Discontinuation of disease-modifying anti-rheumatic drugs and clinical outcomes in the Rheumatoid Arthritis DMARD Intervention and Utilisation Study 2 (RADIUS 2)

A. Gibofsky[1], G.W. Cannon[2], D.J. Harrison[3], G. Joseph[3], B. Bitman[3], S. Chaudhari[4], D.H. Collier[3]

[1]Hospital for Special Surgery, New York, NY; [2]Veterans Affairs Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT; [3]Amgen Inc., Thousand Oaks, CA; [4]KForce Clinical Research, Tampa, FL, USA.

Abstract

Objective

The purpose of this analysis was to examine discontinuation and reasons for discontinuation from disease-modifying anti-rheumatic (DMARD) therapies in the RADIUS 2 registry, a long-term, open-label, observational study of patients with moderate to severe rheumatoid arthritis (RA).

Methods

Patients who participated in RADIUS 2 initiated etanercept (ETN) therapy at study entry and were followed for 5 years. In this post hoc analysis, patients who had received ETN continuously from entry to month 4 were categorised by treatment at month 4: ETN monotherapy, ETN+methotrexate (MTX), ETN+MTX+other DMARDs (OTH), or ETN+OTH. Outcomes were assessed at month 4 and at the time of any subsequent treatment change, and included Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire Disability Index (HAQ-DI).

Results

Of 3,484 patients analysed (982 ETN; 1,356 ETN+MTX; 537 ETN+MTX+OTH; 609 ETN+OTH), baseline demographic and clinical characteristics were similar across treatments. No treatment change occurred in 62.3%, 49.9%, 33.3%, and 37.1% of ETN, ETN+MTX, ETN+MTX+OTH, and ETN+OTH patients, respectively. The mean time on therapy from month 4 was longer for patients receiving ETN (23.3 months) or ETN+MTX (23.7 months) than those receiving ETN+MTX+OTH (18.0 months) or ETN+OTH (18.3 months). The greatest improvements in CDAI and HAQ-DI were seen in patients who continued on ETN. The most common reasons for discontinuing DMARD therapy were cost and ineffective treatment.

Conclusion

Most patients who had received ≥4 months of ETN continued on ETN throughout the 5-year observation period. Patients with greatest clinical and disability improvements tended to continue on ETN.

Key words

arthritis, rheumatoid, biological therapy, etanercept, anti-rheumatic agents

Allan Gibofsky, MD
Grant W. Cannon, MD
David J. Harrison, PhD
*George Joseph, PhD**
Bojena Bitman, MS
*Sandeep Chaudhari, MS***
David H. Collier, MD

**Current affiliation Sanofi, Bridgewater, NJ, USA.*
***Current affiliation PRA International, Raleigh, NC, USA.*

Please address correspondence to:
Allan Gibofsky, MD,
Hospital for Special Surgery,
Dept. of Medicine and Public Health,
535 East 70th Street,
New York, NY 10021, USA.
E-mail: gibofskya@hss.edu

Received on September 10, 2013; accepted in revised form on January 22, 2014.

Funding: this study was funded by Immunex, a wholly owned subsidiary of Amgen Inc. and by Wyeth, which was acquired by Pfizer in October 2009.

Competing interests:
A. Gibofsky is a shareholder of Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, and Pfizer Inc.; is a consultant for Abbott Laboratories, Amgen Inc., Genentech/Roche, and Pfizer Inc.; and serves on speakers' bureaus for Abbott Laboratories, Amgen Inc, Genentech/Roche, Pfizer Inc., and UCB.
G.W. Cannon has received research funding from Amgen Inc.
D.J. Harrison, B. Bitman, and D.H. Collier are employees and shareholders of Amgen Inc.
G. Joseph is a former employee of Amgen Inc. and is a shareholder of Amgen Inc. and Pfizer.
S. Chaudhari is a former employee of KForce Clinical Research, which received funding for this study from Amgen Inc.

Introduction

Tumour necrosis factor (TNF) blockers have been shown to be effective in reducing clinical signs of inflammation in patients with moderate to severe rheumatoid arthritis (RA) (1); however, these agents are not universally effective in all patients (2). Treatment is not intended to be short-term, but discontinuation rates of up to 50% in the first year of treatment have been reported for patients taking TNF blockers (3-6). The reasons for discontinuation are not well characterised since they are not captured in commercial databases or most cohort studies. RA is a chronic disease requiring long-term treatment, so selection of an appropriate first-course TNF blocker is important for patients (to provide effective relief from RA symptoms and to inhibit progression of disease), for clinicians (to effectively manage treatment), and for payers (to anticipate and manage costs).

The TNF blocker etanercept (ETN) is used for the treatment of moderate to severe RA (7). ETN can be initiated in combination with methotrexate (MTX) or used alone (7). Data from medical claims databases, representing real-world prescribing practices, have shown that regimen modifications are common (3, 8). The Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilisation Study 2 (RADIUS 2) registry collected data on disease-modifying anti-rheumatic drug (DMARD) utilisation patterns (9) as well as reasons for treatment changes in patients with RA. The objective of this analysis was to examine discontinuation, duration of therapy, and switching patterns for biologic and non-biologic DMARDs and to assess clinical outcomes in patients with moderate to severe RA initiating ETN therapy in the RADIUS 2 registry.

Patients and methods

Patients

RADIUS 2 was a prospective, multicenter, observational registry that enrolled patients with RA between October 2002 and June 2003 (9, 10) and was designed to provide information on use patterns, effectiveness, and safety of DMARDs, biologics, and combination therapies used to manage RA in clinical practice. Eligible adults with RA met the 1987 American Rheumatism Association criteria for RA (11) and were appropriate candidates to initiate or add ETN to their treatment regimen. Patients enrolled in RADIUS 2 received ETN at study baseline and were followed for up to 5 years. Patients initiated ETN therapy alone or in addition to their current therapy at the beginning of the study. Patients were provided with a 12-week supply of ETN at the beginning of the study.

For these analyses, patients were categorised by treatment at month 4 (index date) into four mutually exclusive groups: ETN monotherapy, ETN plus methotrexate (ETN+MTX), ETN plus MTX plus other DMARDs (ETN+MTX+OTH), or ETN plus other DMARDs (ETN+OTH). The 4-month index date was selected as the time at which patients were categorised to allow for treatment changes that occurred after ETN was no longer provided free of charge. Patients could have had other drug combinations between the study baseline and the 4-month index date when they were categorised. Patients were followed to the end of the study (up to 5 years).

Outcomes

At the time of any DMARD treatment changes occurring after month 4, clinical outcome was assessed using the Clinical Disease Activity Index (CDAI) and disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). The CDAI is a composite index of disease severity in which higher scores indicate more severe disease (range 0–76) (12). The HAQ-DI is a generic patient-reported assessment of disability in which higher scores indicate greater disability (range 0–3) (13).

Treatment changes included gaps in ETN therapy ≥60 days with and without subsequent resumption of ETN, discontinuation of ETN and initiation of another biologic or non-biologic DMARD, discontinuation of MTX, and switching, discontinuing, or adding a non-biologic DMARD. CDAI and HAQ-DI scores were analysed only at

the first treatment change. Scores were within 30 days of treatment change. If more than one score occurred within 30 days of treatment change, the record nearest the treatment change – either before or after – was selected.

Statistical considerations

No statistical tests were performed for this analysis. Data were analysed as observed without imputation for missing data. All conclusions were based on interpretation of summary statistics: for continuous variables, these included means and standard deviations (SDs); for categorical variables, these included counts and percentages. Descriptive statistics were performed for patient characteristics. Summary statistics of treatment change as well as prior MTX use by 4-month index date treatment group were generated; summary statistics for CDAI, HAQ-DI, and time on 4-month index treatment were generated by treatment change, and treatment change was stratified by the 4-month index treatment group. Kaplan-Meier methodology was used for time-to-event analyses.

Table I. Patient demographics and clinical characteristics at study baseline and month 4 index date.

	ETN (n=982)	ETN+MTX (n=1,356)	ETN+MTX+OTH (n=537)	ETN+OTH (n=609)
Sex, n women (%)	734 (74.8)	1,071 (79.0)	407 (75.8)	474 (77.8)
Race, n white (%)	809 (82.4)	1,107 (81.6)	433 (80.6)	499 (81.9)
Age at disease onset, mean years (SD)	43.1 (15.4)	44.6 (13.6)	43.1 (12.9)	42.9 (13.9)
Disease duration, mean years (SD)	9.0 (9.9)	7.6 (8.7)	8.3 (8.5)	9.8 (9.7)
Rheumatoid Factor positive, n (%)	633 (72.1)	958 (76.5)	363 (76.6)	411 (75.7)
CDAI, mean score (SD)				
At study baseline	35.6 (16.5)	36.0 (15.8)	35.4 (15.1)	36.0 (15.5)
At month 4 index*	18.7 (15.1)	18.2 (14.5)	18.8 (13.6)	19.5 (16.0)
HAQ-DI, mean score (SD)				
At study baseline	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
At month 4 index*	0.9 (0.7)	1.0 (0.7)	1.0 (0.7)	1.0 (0.7)

*The closest record prior to the 4-month index date was selected. CDAI: Clinical Disease Activity Index; ETN: etanercept; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; OTH: other; SD: standard deviation.

Results

Patients

A total of 3,484 patients were included in the analysis (982 ETN; 1,356 ETN+MTX; 537 ETN+MTX+OTH; 609 ETN+OTH). Demographic and clinical characteristics were similar among treatment groups at baseline (Table I). Most patients were women (77%) and the patient population was predominantly white (82%).

Time on treatment

Longer mean times on treatment following the 4-month index date were seen in patients receiving ETN (23.3 months; SD, 19.4) or ETN+MTX (23.7 months; SD, 19.5) than in patients on ETN+MTX+OTH (18.0 months; SD, 17.9) or ETN+OTH (18.3 months; SD, 18.2).

ETN and DMARD treatment changes and discontinuations

Fewer treatment changes after the 4-month index date were seen in the ETN monotherapy group than in the ETN+MTX, ETN+MTX+OTH, or ETN+OTH groups (Table II). Fewer discontinuations were observed in the ETN group after the 4-month index date than in the other groups (Table II). ETN was not discontinued in 84.4% of patients in the ETN group, 73.3% in the ETN+MTX group, 72.6% in the ETN+MTX+OTH group, and 73.9% in the ETN+OTH group. Across all treatment groups, the most common reasons for discontinuing ETN were cost and ineffective treatment. The most common reasons for discontinuation of a non-biologic DMARD (OTH groups) were patient decision and other/unknown/missing reasons. Few patients receiving MTX added a non-biologic DMARD.

Clinical outcomes

At study baseline, mean CDAI and HAQ-DI scores were similar across treatment groups and between patients who continued on ETN and those who discontinued ETN after the 4-month index date (Table III). Mean CDAI and HAQ-DI scores at the 4-month index date and at the time of treatment change were greater in patients who continued on ETN compared with patients who discontinued ETN.

Discussion

Nearly two-thirds of patients on ETN monotherapy stayed on their initial 4-month index date therapy throughout the 5-year study, whereas only half of patients on ETN+MTX and a third of patients on ETN+MTX+OTH or ETN+OTH continued on therapy to the end of the study. Patients on ETN monotherapy or ETN+MTX had a longer mean duration of therapy than patients receiving ETN+MTX+OTH or ETN+OTH. Patients who did not discontinue ETN had better CDAI and HAQ-DI scores at study baseline and showed greater improvements in CDAI and HAQ-DI scores at the 4-month index date than patients who discontinued ETN.

The potential effects of discontinuation from biologic therapies (such as flares or resumption of structural damage) for the treatment of RA are not currently known. There is evidence, however, that discontinuation of biologic therapy in some patients who are in remission or have very low disease activity is possible (14, 15). Our data showed that patients who discontinued etanercept had less clinical improvement than those who continued on etanercept, suggesting that clinicians were not withdrawing etanercept in patients because they were in remission at the time of RADIUS 2.

Unlike data from commercial healthcare plans or Pharmacy Benefit Management programs, RADIUS 2 provided real-world data that has captured treatment patterns in everyday clinical practice. Our findings indicate that cost was one of the most common reasons for discontinuing treatment in some patients. Although studies have shown that biologic agents are cost effective for the treatment of RA (16), the pa-

Table II. Treatment changes after the 4-month index date.

Treatment change and reasons, n (%)	ETN (n=982)	ETN+MTX (n=1,356)	ETN+MTX+OTH (n=537)	ETN+OTH (n=609)
No change in treatment	612 (62.3)	676 (49.9)	179 (33.3)	226 (37.1)
ETN discontinued	153 (15.6)	362 (26.7)	147 (27.4)	159 (26.1)
Adverse event	26 (2.7)	63 (4.7)	26 (4.8)	36 (5.9)
Cost	28 (2.9)	77 (5.7)	28 (5.2)	30 (4.9)
Ineffective	61 (6.2)	134 (9.9)	54 (10.1)	57 (9.4)
Patient decision	27 (2.8)	56 (4.1)	19 (3.5)	21 (3.5)
Other/Unknown/Missing	11 (1.1)	32 (2.4)	20 (3.7)	15 (2.5)
Treatment gap >60 days, ETN not resumed	51 (5.2)	17 (1.3)	1 (0.2)	7 (1.1)
Adverse event	14 (1.4)	6 (0.4)	0	1 (0.2)
Cost	11 (1.1)	2 (0.2)	0	1 (0.2)
Ineffective	13 (1.3)	4 (0.3)	0	1 (0.2)
Patient decision	10 (1.0)	2 (0.2)	0	0
Other/Unknown/Missing	3 (0.3)	3 (0.2)	1 (0.2)	4 (0.7)
Treatment gap >60 days, ETN resumed	46 (4.7)	41 (3.0)	4 (0.7)	11 (1.8)
Adverse event	13 (1.3)	8 (0.6)	0	1 (0.2)
Cost	5 (0.5)	1 (0.1)	0	0
Ineffective	4 (0.4)	1 (0.1)	1 (0.2)	0
Patient decision	6 (0.6)	5 (0.4)	0	0
Other/Unknown/Missing	18 (1.8)	26 (1.9)	3 (0.6)	10 (1.6)
Drop ETN for another biological DMARD	81 (8.2)	121 (8.9)	51 (9.5)	49 (8.0)
Adverse event	7 (0.7)	6 (0.4)	4 (0.7)	1 (0.2)
Cost	11 (1.1)	7 (0.5)	2 (0.4)	4 (0.7)
Ineffective	43 (4.4)	81 (6.0)	40 (7.5)	38 (6.2)
Patient decision	14 (1.4)	19 (1.4)	2 (0.4)	4 (0.7)
Other/Unknown/Missing	6 (0.6)	8 (0.6)	3 (0.6)	2 (0.3)
Drop ETN for non-biological DMARD	21 (2.1)	224 (16.5)	95 (17.7)	103 (16.9)
Adverse event	5 (0.5)	51 (3.8)	22 (4.1)	34 (5.6)
Cost	6 (0.6)	68 (5.0)	26 (4.8)	25 (4.1)
Ineffective	5 (0.5)	49 (3.6)	14 (2.6)	18 (3.0)
Patient decision	3 (0.3)	35 (2.6)	17 (3.2)	17 (2.8)
Other/Unknown/Missing	2 (0.2)	21 (1.6)	16 (3.0)	9 (1.5)
Drop MTX	NA	235 (17.3)	81 (15.1)	NA
Adverse event	NA	59 (4.4)	20 (3.7)	NA
Cost	NA	4 (0.3)	1 (0.2)	NA
Ineffective	NA	13 (1.0)	6 (1.1)	NA
Patient decision	NA	95 (7.0)	33 (6.2)	NA
Other/Unknown/Missing	NA	64 (4.7)	21 (3.9)	NA
Switch non-biological DMARD	NA	6 (0.4)	2 (0.4)	16 (2.6)
Adverse event	NA	3 (0.2)	0	4 (0.7)
Cost	NA	0	0	0
Ineffective	NA	1 (0.1)	2 (0.4)	8 (1.3)
Patient decision	NA	1 (0.1)	0	4 (0.7)
Other/Unknown/Missing	NA	1 (0.1)	0	0
Drop non-biological DMARD	NA	NA	117 (21.8)	143 (23.5)
Adverse event	NA	NA	18 (3.4)	30 (4.9)
Cost	NA	NA	3 (0.6)	4 (0.7)
Ineffective	NA	NA	21 (3.9)	30 (4.9)
Patient decision	NA	NA	32 (6.0)	50 (8.2)
Other/Unknown/Missing	NA	NA	43 (8.0)	29 (4.8)
Add non-biological DMARD	171 (17.4)	36 (2.7)	7 (1.3)	54 (8.9)
Adverse event	1 (0.1)	1 (0.1)	0	0
Cost	0	0	0	0
Ineffective	0	1 (0.1)	0	0
Patient decision	0	0	0	0
Other/Unknown/Missing	170 (17.3)	34 (2.5)	7 (1.3)	54 (8.9)

DMARD: disease-modifying anti-rheumatic drug; ETN: etanercept; MTX: methotrexate; NA: not applicable; OTH: other.

tient's share of the costs is quite high and led to discontinuation of etanercept in approximately 5% of patients in RADIUS 2. Nevertheless, nearly two-thirds of patients on ETN monotherapy stayed on their initial 4-month index therapy throughout the 5-year study and patients with the greatest improvements in clinical and disability outcomes tended to continue on ETN.

Acknowledgements

We thank Edward Mancini of Amgen Inc. and Julia R. Gage on behalf of Amgen Inc. for assistance with writing the manuscript. Assistance with formatting the manuscript to meet journal specifications was provided by Shobana Ganesan, CACTUS Communications, on behalf of Amgen Inc.

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Table III. Clinical outcomes.

	ETN (n=982)	ETN+MTX (n=1,356)	ETN+MTX+OTH (n=537)	ETN+OTH (n=609)
CDAI, mean score (SD)				
Patients who continued on ETN				
Study baseline	35.1 (16.3)	35.2 (15.6)	35.1 (15.2)	35.3 (15.8)
4-month index date	18.0 (14.8)	17.5 (14.3)	17.6 (13.3)	18.0 (15.1)
Time of treatment change*	16.3 (15.2)	13.4 (13.0)	14.3 (12.4)	16.0 (14.6)
Patients who discontinued ETN				
Study baseline	38.8 (17.0)	38.6 (16.0)	36.5 (14.7)	38.7 (14.0)
4-month index date	22.7 (16.4)	20.3 (14.7)	22.0 (13.7)	24.0 (17.5)
Time of treatment change*	23.7 (17.5)	25.3 (15.9)	24.6 (16.1)	26.3 (16.8)
HAQ-DI, mean score (SD)				
Patients who continued on ETN				
Study baseline	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
4-month index date	0.9 (0.7)	0.9 (0.7)	0.9 (0.7)	0.9 (0.7)
Time of treatment change*	0.9 (0.8)	0.9 (0.7)	0.9 (0.7)	1.0 (0.8)
Patients who discontinued ETN				
Study baseline	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	1.5 (0.6)
4-month index date	1.1 (0.8)	1.1 (0.7)	1.2 (0.8)	1.3 (0.7)
Time of treatment change*	1.2 (0.8)	1.2 (0.7)	1.2 (0.7)	1.5 (0.7)

*Treatment changes included gaps in ETN therapy ≥60 days with and without subsequent resumption of ETN, discontinuation of ETN and initiation of another biologic or non-biologic DMARD, discontinuation of MTX, and switching, discontinuing, or adding a non-biologic DMARD.
CDAI: Clinical Disease Activity Index; ETN: etanercept; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; OTH: other; SD: standard deviation.

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