization (HCRU) and costs in patients with RA and T2DM.

Methods: This retrospective study used 100% Medicare Fee-for-Service claims (parts A/B/D) to identify patients ≥ 65 age, diagnosed with RA and T2DM, and were either TNFi-experienced (switched from a TNFi to another tDMARD) or tDMARD-naïve, initiating their first tDMARD (abatacept, TNFi, or non-TNFi) between 2010 and 2017. Abatacept users were propensity-score (PS) matched to TNFi and other non-TNFi users separately on baseline demographics, comorbidities, medications, T2DM-related HCRU, and costs. Post-index follow-up: until discontinuation of index treatment, disenrollment, death, or end of study period, whichever occurred first. T2DM-related complications and HCRU were assessed. Costs were normalized to per-patient-per-month (PPPM) and inflated to 2019 US$.

Results: The TNFi-experienced group included 2169 abatacept/TNFi and 2118 abatacept/other non-TNFi PS-matched pairs; the tDMARD-naïve group included 2667 abatacept/TNFi and 2247 abatacept/other non-TNFi PS-matched pairs. For TNFi-experienced patients, T2DM-related complication rates for inpatient settings PPPM trended lower for abatacept than TNFi (21 vs. 24, $p = 0.046$) and other non-TNFi groups (21 vs. 26; $p < 0.0001$). T2DM-related total costs PPPM for TNFi-experienced patients demonstrated lower trends for abatacept than TNFi ($489 vs. $594, $p = 0.016$) and other non-TNFi users ($493 vs. $606, $p = 0.012$).

Conclusions: Medicare beneficiaries with RA and T2DM who switch to/initiate abatacept as their first tDMARD have directionally lower rates and costs of T2DM-related complications compared with patients switching to/initiating other tDMARDs. Abatacept treatment may help

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reduce clinical and economic burdens associated with T2DM in patients with RA.

Keywords: Abatacept; DMARD; Healthcare resource utilization; Rheumatoid arthritis; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Abatacept treatment of patients with non-diabetic rheumatoid arthritis (RA) reported improved whole-body insulin sensitivity, reduced HbA1c levels, and a decreased risk of developing diabetes.

The use of tDMARDs in patients with RA has the potential to decrease the progression and risk of type 2 diabetes mellitus (T2DM), however, there is limited information regarding the comparative economic impact of tDMARDs on patients with RA and T2DM.

The impact of initiation or switch to abatacept, TNFis, and other non-TNFis on T2DM-related costs and HCRU complications was evaluated.

What was learned from this study?

T2DM-related complication rates and costs trended lower for patients treated with abatacept compared with TNFi and other non-TNFi, which indicates that abatacept could potentially be more effective in reducing diabetes-related complications and hence the economic burden associated with them.

The results reported here suggest that use of abatacept treatment may improve the clinical and economic burden associated with T2DM in patients with RA.

PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis (RA) is an autoimmune disease – a disease that causes the immune system to attack an individual's own body. RA causes inflammation and damage of the joints, which can severely impact a patient's quality of life. Studies have shown that inflammation may lead to insulin resistance, a precursor of type 2 diabetes mellitus (T2DM). Therefore, patients with RA are at higher risk of developing T2DM. The combination of RA and T2DM increases the burden on healthcare systems. Symptoms of RA can be reduced with a group of medications called targeted disease-modifying antirheumatic drugs (tDMARDs). These tDMARDs can slow the progression of RA and may decrease the risk of a patient developing T2DM; more research is needed on the impact of tDMARDs on the progression of T2DM-related complications. This observational study examined real-life patient data from the CMS Medicare insurance database to compare differences in the use of healthcare (such as outpatient visits and antidiabetic medications) associated with T2DM complications. It is important to understand the benefits of tDMARDs beyond RA because patients with RA have a higher burden of comorbidities than the general population. Patients were treated with tDMARDs: abatacept, a tumor necrosis factor inhibitor (TNFi), or other tDMARDs. This study found the use of healthcare associated with T2DM complications in patients treated with abatacept were numerically lower than for patients treated with TNFi or other tDMARDs. These findings suggest that use of abatacept could help reduce the clinical and economic burden associated with T2DM in patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting nearly 1.3 million people in the United States (US) [1]. RA is characterized by chronic inflammation of the joints which can ultimately lead to cartilage and bone destruction [2]. Though not directly life threatening, RA severely impacts patients'

quality of life and imparts a major economic burden on healthcare systems and society [3]. One US study estimated that RA contributes $19.3 billion in direct and indirect costs in the US annually [4].

RA is typically managed with a group of medications known as disease-modifying antirheumatic drugs (DMARDs). Initial treatment of active RA is typically a conventional DMARD (cDMARD) such as methotrexate, sulfasalazine, or leflunomide [5, 6]. Patients who are intolerant or show an inadequate response to cDMARDs are often treated with targeted DMARDs (tDMARDs). There are various tDMARDs with unique mechanism of action (MOA) such as tumor necrosis factor-α inhibitors (TNFi), including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, anti-interleukin-6 receptor agents (tocilizumab), anti-CD20 agents (rituximab), T-cell co-stimulation modulators (abatacept), and Janus kinase (JAK) inhibitors (baricitinib and tofacitinib) [7]. Studies have associated inflammatory activity with insulin resistance, which, in turn, is more prevalent among RA patients, particularly those with longstanding disease [8, 9]. Prevalence of diabetes mellitus is higher in patients with RA (35.3%) [10] compared with the general population (20.8%) [11] who are ≥ 65 years of age, which is a significant economic burden of diabetes mellitus in the elderly population [12]. Type 2 diabetes mellitus (T2DM)-related complications are costly. A previous study in 2011 estimated the 24 months medical cost of managing complications at US$6,997.0–$19,971.6 in Medicare Advantage beneficiaries [13].

The use of tDMARDs in patients with RA has the potential to decrease the progression and risk of T2DM. Studies that investigated the treatment of non-diabetic RA patients with abatacept reported improved whole-body insulin sensitivity, reduced HbA1c levels, and a decreased risk of developing diabetes [14–17]. However, there is lack of information regarding the comparative economic impact of tDMARDs on patients with RA and T2DM. The current study used 100% Medicare Fee-for-Service (FFS) claims database to evaluate the impact of tDMARDs in patients with RA and T2DM on T2DM-related cost and healthcare resource utilization (HCRU) during follow-up. Ideally, a specific drug versus drug comparison would facilitate inferences regarding cost difference not just between MOA classes but also within each MOA class. However, due to sample size constraints, we grouped adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab into the TNFi group based on their common MOA [10, 16]. Abatacept has a unique MOA and is widely used in the Medicare population [16]; this allowed us to retain abatacept in itself as a separate treatment arm. Tocilizumab, rituximab, tofacitinib, and baricitinib have separate MOAs and are not widely used within the Medicare population [16, 18]. Therefore, we grouped these tDMARDs into other non-TNFi group due to sample size constraints. More specifically, in patients who were either TNFi-experienced or tDMARD-naïve, we evaluated the impact of initiation or switch to abatacept, TNFis, and other non-TNFis on T2DM-related costs and HCRU complications.

METHODS

Study Design and Data Source

This was a retrospective observational study using 100% Medicare FFS (Part A, B, and D) claims and enrollment data from January 1, 2009 through December 31, 2017. The study cohort was derived from the 100% sample of the Medicare research identifiable files, which included Part A and Part B FFS claims data, and prescription drug event (PDE) data for all Part D plans. The claims data comprised all medical and pharmacy encounters including hospital claims, emergency department (ED) visits, skilled nursing facility stays, hospital outpatient services/ambulatory surgical center services, physician office visits (including physician administered treatments), home health services/durable medical equipment, hospice care, and pharmacy utilization.

Study Population

Beneficiaries ≥ 65 years of age with a primary or secondary diagnosis of RA (≥ 2 International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] or ICD, Tenth Revision, CM [ICD-10-CM] diagnoses) in an outpatient or inpatient setting and T2DM (≥ 1 primary or secondary diagnosis of T2DM or use of antidiabetic drugs prior to initiating targeted DMARD) were eligible for the study. TNFi's included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, while other non-TNFi's included anakinra, sarilumab, tocilizumab, baricitinib, rituximab, and tofacitinib. The study cohorts consist of (1) patients who were TNFi-experienced were required to have used a prior (but not same) TNFi in the 12-month pre-index period and switched to a subsequent different tDMARD treatment (≥ 1 National Drug Code [NDC] or Healthcare Common Procedure Coding System [HCPCS] claim for a tDMARD between January 1, 2009 through December 31, 2017, subsequent tDMARD claim served as an index), and (2) patients who were tDMARD-naïve and initiated either abatacept, TNFi, or other non-TNFi as their first tDMARD (≥ 1 NDC or HCPCS claim between January 1, 2009 through December 31, 2017, first tDMARD claim served as an index). Patients with evidence of type 1 diabetes or cancer during 12-month pre-index period were excluded from the study. Patients treated with more than one tDMARD on index or had prior dispensing for index drug within 12 months prior to index date were excluded from the study. Among tDMARD-naïve RA patients, beneficiaries with use of any tDMARD within 12 months before the index date were excluded from the study. The follow-up periods for TNFi-experienced and tDMARD-naïve groups were variable and ended at the earliest of (1) patient disenrollment; (2) end of study period; (3) discontinuation or switch of index treatment; (4) death during follow-up. Discontinuation was defined as a gap from end of days' supply of index drug to ≥ 60 days of following prescription. For patients who discontinued the index drug, the last date of follow-up was the last day of supply for index drug (index drug + days' supply). For patients who switched to another tDMARD during follow-up, the last date of follow-up was the drug switching date.

Compliance with Ethics Guidelines

This retrospective study was carried out in accordance with the Declaration of Helsinki. The study was limited to data without identifiers to ensure confidentiality, and no personal health information was collected. Because of the retrospective study design using previously collected de-identified data, formal consent and institutional review board approval was not necessary for this study.

Study Outcomes

T2DM-related consequences or complications included retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and glucose complications. These complications constitute the Diabetes Complications Severity Index (DCSI) that has been validated to predict HCRU in patients with diabetes [19]. T2DM-related HCRU and costs in the follow-up period were derived by identifying relevant diagnosis codes for T2DM-related complications at primary or secondary position on all medical claims and were computed for outpatient visits, ER visits, physician office visits, antidiabetic medications, other service use (defined as skilled nursing facility (SNF), home health, hospice, durable medical equipment), inpatient admissions/readmissions, and length of inpatient stay. Rates of T2DM-related complications were reported as per 1000 patients per month (P1000PPM). Utilization of antidiabetic medications during follow-up were identified through NDC or HCPCS claims for antidiabetic therapies (i.e., alpha-glucosidase inhibitors, amylin analogs, antidiabetic combinations, biguanides, ddp-4 inhibitors, GLP-1 receptor agonists, insulin, meglitinides, SGLT-2 inhibitors, sulfonylureas, and TZHs). We adopted a payer perspective for the cost estimates. Direct healthcare costs were inflation adjusted to 2019 US$ using the Consumer Price Index and represented as per-patient-per-month (PPPM).

Table 1 Pre-index PS-matched patient characteristics

Patient characteristics	TNFi-experienced patient cohort								tDMARD-naïve patient cohort							
	Abatacept vs. TNFi				Abatacept vs. other non-TNFi				Abatacept vs. TNFi				Abatacept vs. other non-TNFi			
	Abatacept (*N* = 2169)		TNFi (*N* = 2169)		Abatacept (*N* = 2118)		Other non-TNFi (*N* = 2118)		Abatacept (*N* = 2667)		TNFi (*N* = 2667)		Abatacept (*N* = 2247)		Other non-TNFi (*N* = 2247)	
Variable	*N*		%		*N*		%		*N*		%		*N*		%	
Age (years)																
Mean age (SD)	73.0 (5.8)		72.9 (5.8)		72.8 (5.6)		72.7 (5.5)		73.7 (5.9)		73.9 (6.1)		73.4 (5.8)		73.4 (73.4)	
Gender																
Female	1758	81.1%	1755	80.9%	1730	81.7%	1730	81.7%	2188	82.0%	2205	82.7%	1806	80.4%	1797	80.0%
Male	411	18.9%	414	19.1%	388	18.3%	388	18.3%	479	18.0%	462	17.3%	441	19.6%	450	20.0%
Region[a]																
South	980	45.2%	984	45.4%	950	44.9%	933	44.1%	1294	48.5%	1275	47.8%	970	43.2%	954	42.5%
Midwest	398	18.3%	389	17.9%	392	18.5%	396	18.7%	478	17.9%	504	18.9%	445	19.8%	451	20.1%
Northeast	416	19.2%	407	18.8%	386	18.2%	392	18.5%	439	16.5%	448	16.8%	403	17.9%	417	18.6%
West	370	17.1%	386	17.8%	386	18.2%	396	18.7%	445	16.7%	421	15.8%	423	18.8%	424	18.9%
Race ethnicity																
White	1745	80.5%	1743	80.4%	1717	81.1%	1701	80.3%	2114	79.3%	2117	79.4%	1761	78.4%	1767	78.6%
Black or African American	209	9.6%	206	9.5%	198	9.3%	199	9.4%	266	10.0%	279	10.5%	253	11.3%	239	10.6%
Other	215	9.9%	220	10.2%	203	9.6%	218	10.3%	287	10.7%	271	10.2%	233	10.4%	241	10.7%
Route of administration																
Intravenous	1742	80.3%	389	17.9%	1691	79.8%	1424	67.2%	2247	84.3%	795	29.8%	1863	82.9%	1652	73.5%
Subcutaneous	427	19.7%	1780	82.1%	427	20.2%	143	6.8%	420	15.7%	1872	70.2%	384	17.1%	99	4.4%
Oral	0	0.0%	0	0.0%	0	0.0%	551	26.0%	0	0.0%	0	0.0%	0	0.0%	496	22.1%

Table 1 continued

Patient characteristics	TNFi-experienced patient cohort								tDMARD-naïve patient cohort							
	Abatacept vs. TNFi				Abatacept vs. other non-TNFi				Abatacept vs. TNFi				Abatacept vs. other non-TNFi			
	Abatacept (*N* = 2169)		TNFi (*N* = 2169)		Abatacept (*N* = 2118)		Other non-TNFi (*N* = 2118)		Abatacept (*N* = 2667)		TNFi (*N* = 2667)		Abatacept (*N* = 2247)		Other non-TNFi (*N* = 2247)	
CCI Score																
Mean (SD)	4.4 (2.1)		4.4 (2.1)		4.4 (2.1)		4.5 (2.1)		4.8 (2.2)		4.8 (2.2)		4.8 (2.2)		4.7 (2.2)	
Baseline T2DM-related complications																
Cardiovascular	1114	51.4%	1108	51.1%	1113	52.5%	1118	52.8%	1557	58.4%	1536	57.6%	1300	57.9%	1311	58.3%
Cerebrovascular	362	16.7%	344	15.9%	344	16.2%	348	16.4%	496	18.6%	498	18.7%	401	17.8%	397	17.7%
Metabolic	52	2.4%	52	2.4%	44	2.1%	47	2.2%	59	2.2%	66	2.5%	56	2.5%	49	2.2%
Nephropathy	557	25.7%	575	26.5%	559	26.4%	566	26.7%	782	29.3%	776	29.1%	659	29.3%	650	28.9%
Neuropathy	730	33.7%	728	33.6%	738	34.8%	748	35.3%	1036	38.8%	1029	38.6%	852	37.9%	853	38.0%
Peripheral vascular disease	539	24.9%	523	24.1%	483	22.8%	482	22.8%	779	29.2%	761	28.5%	654	29.1%	642	28.6%
Retinopathy	285	13.1%	289	13.3%	276	13.0%	287	13.6%	358	13.4%	346	13.0%	296	13.2%	298	13.3%
Baseline cardiovascular conditions																
Cardiac arrhythmias	523	24.1%	545	25.1%	530	25.0%	522	24.6%	810	30.4%	809	30.3%	708	31.5%	684	30.4%
Congestive heart failure	421	19.4%	388	17.9%	413	19.5%	393	18.6%	647	24.3%	556	20.8%	548	24.4%	552	24.6%
Coronary heart disease	586	27.0%	582	26.8%	600	28.3%	603	28.5%	867	32.5%	873	32.7%	734	32.7%	716	31.9%
Hypertension	1972	90.9%	1965	90.6%	1910	90.2%	1914	90.4%	2436	91.3%	2475	92.8%	2038	90.7%	2043	90.9%
Stroke	377	17.4%	367	16.9%	357	16.9%	380	17.9%	522	19.6%	527	19.8%	426	19.0%	436	19.4%
COPD	653	30.1%	694	32.0%	618	29.2%	681	32.2%	864	32.4%	949	35.6%	733	32.6%	787	35.0%
Baseline comorbid conditions																
Chronic liver disease	299	13.8%	229	10.6%	295	13.9%	251	11.9%	364	13.6%	354	13.3%	305	13.6%	276	12.3%
Neutropenia	30	1.4%	14	0.6%	27	1.3%	26	1.2%	32	1.2%	29	1.1%	29	1.3%	39	1.7%
Renal disease	476	21.9%	490	22.6%	479	22.6%	509	24.0%	688	25.8%	689	25.8%	585	26.0%	568	25.3%

Table 1 continued

Patient characteristics	TNFi-experienced patient cohort								tDMARD-naïve patient cohort							
	Abatacept vs. TNFi				Abatacept vs. other non-TNFi				Abatacept vs. TNFi				Abatacept vs. other non-TNFi			
	Abatacept (*N* = 2169)		TNFi (*N* = 2169)		Abatacept (*N* = 2118)		Other non-TNFi (*N* = 2118)		Abatacept (*N* = 2667)		TNFi (*N* = 2667)		Abatacept (*N* = 2247)		Other non-TNFi (*N* = 2247)	
Baseline medication use																
Glucocorticoids	1750	80.7%	1748	80.6%	1756	82.9%	1741	82.2%	2193	82.2%	2180	81.7%	1869	83.2%	1884	83.8%
Hydroxychloroquine	349	16.1%	354	16.3%	353	16.7%	355	16.8%	718	26.9%	708	26.5%	549	24.4%	554	24.7%
Other cDMARDs	1554	71.6%	1549	71.4%	1522	71.9%	1530	72.2%	2017	75.6%	2029	76.1%	1656	73.7%	1645	73.2%
Antidiabetics	1256	57.9%	1260	58.1%	1234	58.3%	1238	58.5%	1461	54.8%	1460	54.7%	1260	56.1%	1227	54.6%

[a]Regions (as defined by United States Census Bureau) included the following states: South—Oklahoma, Arkansas, Kentucky, West Virginia, Delaware, Maryland, Virginia, North Carolina, Tennessee, South Carolina, Georgia, Alabama, Mississippi, Louisiana, Florida, and Texas; Midwest—Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; Northeast—Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania; and West—Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Idaho, Nevada, Washington, Oregon, California, Alaska, and Hawaii. *CCI* Charlson Comorbidity Index, *cDMARD* conventional DMARD, *COPD* chronic obstructive pulmonary disease, *DMARD* disease-modifying antirheumatic drug, *PS* propensity score, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *tDMARD* targeted DMARD, *TNFi* tumor necrosis factor-α inhibitor

Table 2 T2DM-related HCRU during follow-up

Variable	TNFi-experienced patient cohort						tDMARD-naïve patient cohort					
	Abatacept vs. TNFi			Abatacept vs. other non-TNFi			Abatacept vs. TNFi			Abatacept vs. other non-TNFi		
	Abatacept (*N* = 2169)	TNFi (*N* = 2169)	*p* value	Abatacept (*N* = 2118)	Other non-TNFi (*N* = 2118)	*p* value	Abatacept (*N* = 2667)	TNFi (*N* = 2667)	*p* value	Abatacept (*N* = 2247)	Other non-TNFi (*N* = 2247)	*p* value
Mean (SD) T2DM-related rate of visits P1000PPM during follow-up												
Inpatient visit	21.3 (64.5)	24.0 (72.0)	**0.046**	21.5 (67.2)	25.6 (70.9)	**< 0.0001**	23.1 (69.6)	25.6 (73.9)	0.821	23.6 (71.4)	34.5 (93.9)	0.271
Cardiovascular	17.5 (57.2)	18.9 (65.8)	0.816	17.7 (60.5)	20.3 (64.5)	0.678	18.6 (63.7)	20.6 (66.2)	0.971	18.9 (65.7)	27.7 (84.0)	0.595
Cerebrovascular	1.9 (15.8)	2.3 (20.2)	0.489	1.7 (13.6)	1.9 (16.3)	0.327	1.8 (18.6)	2.2 (15.8)	0.532	1.8 (17.6)	2.5 (24.3)	0.354
Glucose complications and variability	0.7 (10.7)	0.3 (7.2)	0.136	0.6 (10.8)	0.5 (5.0)	0.784	0.5 (8.2)	0.4 (9.4)	0.333	0.6 (9.0)	0.7 (10.5)	0.205
Nephropathy	6.8 (36.8)	8.5 (44.5)	0.141	7.1 (40.9)	9.3 (44.5)	0.205	8.6 (44.5)	10.2 (49.5)	0.551	9.3 (46.2)	11.7 (61.6)	0.261
Neuropathy	3.6 (25.2)	2.9 (23.8)	0.424	3.3 (25.6)	4.0 (25.6)	0.526	3.5 (25.7)	4.2 (25.6)	0.131	3.8 (27.2)	5.6 (34.5)	0.794
Peripheral vascular disease	2.0 (15.4)	3.0 (23.8)	0.172	2.0 (18.9)	3.1 (25.1)	0.532	2.7 (24.1)	3.4 (24.4)	0.492	2.5 (22.6)	4.5 (36.2)	0.403
Retinopathy	0.5 (9.1)	0.5 (9.9)	0.528	0.4 (7.6)	0.4 (5.4)	0.462	0.5 (10.8)	0.6 (7.9)	0.244	0.5 (11.3)	0.9 (10.8)	0.448
Inpatient LOS; (days)	5.2 (5.8)	6.2 (7.7)	0.062	5.3 (6.2)	6.2 (8.7)	0.083	6.4 (8.4)	5.8 (6.4)	0.902	6.3 (8.6)	6.8 (8.8)	**0.030**
ER Visit	15.6 (56.5)	13.9 (50.7)	0.181	15.9 (58.7)	14.3 (50.2)	0.228	15 (54)	16 (67)	0.378	17 (57)	19 (62)	0.593
Outpatient visit	119.8 (313.7)	108.5 (245.3)	0.167	118.8 (273.7)	120.7 (287.1)	0.441	118.5 (265.4)	125.3 (321.5)	0.530	122.1 (263.5)	144.2 (376.6)	**0.014**
Physician office visit	513.8 (765.1)	547.8 (820.5)	0.563	520.4 (805.0)	578.3 (995.0)	0.512	602.2 (863.5)	621.6 (921.8)	0.216	599.4 (879.3)	671.1 (1061.2)	**< 0.0001**

p values in bold show significance (< 0.05). *p* values were calculated based on GLMs with negative binomial distribution and log link

ER emergency room, *GLM* generalized linear model, *HCRU* healthcare resource utilization, *LOS* likelihood of superiority, *P1000PPM* per 1000 patients per month, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *tDMARD* targeted disease-modifying antirheumatic drug, *TNFi* tumor necrosis factor-α inhibitor

Table 3 T2DM-related PPPM healthcare costs during baseline & follow-up

Variable	TNFi-experienced patient cohort				tDMARD-naïve patient cohort			
	Abatacept vs. TNFi		Abatacept vs. other non-TNFi		Abatacept vs. TNFi		Abatacept vs. other non-TNFi	
	Abatacept (*N* = 2169)	TNFi (*N* = 2169)	Abatacept (*N* = 2118)	Other non-TNFi (*N* = 2118)	Abatacept (*N* = 2667)	TNFi (*N* = 2667)	Abatacept (*N* = 2247)	Other non-TNFi (*N* = 2247)
Total medical								
Baseline	$572 ($1453)	$569 ($1385)	$633 ($1554)	$633 ($1528)	$794 ($1739)	$781 ($1752)	$836 ($1791)	$794 ($1739)
Follow-up	$489 ($1313)*	$594 ($1822)*	$493 ($1338)*	$606 ($1866)*	$590 ($2030)	$609 ($1739)	$598 ($2113)*	$854 ($2371)*
Inpatient								
Baseline	$312 ($1042)	$284 ($891)	$357 ($1118)	$337 ($1048)	$422 ($1212)	$412 ($1147)	$446 ($1192)	$422 ($1212)
Follow-up	$255 ($984)*	$334 ($1547)*	$255 ($1001)	$322 ($1525)	$314 ($1716)	$316 ($1365)	$319 ($1783)*	$502 ($1868)*
Outpatient								
Baseline	$59 ($262)	$62 ($259)	$67 ($295)	$73 ($323)	$93 ($367)	$84 ($322)	$95 ($368)	$93 ($367)
Follow-up	$75 ($285)	$61 ($234)	$81 ($306)	$81 ($337)	$80 ($310)	$89 ($389)	$85 ($322)	$93 ($399)
ER								
Baseline	$13 ($50)	$15 ($68)	$15 ($60)	$14 ($64)	$18 ($65)	$21 ($84)	$18 ($65)	$17 ($61)
Follow-up	$14 ($70)	$14 ($60)	$14 ($72)	$13 ($73)	$16 ($117)	$14 ($71)	$17 ($126)	$18 ($70)
Physician office								
Baseline	$85 ($178)	$82 ($169)	$88 ($186)	$97 ($233)	$102 ($179)	$99 ($191)	$100 ($208)	$102 ($179)
Follow-up	$79 ($159)	$87 ($182)	$80 ($168)	$94 ($277)	$97 ($217)	$93 ($204)	$96 ($212)	$101 ($222)
Other[a]								
Baseline	$103 ($467)	$126 ($520)	$106 ($461)	$113 ($419)	$159 ($544)	$165 ($596)	$177 ($635)	$159 ($544)
Follow-up	$66 ($371)*	$99 ($423)*	$64 ($384)*	$95 ($399)*	$82 ($501)	$96 ($486)	$82 ($536)*	$141 ($607)*

Table 3 continued

Variable	TNFi-experienced patient cohort				tDMARD-naïve patient cohort			
	Abatacept vs. TNFi		Abatacept vs. other non-TNFi		Abatacept vs. TNFi		Abatacept vs. other non-TNFi	
	Abatacept ($N = 2169$)	TNFi ($N = 2169$)	Abatacept ($N = 2118$)	Other non-TNFi ($N = 2118$)	Abatacept ($N = 2667$)	TNFi ($N = 2667$)	Abatacept ($N = 2247$)	Other non-TNFi ($N = 2247$)
Antidiabetic medication								
Baseline	$55 ($141)	$62 ($173)	$55 ($143)	$63 ($168)	$41 ($122)	$43 ($121)	$43 ($130)	$41 ($122)
Follow-up	$62 ($169)	$66 ($180)	$67 ($181)	$66 ($191)	$45 ($126)	$54 ($150)	$48 ($134)	$55 ($163)

All data are mean (SD). *p* values were calculated based on GLMs with gamma distribution and log link (note: hypothesis testing was conducted only for post-index outcomes)

*indicates statistical significance (< 0.05)

[a]Other includes costs related to skilled nursing facility, home health and durable medical equipment, and hospice utilization. *ER* emergency room, *GLM* generalized linear model, *PPPM* per-patient-per-month, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *tDMARD* targeted disease-modifying antirheumatic drug, *TNFi* tumor necrosis factor-α inhibitor

Statistical Analysis

Propensity score (PS) matching was utilized to match abatacept users to the TNFi and other non-TNFi users on demographic and clinical characteristics. Multivariable logistic regression was used to generate PS, with the dependent variable comprising of the tDMARD type (abatacept vs. TNFi and abatacept vs. other non-TNFi) and independent variable (covariates) including baseline patient characteristics including age, gender, race, U.S. geographic region (as defined by United States Census Bureau), index year, DCSI complications, Charlson Comorbidity Index (CCI) score, baseline HCRU, concomitant cDMARD use, previous glucocorticoid use, and comorbid conditions. After 1:1 PS matching, the patient characteristics were balanced. Among the matched cohorts, descriptive statistics were used to evaluate differences in patient demographics, clinical characteristics, HCRU, and costs for the study cohorts. Means, standard deviations, interquartile ranges, and medians were calculated for continuous variables; patient counts and percentages were calculated for categorical variables. Generalized linear models were estimated to examine differences in HCRU and cost between cohorts. A p value of < 0.05 was considered statistically significant.

RESULTS

Cohort Selection and Baseline Characteristics

A total of 8105 Medicare FFS patients who previously used a TNFi met the study criteria among the TNFi-experienced patient cohort of whom 2488 patients switched to abatacept, 3216 switched to TNFi, and 2401 switched to other non-TNFi (Supplementary Fig. S1 in Supplementary Material). After PS matching, 2169 matched pairs of abatacept and TNFi's, and 2118 matched pairs of abatacept and other non-TNFi's were identified. The tDMARD-naïve patient cohort consisted of a total of 16,316 Medicare FFS patients, of whom 2688 patients initiated abatacept, 10,659 initiated TNFi, and

Table 4 Inpatient T2DM-related complication costs during follow-up

Variable	TNFi-experienced patient cohort						tDMARD-naïve patient cohort					
	Abatacept vs. TNFi			Abatacept vs. Other Non-TNFi			Abatacept vs. TNFi			Abatacept vs. Other Non-TNFi		
	Abatacept (*N* = 2169)	TNFi (*N* = 2169)	*p* value	Abatacept (*N* = 2118)	Other non-TNFi (*N* = 2118)	*p* value	Abatacept (*N* = 2667)	TNFi (*N* = 2667)	*p* value	Abatacept (*N* = 2247)	Other non-TNFi (*N* = 2247)	*p* value
Mean (SD) T2DM-related PPPM costs during follow-up												
Inpatient visit	$255 ($984)	$334 ($1547)	**0.047**	$255 ($1001)	$322 ($1525)	0.072	$314 ($1716)	$316 ($1365)	0.897	$319 ($1783)	$502 ($1868)	**0.001**
Cardiovascular	$213 ($905)	$271 ($905)	0.124	$213 ($925)	$250 ($1412)	0.281	$243 ($1561)	$254 ($1219)	0.691	$247 ($1660)	$420 ($1745)	**0.001**
Cerebrovascular	$20 ($178)	$27 ($446)	0.369	$18 ($161)	$21 ($232)	0.68	$24 ($306)	$29 ($338)	0.526	$24 ($277)	$30 ($448)	0.610
Glucose complications and variability	$5 ($93)	$2 ($72)	0.275	$5 ($94)	$4 ($50)	0.738	$6 ($85)	$9 ($564)	0.623	$7 ($94)	$7 ($120)	0.952
Nephropathy	$84 ($523)	$111 ($967)	0.203	$87 ($556)	$122 ($804)	0.152	$119 ($975)	$136 ($942)	0.502	$128 ($980)	$158 ($1090)	0.325
Neuropathy	$42 ($306)	$38 ($328)	0.729	$38 ($301)	$53 ($509)	0.295	$44 ($411)	$45 ($443)	0.903	$47 ($442)	$79 ($719)	0.123
Peripheral vascular disease	$31 ($289)	$53 ($710)	0.158	$29 ($303)	$38 ($350)	0.459	$34 ($521)	$42 ($369)	0.482	$32 ($460)	$65 ($618)	0.077
Retinopathy	$5 ($125)	$5 ($111)	0.906	$3 ($123)	$4 ($79)	0.877	$7 ($120)	$8 ($143)	0.703	$7 ($124)	$12 ($223)	0.442

p values in bold show significance (< 0.05). *p* values were calculated based on GLMs with gamma distribution and log link

GLM generalized linear model, *PPPM* per-patient-per-month, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *tDMARD* targeted disease-modifying antirheumatic drug, *TNFi* tumor necrosis factor-α inhibitor

2969 initiated other non-TNFi. After PS matching, 2667 matched pairs of abatacept and TNFi's, and 2247 matched pairs of abatacept and other non-TNFi's were identified (Supplementary Fig. S1 in Supplementary Material). Table 1 presents patient characteristics among TNFi-experienced and treatment-naïve matched patient cohorts with stratification comparison of abatacept with TNFi users and abatacept with other non-TNFi users. For both TNFi-experienced and tDMARD-naïve patient cohorts, abatacept (> 80%) and other non-TNFi's (~ 70%) were primarily administered by intravenous route, while TNFi's (> 70%) were administered majorly through subcutaneous route. Majority of the study patients were white and female, located in the southern region of the US with an average age of 73 years. The mean CCI scores were non-differential (between 4 and 5) through all tDMARD groups. The majority of patient cohorts experienced T2DM-related complications during baseline, about 90% of patients for each study cohort had hypertension and > 50% had cardiovascular complications. About a third of the patients in each cohort had chronic obstructive pulmonary disease (COPD). A large percent of patients in each cohort used glucocorticoids (> 80%), other cDMARDs (> 71%) and antidiabetic medication (> 55%) during baseline (Table 1).

T2DM-Related Complications During Follow-Up

During the follow-up period, T2DM-related complication rates in inpatient visits P1000PPM trended lower in abatacept compared with TNFi (21 vs. 24; $p = 0.046$ and 23 vs. 26; $p = 0.821$, respectively, for TNFi-experienced and tDMARD-naïve patient cohorts) and other non-TNFi groups (21 vs. 26; $p \leq 0.0001$ and 24 vs. 34; $p = 0.271$, respectively, for TNFi-experienced and tDMARD-naïve patient cohorts) (Table 2). A similar trend favoring abatacept was observed for physician visits in both patient cohorts; however, ER visits and outpatient visits were lower in abatacept users only in the tDMARD-naïve cohort.

During follow-up, abatacept users demonstrated trends for lower total T2DM-related PPPM costs than TNFi in TNFi-experienced patients (tDMARD-naïve: $590 vs. $609, $p = 0.562$; TNFi-experienced: $489 vs. $594, $p = 0.016$) and other non-TNFi users for both cohorts (tDMARD-naïve: $598 vs. $854, $p < 0.0001$; TNFi-experienced: $493 vs. $606, $p = 0.012$) (Table 3).

The major driver of healthcare costs was the utilization of inpatient services, which was in turn driven mostly by cardiovascular events. Among TNFi-experienced patients during follow-up, abatacept users had a significantly lower T2DM-related PPPM cost for inpatient stay and other services compared with TNFi users, while compared with non-TNFi users, only cost for other services was statistically significant (Table 3). In tDMARD-naïve patients, abatacept users demonstrated a trend for lower T2DM-related PPPM cost for other services compared to TNFi users, while in comparison with other non-TNFi users, T2DM-related PPPM costs for inpatient stays and other services trended lower for abatacept users at all settings of care (Table 3).

Among tDMARD-naïve patients, inpatient T2DM-related PPPM cardiovascular costs were significantly lower for abatacept users ($247) compared with other non-TNFi users ($420; $p = 0.001$), while there were no significant differences compared with TNFi users ($243 vs. $254; $p = 0.691$, respectively) (Table 4). Among TNFi-experienced patients, inpatient T2DM-related PPPM cardiovascular costs were lower for abatacept users ($213) compared with other non-TNFi users ($250; $p = 0.281$) and TNFi users ($271; $p = 0.124$); however, results were not statistically significant (Table 4).

Sensitivity analysis was performed by varying the duration of follow-up to allow for additional days after discontinuation and evaluate its impact on T2DM-related rate of inpatient visits and total medical cost (Supplementary Table S1 in Supplementary Material). In the original analysis, for patients who discontinued the index medication, the last day of follow-up was index drug + days' supply. For the sensitivity analysis, last day of follow-up was extended an additional 90 days

(index drug + days' supply + 90 days). Among both TNFi-experienced and tDMARD-naïve patients, by adding an additional 90 days following discontinuation of index treatment, the rate of inpatient visits P1000PPM and total medical costs PPPM trended upwards among all cohorts without impacting the directionality of results (Supplementary Table S1 in Supplementary Material).

DISCUSSION

T2DM-related healthcare complications in elderly patients with RA are associated with a significant economic burden to the healthcare system in the US [12]. As a result, it is important to investigate the clinical and economic burden associated with T2DM among tDMARD-treated Medicare FFS beneficiaries with RA and T2DM on the US healthcare systems. To our knowledge, this is the first real-world study that utilized the 100% sample of Medicare FFS beneficiaries to assess HCRU and costs of T2DM-related complications in RA + T2DM patients who were either (1) TNFi-experienced, who switched to abatacept or other tDMARDs, or (2) tDMARD-naïve patients, who initiated either abatacept, TNFi, or other non-TNFi.

The key finding of this study was that patients treated with abatacept showed a trend towards lower T2DM-related HCRU and costs compared with TNFi and other non-TNFi. Although not all differences were statistically significant, trends and directionality of results indicate a reduction in T2DM-related complications for patients treated with abatacept. The results from this retrospective cohort study indicate that Medicare patients with RA have a high prevalence of T2DM-related cardiovascular complications (> 50%) and hypertension (~ 90%) at pre-index. Additionally, other less significant T2DM-related complications were observed in our study population, which included congestive heart failure (< 25%), coronary heart disease (< 33%), and stroke (< 20%). Further, one-third of our study population also presented with COPD (~ 33%). An important observation in this study was that the total costs were driven mostly by inpatient stays; the majority of inpatient stays and costs were due to cardiovascular events. Although the differences in cardiovascular-related stays and costs were not statistically significant in all comparisons, the trends indicate that abatacept-treated patients experienced numerically lower costs compared to the other groups. Compared with the TNFi group, the abatacept group had significantly lower inpatient costs in the TNFi-experienced population, but not in the tDMARD-naïve cohort. A potential explanation may be that TNFi-experienced patients treated with another round of TNFi may no longer derive benefit from the treatment; however, switching to abatacept may offer some benefit due to the unique MOA. For example, a recent hypothesis suggests abatacept treatment may directly influence glucose metabolism [20]. This was based on the observation that abatacept use, compared with TNFi use, was associated with a lower risk of incident diabetes mellitus in patients with RA [20]. Together, the current and aforementioned studies suggest that treatment with abatacept may provide an approach for ameliorating the consequences of T2DM amongst patients with RA. Our findings indicate that TNFi-cycling may not benefit RA patients in terms of reducing the T2DM-related complications.

Medicare Part A data provide the total cost per inpatient stay but not the cost of each diagnosis. Of note, total cost per inpatient stay is typically a function of both primary and secondary diagnoses. Total costs for inpatient stays with a diagnosis code for T2DM-related complications may also be impacted by the presence of other comorbidities, leading to a significant variation (standard deviation) in observed costs. This may have impacted the statistically significant findings of our study. However, the inclusion of inpatient stays with only a primary diagnosis for T2DM-related complications was not feasible as the majority of the secondary events experienced during a hospital stay would be missed.

To the best of our knowledge, no previous study has examined the HCRU and costs associated with T2DM-related complications in patients with RA. One previous study estimated the cost associated with each episode of DCSI

complication using Truven MarketScan® data [21]. Consistent with our study, Candrilli 2015 observed inpatients costs to account for majority (~ 90% for cardiovascular) of the total costs. Cardiovascular events ($24,305 per episode) contributed the most towards inpatient costs. Chang 2012 used claims from 7 Blue Cross Blue Shield plans to estimate the costs by increments in DCSI score (0, 1, 2, 3 +) [22]. Forty to fifty percent of the total costs were attributed to inpatient stay. Higher costs were observed in patients with a score of 3 + ($25,900) compared with patients with a score of 0 ($3200), indicating that the DCSI index may be a good measure of T2DM severity. A direct comparison of results with the studies described above was challenging due to differences in the patient population and data sources. In addition, the HCRU and costs varied by the index treatment regimen (abatacept vs. other tDMARDs) in our study. Our findings align with previous research that have shown abatacept to be associated with increased insulin sensitivity [23]. Ursini 2015 study had reported patients with RA treated with abatacept have a significant insulin sensitivity index increase from 3.7 ± 2.6 to 5.0 ± 3.2 ($p = 0.003$) [23]. Further, reduction in glucose and insulin values as well as significant improvements in glycated hemoglobin were found among these treated patients, indicating an increased whole-body insulin sensitivity associated with abatacept use [23]. Real-world evidence from our study shows directionality and trends towards the cost of care and HCRU being lower in patients with RA receiving abatacept, which helps make a case for abatacept to be more effective in reducing diabetes-related complications and hence the economic burden associated with them.

There are several important strengths of this current study. The study benefits from the use of data from a large, nationally representative US Medicare claims database. The dataset is comprehensive, incorporating all medical and pharmacy claims of Medicare FFS patients and allows for the longitudinal analysis of a large US patient sample. A key strength is that retrospective analyses provide a better understanding of the RA population in real-world clinical practice as compared with the controlled conditions of a clinical trial. Retrospective database studies allow observation of patients who are often under-represented in clinical trials, such as those with comorbidities and the elderly. Since prescribing patterns in the real-world are broader and less limiting, the retrospective analysis provides a more comprehensive picture of how medications are used by clinicians in routine practice and the adherence of treatments. Many of the medications being studied are relatively new to the market, and this database captures the utilization of these newer drugs.

Some limitations associated with this study and observational studies in general need to be acknowledged. As claims data exist mainly for billing and reimbursement purposes, there is a possibility for errors in documentation of medical conditions and outcomes. For example, given the similarity between RA- and T2DM-related HCRU, it remains inherently difficult to distinguish HCRU by RA or T2DM separately. This can lead to patient misclassification either due to miscoding or misdiagnosis. For this study, identification of patients with RA and T2DM disease and other conditions relied heavily on available diagnosis codes. To minimize the extent of misclassification, we included patients who had at least two diagnoses for RA and excluded patients with type 1 diabetes mellitus. This retrospective cohort study has higher internal validity in comparison with cross-sectional and case–control study design. However, results from this study cannot be generalized to patients who have limited access to the healthcare system or who are uninsured and less likely to be captured in the data. For patients in this observational study, as for all observational studies, treatments are prescribed on the basis of clinical judgment. Patients receiving one tDMARD were likely to be different in many ways from patients receiving other tDMARDs. Therefore, comparisons of patients on different treatment regimens may be confounded by factors such as disease severity and baseline risk of the events of interest. Additionally, despite abatacept and TNFi treatments demonstrating similar efficacy among the overall RA cohort [24], the absence of disease activity outcomes and potential baseline

differences among patients included in this analysis may introduce selection bias. Potential confounding variables were controlled for via appropriate study design and statistical modeling. However, the possibility of residual confounding from unmeasured factors cannot be excluded.

Total cost per inpatient stay is typically a function of both primary and secondary diagnoses. Total costs for inpatient stays with a diagnosis code for T2DM-related complications may also be impacted by the presence of other comorbidities, leading to a significant variation (standard deviation) in observed costs. This may have impacted the statistical significance of findings in our study. However, the inclusion of inpatient stays with only a primary diagnosis for T2DM-related complications was not feasible as the majority of the secondary events experienced during a hospital stay would be missed.

CONCLUSIONS

Among TNFi-experienced Medicare FFS beneficiaries with RA and T2DM, patients who switched to abatacept demonstrated trends for lower rates and costs of hospitalizations associated with T2DM-related complications in comparison with patients who switched to TNFi or other non-TNFi. tDMARD-naïve abatacept initiators also demonstrated trends for lower rates and costs of T2DM-related complications compared with initiators of other non-TNFi. Overall in this analysis, the results indicate direct T2DM-related healthcare benefits associated with use of abatacept in comparison with other tDMARDs in TNFi-experienced patients. Thus, these results suggest that use of abatacept instead of other tDMARDs could potentially help reduce the clinical and economic burden associated with T2DM in patients with RA.

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Compliance with Ethics Guidelines. This retrospective study was carried out in accordance with the Declaration of Helsinki. The study was limited to data without identifiers to ensure confidentiality, and no personal health information was collected. Because of the retrospective study design using previously collected de-identified data, formal consent and institutional review board approval was not necessary for this study.

Data Availability. The data described in this paper are sourced from CMS Medicare Fee-for-Service claims and enrollment data. The datasets generated during and/or analyzed during the current study are not publicly available due to protection of patient privacy. Researchers may request use of CMS data through ResDAC.

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