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TNF Antagonist Responsiveness in a United States Rheumatoid Arthritis Cohort

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Abstract

Objective—To investigate responsiveness according to whether patients satisfy eligibility criteria from randomized controlled trials of tumor necrosis factor (TNF) antagonists in a multi-centered United States cohort

Methods—Biologic-naïve rheumatoid arthritis patients prescribed TNF antagonists (n=465) in the Consortium of Rheumatology Researchers of North America registry were included. Patients were stratified by whether they met eligibility criteria from 3 major TNF antagonist trials. Two cohorts were examined: cohort A (n=336) included patients with complete American College of Rheumatology response criteria except acute phase reactants; and cohort B (n=129) with the complete response criteria. Study outcomes included modified American College of Rheumatology 20% and 50% improvement responses (Cohort A) and standard American College of Rheumatology improvement (Cohort B).

Results—A minority of patients (5.4% to 19.4%) prescribed TNF antagonists met trial eligibility criteria, and predominantly had high disease activity (78.5% to 100%). In cohort A for patients who met eligibility criteria, rates of 20% improvement (52.3% to 63.6%) and 50% improvement (30.8% to 45.5%) were achieved. Among patients failing to meet eligibility criteria, rates of 20% improvement (16.2% to 20.4%) and 50% improvement (8.9% to 10.8%) were consistently inferior ($p<0.05$ all comparisons). For cohort B, similar differences were observed.

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Conclusion—This multi-centered U.S. cohort study demonstrates that the majority of patients receiving TNF antagonists would not meet trial eligibility criteria and achieve lower clinical responses. These findings highlight the tradeoff between defining treatment responsive populations and achieving results that can be generalized for broader patient populations.

Keywords

TNF antagonist; rheumatoid arthritis; trial eligibility

INTRODUCTION

Randomized, controlled trials have clearly demonstrated the efficacy of tumor necrosis factor (TNF) antagonists for treatment of active rheumatoid arthritis.[1–4] However, concerns that patients in clinical practice differ from participants in randomized controlled trials have been raised.[5] Two recent studies from European registries have confirmed that a substantial proportion of patients receiving TNF antagonists in European countries would not meet eligibility criteria for enrollment in TNF antagonist randomized controlled trials. Whereas studies of TNF antagonist utilization patterns and effectiveness in European countries have been extensively published, few comparable studies from U.S. cohorts have been reported.[6–17] As a result, there is little data available on whether or not the broader utilization patterns of TNF antagonists by U.S. rheumatologists translate into improved patient outcomes similar to those achieved in the TNF antagonist randomized controlled trials.

The evidence supporting TNF antagonist effectiveness in clinical practice has been derived primarily from European countries,[6–13] many of whom require fulfillment of explicit disease activity requirements for receiving access to biologic agents.[18, 19] These studies have consistently reported that the majority of patients prescribed TNF antagonists in these countries had high baseline disease activity.[6, 7, 9, 10] In contrast, formal requirements for minimum disease activity levels to be prescribed these agents among U.S. health and government insurance plans are highly variable, and are defined differently by individual health plans and states. These requirements are frequently based on the rheumatologist's assessment of "treatment failure" or "persistent disease activity" despite treatment with non-biological disease modifying anti-rheumatic drugs.[14, 15]

Clinical studies in other chronic conditions including atherosclerotic heart disease, stroke, asthma and malignancies have demonstrated that patient selection and inclusion criteria may compromise the external validity or generalizability of clinical trial results to clinical practice.[20–23] In the discipline of rheumatology, randomized controlled trials of biologic agents, including TNF antagonists, have consistently required that patients meet inclusion criteria defining a minimal level of disease activity for study eligibility.[1–3, 5]

The purpose of this study was to investigate responsiveness to TNF antagonists according to whether patients satisfied eligibility criteria from randomized controlled trials in a multi-centered United States cohort of rheumatoid arthritis patients. We applied eligibility criteria from three major randomized controlled trials to patients prescribed these agents who were enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Thereafter, we examined whether clinical response rates to TNF antagonists differed between patients who met and those who failed to meet eligibility criteria from these randomized controlled trials.

METHODS

Patients with a diagnosis of rheumatoid arthritis and no prior biologic agent utilization who were enrolled in the registry and prescribed a TNF antagonist for the first time were included. The study period was from March 2002 to May 2006. The Consortium of Rheumatology Researchers of North America (CORRONA) registry is a prospective observational study of arthritis patients enrolled by participating rheumatologists at both academic and private practice sites; details have been previously described.[24, 25] Approvals for data analyses were obtained for academic and private practice sites from local and central Institutional Review Boards, respectively.

Study Population and Cohorts

The study population included 465 biologic naïve rheumatoid arthritis patients selected from a total of 854 patients prescribed a new TNF antagonist from rheumatology practices participating in the consortium registry. No disease activity or comorbidity exclusion criteria were required for enrollment into the consortium registry. Consecutive patients in the registry with baseline evaluations prior to prescription of a new TNF antagonist and at least one follow-up evaluation within 3 and 6 months were studied, selecting the last observation during the 6 month follow-up period. Patients who discontinued the TNF antagonist prior to the first follow-up visit at 3 months were included as well, using a nonresponder imputation as previously defined.[13] Two cohorts were defined for the purposes of this study: cohort A (n=336) included patients with measures for all components of the American College of Rheumatology response criteria except acute phase reactants and cohort B (n=129) for whom complete American College of Rheumatology response criteria were available. In cohort B, erythrocyte sedimentation rate (ESR) was selected as the acute phase reactant for the purposes of this study.

Medication and Clinical Data

Data were prospectively collected during the study period from physician assessments and patient questionnaires completed during clinical encounters. Disease modifying drug and biologic agent data, including TNF antagonist agents, are recorded at the time of the clinical encounter. Data collected also includes the seven components of the American College of Rheumatology response criteria including 28 tender and swollen joint counts, physician and patient global assessments of disease activity, patient assessment of pain, the modified Health Assessment Questionnaire assessing physicial function and an acute phase reactant. Acute phase reactant data are recorded from laboratory tests obtained within 14 days of the clinical encounter, but collection of laboratory data are not mandated by the study protocol. As a result of the missing acute phase reactant data for cohort A, different composite measures of disease activity and response were selected for the two cohorts. For cohorts A and B, disease activity for each patient was stratified into low, moderate or high disease activity categories based on previously published cutpoints for the Clinical Disease Activity Index (CDAI) and Disease Activity Score (DAS)-28, respectively.[26, 27] For cohort A responses, achievement of a modified American College of Rheumatology 20% improvement was defined for this study requiring ≥20% improvement in tender and swollen joint counts, as well as ≥20% improvement in 2 of 4 remaining components (excluding the erythocyte sedimentation rate, as previously defined).[28] For cohort B, achievement of standard American College of Rheumatology 20% responses required ≥20% improvement in tender and swollen joint counts, as well as ≥20% improvement in 3 of 5 remaining components. These definitions of modified and standard American College of Rheumatology responses were applied to the 50% improvement responses as well.

Definitions of Randomized Controlled Trial Eligibility Criteria

Patients were stratified in both cohorts based on whether or not they met the eligibility criteria from three major published randomized controlled trials, one for each of the approved TNF antagonists: the infliximab Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, one of the Phase III etanercept monotherapy trials and the Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis (ARMADA) trial for adalimumab.[1–3] Eligibility criteria from each trial were applied to the baseline disease characteristics in cohorts A and B. Because the registry records 28-joint counts, we estimated 28-joint count equivalents for the randomized controlled trial 66-joint count requirements based on the 28-joint validation study by Smolen et al.[29] For 66-joint count thresholds of 6, 9, 10 and 12 tender and swollen joints, we applied the estimated 28-joint count equivalents of 4, 5, 6 and 8 joints, respectively as previously described. Functional class, previous number of disease modifying antirheumatic drugs failed and corticosteroid dose eligibility criteria from each of the trials were applied to both cohorts. Acute phase reactant eligibility thresholds were applied only to patients in cohort B.

Statistical Analysis

We compared baseline characteristics of cohort A and B using Fisher's exact tests and Student's t-tests for categorical and continuous variables, respectively. Baseline values were stratified into disease activity categories (low, moderate and high). Rates of modified American College of Rheumatology 20% and 50% improvement in cohort A were compared between patients meeting trial eligibility requirements and those failing to meet eligibility requirements using Fisher's exact test. Similar methods for comparing rates of standard American College of Rheumatology 20% and 50% improvement were applied to cohort B. All analyses were performed using Stata, version 9.2 (Stata Corporation, College Station, TX).

RESULTS

Patient and Baseline Disease Activity Characteristics

Baseline characteristics and disease activity levels of patients in cohorts A and B are summarized and compared in Table 1, showing no significant differences with the exception that patients in cohort A were less frequently rheumatoid factor positive (69.8% versus 82.8%, p=0.016). Similar proportions of patients prescribed TNF antagonists in cohorts A (27.9%) and B (28.4%) had high clinical disease activity index (CDAI) scores at baseline. The proportion of patients in cohort A with low, moderate and high baseline disease activity levels was 43.2%, 27.1%, 29.8%, respectively. These proportions were similar to cohort B, for whom the distribution of low, moderate and high disease activity patients was 42.6%, 29.5% and 27.9%, respectively.

Clinical Trial Eligibility and Disease Activity Levels

A minority of patients in both cohorts met the eligibility criteria cited for the TNF antagonist randomized controlled trials (Table 2). In cohort A, the proportion of patients meeting eligibility criteria for the selected infliximab, etanercept and adalimumab trials were 19.4%, 11.3% and 6.6%, respectively. In cohort B, the proportion of patients who met eligibility criteria for the three randomized controlled trials ranged from 5.4% to 10.1%. Eligibility criteria that consistently excluded a majority of patients in both cohorts included tender joint count (range 28.6% to 46.8% met eligiblity criteria), morning stiffness (40.8% to 42.0%) and erythrocyte sedimentation rate (29.2% in cohort A). Swollen joint counts, number of prior disease-modifying drugs and functional class eligibility criteria were more commonly met by patients in both cohorts.

The majority of patients who met eligibility criteria of TNF antagonist trials had high baseline disease activity (Table 3): 80% to 100% of patients in cohort A and 62.3% to 100% in cohort B. In contrast, among those who failed to meet eligibility criteria, the proportion of patients with high disease activity ranged from 20.4% to 30.4% in the two cohorts.

Responsiveness to TNF Antagonists

Among patients in Cohort A meeting eligibility criteria ("trial eligible" patients), modified American College of Rheumatology 20% and 50% responses were superior to those who did not ("trial ineligible patients"), as described in Table 3. According to the infliximab trial eligibility criteria, modified 20% responses were achieved more frequently in trial eligible (52.3%) than trial ineligible patients (16.2%), $p<0.001$. Similar differences in responsiveness were observed using the etanercept trial eligibility criteria, with 60.5% of patients achieving modified 20% responses in trial eligible versus 18.5% for ineligible patients, $p<0.002$. Using the adalimumab trial criteria, 63.6% of trial eligible patients achieved the modified 20% response versus 20.4% in ineligible patients, ($p<0.001$). Higher response rates were also evident for modified American College of Rheumatology 50% improvement responses for trial eligible versus eligible patients (Table 4). The observed differences between trial eligible and trial ineligible patients in the smaller Cohort B were generally similar, although these differences achieved statistical significance for three of the six comparisons.

DISCUSSION

In this multi-centered, U.S.-based cohort study of rheumatoid arthritis patients prescribed TNF antagonists, we had two principal findings. First, we observed that fewer than one-fifth of rheumatoid arthritis patients in the study cohorts prescribed a TNF antagonist would have met the eligibility requirements from three major TNF antagonist trials, primarily due to disease activity requirements. The proportion of rheumatoid arthritis patients satisfying requirements for trial eligibility in this U.S. cohort study were markedly lower than estimates reported from European registries. The second principal finding of this study was that response rates to TNF antagonist therapies were markedly attenuated in those patients who did not meet trial eligibility criteria.

Two recent studies from a single academic site in the U.S. reported that the majority of rheumatoid arthritis patients in their practice would not meet the entry criteria for TNF antagonist clinical trials due to lower than required disease activity.[30, 31] Similar findings have also been reported in rheumatoid arthritis cohorts from other countries.[5, 12, 13, 32] In our study, we examined the baseline disease activity of patients who were actually prescribed TNF antagonists, which has not been examined in a U.S. cohort to date. We observed that fewer than one-fifth (9.4% – 18.6%) of patients prescribed TNF antagonists would have met eligibility criteria. These estimates are markedly lower than the observations from European registries. In the German biologics registry, Zink and colleagues reported that 21% to 33% of patients prescribed TNF antagonists met eligibility criteria.[12] Similarly, the Dutch registry reported a higher proportion of patients meeting TNF antagonist trial eligibility criteria, ranging from 24% to 79% of patients in their registry. The fact that the rates of trial eligibility in this U.S. cohort are the lowest reported to date suggests that the generalizability of TNF antagonist trials may be more problematic for rheumatoid arthritis patients treated in U.S. practices.

Our second principal finding was that the response to TNF antagonists was attenuated in patients who fail to meet trial eligibility criteria. These results confirm the findings of both the German and Dutch registry studies in a multi-centered U.S.-based cohort. When outcomes differ among those who are eligible versus ineligible for trials, it suggests that caution may be warranted regarding the external validity of trial results. Specifically, clinical trial designs that exclude serious medical comorbidities or employ "enrichment strategies" to improve the

likelihood of detecting a therapeutic effect may compromise the external validity of a study's findings.[23, 33] Concerns regarding the generalizability of clinical trial results have been raised in other subspecialties, including issues relating to patient selection and inclusion criteria.[20–23] While the response rate differences observed in our study may be partly explained by floor effects for individual outcome measures, they are unlikely to fully explain our findings. These findings further emphasize the need to identify clinical and biomarker predictors of TNF antagonist responsiveness to avoid utilization of expensive biologic agents in patients who are unlikely to respond.

The strengths of this study include the large patient population available for analysis, based on the number of participating rheumatologists in the consortium. In addition, the detailed clinical data collected from both physicians and patients, including the components of the American College of Rheumatology response criteria, were another strength that permitted determination of trial eligibility. The collection of these components in a prospective, standardized manner allowed us to stratify patients by disease activity level, as well as determine responsiveness, using validated instruments frequently applied in randomized controlled trials.

We also recognize a number of limitations. The consortium registry for this study does not mandate regular collection of laboratory values, but captures 'real-world' therapeutic prescribing and laboratory monitoring. Acute phase reactants were not routinely ordered and therefore prevented calculation of standard American College of Rheumatology responses in cohort B. However, our study findings were generally similar in both cohorts, indicating that these findings are likely to be robust. A second limitation is that the registry requires measurement of 28-joint counts, whereas most trial eligibility criteria apply 66/68 joint counts. However, the validity of 28 joint counts has been previously utilized in several randomized controlled trials in rheumatoid arthritis, and we applied a published nomogram for converting 66/68 to 28 joint counts.[26, 29] This approach has been adopted by other rheumatoid arthritis registries in their published work.[12,13] Finally, the Consortium of Rheumatology Researchers of North America registry may not be representative of rheumatoid arthritis patients treated across the United States. However, the patients in the consortium registry are enrolled from a large number of practices located across the United States, representing the largest U.S.-based cohort of rheumatoid arthritis patients with both physician and patient reported data. This suggests that these findings are likely to be applicable to other rheumatoid arthritis cohorts in the U.S., but further studies are required to confirm these findings.

In conclusion, this study of a large U.S. rheumatoid arthritis cohort indicates that fewer than one-fifth of patients prescribed TNF antagonists meet typical eligibility requirements from TNF antagonist trials, and that patients failing to meet these criteria achieve inferior responses. These findings highlight the tradeoff between defining a treatment responsive population and generalizing data from randomized controlled trials to the larger population of patients with rheumatoid arthritis treated in clinical practice.

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Table 1

Characteristics of patients prescribed TNF antagonists in the study cohorts

	Cohort A (n=336)	Cohort B (n=129)	P value
Age, years ± SD	57.7 ± 13.7	57.4 ± 15.0	0.834
Female (%)	77.5	74.0	0.460
Caucasian (%)	84.1	84.9	0.886
Rheumatoid factor positive (%)	69.8	82.8	0.016
Duration of RA, years ± SD	10.7 ± 10.6	9.3 ± 9.6	0.189
Prescribed methotrexate (%)	67.3	69.0	0.741
Prescribed prednisone (%)	37.1	36.4	0.915
Number of prior DMARDs ± SD	1.9 ± 1.2	1.7 ± 1.3	0.188
Distribution of disease activity*			0.859
Low (%)	43.2	42.6	
Moderate (%)	27.1	29.5	
High (%)	29.8	27.9	
Tender joint count (0–28) ± SD	4.8 ± 6.0	5.2 ± 7.0	0.527
Swollen joint count (0–28) ± SD	5.8 ± 6.3	6.0 ± 6.5	0.792
Physician global (0–100) ± SD	29.3 ± 22.2	27.1 ± 21.9	0.346
Patient global (0–100) ± SD	28.9 ± 23.1	26.8 ± 24.0	0.405
Patient pain (0–100) ± SD	32.8 ± 24.9	31.5 ± 25.2	0.628
ESR, mm/hr ± SD	---	20.7 ± 20.3	---
mHAQ score (0–3) ± SD	0.4 ± 0.4	0.4 ± 0.5	0.328

Abbreviations: DMARDs = Disease-modifying Anti-Rheumatic Drugs; ESR = erythrocyte sedimentation rate; mHAQ = modified Health Assessment Questionnaire

* Based on cutpoints of the Clinical Disease Activity Index (CDAI).

Table 2

Proportion of patients prescribed TNF antagonists who meet trial eligibility criteria

	Cohort A (n=336)	Cohort B (n=129)
Complete RCT eligibility criteria*		
Infliximab ATTRACT criteria	65 (19.4%)	7 (5.4%)
Etanercept monotherapy criteria	38 (11.3%)	13 (10.1%)
Adalimumab ARMADA criteria	22 (6.6%)	12 (9.3%)
Tender joint count criteria		
Infliximab ATTRACT criteria	152 (45.2%)	49 (38.0%)
Etanercept monotherapy criteria	87 (25.9%)	35 (27.1%)
Adalimumab ARMADA criteria	117 (34.8%)	49 (38.0%)
Swollen joint count criteria		
Infliximab ATTRACT tender joint count	185 (55.1%)	67 (51.9%)
Etanercept monotherapy tender joint count	147 (43.8%)	52 (40.3%)
Adalimumab ARMADA tender joint count	185 (55.1%)	67 (51.9%)
Other common eligibility criteria		
Morning stiffness ≥45 minutes	123 (36.6%)	44 (34.1%)
ESR ≥28 mm/hr	--	30 (23.3%)
Number of prior DMARDS ≥1 and ≤ 4	289 (86.0%)	109 (84.5%)
Corticosteroid dose ≤ 10 mg prednisone	316 (94.1%)	120 (93.0%)
Functional Class ≤ 3	331 (98.5%)	125 (96.9%)

Abbreviations: ATTRACT = Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy; ARMADA = Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis; DMARDs = Disease-modifying Anti-Rheumatic Drugs; ESR = erythrocyte sedimentation rate; mHAQ = modified Health Assessment Questionnaire

Table 3

Baseline disease activity based on RCT eligibility criteria

	Cohort A (n=336) Baseline Disease Activity level			Cohort B (n=129) Baseline Disease Activity level		
	Low	Moderate	High	Low	Moderate	High
Infliximab ATTRACT criteria						
Patients meeting eligibility criteria	0.0	21.5	78.5	0	16.7	83.3
Patients not meeting eligibility criteria	53.5	28.4	18.1	49.6	30.4	20.0
Etanercept monotherapy RCT criteria						
Patients meeting eligibility criteria	0.0	0.0	100.0	0.0	0.0	100.0
Patients not meeting eligibility criteria	48.7	30.5	20.8	52.3	33.0	14.7
Adalimumab ARMADA criteria						
Patients meeting eligibility criteria	0.0	13.6	86.4	0.0	8.3	91.7
Patients not meeting eligibility criteria	46.2	28.0	25.8	52.3	32.1	15.6

Abbreviations: ATTRACT = Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy; ARMADA = Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis

Table 4

Response to TNF antagonist drugs based on whether patients met trial eligibility criteria

	Cohort A (n=336) Modified ACR Response Rates			Cohort B (n=129) Standard ACR Response Rates		
	Eligible	**Ineligible**	**P-value**	**Eligible**	**Ineligible**	**P-value**
20% Improvement						
Infliximab ATTRACT	34/65 (52.3)	44/271 (16.2)	<.001	3/7 (42.9)	20/122 (16.4)	.075
Etanercept Monotherapy	23/38 (60.5)	55/298 (18.5)	<.001	7/13 (53.9)	16/116 (13.8)	<.001
Adalimumab ARMADA	14/22 (63.6)	64/314 (20.4)	<.001	7/12 (58.3)	16/117 (13.7)	<.001
50% Improvement						
Infliximab ATTRACT	20/65 (30.8)	24/271 (8.9)	<.001	0/7 (0.0)	10/122 (8.2)	.430
Etanercept Monotherapy	14/38 (36.8)	30/298 (10.1)	<.001	2/13 (15.4)	8/116 (6.9)	.278
Adalimumab ARMADA	10/22 (45.5)	34/314 (10.8)	<.001	4/12 (33.3)	6/117 (5.1)	.001

Abbreviations: ACR = American College of Rheumatology; ATTRACT = Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy; ARMADA = Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis