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Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug

A Randomized Clinical Trial

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IMPORTANCE One-third of patients with rheumatoid arthritis show inadequate response to tumor necrosis factor α (TNF- α) inhibitors; little guidance on choosing the next treatment exists.

OBJECTIVE To compare the efficacy of a non-TNF-targeted biologic (non-TNF) vs a second anti-TNF drug for patients with insufficient response to a TNF inhibitor.

DESIGN, SETTING, AND PARTICIPANTS A total of 300 patients (conducted between 2009-2012) with rheumatoid arthritis, with persistent disease activity (disease activity score in 28 joints-erythrocyte sedimentation rate [DAS28-ESR] ≥ 3.2 [range, 0-9.3]) and an insufficient response to anti-TNF therapy were included in a 52-week multicenter, pragmatic, open-label randomized clinical trial. The final follow-up date was in August 2013.

INTERVENTIONS Patients were randomly assigned (1:1) to receive a non-TNF-targeted biologic agent or an anti-TNF that differed from their previous treatment. The choice of the biologic prescribed within each randomized group was left to the treating clinician.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients with good or moderate response according to the European League Against Rheumatism (EULAR) scale at week 24. Secondary outcomes included the EULAR response at weeks 12 and 52; at weeks 12, 24, and 52; DAS28ESR, low disease activity (DAS28 ≤ 3.2), remission (DAS28 ≤ 2.6); serious adverse events; and serious infections.

RESULTS Of the 300 randomized patients (243 [83.2%] women; mean [SD] age, 57.1 [12.2] years; baseline DAS28-ESR, 5.1 [1.1]), 269 (89.7%) completed the study. At week 24, 101 of 146 patients (69%) in the non-TNF group and 76 (52%) in the second anti-TNF group achieved a good or moderate EULAR response (OR, 2.06; 95% CI, 1.27-3.37; $P = .004$, with imputation of missing data; absolute difference, 17.2%; 95% CI, 6.2% to 28.2%). The DAS28-ESR was lower in the non-TNF group than in the second anti-TNF group (mean difference adjusted for baseline differences, -0.43 ; 95% CI, -0.72 to -0.14 ; $P = .004$). At weeks 24 and 52, more patients in the non-TNF group vs the second anti-TNF group showed low disease activity (45% vs 28% at week 24; OR, 2.09; 95% CI, 1.27 to 3.43; $P = .004$ and 41% vs 23% at week 52; OR, 2.26; 95% CI, 1.33 to 3.86; $P = .003$).

CONCLUSIONS AND RELEVANCE Among patients with rheumatoid arthritis previously treated with anti-TNF drugs but with inadequate primary response, a non-TNF biologic agent was more effective in achieving a good or moderate disease activity response at 24 weeks than was the second anti-TNF medication.

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Tumor necrosis factor α (TNF- α) inhibitors have improved the quality of life for patients with rheumatoid arthritis who show insufficient response to methotrexate.¹ However, as many as one-third of patients^{2,3} have persistent disease activity and insufficient (inadequate) response to anti-TNF agents according to international recommendations.⁴ Therefore, alternatives are needed.

Switching to a non-TNF-targeted therapy can be an acceptable strategy, as was reported in 3 placebo-controlled trials.⁵⁻⁷ The most frequently used non-TNF biologics are abatacept, an inhibitor of T-cell costimulation; rituximab, a β -cell-depleting agent; and tocilizumab, an inhibitor of interleukin 6 (IL-6) receptor. Tofacitinib could also be an option⁸ but has not been approved in most European countries, including France. Cycling to a second anti-TNF agent after failure of a first anti-TNF agent is a reasonable alternative. The molecular structure of TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) and their affinity for membrane and soluble TNF- α differ. Etanercept targets TNF as well as lymphotoxin- α . In addition, loss of efficacy of monoclonal antibodies might result from the secretion of antidrug antibodies.⁹ Therefore, the lack of efficacy of one anti-TNF drug does not preclude the potential efficacy of another. Two randomized placebo-controlled trials reported that approximately half of patients with rheumatoid arthritis with insufficient response to a TNF- α inhibitor responded to a second anti-TNF drug.^{10,11}

Four observational studies compared a non-TNF biologic vs a second anti-TNF agent in patients with rheumatoid arthritis with insufficient response to a TNF- α inhibitor.¹²⁻¹⁵ However, no randomized controlled trial has compared the 2 strategies in such patients.

Therefore, the Rotation or Change (ROC) trial was designed to compare the efficacy of 2 therapeutic strategies in patients with rheumatoid arthritis after an initial anti-TNF agent failed to reduce their symptoms: a non-TNF-targeted biologic or a second anti-TNF agent.

Methods

Design

The ROC trial was a 52-week pragmatic, multicenter, open, parallel-group, randomized clinical trial with a superiority design. Patients with insufficient response to an anti-TNF drug were randomly assigned in a 1:1 ratio to receive a non-TNF-targeted biologic or a second anti-TNF agent. Patients were recruited from December 2009 to August 2012 (Trial Protocol Supplement 1).

Ethics

The trial was approved by the institutional review board of the Comité de Protection des Personnes-Est 1, Strasbourg, France. The study was conducted according to the current regulations of the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki. All patients gave written informed consent after receiving oral and written information about the trial.

Key Points

Question For patients with rheumatoid arthritis and an inadequate response to an anti-tumor necrosis factor (TNF) drug, is a non-TNF-targeted biologic drug more effective than a second anti-TNF drug?

Findings In this randomized clinical trial involving 300 adults, 69% of patients achieved an effective clinical response with a non-TNF biologic vs 52% of patients who took a second anti-TNF drug.

Meaning For patients with rheumatoid arthritis and an insufficient response to anti-TNF therapy, a non-TNF biologic agent may be more effective than a second anti-TNF drug.

Randomization

A computer-generated list (random permuted block design using block sizes of 2, 4, or 6, randomly selected with equal probability) was generated by an independent statistician. Concealed allocation of treatments involved a web-based system that confirmed eligibility criteria before issuing a treatment assignment.

Patients

From December 2009 to August 2012, patients who were at least 18 years old were recruited from 47 French clinical centers belonging to the Club des Rhumatismes et Inflammation (a section of the French Society of Rheumatology)-IMIDIATE Clinical Research Network. To meet the inclusion criteria patients needed to have (1) a diagnosis of rheumatoid arthritis according to the 1987 American College of Rheumatology criteria; (2) presence of erosions; (3) a disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) of 3.2 or more (DAS28-ESR is a composite score that ranges from 0-9.3 by taking into account the number of tender joints [range, 0-28], number of swollen joints [range, 0-28], patient global assessment of disease activity [numeric analog scale range, 0-10, with 0 representing the best and 10 the worst], and the ESR); (4) insufficient response to anti-TNF according to the physician, who usually considers the response to be insufficient (inadequate) with one or several of the following conditions: persistent tender and swollen joints, persistent disease activity according to patient global assessment, elevated levels of acute-phase reactants, and dependence on analgesics, nonsteroidal anti-inflammatory drugs or corticosteroids. International recommendations state that a DAS28-ESR score greater than 3.2 indicates insufficient control of disease activity and justifies changing the rheumatoid arthritis treatment⁴; (5) stable dose of oral corticosteroids of 15 mg/d or less of equivalent prednisone within 4 weeks before enrollment; (6) stable dose of synthetic disease-modifying antirheumatic drugs (DMARDs) within 4 weeks of enrollment; and (7) informed written consent.

The exclusion criteria were discontinuation of the first anti-TNF agent due to an adverse event only; previous treatment with 2 or more anti-TNF agents; previous treatment with abatacept, rituximab, or tocilizumab; contraindication to all anti-TNF agents and other biologics (ongoing infection; history of

recent cancer <5 years before enrollment, except for cured non-melanoma skin cancer); pregnancy; and breastfeeding.

Interventions

Patients were randomly assigned to receive either a non-TNF biologic (ie, abatacept, rituximab, or tocilizumab) or a second anti-TNF agent (adalimumab, certolizumab, etanercept, infliximab, or golimumab). The choice of the biologic prescribed within each randomized group was left to the treating clinician. The initial dose and frequency of treatment were defined for each drug as follows. In the non-TNF group, the biologic could be abatacept (500 to 1000 mg intravenously, dosed according to the patient's weight, every 14 days until week 4 and once monthly thereafter), rituximab (1-g infusion intravenously followed by another 2 weeks later), or tocilizumab (8 mg/kg monthly, intravenously).

Patients receiving an anti-TNF that differed from their initial treatment could receive adalimumab (40 mg subcutaneously every 14 days), certolizumab (400 mg subcutaneously every 14 days until week 4, then 200 mg every 14 days), etanercept (50 mg subcutaneously every 7 days), or infliximab (3 mg/kg intravenously initially, with the possibility of ascending doses at weeks 2 and 6 and every 8 weeks thereafter). A fifth anti-TNF agent, golimumab, was not available at the time of the study. According to the marketing authorization, the choice of subsequent dose and frequency adjustment of the treatment was left to the treating physician in both groups. The assigned treatment had to be continued for 12 months within the study protocol but could be discontinued for inefficacy, for adverse events, or by patient choice. Dose adjustments of oral corticosteroids and glucocorticoid intra-articular injections were allowed for both groups.

End Points

The primary end point was the proportion at week 24 of patients with a good or moderate European League Against Rheumatism (EULAR) response.¹⁶ A good EULAR response is defined as a decrease in DAS28-ESR of more than 1.2 points, resulting in a score of 3.2 or less. A moderate EULAR response is defined as a decrease of more than 0.6 and resulting in a score of 5.1 points or lower.¹⁶ Twenty-four weeks was chosen for the primary end point to ensure that changes in disease activity were due to the initially assigned biologic treatment. Because clinicians evaluate therapeutic response and safety within 24 weeks of drug initiation and change treatments in case of insufficient response or serious adverse event, the study duration was 52 weeks to allow the evaluation of longer-term end points, such as therapeutic maintenance.

Prespecified secondary end points included the EULAR response at weeks 12 and 52; DAS28-ESR at weeks 12, 24, and 52; low disease activity (DAS28-ESR<3.2) and remission (DAS28-ESR<2.6) at weeks 12, 24, and 52; mean oral corticosteroid use at weeks 24 and 52; therapeutic maintenance (defined as the proportion of patients who did not discontinue the assigned biologic treatment) at weeks 24 and 52; and health assessment questionnaire¹⁷ (HAQ) score (range, 0-3, with 0 representing the best and 3 the worst outcomes) at weeks 12, 24, and 52. Structural radiographic progression,

initially listed in the protocol, was not available for half of the recruited patients and was not analyzed or reported herein.

Safety was evaluated throughout the study. Serious adverse events were defined as life-threatening or resulting in death, hospitalization, or persistent disability. Serious infections were defined as requiring intravenous antibiotics, or resulting in hospitalization, or in death.

Statistical Analysis

Among patients with insufficient response to a TNF- α inhibitor, the EULAR response was approximately 50% in one placebo-controlled study of a second anti-TNF (golimumab)¹⁰ and 66% in 2 placebo-controlled studies of rituximab⁵ and tocilizumab.⁶ Therefore, we assumed that 50% of patients with insufficient response to anti-TNF therapy would respond to a second anti-TNF agent and that 66% would respond to a non-TNF-targeted biologic. We hypothesized an absolute increase of 16% in EULAR response (ie, odds ratio [OR], 1.94) in the non-TNF-targeted group, with an α risk of .05 and a β risk of .20. This hypothesis required randomizing 300 patients (150 patients per group).

Data were analyzed on an intention-to-treat basis. In case of missing data for the primary end point, we decided, before the study data were made available to the statistical team, to use multiple imputation by chained equation with $m = 50$ imputations instead of a last-observation-carried-forward approach, as specified in the initial protocol. Since the protocol was written, multiple imputation has become widely accepted as a vastly superior method to the last-observation-carried-forward approach.¹⁸ Given the low number of missing data and the fact that they were well balanced, secondary end points were not imputed. For mixed models of longitudinal data, multiple imputation has been shown to not improve the results and a mixed model for imputed data could sometimes lead to unstable results.¹⁹ During follow-up, patients who received any biologic agent different from the treatment initially assigned, for any reason, were continued in the study and were considered nonresponders.

Categorical variables are described with frequencies and percentages and quantitative variables with mean (SD) or, for data that did not have normal distribution, median (interquartile range [IQR] percentile). Mixed logistic regression models were used to assess differences between the 2 groups for categorical variables at weeks 12, 24, and 52 with a random effect on each center to account for the potential correlation between centers. To assess mean differences between groups at weeks 12, 24, and 52, we used a constrained longitudinal analysis with random effects on patient and center. In this model, both the baseline and postbaseline values were modeled as dependent variables and the true baseline means were constrained to be the same for the 2 treatment groups. Hence, this analysis provides an adjustment for the observed baseline difference in estimating the treatment. If the hypotheses for the mixed model were not satisfied, nonparametric analysis was used; differences between week 0 and the week of interest between the 2 groups were compared by Wilcoxon test.

A comparison of the primary end point between the 3 biologics in the non-TNF-targeted group was also performed.

To handle the fact that the choice of the biologic prescribed was left to the clinician (and not randomized), inverse probability weighting was used; each observation was weighted by the inverse of the predicted probability of receiving the biologic prescribed (abatacept, rituximab, or tocilizumab) for each patient. Therapeutic maintenance was analyzed by Kaplan-Meier curves and compared with a marginal Cox model to take into account the center effect. All statistical tests were 2-sided with P values $<.05$ considered statistically significant. Statistical analysis involved use of R 3.0.1 (<http://www.R-project.org>, the R Foundation for Statistical Computing).

Results

Baseline Characteristics of Patients

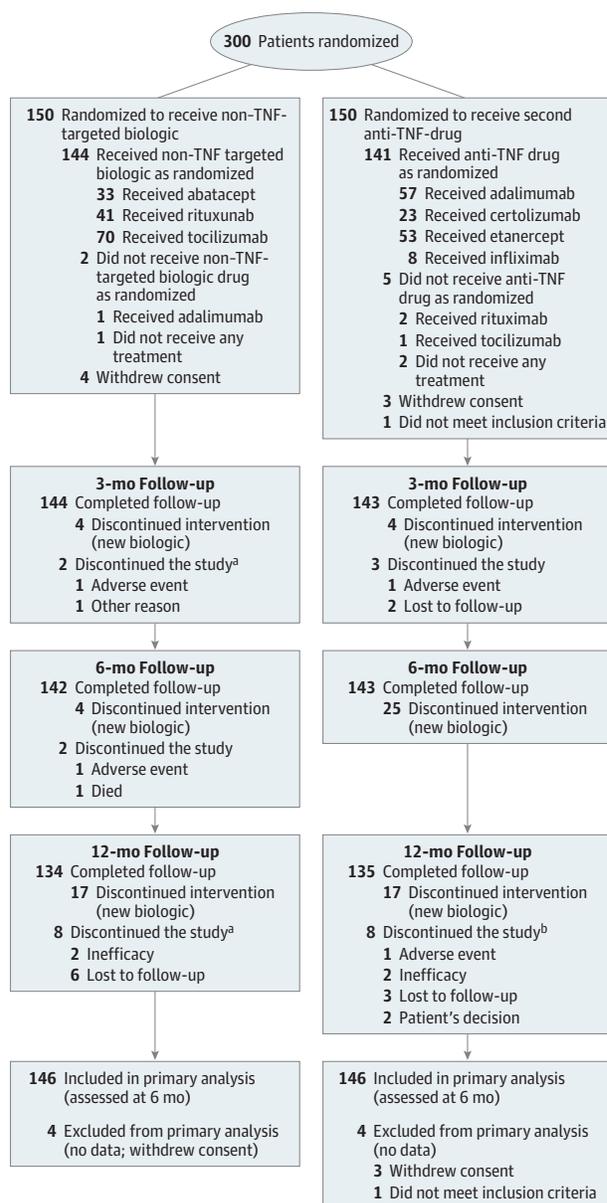
From December 2009 to August 2012, 300 patients (150 in each group) were randomized; 7 patients withdrew their consent for use of data and 1 patient did not meet inclusion criteria and was wrongly included. The final follow-up testing was in August 2013. On-site monitoring of all patients in all 47 centers was completed in February 2015. Overall, data for 146 patients in each group could be analyzed; 144 and 141 patients received the allocated intervention in the non-TNF-targeted and second anti-TNF groups, respectively (Figure 1). The 2 groups were not different in demographic and disease characteristics, such as sex, age, disease duration, rheumatoid factor, and anticyclic citrullinated peptide positivity, number of previous synthetic DMARDs taken, baseline DAS28-ESR, and HAQ score (Table 1).

Treatments Received

In the non-TNF group, 33 of 146 patients (23%) received abatacept; 41 (28%) rituximab, and 70 (48%), tocilizumab. Two patients (1%) did not receive the intervention as allocated; 1 patient received adalimumab and 1 patient received no treatment. In the second anti-TNF group, 57 of 146 patients (39%) received adalimumab; 23 (16%), certolizumab, 53 (36%), etanercept; and 8 (5%), infliximab. Five patients (3%) did not receive the intervention as allocated; 2 patients received rituximab, 1 patient received tocilizumab, and 2 patients received no treatment. At enrollment, 112 patients (77%) in each group received a concomitant synthetic DMARD: 95 patients (65%) in the non-TNF group and 88 (60%) in the second anti-TNF group concomitantly received methotrexate; and 80 (55%) in the non-TNF group received a mean (SD) dose of 7.3 (2.9) mg/d and 75 (51%) in the second anti-TNF group received 7.2 (3.1) mg/d of oral corticosteroids.

At week 24, 104 of 140 patients (74%) in the non-TNF group and 112 of 141 patients (79%) in the second anti-TNF group concomitantly received a synthetic DMARD, including 89 (63.6%) in the non-TNF group and 88 (62.4%) in the second anti-TNF group who received methotrexate. At week 24, 79 of 142 patients (56%) in the non-TNF group concomitantly received a mean (SD) dose of 6.81 (4.26) mg/d of prednisone and 79 of 141 patients (56%) in the second anti-TNF group 6.69 (2.93) mg/d.

Figure 1. Flow Diagram of Progress Through Phases of the Randomized Trial Comparing a Non-Tumor-Necrosis Factor (TNF)-Targeted Biologic or a Second Anti-TNF Agent Among Patients With Rheumatoid Arthritis and an Insufficient Response to a First Anti-TNF Agent



The number of patients screened for eligibility, number excluded, and reasons for exclusion are not available. Patients who during follow-up received any biologic agent different from the treatment initially assigned for any reason continued to be followed up and were considered nonresponders. TNF indicates tumor necrosis factor.

^a One patient at 3 months and 1 patient at 12 months who discontinued the study discontinued the intervention (new biologic).

^b Two patients who discontinued the study discontinued the intervention (new biologic).

At week 52, 98 of 132 patients (74%) in the non-TNF group concomitantly received a synthetic DMARD, including 84 (64%) who received methotrexate, and 106 of 130

Table 1. Baseline Characteristics of Patients Randomized to Receive a Non-TNF Biologic or a Second Anti-TNF Drug

Characteristics	Non-TNF Biologic (n = 146)	Second Anti-TNF Drug (n = 146)	Total (N = 292)
Women, No. (%)	120 (82)	123 (84)	243 (83)
Age, mean (SD), y	58.2 (11.1)	55.9 (13.1)	57.1 (12.2)
Disease duration, median (IQR), y	10.0 (4.0-17.8)	11.0 (4.0-19.0)	10.0 (4.0-18.0)
Rheumatoid factor positive, No. (%)	121 (85)	111 (77)	232 (81)
Anti-CCP positive, No. (%)	115 (83)	112 (80)	227 (82)
No. of previous synthetic DMARDs, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
First anti-TNF prescribed, No. (%)			
Adalimumab	40 (27)	45 (31)	85 (29)
Etanercept	80 (55)	77 (53)	157 (54)
Infliximab	21 (14)	20 (14)	41 (14)
Certolizumab	2 (1)	3 (2)	5 (2)
Golimumab	3 (2)	0	3 (1)
Missing data	0	1 (1)	1 (0.3)
Duration of treatment with first anti-TNF, median (IQR), mo	19.5 (6.2-53.0)	24.0 (9.0-51.8)	20.5 (7.0-53.0)
Cause for discontinuation of first anti-TNF, No. (%)			
Primary nonresponders ^a	24 (18)	20 (14)	44 (16)
Secondary nonresponders ^b	102 (75)	110 (78)	222 (76)
Inefficacy and adverse event ^c	10 (7)	11 (8)	21 (8)
No. of joints (28), median (IQR)			
Tender	8.0 (4.0-12.0)	6.0 (3.0-10.0)	7.0 (4.0-11.0)
Swollen	5.0 (3.0-8.0)	4.0(2.2-7.0)	5.0 (3.0-7.0)
Patient global assessment of disease activity, NAS (0-10), mean (SD)	6.2 (1.9)	6.3 (1.7)	6.2 (1.8)
ESR, median (IQR), mm	27.0 (11.0-45.0)	22.0 (10.0-44.0)	24.0 (11.0-45.0)
CRP level, median (IQR), mg/L	7.7 (3.0-26.3)	8.8 (4.0-20.0)	8.1 (4.0-22.0)
DAS28, mean (SD)			
ESR ^d	5.2 (1.2)	5.0 (1.1)	5.1 (1.1)
CRP ^e	4.8 (1.1)	4.7 (0.9)	4.7 (1.0)
Health assessment questionnaire, mean (SD) ^f	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
Concomitant treatment with a synthetic DMARD, No. (%)	112 (77)	112 (77)	224 (77)
Methotrexate	95 (65)	88 (60)	183 (63)
Concomitant treatment with oral corticosteroids, No. (%)	80 (55)	75 (51)	155 (53)
Dosage of corticosteroids or prednisone, mean (SD), mg/d	7.3 (2.9)	7.2 (3.1)	7.3 (3.0)

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; NAS, numeric analog scale; TNF, tumor necrosis factor.

^a Primary nonresponders are those with both initial and persistent absence of response to first anti-TNF.

^b Secondary nonresponders are those with an initial response but later lose the response to the first anti-TNF.

^c Discontinuation of the first anti-TNF agent related to the association of inefficacy and adverse events.

^d Represents a composite score of DAS in 28 joints and ESR (See the Methods section for the DAS28-ESR score ranges).

^e Represents a composite score of DAS28 and CRP level (See the Methods section for the DAS28 score ranges).

^f A patient-related score of functional status (disability) from 0 (best) to 3 (worst).

patients (82%) in the second anti-TNF group, concomitantly received a synthetic DMARD, including 84 (65%) who received methotrexate. At week 52, 67 of 127 patients (53%) in the non-TNF group concomitantly received prednisone at a mean (SD) dosage of 7.83 (6.99) mg/d and 73 of 131 patients (56%) in the second anti-TNF group concomitantly received 7.23 (4.45) mg/d.

All changes in conventional DMARDs and oral corticosteroids throughout the study are summarized in eTable in Supplement 2.

Efficacy

At week 24, 101 of 146 patients (69%) in the non-TNF group and 76 (52%) in the second anti-TNF group achieved a good or moderate EULAR response, the primary end point of the trial,

with 39% with a good response and 30% with a moderate response in the non-TNF group and 21% with a good response and 31% with a moderate response in the second anti-TNF group (OR, 2.12; 95% CI, 1.31-3.46; $P = .003$; absolute difference, 17.6%; 95% CI, 6.4-28.8, without imputation of missing data; OR, 2.06; 95% CI, 1.27-3.37; $P = .004$; absolute difference, 17.2%; 95% CI, 6.2%-28.2%, with imputation of missing data (4 in each group). At week 12, 64% of patients in the non-TNF vs 48% of patients in the second anti-TNF group showed good or moderate EULAR response (good response, 28% vs 13%; moderate response, 37% vs 35%, respectively; OR, 2.01; 95% CI, 1.23-3.32; $P = .005$; absolute difference, 16.4; 95% CI, 4.8-28.1) (Table 2). At week 52, 60% of patients in the non-TNF group vs 43% in the second anti-TNF group showed good or moderate EULAR response (good response, 38% vs 21%;

Table 2. Response Criteria in the Non-TNF Biologic and Second Anti-TNF Groups

Week of Follow-up	Non-TNF Biologic Group (n = 146)		Second Anti-TNF Group (n = 146)		Absolute Difference (95% CI), %	OR (95% CI)	P Value
	No.	No. (%)	No.	No. (%)			
EULAR good or moderate response^a							
12	137	88 (64)	136	65 (48)	16.4 (4.8 to 28.1)	2.01 (1.23 to 3.32)	.005
24	142	99 (70)	142	74 (52)	17.6 (6.4 to 28.8)	2.12 (1.31 to 3.46)	.003
24 (imputed) ^b	146	101 (69)	146	76 (52)	17.2 (6.2 to 28.2)	2.06 (1.27 to 3.37)	.004
52	131	78 (60)	134	57 (43)	17.0 (5.1 to 28.9)	1.99 (1.22 to 3.25)	.006
Low Disease Activity (DAS28-ESR <3.2)							
12	137	42 (31)	134	31 (23)	7.7 (-2.8 to 18.2)	1.48 (0.86 to 2.57)	.16
24	139	62 (45)	140	39 (28)	16.7 (5.6 to 27.9)	2.09 (1.27 to 3.43)	.004
52	130	53 (41)	133	31 (23)	17.5 (6.4 to 28.6)	2.26 (1.33 to 3.86)	.003
DAS28 Remission (DAS28-ESR <2.6)							
12	137	28 (20)	135	13 (10)	10.8 (2.4 to 19.2)	2.41 (1.19 to 4.89)	.02
24	139	38 (27)	140	26 (19)	8.7 (-1.1 to 18.6)	1.65 (0.94 to 2.91)	.08
52	130	35 (27)	133	18 (14)	13.4 (3.8 to 23.0)	2.36 (1.25 to 4.43)	.008

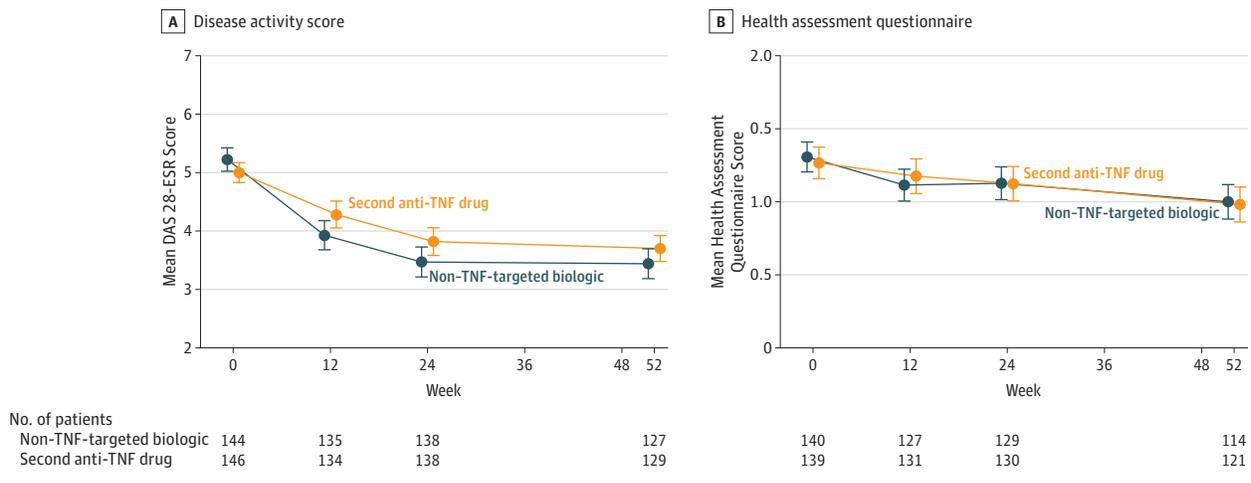
Abbreviations: DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; TNF, tumor necrosis factor.

^a A good EULAR response is a decrease in DAS28-ESR by more than 1.2 points and resulting in a DAS28 of 3.2 or less. A moderate EULAR response is a decrease in DAS-ESR of more than 0.6 points and resulting in a DAS28

of 5.1 or less. (See the Methods section for definition of DAS28-ESR.) We imputed missing values only when indicated for the primary outcome. All the other results presented in the Table and in the manuscript consistently use data for completers, without imputation.

^b Primary outcome analysis.

Figure 2. Evolution of Disease Activity Score in 28 Joints-Erythrocyte Sedimentation Rate (DAS28-ESR) and Health Assessment Questionnaire Score in Non-Tumor-Necrosis Factor (TNF) and Second Anti-TNF Groups



The analytic sample sizes shown at baseline in Figure 2 differ from the total number randomized because of missing data. They also differ for DAS28-ESR from the numbers included in the primary analysis (European League Against Rheumatism response) because in the primary analysis, some of the patients with missing data were considered nonresponders because they received during the follow-up a biologic agent different from the treatment initially assigned, as specified in the statistical analysis section. Constrained longitudinal data analyses were used for between-group comparisons for

DAS28-ESR and HAQ. For DAS-28-ESR, the 12-week P value was .008; 24-week, P = .004; and 52-week, P = .01; for HAQ, the 12-week P value was .09; 24-week, P = .44; and 52-week, P = .75. Data markers represent the mean and error bars 95% CIs. See the Methods section for a definition of disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) and range and the Health Assessment Questionnaire (HAQ) definition and score range.

moderate response, 22% vs 22%, respectively; OR, 1.99; 95% CI, 1.22-3.25; P = .006; absolute difference, 17.0; 95% CI, 5.1-28.9) (Table 2).

Overall the mean DAS28-ESR change from baseline was greater for patients in the non-TNF group than for patients in the second anti-TNF group with a week-12 mean difference of

-0.40 (95% CI, -0.70 to -0.10; P = .008); 24-week mean difference of -0.43 (95% CI, -0.72 to -0.14; P = .004), and week-52 mean difference of -0.38 (95% CI, -0.69 to -0.08; P = .01) (Figure 2).

At week 24, 62 of 139 patients (45%) in the non-TNF group vs 39 of 140 patients (28%) in the second anti-TNF group

showed low disease activity with a DAS28-ESR of less than 3.2 (OR, 2.09; 95% CI, 1.27-3.43; $P = .004$). At week 52, 53 of 130 patients (41%) in the non-TNF group vs 31 of 133 patients (23%) in the anti-TNF group showed low disease activity (OR, 2.26; 95% CI, 1.33-3.86; $P = .003$).

At week 12, 28 of 137 patients (20%) in the non-TNF group vs 13 patients of 135 (10%) in the second anti-TNF group showed DAS28-ESR remission with a score of 2.6 or less (OR, 2.41; 95% CI, 1.19; 4.89; $P = .02$). At week 52, 35 of 130 patients (27%) in the non-TNF group vs 18 of 133 (14%) in the second anti-TNF group had a DAS28-ESR remission (OR, 2.36; 95% CI, 1.25-4.43; $P = .008$) (Table 2).

The health assessment questionnaire scores did not differ between the 2 groups: the mean difference adjusted for baseline difference at week 12 was -0.09 (95% CI, -0.20 to 0.01 ; $P = .09$); week 24, -0.04 (95% CI, -0.15 to 0.07 ; $P = .44$), and week 52, -0.02 (95% CI, -0.13 to 0.09 ; $P = .75$).

At week 24, the median change from baseline in erythrocyte sediment rate was -10 (interquartile range [IQR], -28 to -1) in the non-TNF group vs -2 (IQR, -13 to 3) in the second anti-TNF group ($P < .001$). The median change in C-reactive protein (CRP) level was -3 (IQR, -18 to 0) in the non-TNF group vs -2 (IQR, -10 to -1) in the second anti-TNF group ($P = .06$).

The proportion of EULAR good and moderate responders at week 24 did not significantly differ with abatacept, rituximab, and tocilizumab treatment: 67% (22 of 33) of patients, 61% (25 of 41) of patients, and 80% (56 of 70) of patients, respectively (OR tocilizumab vs abatacept, 1.78; 95% CI, 0.59-5.37; $P = .30$; OR tocilizumab vs rituximab, 2.47; 95% CI, 0.92 to 6.62; $P = .07$).

Twenty-seven patients (18%) in the non-TNF group and 48 (33%) in the anti-TNF group (OR, 0.46; 95% CI, 0.27 to 0.79) started a new biologic. In the non-TNF group 14 patients did so because of inefficacy; 12, adverse events, and 1, unknown reasons. In the second anti-TNF group, 40 patients did so because of inefficacy; 6, adverse events; 1, desire to become pregnant; and 1, unknown reasons. At the time of discontinuation, the mean (SD) DAS28-ESR was 4.54 (1.90) in the non-TNF group and 5.25 (1.17) in second anti-TNF, 2 in each group had missing data. The therapeutic maintenance rate, defined as the proportion of patients who continued the biologic treatment as initially assigned, was significantly higher at weeks 24 and 52 in the non-TNF group than in the second anti-TNF group (eFigure in Supplement 2). The mean change from baseline to weeks 24 and 52 in the level of prednisone doses were not significantly different between patients between treatment groups. The mean difference in the level of prednisone doses at week 24 was -0.16 (95% CI, -1.11 to 0.79 ; $P = .74$) and was -0.02 (95% CI, -1.01 to 0.97 ; $P = .97$) at week 52.

Safety

Sixteen patients (11%) in the non-TNF experienced 18 serious adverse events, and 8 patients (5%) in the second anti-TNF group experienced 13 events ($P = .10$). Seven patients (5%) in each group developed serious infections (Table 3). One case of tuberculosis occurred in the second anti-TNF group. Six car-

Table 3. Serious Adverse Events by Treatment Groups

	No./Total (%)	
	Non-TNF Biologic	Second Anti-TNF Drug
≥ 1 Serious adverse events	16/146 (11)	8/146 (5)
No. of serious adverse events		
1	14/146 (10)	4/146 (3)
2	2/146 (1)	3/146 (2)
3	0/146	1/146 (0.7)
Total	18	13
Detail of Serious Adverse Events		
Deaths	1/18 (6)	0/13
Cancer	1/18 (6)	0/13
Lung adenocarcinoma	1/18 (6)	0
Serious infections	7/18 (39)	10/13 (77)
Bronchopulmonary	2/18 (11)	3/13 (23)
Ear, nose, throat	0/18	3/13 (23)
Cutaneous	3/18 (17)	0/13
Osteoarticular (including 1 tuberculosis)	0/18	2/13 (15)
Digestive	0/18	2/13 (15)
Urinary	1/18 (6)	0/13
Articular	1/18 (6)	0/13
Cardiovascular events	6/18 (33)	1/13 (8)
Tachycardia	2/18 (11)	0/13
Strokes	2/18 (11)	0/13
Limb ischemia	2/18 (11)	0/13
Hypertensive crisis	0/18	1/13 (8)
Other events	3/18 (16)	2/13 (15)
Neutropenia	1/18 (6)	0/13
Pruritus	1/18 (6)	0/13
Anorexia	1/18 (6)	0/13
Leukocytic vasculitis	0	1/13 (8)
Anemia	0	1/13 (8)

Abbreviation: TNF, tumor necrosis factor.

diovascular events occurred in the non-TNF group: tachycardia occurred in 1 patient receiving abatacept and 1 receiving tocilizumab; stroke, in 1 patient receiving rituximab and 1 receiving tocilizumab; and 2 episodes of limb ischemia, in 1 patient receiving rituximab. One cardiovascular event occurred in the second anti-TNF group, hypertensive crisis in a patient receiving certolizumab. One patient in the non-TNF group receiving abatacept died of complications stemming from a dissection of an aortic aneurysm.

Discussion

This pragmatic, multicenter, open-label, parallel-group, randomized clinical trial addressed the optimal therapeutic strategy for patients with rheumatoid arthritis and insufficient response to a first anti-TNF drug. The proportion of EULAR response at week 24, the primary end point of the study, was greater among those treated with a non-TNF-targeted biologic than those treated with a second anti-TNF biologic.

The results of the ROC study demonstrate in a pragmatic clinical trial that approximately 50% of patients with insufficient response to a TNF- α inhibitor might respond to a second anti-TNF agent. However, a therapeutic response was more frequent with non-TNF-targeted biologics. In addition to the superiority of the non-TNF treatment for the primary outcome at week 24, the non-TNF treatment was associated with a better EULAR response than a second anti-TNF drug at weeks 12 and 52. Consistent with these findings, the DAS28-ESR and proportion of patients achieving low disease activity status were greater at months 6 and 12 than in the non-TNF group in the second anti-TNF group.

Tocilizumab is the only drug with a direct effect on CRP levels due to inhibition of IL-6, independent of clinical response. Of note, the 2 groups did not differ in changes in their CRP levels. Thus, the differences in the primary and most of the secondary outcomes were not likely to be due to the biological effect of tocilizumab.

The main strength of the study is its pragmatic design. Physicians commonly choose one drug rather than another for multiple reasons (habits, characteristics of patients). We chose to compare strategies instead of individual drug prescriptions because this issue corresponds to the therapeutic question clinicians face in daily practice. Therefore, the choice of the biologic within each randomized group and the concomitant synthetic DMARDs was left to the clinicians.

The study also has several limitations. First, a primary limitation is the lack of blinding of participants. However, in this trial including multiple biologics, a blinded design could not

be easily performed given the number of different placebos that would have been needed. Second, some biologic agents were not allowed (eg, golimumab because this drug was not marketed in France at the time of enrollment in the study or anakinra because this drug is less frequently used than other biologics to treat rheumatoid arthritis). Third, the study was not powered to compare the safety profile of non-TNF-targeted drugs and anti-TNF agents or to detect differences between individual drugs. Therefore, no conclusions can be made regarding individual drug efficacy. Fourth, approximately 40% of patients in each group did not receive concomitant treatment with methotrexate. Methotrexate improves the clinical efficacy of most biologics, with tocilizumab perhaps the least likely to benefit from its concomitant use. Fifth, treatment adherence might have differed between the 2 groups because all non-TNF drugs were given as infusions under observation, whereas most of the anti-TNF drugs (except infliximab) were self-injected by patients.

Conclusions

Among patients with rheumatoid arthritis previously treated with anti-TNF drugs but considered for a second medication due to inadequate primary response, a non-TNF biologic agent was more effective in achieving a good or moderate disease activity response at 24 weeks. However, a second anti-TNF drug to treat these patients was often effective in producing a clinical improvement.

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