Effectiveness and healthcare costs among stabilised rheumatoid arthritis patients with dose reduction of adalimumab or etanercept in real world

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Abstract

Objective

We assessed the level of maintained effectiveness and associated healthcare costs in stabilised rheumatoid arthritis (RA) patients who reduced doses of adalimumab or etanercept.

Methods

Eligible patients were identified from a U.S. commercial insurance database using the following criteria: adults with ≥2 RA diagnoses; effectively treated on standard dose of adalimumab or etanercept for a 6-month baseline period; and ≥3 months of dose reduction within a 6-month assessment period following the index date (date of the first reduced dose). Effectiveness was estimated using a validated claims-based algorithm. Multivariate regression models were used to assess maintained effectiveness and healthcare costs in the short-term (months 7–12) and long-term (months 13–24) following the index date, while adjusting for baseline characteristics. Cost per patient maintaining effective treatment (CPME) was calculated as the average total healthcare costs divided by the proportion of patients with maintained effectiveness.

Results

Both groups (etanercept=375; adalimumab=610) had 70% females and a mean age of 48 years. Adjusted rates of maintained effectiveness for etanercept vs. adalimumab were 57.5% vs. 64.7% (p=0.028) in the short-term and 44.3% vs. 51.9% (p=0.047) in the long-term. Adjusted healthcare costs were similar for etanercept- and adalimumab-treated patients (short-term: $15,043 vs. $15,041; long-term: $31,461 vs. $30,449). The CPME was $2,915 higher with etanercept-treated patients in short-term and $12,349 higher in long-term compared with adalimumab-treated patients.

Conclusion

Among stabilised RA patients who reduced biologic dosing, a greater proportion of adalimumab-treated patients maintained effectiveness than etanercept-treated patients. Adalimumab was associated with a lower total CPME than etanercept.

Key words

rheumatoid arthritis, dose reduction, adalimumab, etanercept

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Introduction

Rheumatoid arthritis (RA) is a chronic, debilitating disease characterised by inflammation and destruction of joints and surrounding tissues. It can result in significant impairment of a patient's quality of life and the ability to carry out daily activities (1). Treatment of RA aims to achieve and maintain remission or low disease activity (2). Over the past two decades, a number of innovative biological agents have been approved to treat RA, making the treatment goal of achieving and maintaining remission or low disease activity possible for many patients. These new therapies have been effective in improving inflammation control, preventing/delaying structural joint damage, and maintaining patient function, when compared with traditional/synthetic disease-modifying anti-rheumatic drugs (DMARDs) (3-5). On the other hand, due to reasons such as tolerability, healthcare costs, and patient preferences various RA treatment guidelines and recommendations have discussed the tapering or withdrawing of biologics among patients who have achieved remission or low disease activity in RA (2, 6-12).

Adalimumab and etanercept are the most widely used biologics for the treatment of RA (13). As recent as 2014, a systematic review of clinical trials of dose reduction and/or discontinuation of anti-TNF agents in RA patients who achieved low disease activity (LDA) (14) concluded that dose reduction (etanercept to half of the standard dose) could be a sensible approach in some patients, while stopping (adalimumab or etanercept) was not yet supported by clinical evidence. On the other hand, evidence from the real-world practice is emerging that biologic dose tapering/withdrawing could be associated with an increased risk of disease flares in RA patients (15, 16). A multicentre chart review study in Taiwan also found that tapering adalimumab or etanercept in stabilied RA patients could, at least in the short-term, lead to an increase in healthcare resource utilisation (15).

More real-world research assessing the impact of biologic dose reduction/biologic tapering is needed. The present study applied a validated administrative claims-based algorithm for assessing effectiveness (17) to compare the short- and long-term real-world effectiveness and costs associated with adalimumab or etanercept dose reduction.

Materials and methods

Data source

This retrospective cohort study used administrative claims data from the Truven Health Analytics MarketScan® Database (Q1 2000 to Q3 2013). The database contains medical encounters (inpatient and outpatient services) and pharmacy claims of insured employees and dependents, and Medicare-eligible retirees with employer-provided Medicare Supplemental plans. Data are available for approximately 30 million unique patients annually in over 130 commercial insurance plans in the U.S.

Curtis effectiveness algorithm

An administrative claims-based algorithm was developed and validated by Curtis *et al*. to estimate the effectiveness of newly initiated biologic treatments using the Veterans Affairs RA registry (17). The algorithm considers biologic switching, biologic dose/frequency increase, new use of non-biologic DMARDs, glucocorticoid injection use, new use/increase in oral glucocorticoid, and suboptimal adherence as the criteria of failing the effectiveness assessment within one year of newly initiated biologic therapy. It was initially validated against the Disease Activity Score using 28 joint counts (DAS28) as the criterion for LDA and was found to have a positive predictive value of 75% and negative predictive value of 90%. This algorithm has been further applied in other administrative claims databases (18, 19). The algorithm provides an opportunity to assess effectiveness in administrative databases.

In the current study, the Curtis effectiveness algorithm was used in two ways: 1) as part of the patient selection criteria to determine whether a patient had demonstrated effectiveness on biologic therapy prior to dose reduction; and 2) to estimate the rate of maintained effectiveness after biologic dose reduction.

Sample selection

Patients were included in the analysis if they met the following criteria:

- Had at least two claims including a diagnosis for RA (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 714.0x);
- Was 18 years or older at the time of the first RA diagnosis in claims history;
- Initiated on adalimumab or etanercept on or after the first RA claim;
- Stabilised on the FDA approved dosing schedule for adalimumab or etanercept for at least six months before dose reduction
  - o Adalimumab: 40 mg ± 15% every other week;
  - o Etanercept: 50 mg ± 15% weekly;
- Demonstrated effectiveness during the baseline period (*i.e.* six months before dose reduction)
  - o Did not add or switch to any other biologic agent;
  - o Did not have an increase use of oral glucocorticoid;
  - o Did not have more than 1 glucocorticoid injection;
  - o Did not have an addition of non-biologic DMARD agent; and
  - o Did not have a RA-related urgent care visit (diagnosis with ICD-9-CM code 714.0x).
- Had at least 12 months of follow-up after the start of dose reduction with at least three months on the reduced dose schedule within the first six months
  - o Adalimumab: 40 mg ± 15% every three weeks
  - o Etanercept: 25 mg ± 15% weekly

These definitions are consistent with prior research for etanercept (20, 21) and adalimumab (15, 22). The first claim date with the reduced dose schedule was defined as the index date. RA patients stabilised on the adalimumab or etanercept standard regimen who met the sample selection criteria were classified into two mutually exclusive cohorts based on whether they were first treated with adalimumab or etanercept (*i.e.*, the index biologic).

Study design

Figure 1 provides the study design schema for assessing the short-term and long-term outcomes following dose reduction. The baseline period was defined as the 6 months prior to the index date. The 6-month period immediately following baseline was designated as an assessment period for exposure to dose reduction for at least 3 months. Outcomes were measured following this 6-month assessment period.

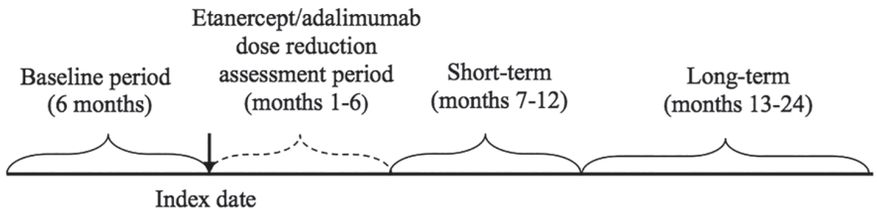

Fig. 1. Study design schema.

Outcomes in two study periods were evaluated, including a short-term study period for months 7 through 12 following the dose reduction assessment period, and a long-term study period from months 13 through 24 following the short-term period. Patients included in the short-term and long-term study periods were required to maintain continuous enrolment in their health plan for 12 months and 24 months, respectively, after the index date.

Outcomes of interest and statistical analyses

Applying the algorithm developed by Curtis *et al*. (19), maintained effectiveness was defined as the percentages of patients in each study cohort who met all of the effectiveness standards during the short-term and long-term study periods, respectively. Specifically, a patient was considered to have maintained effectiveness when the patient did not have an increase in biologic dose or frequency to twice the standard dose of the biologic (adalimumab: 40 mg once weekly; etanercept: 50 mg twice weekly), did not initiate non-index biologics, did not add new non-biologic DMARDs, did not increase oral glucocorticosteroid use, did not have more than one glucocorticosteroid injection, and did not fail the criterion of high adherence to index biologic. High adherence was defined as having a medication possession ratio (MPR) ≥80% during a study period. An increased use of oral glucocorticoid was defined in two ways: 1) if the patient increased the baseline cumulative oral steroid dose by 20% or more; or 2) if the patient did not have any oral glucocorticoid prescriptions during the baseline period but had ≥30 days of oral glucocorticoid supply in the study period.

Healthcare costs (in 2013 USD) were reported and adjusted for inflation using the medical care component of the U.S. consumer price index (CPI). Cost estimation included medical service costs (inpatient admissions, emergency department visits, and outpatient visits) and pharmacy costs (biologics, non-biologic DMARDs, and other medications), incurred during the study periods. In addition, the total health care costs were assessed and compared between cohorts in each study period. Cost per patient maintaining effective treatment (CPME) was then calculated in both study periods as the mean total healthcare cost divided by the rate of maintained effectiveness.

Statistical comparisons across cohorts were conducted using Wilcoxon rank-sum tests for continuous cost variables and chi-square tests for categorical variables. Chi-squared tests were used to compare the rate of maintained effectiveness between cohorts. Multivariable logistic regression models were used to adjust comparisons for baseline age, gender, region, health plan type, index year, disease duration, Charlson comorbidity index (CCI), comorbidities significantly different between cohorts, and non-biologic DMARDs use. Healthcare costs (medical services costs, pharmacy costs, and the total healthcare costs) were adjusted for the same baseline characteristics plus the log of the respective baseline costs, using multivariable generalised linear models (GLM) with gamma distribution and log link. Statistical testing was conducted in mul-

tivariate analyses of cost estimation using non-parametric bootstrapping with 1000 iterations. All statistical analyses were conducted using the Statistical Analysis System (SAS) (v. 9.3, SAS Institute, Inc., Cary, NC).

Results

A total of 610 adalimumab-treated patients and 375 etanercept-treated patients met the study sample selection criteria and were included for analysis of the short-term period (Fig. 2). Data from a total of 500 adalimumab-treated patients (82% from the short-term period) and 289 etanercept patients (77% from the short-term period) were available to be included for the long-term period analyses. The majority of the patients (adalimumab *vs*. etanercept) were female (70.3% *vs*. 70.7%), and the mean age of the patients was in the late forties (48.2 *vs*. 48.0 years) (Table I).

At baseline, adalimumab-treated patients had on average a higher CCI score than etanercept-treated patients (0.93 *vs*. 0.86; $p<0.01$), and a higher rate of gastrointestinal diseases (15.9% *vs*. 7.7%; $p<0.01$). In both cohorts, the majority of patients had concomitant non-biologic DMARDs use (adalimumab *vs*. etanercept: 70.3% *vs*. 56.3%; $p<0.01$); in particular, concomitant methotrexate was used more commonly in adalimumab-treated patients than in etanercept-treated patients (58.7% *vs*. 42.9%; $p<0.01$). Healthcare costs were similar for adalimumab-treated patients *vs*. etanercept-treated patients during the 6-month baseline period with mean total healthcare costs of $15,116 *vs*. $15,269 (median: $13,133 *vs*. $13,011), pharmaceutical costs of $12,066 *vs*. $12,331 (median: $11,812 *vs*. $11,858), and medical service costs of $3,050 *vs*. $2,938 (median: $968 *vs*. $960) (Table I). Few patients incurred inpatient costs and emergency department costs during this time period. The costs of biologics incurred during the 6-month baseline period were also similar for adalimumab-treated patients *versus* etanercept-treated patients ($10,622 *vs*. $10,690).

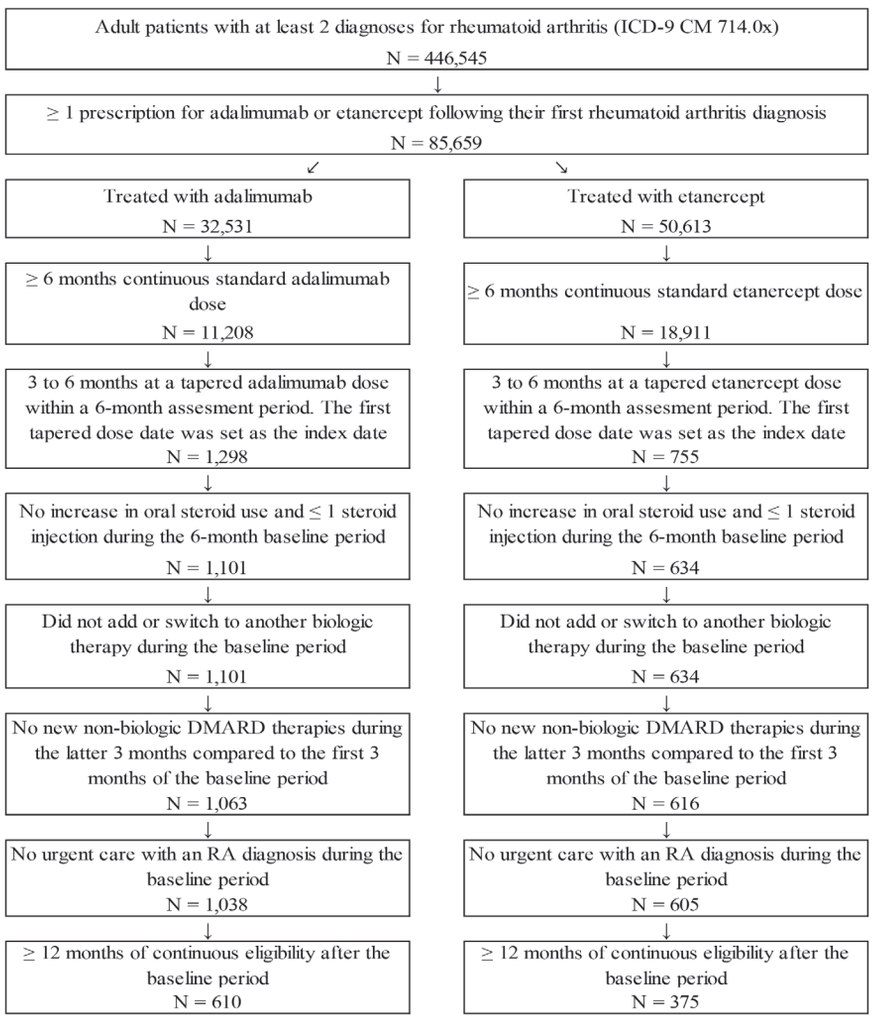

Fig. 2. Sample selection of rheumatoid arthritis patients who attempt to reduce doses for adalimumab or etanercept.

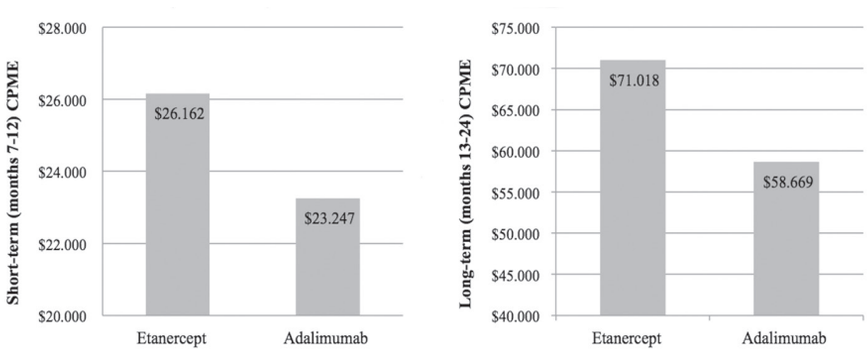

Fig. 3. Short-term (months 7–12) and long-term (months 13–24) cost per patient maintaining effective treatment.

Short-term outcomes after dose reduction

During the 6-month short-term study period (months 7 through 12 after dose reduction), a greater proportion of patients maintaining effectiveness in the adalimumab cohort than in the etanercept cohort (65.1% *vs*. 56.5%; $p=0.007$) (Table II). Between 93% and 99% of patients in the two cohorts satisfied five of the six effectiveness criteria. Failing the high adherence criterion was the main reason for patients not having maintained effectiveness, with a higher failing rate observed in etanercept-treated patients (33.3% *vs*. 24.9%; $p=0.004$). Additionally, more etanercept-treated

Table I. Baseline patient characteristics and healthcare costs (6-month) by index treatment.

Baseline characteristics	Etanercept	Adalimumab	*p*-value[1]
Female, n (%)	265 (70.7%)	429 (70.3%)	0.910
Age, mean ± SD	48.0 ± 9.2	48.2 ± 8.6	0.945
Region, n (%)			0.140
Northeast	49 (13.1%)	76 (12.5%)	
North Central	125 (33.3%)	202 (33.1%)	
South	127 (33.9%)	232 (38.0%)	
West	71 (18.9%)	100 (16.4%)	
Insurance type, n (%)			0.051
Comprehensive[2]	54 (14.4%)	57 (9.3%)	
Exclusive provider organisation	2 (0.5%)	10 (1.6%)	
Non-capitated point-of-service	58 (15.5%)	119 (19.5%)	
Preferred provider organisation	251 (66.9%)	405 (66.4%)	
Consumer-driven health plan	6 (1.6%)	15 (2.5%)	
Health deductible health plan	4 (1.1%)	4 (0.7%)	
Index year, n (%)			<0.001*
2001-2004	46 (12.3%)	18 (3.0%)	
2005-2008	149 (39.7%)	226 (37.0%)	
2009-2012	180 (48.0%)	366 (60.0%)	
Charlson Comorbidity Index, mean ± SD	0.86 ± 0.53	0.93 ± 0.44	0.007*
Comorbidities, n (%)			
Chronic obstructive pulmonary disease	23 (6.1%)	32 (5.2%)	0.556
Depressive disorders	15 (4.0%)	40 (6.6%)	0.090
Diabetes	26 (6.9%)	53 (8.7%)	0.325
Dyslipidaemia	63 (16.8%)	104 (17.0%)	0.919
Gastrointestinal disease[3]	29 (7.7%)	97 (15.9%)	<0.001*
Hypertension	67 (17.9%)	99 (16.2%)	0.505
Osteoarthritis	35 (9.3%)	51 (8.4%)	0.600
Psoriatic arthritis	36 (9.6%)	41 (6.7%)	0.102
Concomitant non-biological DMARDs, n (%)	211 (56.3%)	429 (70.3%)	< 0.001*
Methotrexate	161 (42.9%)	358 (58.7%)	< 0.001*
Hydroxychloroquine	33 (8.8%)	73 (12.0%)	0.119
Leflunomide	23 (6.1%)	43 (7.0%)	0.577
Sulfasalazine	20 (5.3%)	23 (3.8%)	0.244
Total costs (2013 USD), mean ± SD	15,269 ± 11,805	15,116 ± 9,551	0.547
median (IQR)	13,011 (11,718-15,635)	13,133 (11,758-15,698)	
Medical services costs	2,938 ± 10,995 960 (416-1,994)	3,050 ± 9,077 968 (483-2,472)	0.130
Inpatient costs	894 ± 9,038 0 (0-0)	805 ± 8,091 0 (0-0)	0.302
Emergency department costs	29 ± 146 0 (0-0)	86 ± 548 0 (0-0)	0.404
Outpatient visits costs	2,015 ± 3,679 940 (416-1,942)	2,158 ± 3,456 929 (480-2,311)	0.225
Pharmacy costs	12,331 ± 2,418 11,858 (10,874-13,318)	12,066 ± 2,099 11,812 (10,775-12,998)	0.273
Biologics	10,690 ± 1,408 10,663 (9,799-11,605)	10,622 ± 1,377 10,622 (9,831-11,498)	0.724

[1]*p*-values were computed using the chi-square test for discrete variables and the Wilcoxon rank-sum test for continuous variables.
[2]Comprehensive insurance is an insurance plan where patients do not have incentives to use particular providers and coverage is handled by one policy that has a fixed deductible and coinsurance amount.
[3]Gastrointestinal disease includes oral disease, oesophageal disease, gastric disease, and intestinal disease, Crohn's disease, ulcerative colitis, among others.
*denotes statistical significance at $\alpha = 0.05$ level.

patients switched to a non-index biologic (4.3% *vs*. 1.8%; *p*=0.021) than adalimumab-treated patients. A small but higher proportion of adalimumab-treated patients increased their dose to twice the standard dose after the initial dose reduction (2.3% *vs*. 0.5%; *p*=0.034). After adjusting for baseline characteristics, maintained effectiveness in the short-term study period remained higher in adalimumab-treated patients than in etanercept-treated patients (64.7% *vs*. 57.5%; *p*=0.028).

Within the 6-month short-term period, the incurred healthcare costs remained similar between cohorts. After adjusting for baseline characteristics, the total healthcare costs for adalimumab-treated patients compared with etanercept were $15,041 *vs*. $15,043, pharmacy costs were $11,046 *vs*. $10,829, and medical services costs were $4,157 *vs*. $4,137 per patient (Table III).

The CPME was $2,915 lower for adalimumab-treated patients compared with etanercept-treated patients in the 6-month short-term study period ($23,247 *vs*. $26,162) (Fig. 3).

Long-term outcomes after dose reduction

During the subsequent 12-month period (months 13 through 24), similar to the short-term study period, a greater proportion of the adalimumab cohort maintained effectiveness compared to the etanercept cohort (51.2% *vs*. 45.3%; *p*=0.112) (Table II). Between 87% and 98% of patients in the two cohorts satisfied five of the six effectiveness criteria. Similar to the findings from the short-term period, failing the high adherence criterion remained the main reason for effectiveness failure, with a higher failing rate observed in etanercept-treated patients (30.4% *vs*. 38.1%; *p*=0.028). During this period, a small but greater proportion of adalimumab-treated increased their dose to twice the standard dose than etanercept patients (5.0% *vs*. 1.7%; *p*=0.021); the percentage dose increases were similar to those observed in the short-term period. After adjusting for baseline characteristics, the maintained effectiveness among adalimumab-treated patients was significantly higher than etanercept-treat-

Table II. Comparison of short-term and long-term maintained effectiveness.

Maintained effectiveness	Etanercept	Adalimumab	*p*-value[1,2]
6-month short-term in 2nd half of the first year	n=375	n=610	
Unadjusted maintained effectiveness, n (%)	212 (56.5%)	397 (65.1%)	0.007*
Adjusted maintained effectiveness[2], %	57.5%	64.7%	0.028*
Unadjusted effectiveness criterion, n (%)			
High adherence	250 (66.7%)	458 (75.1%)	0.004*
No increased biologic dose	373 (99.5%)	596 (97.7%)	0.034*
No biologic switch	359 (95.7%)	599 (98.2%)	0.021*
No new DMARD	370 (98.7%)	600 (98.4%)	0.703
No new/increased oral glucocorticoid	350 (93.3%)	568 (93.1%)	0.895
<2 glucocorticoid injections	359 (95.7%)	581 (95.2%)	0.722
12-month long-term in the 2nd year	n=289	n=500	
Unadjusted maintained effectiveness, n (%)	131 (45.3%)	256 (51.2%)	0.112
Adjusted maintained effectiveness[2], %	44.3%	51.9%	0.047*
Unadjusted effectiveness criterion, n (%)			
High adherence	179 (61.9%)	348 (69.6%)	0.028*
No increased biologic dose	284 (98.3%)	475 (95.0%)	0.021*
No biologic switch	266 (92.0%)	472 (94.4%)	0.194
No new DMARD	284 (98.3%)	485 (97.0%)	0.274
No new/increased oral glucocorticoid	266 (92.0%)	451 (90.2%)	0.387
<2 glucocorticoid injections	259 (89.6%)	434 (86.8%)	0.243

[1]Unadjusted maintained effectiveness was compared using the chi-square test.
[2]A multivariable logistic model was conducted and the adjusted Curtis effectiveness percentage was generated based on the model. The following covariates at baseline were included: age, gender, region, insurance plan type, index year, CCI, gastrointestinal disease, and use of non-biologic DMARDs.
* denotes statistical significance at $\alpha = 0.05$ level.

Table III. Comparison of short-term and long-term healthcare costs.

Healthcare costs (2013 USD)	Etanercept	Adalimumab	*p*-value[1,2]
6-month short-term in 2nd half of the first year	n=375	n=610	
Unadjusted total costs, mean ± SD	14,709 ± 8,748	15,194 ± 9,680	0.131
Medical services costs	3,860 ± 8,123	4,154 ± 8,967	0.218
Inpatient costs	996 ± 5,371	1,070 ± 6,227	0.659
Emergency department costs	125 ± 652	138 ± 908	0.785
Outpatient visits costs	2,739 ± 5,050	2,946 ± 5,229	0.237
Pharmacy costs	10,849 ± 3,584	11,039 ± 3,680	0.131
Biologics	9,325 ± 3,144	9,613 ± 3,390	0.036
Adjusted total costs[2], mean ± SD			
Total costs	15,043 ± 2,898	15,041 ± 2,802	0.498
Medical services costs	4,137 ± 2,412	4,157 ± 2,384	0.443
Pharmacy costs	10,829 ± 1,642	11,046 ± 1,603	0.173
12-month long-term in the 2nd year	n=289	n=500	
Unadjusted total costs, mean ± SD	30,906 ± 27,667	30,579 ± 23,575	0.250
Medical services costs	9,874 ± 25,754	9,811 ± 22,046	0.098
Inpatient costs	3,852 ± 19,447	2,732 ± 14,168	0.992
Emergency department costs	203 ± 802	302 ± 1,438	0.302
Outpatient visits costs	5,820 ± 10,413	6,777 ± 12,920	0.074
Pharmacy costs	21,032 ± 7,583	20,768 ± 8,456	0.989
Biologics	17,896 ± 6,591	17,827 ± 7,870	0.620
Adjusted total costs[2], mean ± SD			
Total costs	31,461 ± 12,986	30,449 ± 12,548	0.282
Medical services costs	9,388 ± 6,346	9,546 ± 7,257	0.407
Pharmacy costs	21,213 ± 3,414	20,650 ± 3,257	0.160

[1]Unadjusted costs were compared using Wilcoxon rank-sum tests.
[2]Multivariable GLM models with gamma distribution and log link were conducted and adjusted health care costs were estimated. The following covariates at baseline were included: age, gender, region, insurance plan type, index year, CCI, gastrointestinal disease, use of non-biologic DMARDs.
Non-parametric bootstrapping using 1000 iterations was used to estimate the sampling distribution.

ed patients during the long-term study period (51.9% *vs*. 44.3%; *p*=0.047).

During the long-term study period, the incurred healthcare costs were largely similar between cohorts. The adjusted total healthcare costs for adalimumab-treated patients compared with etanercept-treated patients were $30,449 *vs*. $31,461, pharmacy costs $20,650 *vs*. $21,213, and medical services costs $9,546 *vs*. $9,388 (Table III). While there was some reduction in pharmacy costs during the 6-month short-term and 12-month long-term period in both cohorts when compared to the 6-month baseline period, the total costs remained almost constant owing to the increase in medical services costs.

Similar to the findings from the short-term period, the CPME remained lower for adalimumab-treated patients in the long-term study period ($58,669 *vs*. $71,018), resulting in $12,349 less per maintained effectiveness during the second year after the initiation of dose reduction (Fig. 3).

Discussion

The potential for optimising use of anti-TNF therapies has attracted significant interest in recent years from both clinical and economic perspectives. The present retrospective study compared RA patients on stabilised adalimumab or etanercept who reduced the doses for their respective anti-TNF agents. Upon the initial dose reduction attempt, nearly two-thirds of adalimumab-treated patients maintained effectiveness at the end of the first year and half of the patients maintained the effectiveness at the end of second year; slightly over half of etanercept-treated patients maintained effectiveness at the end of the first year and less than half of the patients maintained effectiveness at the end of the second year.

It is noteworthy that whereas a higher proportion of adalimumab-treated patients maintained effectiveness compared to etanercept-treated patients in our study, a large number of patients in both groups were not effectively maintained on the reduced dose of these biologics. This finding indicates the need to *a priori* assess the risk-benefit of dose reduction of biologics in RA patients.

To minimise the risk-benefit of dose reduction of biologics, the American College of Rheumatology in its 2015 RA treatment guidelines recommends: "Patients' values and preferences should drive decisions related to tapering" and "Prior to tapering, RA patients, including those in sustained remission, are informed of the risk of flare."(11)

Our findings are in line with the rate of maintained LDA reported in patients with etanercept dose reduction in the DOSERA trial (44% over 48 weeks), which had a patient population similar to that commonly seen in clinical practice (23). Two etanercept studies reported higher maintained LDA rates, both of which had somewhat different patient populations: the PRESERVE trial reported that 79% etanercept-treated patients maintained LDA after one year on the dose reduction schedule among moderate RA patients naïve to biologic therapy (21); the PRIZE study reported that 89% etanercept-treated patients maintained LDA after 39 weeks of dose reduction among early RA patients naïve to both biologics and methotrexate (20).

Although the clinical trials evidence for dose reduction of adalimumab is unavailable, a few studies reported the effects on maintaining LDA in adalimumab discontinuing patients but little was known about the effects of adalimumab dose reduction on maintaining low disease activity. For instance, the HONOR study reported that 62% of patients maintained LDA 52 weeks after discontinuing adalimumab among moderate to severe RA patients who had inadequate response to methotrexate and achieved remission on adalimumab (24); the OPTIMA trial reported that 83% of patients maintained LDA 52 weeks after discontinuing adalimumab among early RA patients naïve to both biologics and methotrexate (25). The rates observed in the present study on the maintained effectiveness among adalimumab-treated patients with dose reduction are not directly comparable to findings from these prior adalimumab discontinuation studies conducted in different types of RA patient populations.

Applying the effectiveness algorithm in two studies, Curtis *et al*. estimated the first year biologic CPME to be between $50K and $57K for RA patients initiated on adalimumab or etanercept (18, 19). In both studies, the authors only considered the costs of biologics but not the costs of other pharmacy claims and the costs of medical services. The present study took into account all healthcare costs incurred by stabilised RA patients after the initial dose reduction attempt. There appears to be some reduction during the short-term in the CPME after dose reduction for months 7 through 12. It is worth noting the trend in the decrease of biologic drug costs over time in both cohorts. However, in the second year, a substantial increase was observed in the total CPME over the 12-month period, particularly for etanercept-treated patients at $71K compared with adalimumab-treated patients at $59K. The increase in the CPME is largely attributable to a decrease in the maintained effectiveness in the second year and an increase in the medical services costs.

Important limitations should be noted when interpreting findings from this study. First, a proxy of effectiveness was used instead of an actual clinical outcome measure such as the DAS28 score. On the other hand, the Curtis algorithm was developed and validated against the DAS28 score in a large RA registry (17) and was further evaluated in two separate commercial databases (18, 19). Comparing to the Curtis studies, the percentages of patients meeting the individual criteria were higher in the present study, as well as the overall proportion of patients meeting all six criteria. This is not surprising because our study sample were RA patients who had already met the effectiveness criteria and were on standard biologic dose for at least six months prior to dose reduction, whereas both Curtis studies focused on RA patients who newly initiated biologic therapy.

Second, the dose reduction schedules set for etanercept and for adalimumab were not the same. The existing literature has commonly set the etanercept dose reduction to be half of its standard dose (20, 21). Few studies are available on adalimumab dose reduction. van Herwaarden *et al*. included the adalimumab down-titration schedule with 40 mg every 3 weeks, every 4 weeks and stop (13). The biologic tapering policy in Taiwan has a similar tapering schedule (15). However, neither was on maintaining adalimumab dose reduction. Currently, there is one ongoing Phase 4 trial assessing the effect of adalimumab dose reduction to 40mg every 3 weeks among RA patients in clinical remission (22). In the present study, adalimumab 40mg every 3 weeks was set to be the dose reduction schedule. Despite the difference in the dose reduction schedule, the costs of biologics were similar between cohorts during the short-term period and the long-term period.

Additionally, patients meeting adalimumab and etanercept dose reduction criteria were identified based on the average monthly dosing within the 6-month assessment period. Patients with persistently low adherence to their index biologic could have been miscategorised as having dose reduction. However, given this was a longitudinal cohort study, such behavioural impact could be minimal and would likely be comparable across cohorts. Furthermore, one should note that when assessing maintained effectiveness in the current study, the long-term period effectiveness was evaluated independently and was not conditioned upon the effectiveness status during the short-term period.

Lastly, this study assessed the effects of biologics dose reduction in the real world using a commercial insurance claims database in the US. Results may not be directly generalisable to other RA patient populations such as elderly patients enrolled in Medicare or patients enrolled in Medicaid. Data limitations also prevented a number of patient characteristics from being observed (*e.g*. socioeconomic profile, duration of RA), and as a result these characteristics could not be controlled for in adjusted analyses.

Conclusion

A large percentage of the studied RA patients did not maintain effectiveness upon dose reduction of adalimumab or etanercept; however, adalimumab dose reduction was associated with

higher rates of real-world maintained effectiveness and potential economic benefits compared with etanercept dose reduction. The questions of which biologic(s) can have dose reduction, which level of dose reduction should be considered, and which patients should be candidates for dose reduction warrants further investigation.

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