Real-world Effectiveness of Biologic Disease-modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis After Etanercept Discontinuation in the United Kingdom, France, and Germany

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ABSTRACT

Purpose: The purpose of this study was to assess the real-world effectiveness of patients with rheumatoid arthritis (RA) who discontinued etanercept treatment and subsequently received another tumor necrosis factor α (TNF-α) inhibitor or a non–TNF-α biologic in the United Kingdom, France, and Germany.

Methods: Medical record data of patients with RA were collected from a panel of rheumatologists in the United Kingdom, France, and Germany. Patients were required to have a diagnosis of RA, be ≥18 years old, and have initiated use of another TNF-α inhibitor (adalimumab, certolizumab pegol, golimumab, or infliximab) or a non–TNF-α biologic (abatacept or tocilizumab) between January 2014 and May 2015 after discontinuing use of etanercept. Reasons for discontinuing use of etanercept and selecting a second biologic disease-modifying antirheumatic drug (DMARD) were described. Study outcomes included European League Against Rheumatism (EULAR) response and change in Clinical Disease Activity Index (CDAI) score. The study outcomes were compared among treatment groups (ie, TNF-α inhibitors and non–TNF-α biologics) using descriptive and multivariable-adjusted analyses. As a secondary analysis, the study outcomes were also descriptively compared between each of the TNF-α inhibitors. Because adalimumab is one of the most commonly used TNF-α inhibitor to treat RA, a secondary analysis was conducted to compare the outcomes among adalimumab, other TNF-α inhibitors, and non–TNF-α inhibitors.

Findings: Patient characteristics before initiating treatment with a second DMARD were similar across treatment groups (all TNF-α inhibitors [n = 296] and non–TNF-α biologics [n = 276]). The most common reasons for discontinuing etanercept treatment were inadequate response, adverse effects, and patient preference. After etanercept, TNF-α inhibitors overall were associated with a significantly lower EULAR good response rate (56.0% vs. 64.4%, $P < 0.05$) and smaller CDAI score change (−6.3 vs −7.3, $P = .06$) relative to non–TNF-α biologics. However, the proportion of patients achieving an EULAR good response was numerically higher for adalimumab versus other TNF-α inhibitors (61.1% vs 51.6%, $P = 0.11$) and comparable versus non–TNF-α biologics (61.1% vs 64.4%, $P = 0.52$). Adalimumab was also associated with a CDAI score change significantly greater than that of other TNF-α inhibitors (−7.1 vs −5.8, $P < 0.05$) and comparable to that of non–TNF-α biologics (−7.1 vs −7.3, $P = 0.79$). The results were consistent in the multivariable-adjusted analysis and secondary analysis.

Implications: In this retrospective analysis of patients with RA in the United Kingdom, France, and Germany, after discontinuation of etanercept treatment, TNF-α inhibitors as a class were overall less effective as second biologic DMARDs relative to non–TNF-α biologics; however, adalimumab was more or as effective as other TNF-α inhibitors and non–TNF-α biologics. (*Clin Ther.* 2017;39:1618–1627) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammation, pain, stiffness, and swelling of the joints.[1] It is estimated to affect approximately 0.5% to 1% of the world population, with women being 2 to 3 times more likely to be affected than men.[2–4] As a consequence of progressive joint damage, synovitis, and often intense pain, RA is associated with both physical and mental disability, substantially impairing the quality of life of patients.[1,5–7]

The treatment of RA includes primarily disease-modifying antirheumatic drugs (DMARDs), which can be grouped into conventional synthetic DMARDs, such as methotrexate, and biologic DMARDs, such as tumor necrosis factor alpha (TNF-α) inhibitors.[8,9] The most recent European League Against Rheumatism (EULAR) guidelines recommend therapy with conventional synthetic DMARDs be started as soon as a diagnosis of RA is established and a first biologic DMARD be added if inadequate or no response is observed.[10] However, approximately 30% of patients treated with TNF-α inhibitors fail to achieve an improvement of 20% in the American College of Rheumatology criteria (ACR20),[11–14] which typically defines a threshold for response in patients with RA.[15] Although switching to a second biologic DMARD after failure of a first one is generally advocated, no consensus exists on whether patients should switch to a biologic DMARD of the same or different mechanism of action (ie, a TNF-α inhibitor or a non–TNF-α biologic).[16,17] Indeed, the EULAR guidelines consider both switching approaches acceptable.[10] In practice, because TNF-α inhibitors are the most frequently prescribed first biologic DMARDs,[16–18] a therapeutic dilemma that a rheumatologist may face is to whether switch patients from a first TNF-α inhibitor to another TNF-α inhibitor or to a non–TNF-α biologic.[16,19]

Because limited information is available on the most appropriate approach after failure and subsequent discontinuations of use of a first TNF-α inhibitor, more real-world data are needed to optimize treatment strategies in clinical practice.[20] Accordingly, this study aimed to assess the real-world effectiveness outcomes of patients with RA who discontinued etanercept treatment and subsequently received another TNF-α inhibitor (adalimumab, certolizumab pegol, golimumab, or infliximab) or a non–TNF-α biologic (abatacept or tocilizumab) as a second biologic DMARD in the United Kingdom, France, and Germany. An additional objective of this study was to compare the effectiveness of switching from etanercept to adalimumab (one of the most commonly used biologic DMARDs[18]), another TNF-α inhibitor (certolizumab pegol, golimumab, or infliximab), or a non–TNF-α biologic. Rituximab was not included in the analysis because of unfavorable reimbursement decisions issued by health technology assessment authorities in the United Kingdom and France.[21,22]

PATIENTS AND METHODS

Patient Selection

Medical record data of patients with RA in the United Kingdom, France, and Germany were collected from a panel of rheumatologists. To contribute data to this study, rheumatologists were required to have treated at least 5 adult patients with RA who fulfilled the inclusion criteria described below. These patients were required to have a diagnosis of RA in their medical records, be at least 18 years of age, not be a participant in a clinical trial, and have initiated use of a TNF-α inhibitor (adalimumab, certolizumab pegol, golimumab, or infliximab) or a non–TNF-α biologic (abatacept or tocilizumab) between January 1, 2014, and May 31, 2015, after discontinuation of etanercept therapy. Patients were required to have been biologic naïve before beginning use of etanercept. Patients were required to have at least 1 year of continuous treatment between the initiation of use of their second biologic DMARD and their last available visit while still using this drug. Finally, patients were required to have medical records, including Disease Activity Score 28 (DAS28), available for at least one RA-related visit they had immediately before initiating use of their second biologic DMARD and at least 1 year after initiating use of their second biologic DMARD. Eligibility criteria were verified in the process of data abstraction.

Medical Record Data Collection

A case report form was developed in English and translated to French and German to standardize and

facilitate data collection. After verifying the patient inclusion criteria, each participating rheumatologist was asked to randomly select up to 5 patients with RA to reduce physician fatigue and ensure data quality. Up to one medical record for each biologic DMARD was allowed per physician to ensure a representative sample. The entire case report form was pilot tested by 3 rheumatologists (one each from the United Kingdom, France, and Germany) to ensure that every question was clear and easy to interpret in each language. Stratified sampling was used and a quota was implemented to ensure a sufficient sample size to compare the treatment groups.

The study sponsor and authors were not involved in the selection of physicians or eligible medical records, and the physicians who participated in the study were masked to the identity of the study sponsor. All the medical record data collected in this study were anonymous and nonidentifiable. The study was approved by the New England Institutional Review Board.

Study Measures

Patient characteristics and treatment considerations (listed below) were collected at the time of initiation of use of the second biologic DMARD. Disease characteristics, including physician- and patient-reported outcomes, were collected at the visit patients had immediately before initiating use of their second biologic DMARD (index visit) and at the last available visit while still taking the second biologic DMARD (follow-up visit).

Patient characteristics included age, sex, duration of RA, duration of follow-up, the Charlson comorbidity index (CCI),[23] autoimmune comorbidities (ankylosing spondylitis, celiac disease, Crohn's disease, hidradenitis suppurativa, psoriasis, psoriatic arthritis, and other autoimmune comorbidities), DAS28 score, Clinical Disease Activity Index (CDAI) score, and nonbiologic DMARD use before the index visit. Treatment considerations included reasons for discontinuing use of etanercept and reasons for selecting the second biologic DMARD. On the basis of the current treatment guidelines,[10] EULAR response (good, moderate, none) and change in CDAI scores between the follow-up visit and index visit were included as study outcomes.

Statistical Analyses

In the primary analyses, baseline patient characteristics were summarized for the two treatment groups (TNF-α and non–TNF-α biologics) and compared using t tests for continuous variables and χ^2 tests for categorical variables. Reasons for discontinuing etanercept treatment and selecting the second biologic DMARD were described. The study outcomes (including EULAR response and change in CDAI scores) were compared among treatment groups using descriptive and multivariable-adjusted analyses. The proportion of patients achieving an EULAR response corresponding to good was evaluated using a multivariable-adjusted logistic regression model that controlled for age, sex, country, CCI score, duration of RA at the index visit, and whether the patient had any autoimmune comorbidity. The mean change in CDAI score was assessed using a multivariable-adjusted linear regression model that adjusted for the same factors listed above.

In the secondary analyses, baseline patient characteristics, EULAR response, and change in CDAI scores were descriptively compared between adalimumab and (1) each other TNF-α inhibitors (ie, certolizumab pegol, golimumab, and infliximab), (2) other TNF-α inhibitors as a class, and (3) non–TNF-α inhibitor biologics.

All the analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, North Carolina). $P \leq 0.05$ was considered statistically significant for all comparisons.

RESULTS

Patient Characteristics

Patient characteristics at the index visit were similar across treatment groups (all TNF-α inhibitors [n = 296], including adalimumab [n = 137] and other TNF-α inhibitors [n = 159], and non–TNF-α biologics [n = 276]). The mean age ranged from 47.6 to 50.7 years, most patients were women (TNF-α inhibitors, 68.9%; non–TNF-α biologics, 70.7%), and the mean duration of RA was 4.5 years for the TNF-α inhibitors and 5.0 years for the non–TNF-α biologics (Table I). The mean duration of follow-up between the index visit and the follow-up visit was 1.6 years for the TNF-α inhibitors and 1.5 years for the other TNF-α inhibitors. In addition, in all the treatment groups, the mean CCI score was 0.4, and autoimmune comorbidities were uncommon. Baseline RA severity was also comparable across treatment groups: the

Table I. Patient characteristics at the index visit.[*]

Characteristic	TNF-α Inhibitors			Non–TNF-α Biologics[§] (n = 276)
	All TNF-α Inhibitors[†] (n = 296)	Adalimumab (n = 137)	Other TNF-α Inhibitors[‡] (n = 159)	
Age at index date, y				
Mean (SD)	48.3 (13.2)	47.6 (12.8)	48.9 (13.6)	50.7 (13.1)
Median	47.7	45.6	49.7	50.9
Male	92 (31.1)	44 (32.1)	48 (30.2)	81 (29.3)
Duration of RA at index date, y				
Mean (SD)	4.5 (4.4)	4.4 (4.3)	4.5 (4.4)	5.0 (4.7)
Median	3.1	2.9	3.1	3.6
Duration of follow-up from index date, y				
Mean (SD)	1.6 (0.4)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)
Median	1.5	1.5	1.4	1.4
Charlson comorbidity index, mean (SD)	0.4 (0.8)	0.4 (0.9)	0.4 (0.7)	0.4 (0.9)
Autoimmune				
Ankylosing spondylitis	3 (1.0)	3 (2.2)	0 (0.0)	0 (0.0)
Celiac disease	3 (1.0)	3 (2.2)	0 (0.0)	4 (1.5)
Crohn's disease	2 (0.7)	1 (0.8)	1 (0.6)	2 (0.7)
Hidradenitis suppurativa	1 (0.3)	1 (0.7)	0 (0.0)	1 (0.4)
Psoriasis	13 (4.4)	4 (3.0)	9 (5.7)	6 (2.2)
Psoriatic arthritis	1 (0.3)	1 (0.8)	0 (0.0)	1 (0.4)
Other autoimmune comorbidities	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
DAS28 score				
Mean (SD)	4.8 (1.3)	4.9 (1.3)	4.6 (1.3)	5.0 (1.2)
Median	4.9	5	4.7	5.1
CDAI score				
Mean (SD)	13.3 (3.8)	14.0 (3.4)	12.8 (4.0)	14.1 (3.7)
Median	14	14	14	15
Nonbiologic DMARD used before index date				
Azathioprine	6 (2.0)	3 (2.2)	3 (1.9)	3 (1.1)
Cyclosporine	4 (1.4)	2 (1.5)	2 (1.3)	3 (1.1)
Hydroxychloroquine	41 (13.9)	22 (16.1)	19 (11.9)	55 (19.9)
Leflunomide	39 (13.2)	21 (15.3)	18 (11.3)	50 (18.1)
Methotrexate	252 (85.1)	115 (83.9)	137 (86.2)	231 (83.7)
Sulfasalazine	41 (13.9)	23 (16.8)	18 (11.3)	55 (19.9)
None	23 (7.8)	11 (8.0)	12 (7.5)	27 (9.8)
Steroid treatment initiated on index date	73 (24.7)	32 (23.4)	41 (25.8)	83 (30.1)

CCI = Charlson comorbidity index; CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF-α = tumor necrosis factor α.

[*]Data are presented as number (percentage) of patients unless otherwise indicated. Data are from 572 medical records (163 from the United Kingdom, 251 from France, and 158 from Germany).

[†]Included adalimumab, certolizumab pegol, golimumab, and infliximab.

[‡]Included certolizumab pegol, golimumab, and infliximab.

[§]Included abatacept and tocilizumab.

mean DAS28 was 4.8 for the TNF-α inhibitors and 5.0 for non–TNF-α biologics; the mean CDAI score was 13.3 for the TNF-α inhibitors and 14.1 for the non–TNF-α biologics. The most commonly used nonbiologic DMARD before the index visit was methotrexate (85.1% for TNF-α inhibitors and 83.7% for non–TNF-α biologics). On the index visit, most patients did not initiate use of a steroid (24.7% for TNF-α inhibitors and 30.1% for non–TNF-α biologics).

Table II. Reasons for discontinuing etanercept treatment and choosing a second biologic DMARD.[*]

Reason	TNF-α Inhibitors			Non–TNF-α Biologics[§] (n = 276)
	All TNF-α Inhibitors[†] (n = 296)	Adalimumab (n = 137)	Other TNF-α Inhibitors[‡] (n = 159)	
Reason for discontinuation of etanercept[‖]				
Economic considerations	3 (1.0)	2 (1.5)	1 (0.6)	2 (0.7)
Inadequate response	213 (72.0)	105 (76.6)	108 (67.9)	212 (76.8)
Patient preference	47 (15.9)	15 (10.9)	32 (20.1)	33 (12.0)
Physician preference	23 (7.8)	10 (7.3)	13 (8.2)	14 (5.1)
Adverse effects	64 (21.6)	33 (24.1)	31 (19.5)	62 (22.5)
Other	2 (0.7)	0 (0.0)	2 (1.3)	3 (1.1)
Reasons for choosing second biologic DMARD after etanercept failure[‖]				
Patient comorbidities	15 (5.1)	8 (5.8)	7 (4.4)	36 (13.0)
Cost	8 (2.7)	1 (0.7)	7 (4.4)	3 (1.1)
Efficacy	143 (48.3)	74 (54.0)	69 (43.4)	143 (51.8)
Different mechanism of action	65 (22.0)	26 (19.0)	39 (24.5)	158 (57.2)
Physician experience	190 (64.2)	93 (67.9)	97 (61.0)	136 (49.3)
Patient preference	90 (30.4)	43 (31.4)	47 (29.6)	38 (13.8)
Peer experience	50 (16.9)	24 (17.5)	26 (16.4)	43 (15.6)
Route of administration	70 (23.6)	22 (16.1)	48 (30.2)	38 (13.8)
Tolerability of drug	45 (15.2)	20 (14.6)	25 (15.7)	62 (22.5)
Treatment guidelines	61 (20.6)	32 (23.4)	29 (18.2)	65 (23.6)
Other	2 (0.7)	1 (0.7)	1 (0.6)	2 (0.7)

DMARD = disease-modifying antirheumatic drug; TNF-α: tumor necrosis factor α.
[*]Data are presented as number (percentage) of patients unless otherwise indicated. Data are from 572 medical records (163 from the United Kingdom, 251 from France, and 158 from Germany).
[†]Included adalimumab, certolizumab pegol, golimumab, and infliximab.
[‡]Included certolizumab pegol, golimumab, and infliximab.
[§]Included abatacept and tocilizumab.
[‖]Rates do not sum to 100% because rheumatologists were asked to select all the appropriate response options.

Treatment Considerations

Across the treatment groups, the most common reasons for discontinuing etanercept treatment were inadequate response (TNF-α inhibitors, 72.0%; non–TNF-α biologics, 76.8%), adverse effects (TNF-α inhibitors, 21.6%; non–TNF-α biologics, 22.5%), and patient preference (TNF-α inhibitors, 15.9%; non–TNF-α biologics, 22.5%) (Table II). The 3 most common reasons for selecting any of the TNF-α inhibitors were physician experience (64.2%), efficacy (48.3%), and patient preference (30.4%), whereas those for selecting non–TNF-α biologics were different mechanism of action (57.2%), efficacy (51.8%), and physician experience (49.3%).

Study Outcomes

The proportions of patients achieving various EULAR responses between the index and follow-up visits were generally similar across treatment groups (Table III and Figure). After etanercept, TNF-α inhibitors overall were associated with significantly lower EULAR good response rate (56.0% vs 64.4%, $P < 0.05$) relative to non–TNF-α biologics. However, in the secondary analysis, the proportion of patients achieving an EULAR good response was comparable for adalimumab versus non–TNF-α biologics (61.1% vs 64.4%, $P = 0.52$) and adalimumab versus other TNF-α inhibitors (61.1% vs 51.6%, $P = 0.11$). In multivariable analyses, relative to all the TNF-α inhibitors, the adjusted odds ratio (OR) for achieving an EULAR good response was 1.42 (95% CI, 1.01–1.99; $P = 0.04$) for non–TNF-α biologics; relative to adalimumab in the secondary analysis, the adjusted ORs for achieving an EULAR good response were 0.68 (95% CI, 0.43–1.08; $P = 0.10$) for other TNF-α inhibitors and 1.15 (95% CI, 0.75–1.76; $P = 0.52$) for non–TNF-α biologics, respectively.

After etanercept, TNF-α inhibitors overall were associated with a smaller CDAI score change (−6.3 vs −7.3, $P = 0.06$) relative to non–TNF-α biologics. However, the adalimumab treatment group experienced significantly greater change in CDAI score relative to the other TNF-α treatment group (−7.1 vs −5.8, $P < 0.05$) but comparable change relative to the non–TNF-α biologic treatment group (−7.1 vs −7.3, $P = 0.79$) (Table III). In multivariable analyses, relative to TNF-α inhibitors, the

Table III. EULAR response and CDAI score change from index date to follow-up visit.[*]

Variable	TNF-α Inhibitors			Non–TNF-α Inhibitors[§] (n = 264)
	All TNF-α Inhibitors[†] (n = 296)	Adalimumab (n = 131)	Other TNF-α Inhibitors[‡] (n = 153)	
EULAR response				
Good response[‖]	159 (56.0)	80 (61.1)	79 (51.6)	170 (64.4)[¶]
Moderate response	88 (31.0)	36 (27.5)	52 (34.0)	69 (26.1)
No response[**]	37 (13.0)	15 (11.5)	22 (14.4)	25 (9.5)
CDAI score change, mean (SD)	−6.3 (4.9)	−7.1 (5.0)	−5.8 (4.8)[††]	−7.3 (5.0)

CDAI = Clinical Disease Activity Index; EULAR = European League Against Rheumatism; TNF-α = tumor necrosis factor α.
[*]Data are presented as number (percentage) of patients unless otherwise indicated. Data are from 572 medical records (163 from the United Kingdom, 251 from France, and 158 from Germany).
[†]Included adalimumab, certolizumab pegol, golimumab, and infliximab.
[‡]Included certolizumab pegol, golimumab, and infliximab.
[§]Included abatacept and tocilizumab.
[‖]The Disease Activity Score 28 (DAS28) at the follow-up visit was ≤3.2; the DAS28 change was <−1.2.
[¶]$P < 0.05$ for comparison with all TNF-α inhibitors.
The DAS28 at the follow-up visit was ≤5.1 and >3.2; the DAS28 change was ≥−1.2 and <−0.6.
[**]The DAS28 score at the follow-up visit >5.1; the DAS28 change was ≥−0.6.
[††]$P < .05$ for comparison with adalimumab.

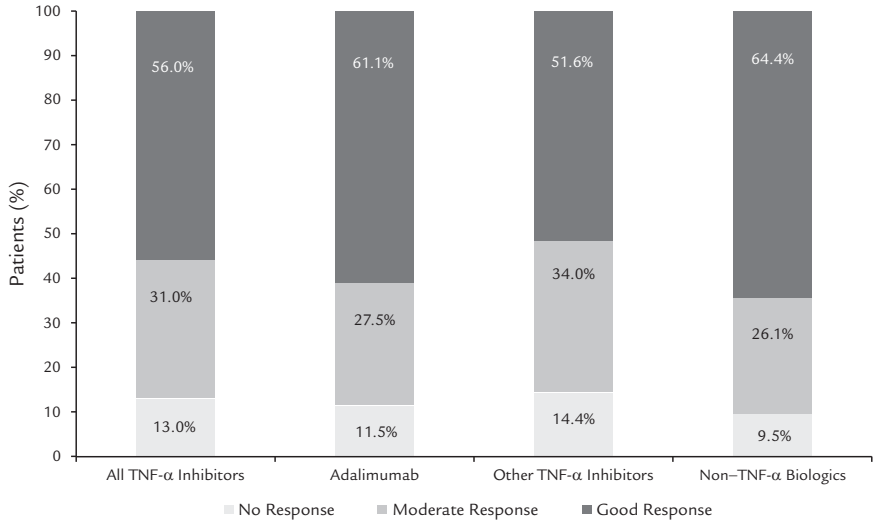

Figure. European League Against Rheumatism response categories by treatment group. TNF-α = tumor necrosis factor α.

adjusted mean difference for CDAI score change was −0.94 (95% CI, −1.88 to 0.00; $P = 0.05$) for non–TNF-α biologics; relative to adalimumab, the adjusted mean differences for CDAI score change were 1.19 (95% CI, −0.12 to 2.50; $P = 0.07$) for other TNF-α inhibitors and −0.26 (95% CI, −1.46 to 0.94; $P = 0.67$) for non–TNF-α biologics, respectively.

In the secondary analyses, compared with each other TNF-α inhibitor, adalimumab exhibited a higher rate of EULAR good response (61.1% vs 52.0% for certolizumab, 40.0% for golimumab, and 58.7% for infliximab) and greater change in CDAI score (−7.1 vs −6.0 for certolizumab, −5.6 for golimumab, and −5.6 for infliximab) (Table IV).

Overall, at the country level, the results related to the EULAR response and CDAI score were directionally similar to those presented above, but no statistical significance was observed because the study was not powered for country-level comparisons.

Table IV. EULAR response and CDAI change for each TNF-α inhibitor from index date to follow-up visit.[*]

Variable	Adalimumab (n = 131)	Certolizumab (n = 50)	Golimumab (n = 40)	Infliximab (n = 63)
EULAR response				
Good response[†]	80 (61.1%)	26 (52.0%)	16 (40.0%)[‡]	37 (58.7%)
Moderate response[§]	36 (27.5%)	17 (34.0%)	19 (47.5%)[‡]	16 (25.4%)
No response[‖]	15 (11.5%)	7 (14.0%)	5 (12.5%)	10 (15.9%)
CDAI score change, mean (SD)	−7.1 ± 5.0	−6.0 ± 4.9	−5.6 ± 4.7	−5.6 ± 4.8

CDAI = Clinical Disease Activity Index; EULAR = European League Against Rheumatism; TNF-α = tumor necrosis factor α.
[*]Data are presented as number (percentage) of patients unless otherwise indicated. Data are from 572 medical records (163 from the United Kingdom, 251 from France, and 158 from Germany).
[†]The Disease Activity Score 28 (DAS28) at the follow-up visit was ≤3.2; the DAS28 change was <−1.2.
[‡]$P < 0.05$ for comparison with adalimumab.
[§]The DAS28 at the follow-up visit was ≤5.1 and >3.2; the DAS28 change was ≥−1.2 and <−0.6.
[‖]The DAS28 score at the follow-up visit >5.1; the DAS28 change was ≥−0.6.

DISCUSSION

This medical record review study assessed real-world effectiveness associated with the use of several TNF-α inhibitors and non–TNF-α biologics after discontinuation of etanercept treatment in patients with RA in the United Kingdom, France, and Germany. Patients receiving TNF-α inhibitors (adalimumab, certolizumab pegol, golimumab, and infliximab) and non–TNF-α biologics (abatacept and tocilizumab) as second biologic DMARDs were found to have similar baseline characteristics and disease severity. The most common reasons for discontinuing etanercept treatment were inadequate response and the presence of adverse effects. After discontinuation of etanercept treatment, the real-world effectiveness, as measured by EULAR response and CDAI score change, was worse among TNF-α inhibitors than non–TNF-α biologics; however, when singling out one of the most commonly used biologics (ie, adalimumab[18]) from the remaining TNF-α inhibitors, the effectiveness of adalimumab was comparable to, if not better than, that associated with the other TNF-α inhibitors and non–TNF-α biologics. In particular, patients treated with adalimumab as a second biologic DMARD experienced a significantly greater change in CDAI score compared with patients treated with all the other TNF-α inhibitors.

Switching biologic DMARDs is common in clinical practice.[17] Several US studies using different methods estimated that 7.8% to 15.4% of patients switched to a second biologic DMARD within 1 year after initiating use of their first biologic DMARD.[18,24–27] As the number of biologic DMARDs approved to treat RA increases, the selection of subsequent biologic DMARDs becomes increasingly challenging.[28] For instance, the 2013 EULAR guidelines recommend a second biologic DMARD be started if no improvement is observed within 3 months or the treatment goal is not achieved within 6 months after initiating use of the first biologic DMARD.[10] However, no guidance is provided regarding which drug and/or drug class should be used as first or second biologic DMARD.[10]

The existing literature on the comparative efficacy or effectiveness of TNF-α inhibitors versus non–TNF-α biologics as second biologic DMARDs has been limited and sometimes contradictory. Several studies supported the beneficial effects of switching to a second TNF-α inhibitor after failure of a first one.[29–32] For example, one study found that 75% of patients who switched from infliximab to adalimumab achieved a 20% response in the American College of Rheumatology criteria after 12 months.[29] In contrast, other studies have reported superior clinical benefits associated with the switch from a TNF-α inhibitor to a non–TNF-α biologic versus the switch from one TNF-α inhibitor to another.[33–36] The findings of the present study indicate that, after etanercept, TNF-α inhibitors overall were less effective relative to non–TNF-α biologics; however, adalimumab was found to have similar or more effectiveness than the other TNF-α inhibitors and non–TNF-α biologics.

Given the conflicting results regarding the benefits of continued TNF-α inhibition versus a non–TNF-α biologic after discontinuing use of a first TNF-α inhibitor, this study provides health care decision makers with important evidence on the real-world comparative effectiveness of TNF-α inhibitors and non–TNF-α biologics after discontinuation of treatment with etanercept, a commonly prescribed biologic DMARDs. Because switching from one TNF-α inhibitor to another is so common, the results reported here are particularly important to help physicians optimize their treatment strategies. More real-world studies that compare different biologic agents used as first and second biologic DMARDs are needed to optimize the treatment algorithm for RA and maximize clinical outcomes, as well as inform policy decisions and clinical guidelines in the United Kingdom, France, and Germany. In particular, future studies should evaluate and compare the clinical outcomes associated with the switch from other commonly used first-line TNF-α inhibitors, such as adalimumab, to another TNF-α inhibitor or a non–TNF-α biologic.

The results of this study should be interpreted in light of some limitations. First, medical record data abstraction might be subject to errors and/or omissions. However, to the extent that all treatment groups were affected in a similar way, no significant bias was expected to affect the current comparative findings. Second, unobserved confounding factors and selection bias could result from the nonrandomization of patients to treatment groups. To minimize this problem, multivariable analyses controlled for patient characteristics commonly found in medical record data and known to be prognostic for outcomes in patients with RA. Third, the EULAR response rates reported here were found to be higher than previous

studies.[37] This is most likely because, in this study, patients were required to have received a second biologic DMARD for at least 1 year in an effort to select only long-term responders (ie, patients in whom a second biologic DMARD failed within a year of treatment initiation were not included in the analysis). However, comparisons among treatment groups were not expected to have been affected because this selection criterion was equally applied to all treatment groups.

CONCLUSIONS

In this retrospective analysis of patients with RA in the United Kingdom, France, and Germany, after discontinuation of etanercept treatment, TNF-α inhibitors as a class were overall less effective as second biologic DMARDs than non–TNF-α biologics; however, adalimumab was more or as effective as other TNF-α inhibitors and non–TNF-α biologics.

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CONFLICT OF INTEREST

K.A. Betts is an employee of Analysis Group, which received payment from AbbVie for participation in this research. N. Li and A.J. Messali were employees of Analysis Group at the time of this research. V. Garg and M. Skup are employees of AbbVie and may hold stocks or stock options in AbbVie. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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