Predictors of Discontinuation of Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis

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ABSTRACT. *Objective.* Tumor necrosis factor-α (TNF) inhibitors have transformed management of rheumatoid arthritis (RA); however, many patients discontinue TNF inhibitors. Our goal was to determine the discontinuation rate of TNF inhibitors and identify predictors associated with discontinuation.

Methods. Enrollees in the Brigham RA Sequential Study (BRASS) formed the eligible cohort. Patients reporting use of a TNF inhibitor with at least 6 months of followup were followed until reporting TNF inhibitor discontinuation or their last study visit if they continued therapy. Potential predictor variables, including demographic and clinical data assessed at baseline and 6 months prior to study endpoint, were identified using a Cox proportional regression.

Results. Among 961 patients in BRASS, 503 were using a TNF inhibitor with at least 6 months of followup in BRASS (mean length of followup 39 mo, SD 13). Two hundred ten patients (42%) reported discontinuation of TNF inhibitor. Higher physician global scores (hazard ratio 1.27, 95% CI 1.18–1.38) and RA Disease Activity Index scores (HR 1.13, 95% CI 1.05–1.22) 6 months prior to stopping the TNF inhibitor and higher number of TNF inhibitors used previously (HR 1.30, 95% CI 1.03–1.66) were associated with discontinuation of TNF inhibitor. Prior use of synthetic disease modifying antirheumatic drugs (HR 0.50, 95% CI 0.34–0.72) and more years of cumulative methotrexate use (HR 0.24, 95% CI 0.12–0.47) were inversely associated with discontinuation of TNF inhibitor.

Conclusion. These data demonstrate that a significant number of patients with RA discontinue TNF inhibitors. Several easily characterized clinical variables have a modest predictive association with reduced probability of TNF inhibitor discontinuation. (First Release July 15 2008; J Rheumatol 2008;35:1737–44)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   TUMOR NECROSIS FACTOR INHIBITOR
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Rheumatoid arthritis (RA) is an inflammatory disease that affects about 1% of the population. RA has a variable clinical course, although the majority of patients experience chronic inflammation of diarthrodial joints. Synovial inflammation often results in cartilage destruction and bone erosions, leading to longterm physical disability. Early aggressive therapy with synthetic disease modifying antirheumatic drugs (DMARD), such as methotrexate (MTX) and sulfasalazine, suppresses disease activity, slows radiographic progression, and improves mortality[1-3].

Inhibitors of tumor necrosis factor-α (TNF) have profoundly transformed the management of RA and improved outcomes for patients. Clinical trials with infliximab, etanercept, and adalimumab have demonstrated an improvement in clinical signs and symptoms, functional and general health status, and the prevention of radiographic progression in patients with established and early RA[4-10]. However, 28%–41% of patients in clinical trials failed to achieve and/or sustain an American College of Rheumatology 20% (ACR20) improvement. Further, several studies following patients in "real life" situations have demonstrated that a substantial number of patients do not respond to TNF

inhibitor therapy or eventually experience increased RA activity despite therapy[11,12].

The inventory of effective therapeutic agents in the management of RA continues to grow. Advances in the understanding of RA pathogenesis have led to the development of novel therapeutics targeting T lymphocytes (CTLA-4-Ig, abatacept) and B cells (rituximab). These agents have been demonstrated to decrease disease activity in RA[13-15]. The growing list of potential therapeutic agents presents physicians caring for patients with RA with decisions as to which agent(s) should be used for each patient. With the increasing appreciation of the importance of early use of DMARD to prevent longterm structural damage[16], it will be clinically useful to identify patients who are likely to respond or not respond to particular agents. Several reports from Europe have described clinical predictors of response to TNF inhibitors in patients with RA. Anti-cyclic citrullinated peptide (anti-CCP) antibody status and titers and a decrease in C-reactive protein (CRP) predicted improvement in disease activity using the Disease Activity Score 28-joint count (DAS28) and ACR20 response, respectively[17,18]. Using the British Society for Rheumatology Biologics Register, MTX, nonsteroidal antiinflammatory drugs (NSAID), nonsmoking status, and low Health Assessment Questionnaire (HAQ) scores were associated with better DAS28 responses to etanercept or infliximab at 6 months[19]. These studies used relatively short periods of followup and focused on clinical scores of RA disease activity (e.g., DAS28 and ACR20).

Treatment decisions in clinical practice are based on a combination of biological, cultural, and sociological factors. These decisions may be significantly influenced by patient and physician preferences and expectations of treatment outcomes in addition to improvement in disease activity levels. It would be clinically useful to identify which RA patients are not only likely to respond to but are also able to continue treatment with particular therapeutic agents. Therefore, we utilized the Brigham Rheumatoid Arthritis Sequential Study (BRASS), a large single-center cohort of RA patients in the United States, to identify clinical predictors associated with discontinuation of TNF inhibitors.

MATERIALS AND METHODS

Study population. A cohort of patients from BRASS was utilized for this study. BRASS is a prospective, observational, single-center cohort with over 960 patients diagnosed with RA by board certified rheumatologists at the Brigham and Women's Center for Arthritis and Joint Diseases (Boston, MA). BRASS seeks to identify biomarkers and genetic indicators to predict disease activity and severity as well as treatment response and toxicity. Patients are prospectively followed and their RA is managed without a specific treatment protocol by the treating rheumatologist. Patients complete a series of questionnaires every 6 months, and their rheumatologists annually carry out a structured physical examination with history, laboratory tests, and radiographs to determine RA activity, functional status, medications, and adverse events. All research has been approved by the Institutional Review Board at Brigham and Women's Hospital.

RA patients enrolled in BRASS reporting current use of a TNF inhibitor (etanercept, infliximab, or adalimumab) with at least 6 months of followup within BRASS formed the current cohort. Both incident and prevalent cases of TNF inhibitor use were included. Patients in the discontinuation group were followed until they reached the endpoint of self-reported discontinuation of the TNF inhibitor as identified in their self-reported semiannual BRASS questionnaire. Patients who switched to another TNF inhibitor during the study were included in the discontinuation group. Only data from the first TNF inhibitor use while in BRASS were included in the study. Patients who did not report discontinuation of a TNF inhibitor on their most recent questionnaire formed the continuation group. Five patients who stopped using the TNF inhibitor due to pregnancy were excluded from the cohort.

Potential predictors of discontinuation of TNF inhibitor. Clinical data were prospectively collected on each patient. Gender, self-reported race/ethnicity, rheumatoid factor (RF) status, anti-CCP antibody status, presence of nodules, presence of erosions on radiographs as determined by a board certified musculoskeletal radiologist, assessment of physical activity, and tobacco smoking history were determined for each patient at entry into BRASS. Assessment of physical activity (metabolic equivalents in hours per week, MET hours/week) was determined using a modified questionnaire that asked about physical activities such as stretching, strength training, walking, swimming, cycling, and aerobic exercises[20]. Age, disease duration, and use of prior DMARD were determined at the study visit when the patients first reported use of a TNF inhibitor or at entry into BRASS if not using a TNF inhibitor. Covariates measuring disease activity, clinical course and disability, including CRP (mg/l), MD-HAQ, DAS28-CRP3 (based on total painful joints, total swollen joints, and CRP), RA Disease Activity Index (RADAI) scores, and concomitant prednisone use were recorded at the time of the study visit when the patient first reported use of a TNF inhibitor (baseline) and 6 months prior to the study endpoint. The RADAI questionnaire was modified for ease of use such that we assessed morning stiffness in the following categories: < 10 min was scored as 1, 10–30 min as 2, 30–60 min as 3, 60–90 min as 4, 90–120 min as 5, 120–150 min as 6, and > 150 min was scored as 7[21].

To identify variables for the final combined model, potential predictors of TNF inhibitor discontinuation were separated into 4 domains: subject characteristics, RA treatment, baseline disease activity and severity, and end of study disease activity. The subject characteristic domain included gender, age, duration of RA in years, RF status, anti-CCP antibody status, presence of nodules, presence of erosions on radiographs, smoking (per 10 pack-yrs), assessment of physical activity, and self-reported race/ethnicity. The RA treatment domain included use of a prior synthetic DMARD (MTX, hydroxychloroquine, sulfasalazine, leflunomide, gold, azathioprine, and cyclosporine), number of TNF inhibitors previously used, current use of MTX, cumulative years of MTX use, concomitant prednisone use, and concomitant NSAID use. The baseline disease activity and severity domain included RADAI, physician global assessment, patient global, CRP levels, DAS28-CRP, number of painful joints, number of swollen joints, MD-HAQ, fatigue scale, and depression scale. The end of study disease activity domain included RADAI, physician global, patient global, CRP levels, DAS28-CRP, number of painful joints, number of swollen joints, MD-HAQ, fatigue scale, depression scale, and infection.

Statistical analysis. Potential predictors of TNF inhibitor discontinuation to be used in the final combined model were determined using univariate and multivariate analyses within the 4 domains noted above (subject characteristics, RA treatment, baseline disease activity and severity, end of study disease activity). First, a univariate analysis was performed on all variables. Potential predictors with an unadjusted p value < 0.2 were carried forward for the domain-specific multivariate analysis. In the domain-specific multivariate model (Model 1), variables were analyzed within each domain. Next, backward selection was performed within each domain (Model 2), and covariates with a p value < 0.05 were carried forward for the final combined multivariate model.

For the final multivariate model, potential predictors of TNF inhibitor discontinuation identified in Model 2, from all domains, were combined

and analyzed together in the same model (combined model). These analyses were followed by backward selection. Age, gender, and disease duration were included in the final combined model regardless of their unadjusted or domain-specific multivariate associations with TNF inhibitor discontinuation.

Hazard ratios (HR) were determined using a Cox proportional hazard regression to identify predictors of TNF inhibitor discontinuation. Cox regression is a suitable method for assessing the relationship between covariates and endpoints in a longitudinal cohort such as BRASS. CRP, MD-HAQ, DAS28, and RADAI scores were used in analyses as continuous variables. The Student t test was used to compare patient characteristics between patients in the BRASS cohort who were currently using a TNF inhibitor and those not currently using a TNF inhibitor.

RESULTS

Study population. A total of 961 patients with RA were enrolled in BRASS at the time of this study, including 922 patients who completed the questionnaires. From this large cohort, 503 (52%) patients reported use of a TNF inhibitor during enrollment in BRASS and formed the current cohort. Of these 503 patients, 333 were prevalent cases and 170 were incident cases. Three hundred four patients reported use of etanercept, 71 reported use of infliximab, and 128 reported use of adalimumab.

Demographic data and clinical characteristics of RA patients reporting use of a TNF inhibitor are summarized and compared to patients not using a TNF inhibitor in Table 1. Patients reporting use of a TNF inhibitor (age 55.4 yrs, SD 13.5) were younger than patients not currently reporting use of a TNF inhibitor (age 59.3 yrs, SD 14.2). A significantly higher number of patients in the TNF inhibitor group were positive for RF, anti-CCP antibodies, and the presence of nodules. In the TNF inhibitor group, 381 patients (76%) reported prior use of a synthetic DMARD and 101 (20%) had previously used another TNF inhibitor. Both groups had similar rates of concomitant MTX use, but the TNF inhibitor group had a higher percentage of patients reporting concomitant prednisone use. Finally, compared to patients not taking a TNF inhibitor, patients reporting use of a TNF inhibitor had slightly higher RADAI, DAS28, and MD-HAQ scores at study entry.

Discontinuation of TNF inhibitor therapy. Of the 503 patients using a TNF inhibitor, 210 (42%) reported discontinuation of TNF inhibitor therapy during the study (discontinuation group). At the time of their last visit in the study, 293 (58%) patients did not discontinue the TNF inhibitor they reported using and remained on the same TNF inhibitor (continuation group). Length of followup in the continuation group was 37.4 months (SD 14.2) and in the discontinuation group 42.1 months (SD 11.0). The mean duration of therapy in the continuation group was 51.9 months (SD 32.1) compared to 28.0 months (SD 24.3) in the discontinuation group. The reason for discontinuation was reported by only 63 patients, including 38 reporting lack of efficacy and 25 reporting an adverse event. Since data regarding reasons for discontinuation were available for only 63 patients and we were interested in the real-life endpoint of treatment discontinuation, all subsequent analyses were performed using patients in the continuation and discontinuation groups regardless of reason for discontinuation.

Predictors of discontinuation of TNF inhibitors: domain-specific multivariate analysis

Subject characteristics. As shown in Table 2, multivariate analysis within this domain with backward selection showed that Hispanic patients were more likely to discontinue treatment with the TNF inhibitor (HR 2.74, 95% CI 1.34–5.63). Interestingly, patients who reported higher levels of physical activity (MET hours/week) were also less likely to discon-

Table 1. Demographics and clinical characteristics of patients in BRASS using a TNF inhibitor.

	Patients Not Using a TNF Inhibitor*	Patients Using a TNF Inhibitor*	p
No. of patients	419	503	
Age, yrs	59.3 ± 14.2	55.4 ± 13.5	< 0.0001
Gender female (%)	333 (79)	427 (85)	0.03
Disease duration, yrs	13.5 ± 12.6	14.7 ± 12.3	0.17
Rheumatoid factor-positive (%)	199 (48)	336 (67)	< 0.0001
Anti-CCP antibody-positive (%)	216 (52)	356 (71)	< 0.0001
Presence of nodules (%)	108 (26)	215 (43)	< 0.0001
Prior use of synthetic DMARD (%)	243 (58)	381 (76)	< 0.0001
No. of prior synthetic DMARD, mean ± SD	1.1 ± 1.2	1.9 ± 1.6	< 0.0001
Prior use of TNF inhibitor (%)	38 (9)	101 (20)	< 0.0001
Concomitant use of prednisone (%)	116 (28)	183 (36)	0.005
Concomitant use of methotrexate (%)	184 (44)	237 (47)	0.33
Concomitant use of NSAID (%)	208 (50)	250 (50)	0.99
RADAI	3.3 ± 2.2	3.7 ± 2.3	0.01
DAS28–CRP3	3.9 ± 1.5	4.2 ± 1.6	0.003
MD-HAQ	0.6 ± 0.5	0.7 ± 0.5	0.001

* Number of patients (%) unless otherwise noted.

Table 2. Domain-specific analysis of predictors of TNF inhibitor discontinuation.

	Model 1*		Model 2 (backward selection)	
	Hazard Ratio[†]	95% CI	Hazard Ratio[†]	95% CI
Subject characteristics				
Female	0.77	0.52–1.15		
Age, yrs, continuous	1.00	0.99–1.01		
Disease duration, yrs	0.99	0.98–1.01		
Presence of nodules	0.82	0.60–1.13		
Presence of erosions	1.09	0.79–1.49		
Pack-years smoking (per 10 pack-yrs)	1.00	0.99–1.01		
Physical activity (MET hours/week)	0.96	0.92–0.99	0.96	0.93–0.99
Race/ethnicity				
African American	0.98	0.39–2.46		
Asian	1.39	0.44–4.39		
Native American	0.42	0.06–3.06		
Hispanic	2.44	1.16–5.15	2.74	1.34–5.63
RA treatment				
Prior use of synthetic DMARD	0.56	0.40–0.79	0.55	0.39–0.77
No. prior TNF inhibitors used	1.45	1.14–1.83	1.48	1.18–1.87
Concomitant use of methotrexate	1.92	1.36–2.71	1.94	1.38–2.74
Cumulative methotrexate use, yrs	0.15	0.07–0.30	0.15	0.07–0.30
Concomitant prednisone use	1.18	0.89–1.57		
Concomitant use of NSAID	0.95	0.71–1.27		
Baseline disease activity and severity				
RADAI (per point)	1.16	1.05–1.28	1.12	1.04–1.20
Physician global (per point, 0–10)	1.10	1.01–1.21	1.13	1.05–1.21
Patient global (per point, 0–10)	0.98	0.89–1.08		
CRP (per 10 mg/l)	1.08	0.99–1.18		
DAS28–CRP (per point)	0.95	0.68–1.31		
Painful joints (per joint)	1.02	0.97–1.06		
Swollen joints (per joint)	1.00	0.97–1.03		
MD-HAQ (per point)	0.92	0.65–1.31		
Fatigue scale (per point)	1.00	0.99–1.00		
End of study disease activity				
RADAI (per point)	1.24	1.12–1.37	1.22	1.11–1.34
Physician global (per point, 0–10)	1.23	1.12–1.35	1.25	1.16–1.34
DAS-28-CRP (per point)	1.03	0.91–1.16		
MD-HAQ (per point)	0.87	0.66–1.14		
Fatigue scale (per point)	1.00	0.99–1.00	0.99	0.99–1.00
Infection	0.85	0.63–1.14		

* Variables identified in univariate analyses using $p < 0.2$. [†] HR > 1.0 indicates more likely to discontinue TNF inhibitor.

tinue treatment with the TNF inhibitor (HR 0.95, 95% CI 0.92–0.99). Age, gender, disease duration, and presence of nodules or erosions were not significant in the multivariate analyses. Further, availability or type of medical insurance was not associated with discontinuation of TNF inhibitors.

RA treatment. Multivariate analysis within this domain revealed that prior use of synthetic DMARD was associated with a reduced risk of discontinuation of TNF inhibitor (HR 0.55, 95% CI 0.39–0.77); however, the number of TNF inhibitors previously used was associated with a significantly higher risk of discontinuation (HR 1.48, 95% CI 1.18–1.87). Surprisingly, concomitant use of MTX was associated with a higher risk of discontinuation of TNF inhibitors (HR 1.94, 95% CI 1.38–2.74). However, cumula-

tive use of MTX (years) was associated with a decreased risk of discontinuation (HR 0.15, 95% CI 0.07–0.30). Use of NSAID and corticosteroids was not associated with discontinuation of TNF inhibitors.

Baseline disease activity and severity. Multivariate analysis within this domain showed that at the time of entry into the study, patients with higher RADAI scores (HR 1.18 per point, 95% CI 1.04–1.20) and physician global assessment scores (HR 1.12 per point of 10-point scale, 95% CI 1.05–1.21) were more likely to discontinue TNF inhibitor use during the study. Other covariates within this domain, including CRP, physician or patient global assessment, DAS28-CRP, painful or swollen joints, MD-HAQ, or fatigue scores were not associated with TNF inhibitor discontinuation.

End of study disease activity. Multivariate analysis within this domain revealed that 6 months prior to the study endpoint, higher physician global scores (HR 1.25 per point of 10-point scale, 95% CI 1.20–1.43) were associated with TNF inhibitor discontinuation. Similar to the baseline assessment, higher RADAI scores (HR 1.22 per point, 95% CI 1.02–1.22) were associated with TNF inhibitor discontinuation. Patients reporting higher levels of fatigue were less likely to discontinue the TNF inhibitor (HR 0.99, 95% CI 0.99–0.99). DAS28-CRP, MD-HAQ, and infection were not associated with discontinuation of TNF inhibitors.

Predictors of discontinuation of TNF inhibitors: combined model
To determine predictors of discontinuation of TNF inhibitors, multivariate analysis of variables identified in the domain-specific models was performed in the final combined model (Table 3). Prior use of synthetic DMARD was associated with a lower risk of discontinuation of TNF inhibitor (HR 0.50, 95% CI 0.34–0.72). Further, cumulative use of MTX (years) was also associated with a decreased risk of TNF discontinuation (HR 0.24, 95% CI 0.12–0.47). In contrast, concomitant use of MTX was associated with discontinuation of TNF inhibitors in the final combined model (HR 1.57, 95% CI 1.09–2.25). Interestingly, the number of prior TNF inhibitors used was associated with increased risk of discontinuation of TNF inhibitors (HR 1.30, 95% CI 1.03–1.66).

With regard to measures of disease activity, baseline RADAI scores were not associated with discontinuation of TNF inhibitors. In contrast, RADAI scores (HR 1.13, 95% CI 1.05–1.22) and physician global scores (HR 1.44 per point, 95% CI 1.33–1.55) 6 months prior to the study end-

point but not at baseline were predictive of TNF discontinuation. Age, gender, disease duration, physical activity, CRP, and infection were not associated with discontinuation of TNF inhibitors. A sensitivity analysis comparing predictors of discontinuation between incident cases and prevalent cases did not reveal any significant differences (data not shown).

DISCUSSION
In our study of RA patients who used a TNF inhibitor, 42% of the patients discontinued treatment with TNF inhibitors, with a mean length of followup of roughly 39 months. Based on multivariate analyses, we were able to identify several variables modestly associated with the discontinuation of TNF inhibitors. Specifically, prior use of another TNF inhibitor was associated with a higher risk of TNF inhibitor discontinuation. In contrast, longer disease duration, prior use of synthetic DMARD, and longer cumulative MTX use were associated with a lower risk of TNF inhibitor discontinuation. Lastly, higher RADAI and physician global scores 6 months prior to discontinuation were associated with discontinuation of a TNF inhibitor.

Consideration should be given to several methodological limitations of our study. The cohort included both new users (incident users) and patients taking a TNF inhibitor prior to study entry (prevalent users). Prevalent users may bias toward a group of patients who are doing well using a TNF inhibitor, and could affect the predictors that were identified in this study. Further, baseline data on disease activity measures obtained on prevalent users already reflects treatment with a TNF inhibitor and may limit the ability to identify associations of discontinuation with disease activity. Although the study did not involve an inception cohort, the

Table 3. Final model of predictors of TNF inhibitor discontinuation.

	Combined Model*		Combined Model (backward selection)		Combined Model (backward selection) with Age and Gender	
	Hazard Ratio[†]	95% CI	Hazard Ratio[†]	95% CI	Hazard Ratio[†]	95% CI
Physical activity**	0.98	0.95–1.01				
Hispanic	1.44	0.70–2.98				
Prior synthetic DMARD	0.48	0.33–0.71	0.43	0.30–0.62	0.50	0.34–0.72
No. prior TNF inhibitors	1.42	1.08–1.82	1.35	1.06–1.72	1.30	1.03–1.66
Concomitant methotrexate	1.54	1.06–2.25	1.70	1.19–2.43	1.57	1.09–2.25
Cumulative methotrexate	0.23	0.11–0.47	0.20	0.10–0.41	0.24	0.12–0.47
Baseline RADAI[††]	1.00	0.92–1.08				
Baseline physician global[††]	1.01	0.92–1.10				
End RADAI[††]	1.14	1.03–1.25	1.11	1.03–1.20	1.13	1.05–1.22
End physician global[††]	1.26	1.15–1.38	1.25	1.15–1.35	1.27	1.18–1.38
Fatigue	1.00	0.99–1.00				
Age, yrs, continuous	0.99	0.98–1.00			0.99	0.98–1.01
Female gender	0.97	0.65–1.45			1.04	0.70–1.53
Disease duration	0.99	0.98–1.00			0.99	0.97–1.00

* Variables identified in domain-specific multivariate analyses using p < 0.05 ** MET hours per week. [†] HR > 1.0 indicates more likely to discontinue TNF inhibitor. [††] Per point.

data described here and the predictors identified provide useful insights into the discontinuation of TNF inhibitors, and a sensitivity analysis of our final model did not reveal any differences between prevalent and incident users. Another limitation to consider is the assessment of disease activity measures 6 months prior to the endpoint, which may limit interpretation of the data as these data may not completely reflect all the disease activity that may have occurred prior to the study endpoint. Another limitation is that we relied on patient self-report of discontinuation in the questionnaires and that patients were not categorized according to reasons for discontinuation. Unfortunately, only 63 patients reported a reason for discontinuation of a TNF inhibitor. Further categorization of discontinuation according to self-reported reason would be limited due to incomplete data and statistical power. However, the study focused on treatment discontinuation and the clinical utility of TNF inhibitors. Therefore, from the perspective of clinical utility of the TNF inhibitor, it remains important to determine predictors of discontinuation independent of the reasons for discontinuation. A final limitation that must be considered is the possibility of residual confounding variables associated with treatment discontinuation. In particular, our adjusted models have variables from many domains, but did not focus on educational, emotional, or social support factors that may contribute to medical decisions.

At present, deciding which synthetic DMARD or biologic response modifiers (BRM) will offer the greater clinical benefit for the individual RA patient is largely determined by patient and physician preferences, toxicity profiles, and cost rather than evidence in the literature. Several studies have focused on identifying clinical predictors of clinical responses to synthetic DMARD; however, the predictors have not been consistently reproduced in observational studies[22-25]. Further, these trials did not evaluate predictors of response to TNF inhibitors or other BRM. Several reports have investigated clinical predictors of response to TNF inhibitors. Anti-CCP antibody status and titers, but not disease duration, RF status, and number of prior DMARD, were reported to be associated with DAS28 responses from 30 patients treated with infliximab for 14 weeks[18]. Another study demonstrated that a decrease in CRP predicted ACR20 response to infliximab at 12 weeks[17]. Recently, using the British Society for Rheumatology Biologics Register, MTX, NSAID, nonsmoking status, and low HAQ scores were associated with better DAS28 responses to etanercept or infliximab at 6 months[19]. These studies focused on clinical scores of RA disease activity (e.g., DAS28 and ACR20) with relatively short lengths of followup.

Our study used a large cohort of patients with RA, in a US academic rheumatology center, being followed prospectively, but the treatment decisions were made by the patients and treating physicians without any specific research protocol. The primary endpoint was discontinuation of TNF inhibitors, which is a multidimensional endpoint that is influenced by a combination of biological and sociological factors, physician practices and preferences, and patient preferences and expectations. The possible cultural influences on treatment discontinuation support the need to investigate multiple registries that include RA patients from different cultures. Given this multidimensionality, treatment discontinuation may not reflect clinical scores of RA disease activity. For example, it is possible that patients who achieve only an ACR20 response, an endpoint common to randomized clinical trials, would discontinue a medication due to continued disease activity or expectations of the risk to benefit ratio. With regard to disease activity, we observed an association of RADAI and physician global scores 6 months prior to the study endpoint with discontinuation of TNF inhibitor, but found no association with DAS28 or CRP. This may be due to the time at which these measures were assessed (e.g., 6 months prior to the study endpoint). Alternatively, it may reflect the complex, multidimensional nature of treatment discontinuation, which is not reflected perfectly in disease activity measures.

We observed that prior use of a TNF inhibitor was modestly associated with the discontinuation of a subsequent TNF inhibitor. It is common clinical practice to prescribe a second TNF inhibitor to RA patients who have failed one TNF inhibitor. Several reports suggest that switching TNF inhibitors results in good clinical responses[26-28]. However, one of these reports also noted an increased rate of discontinuation of the second TNF inhibitor within 2 years in patients who previously reported use of a TNF inhibitor[28]. It is tempting to speculate that a subset of patients who fail a TNF inhibitor, particularly due to continued disease activity, have a form of RA that may be more dependent on other cell populations, inflammatory cytokines, and/or chemokines rather than TNF-α. Indeed, a recent observational study suggested rituximab treatment may be more effective than switching to an alternative TNF inhibitor in RA patients who have active disease despite use of a TNF inhibitor[29]. Additional studies will be helpful to determine if patients who fail a single TNF inhibitor due to lack of efficacy are less likely to respond to a subsequent TNF inhibitor compared to a BRM targeting other molecular pathways.

We noted some interesting observations in the interactions between synthetic DMARD and discontinuation of TNF inhibitors. Previous observations suggest that patients reporting prior use of synthetic DMARD have lower clinical responses to either a subsequent synthetic DMARD or a TNF inhibitor[30,31]. However, in our current study, prior use of DMARD and cumulative use of MTX was associated with a lower risk of discontinuation. One possible explanation for these associations might be related to the availability of alternative treatments. At the time of this study, other BRM (e.g., rituximab, abatacept) were not readily available.

Therefore patients and physicians might choose to continue a treatment, even if the overall benefit was not optimal. Whether the introduction of rituximab and abatacept into clinical practice has substantially changed these associations remains to be determined.

It is also surprising that concomitant use of MTX was associated with discontinuation of TNF inhibitors. Randomized clinical trials and observational studies have demonstrated improved clinical responses with combination therapy, including a recent observational study that also showed that patients receiving combination therapy had better DAS28 responses to TNF inhibitors than those not taking concomitant MTX[16,32-34]. One reason for the apparent conflict between results of our current study and prior observations may be due to the specific outcome measured (treatment discontinuation vs DAS28). Consistent with this hypothesis, a recent longterm study of RA patients who started taking infliximab also failed to observe an association of concomitant use of MTX with infliximab and discontinuation of infliximab[11].

In conclusion, a significant number of patients with RA discontinue TNF inhibitor therapy. These patients will require subsequent disease modifying antirheumatic therapy, which is likely to include other BRM. The ability to predict which patients will respond to specific targeted therapies will be extremely useful in the management of RA. Pharmacogenomic approaches to identifying predictors of TNF inhibitor discontinuation may provide greater insight. Extending our understanding of the biological mechanisms as well as social influences underlying discontinuation of TNF inhibitors is essential so that we can develop clinical models to predict which antirheumatic therapeutic regimen will be of greatest benefit to patients with RA.

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