Current Tumor Necrosis Factor-α Inhibitor Use Is Associated with a Higher Probability of Remissions in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine if current tumor necrosis factor-α (TNF-α) inhibitor use is associated with a higher probability of remission than non-use in patients with rheumatoid arthritis (RA).

Methods. Clinical and demographic data were collected from 322 patients with RA during regularly scheduled clinic visits. Current and past medications were recorded. Disease activity status (remission or not) was determined using American College of Rheumatology preliminary criteria for clinical remission of RA. A logistic regression analysis was used to calculate crude and adjusted odds ratios (OR) for remission for current TNF-α inhibitor users versus non-users. Multivariate analysis included age, gender, race, disease duration, use of nonsteroidal antiinflammatory drugs (NSAID), prednisone dosage, and numbers of previously used disease modifying antirheumatic drugs (DMARD).

Results. Of the 111 patients enrolled in the study who were users of TNF-α inhibitors, 25.2% were found to be in clinical remission. Of the 211 patients who were non-users, 14.7% were in clinical remission. The unadjusted OR for remission in TNF-α inhibitor users was 1.96 (95% confidence interval, CI: 1.10 to 3.48). The adjusted OR was 2.74 (95% CI: 1.40 to 5.34).

Conclusion. Cross-sectional observations from an outpatient arthritis clinic found a significantly higher remission rate in patients with RA taking a TNF-α inhibitor compared to non-users. (J Rheumatol 2005;32:1662–5)

Key Indexing Terms:
TNF-α INHIBITOR RHEUMATOID ARTHRITIS REMISSION RATES
CROSS-SECTIONAL STUDY TREATMENT

Tumor necrosis factor-α (TNF-α) inhibitors have produced dramatic clinical responses for patients with rheumatoid arthritis (RA) in clinical trials[1-4]. However, few trials have indicated how many of these patients satisfied American College of Rheumatology (ACR) preliminary criteria for clinical remission[5]. In the TEMPO trial, when using the disease activity score (DAS) of < 1.6 as the remission criterion[6], 35% of patients taking the combination of methotrexate (MTX) and etanercept were in remission at 52 weeks, compared to 16% and 13% of those on etanercept or MTX alone, respectively. Nonetheless, there are few data comparing TNF-α inhibitors with other traditional disease modifying antirheumatic drugs (DMARD) on the frequency of remission in patients with RA.

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We designed a cross-sectional study to estimate the frequency of remission in patients with RA treated at outpatient arthritis clinics at an academic medical center. We also wanted to determine if current TNF-α inhibitor use as a class of DMARD is associated with a higher probability of remission than non-use.

MATERIALS AND METHODS

Patients and data collection. Names of patients with ICD codes of 714.0 (RA) and 714.9 (inflammatory polyarthropathy) one year prior to February 2003 at Arthritis Clinics of an academic medical center in Chicago were obtained through computer registry. Patient schedules of physicians at this clinic from February 2003 to September 2003 were screened by the research assistant before the clinic started and patients from the above list were identified. The research assistant then asked the physician to verify the diagnosis of RA for identified patients at the time of clinic visit. The treating physician then obtained verbal consent from the patient and verified the diagnosis of RA, and the research assistant asked patients to read and sign the written informed consent and HIPAA agreement approved by the local Institutional Review Board.

Charts of all consenting patients were reviewed to determine if they satisfied the 1987 ACR classification criteria for RA[7]. Presence of fatigue and duration of morning stiffness were obtained by the research assistant by interview, and joint examination was performed by the physician; erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) was ordered if clinically indicated. Patients were determined to be in remission or not according to ACR preliminary criteria for clinical remission[5]. The criteria were (1) morning stiffness < 15 minutes; (2) no fatigue; (3) no joint pain

(by history); (4) no joint tenderness or pain on motion; (5) no soft tissue swelling in joints or tendon sheaths; (6) ESR < 30 (female) or < 20 (male). To satisfy a classification of remission, a patient must have 5 or more of the 6 criteria for at least 2 months and must not have any of the following clinical manifestations of active disease: vasculitis, pericarditis, pleuritis, myositis, weight loss, or fever attributable to RA. Since this was a cross-sectional study, the ACR criteria requirement of 2 months' duration for remission was not ascertained. A normal CRP could be substituted for normal ESR when the ESR was not available.

The following demographic and clinical information was obtained by patient interviews and review of patients' medical records: age, gender, race, age at onset and duration of RA, current DMARD regimen, number of previously used DMARD, current use of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and dose of corticosteroids. Patients were divided into 4 groups according to DMARD usage: (1) TNF-α inhibitor alone; (2) TNF-α inhibitor and concurrently one or several traditional DMARD; (3) one or several traditional DMARD but no TNF-α inhibitors; and (4) no TNF-α inhibitors or traditional DMARD.

There were no patients in remission who had clinical manifestations of vasculitis, pericarditis, pleuritis, myositis, weight loss, or fever.

Statistical analysis. The probability of remission in TNF-α inhibitor users was compared with that in non-users using logistic regression, with calculation of odds ratios (OR) and corresponding 95% confidence intervals (CI). Demographic and other characteristics were also compared between those in remission and those not in remission and in users and non-users of TNF-α inhibitors to select possible confounders for inclusion in additional multiple logistic regression analyses. Variables with a p value of 0.20 or less in either of these comparisons were included in a multiple logistic model along with age and gender. Variables that met this criterion were age, race, use of NSAID, prednisone dosage, disease duration, and number of previously used DMARD. Age at diagnosis also met this criterion, but age at diagnosis plus disease duration is equal to current age, and thus only 2 of these 3 variables can be included in any model of analysis.

RESULTS

Demographics and clinical information of patients with RA. Fourteen hundred and fifty-six patients were identified by the ICD codes 714.0 and 714.9. Three hundred and thirty-eight patients had RA and were asked to participate in this study by treating physicians at this clinic during the recruitment period. Seven patients declined, leaving 331 patients who consented to participate in the study. Age at onset of RA and disease duration for 9 of these 331 patients could not be ascertained. All other clinical variables were available for the remaining 322 patients except presence of rheumatoid factor (RF) and rheumatoid nodules. Two hundred and sixty-eight patients were women (83.2%) and 54 were men (16.8%); average age (range) was 56 years (23-87); average age at disease onset was 44 years (6-86); average disease duration was 11.7 years (0-40.8). Two hundred and sixteen patients (67.1%) were Caucasian and 106 (32.9%) were non-Caucasian, 232 (72.1%) used NSAID, 173 (53.7%) used MTX, and 107 (33.2%) used prednisone. Positive RF was present in 182 of 254 patients (72%) and rheumatoid nodules in 57 of 100 patients (57%). Six percent of our study population had arthritis for 1 year or less and 10% for 2 years or less.

Comparison of clinical variables between TNF-α inhibitor users and non-users. Demographic and clinical variables were compared between the TNF-α inhibitor users and non-users (Table 1). There were no significant differences between groups for gender, frequency of use of NSAID, MTX, prednisone, or dosage of prednisone. However, TNF-α inhibitor users appeared to be younger (4.9 yrs), had a younger age at disease onset (8.2 yrs), had a longer duration of RA (3.3 yrs), and previously used a higher number of DMARD (1.0). Caucasians were more likely to be using TNF-α inhibitors.

Comparison of clinical variables between patients in remission and not in remission. There were no statistically or clinically significant differences in gender, age, age at onset of RA, duration of RA, frequency of use of NSAID, MTX, or prednisone (Table 2). However, patients in remission had used TNF-α inhibitors more frequently, used prednisone at a lower dosage, and had a smaller number of previously used DMARD. Caucasians were more likely to be in remission.

Table 1. Demographics and clinical variables for patients receiving TNF-α inhibitors compared to non-users. Results are expressed as mean ± standard deviation unless otherwise noted.

	TNF-α Inhibitors Users, n = 111	TNF-α Inhibitors Non-users, n = 211	p
Female, %	82.9	83.4	0.90
Age, yrs	52.6 ± 12.4	57.5 ± 14.3	0.002
Age at onset of RA, yrs	38.7 ± 12.1	46.9 ± 14.6	< 0.001
Caucasian, %	76.6	62.1	0.009
Duration of RA, yrs	13.8 ± 10.0	10.5 ± 8.3	0.003
Use of NSAID, %	69.4	73.5	0.44
Use of methotrexate, %	55.0	53.1	0.75
Use of prednisone, %	37.8	30.8	0.20
Average dose of prednisone, mg/day*	3.1 ± 6.7	1.9 ± 3.6	0.096
No. of previously used DMARD	2.6 ± 1.8	1.6 ± 1.8	< 0.001

* Patients not taking prednisone were counted as 0 mg/day.

Table 2. Demographics and clinical variables for patients in remission and not in remission.

	In Remission n = 59	Not in Remission n = 263	p
Female, %	79.7	84.0	0.42
Age, yrs	54.9 ± 13.9	56.0 ± 13.9	0.61
Age at onset of RA, yrs	44.7 ± 13.9	44.0 ± 14.4	0.71
Caucasian, %	81.4	63.9	0.01
Duration of RA, yrs	10.2 ± 8.7	12.0 ± 9.1	0.17
Use of TNF-α inhibitors, %	25.2	14.7	0.020
Use of NSAID, %	64.4	73.8	0.15
Use of methotrexate, %	54.2	53.6	0.93
Use of prednisone, %	28.8	34.2	0.43
Average dose of prednisone, mg/day†	1.4 ± 2.5	2.6 ± 5.3	0.013
No. of previously used DMARD	1.4 ± 1.4	2.1 ± 1.9	0.002

Remission probabilities. Fifty-nine of the 322 patients were in clinical remission by ACR 1981 criteria, with an overall remission rate of 18.3%. Those receiving TNF-α inhibitors had a remission rate of 25.2% compared to 14.7% for non-users (Table 3) with an OR of 1.96 (95% CI: 1.10 to 3.48) in favor of TNF-α inhibitor users. The remission probabilities were also calculated in 4 subgroups: 29% in users of TNF-α inhibitors alone, 23.8% in users of TNF-α inhibitors in combination with other traditional DMARD, 15.1% in users of one or several other traditional DMARD, and 12.5% in those not receiving either TNF-α inhibitors or DMARD (Table 3). After adjustment for age, gender, race, disease duration, use of NSAID, prednisone dosage, and number of previously used DMARD (all of these had a p value < 0.2 in Table 1 and/or Table 2 except gender), the OR increased to 2.74 (95% CI: 1.40 to 5.34) for users of TNF-α inhibitors (Table 4).

DISCUSSION

Our cross-sectional study of patients with longstanding RA (average disease duration 11.7 yrs) revealed a 25.2% probability of remission in users of TNF-α inhibitors compared to 14.7% in those receiving traditional or no DMARD, utilizing ACR preliminary criteria for clinical remission[5]. The OR was 2.74 when adjusted for age, gender, race, disease duration, use of NSAID, prednisone dosage, and number of previously used DMARD. Our findings are unique in that we compared remission rates of TNF-α inhibitors as a class with traditional DMARD, a comparison not previously reported in the literature.

In a study by Wolfe and Hawley in 1988, using ACR remission criteria, 83 of 458 patients (18.1%) experienced at least one remission during the 6-year period of observation[9]. O'Dell, *et al* reported that 12% of patients with longstanding RA were in remission at 5 years with triple DMARD[10]. Results from these studies were similar to our findings with patients using traditional DMARD.

In the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study, a longitudinal study using ACR criteria, Möttönen, *et al* reported that a combination of traditional DMARD achieved higher remission rates than monotherapy in patients with disease of less than 2 years' duration[11]. Remissions were achieved in 25% of patients with combination therapy and 11% of those on single drug therapy after 1 year; the remission frequencies increased to 37% and 18%, respectively, at 2 years. In the followup[12], a 4-month delay of monotherapy reduced the frequency of remission from 35% to 11% at 2 years, but there was no difference in the remission rates when combination therapies were delayed. Our study was a cross-sectional study, and the average disease duration of our patients was 11.7 years, much longer than 2 years. The reported remission rates cannot be compared properly, but their remission rates at 1 year of therapy were similar to ours.

In the TEMPO trial, Klareskog, *et al* reported the combination of MTX and etanercept induced clinical remissions (using a DAS score of < 1.6) in 35% of patients, while either etanercept or MTX alone induced remission in 16% and 13%, respectively, for patients with longstanding RA (average disease duration 6.3 to 6.8 yrs)[6]. Our cross-sectional study did not show a higher probability of remission in those patients receiving combination therapy with TNF-α inhibitors or those receiving TNF-α inhibitors alone (23.8% vs 29%), but we did find that the use of TNF-α inhibitors was associated with a higher remission rate than traditional DMARD.

Our study has some limitations. It was a cross-sectional study so the true remission rates induced by responsible agents were not assessed. Since it was not a longitudinal study the temporal relationship between treatment and remission was not prospectively evaluated. Rather, the assumption was made that if the patient was in remission, the treatment that he/she was on was responsible for the remission. There might be patients who had recently started receiving TNF-α inhibitors who eventually might go on to remission, but did not fulfill remission criteria at the study visit. The fact that TNF-α inhibitors act quickly serves to mitigate this problem somewhat, but not completely.

Another limitation is that clinicians were not blinded to the patient's treatment regimen when evaluating remission status. While some of the remission criteria were subjective, some of the elements were objective, which would minimize but not completely eliminate bias. Other limitations include reliance on data from a single institution (although multiple investigators were involved), different lengths of treatment with each DMARD or combination of DMARD, and varia-

Table 3. Remission rates among different groups.

Group	Possibility of Remission, %
Overall, n = 322	18.3
Any TNF-α inhibitors, n = 111	25.2
TNF-α inhibitors alone, n = 31	29.0
TNF-α inhibitors + other DMARD, n = 80	23.8
No TNF-α inhibitors, n = 211	14.7
One or more traditional DMARD, n = 179	15.1
No DMARD, n = 32	12.5

Table 4. Results of multivariate logistic regression on remission.

	OR	95% CI
Use of TNF-α inhibitors, yes vs no	2.74	1.40–5.34
Age, 10 yrs	1.03	0.81–1.30
Sex, male vs female	1.47	0.69–3.16
Race, Caucasians vs non-Caucasians	2.04	0.97–4.25
Disease duration, 10 yrs	0.84	0.57–1.22
Use of NSAID, yes vs no	0.76	0.40–1.44
Prednisone dosage, 1 mg/day	0.91	0.82–1.01
No. of previously used DMARD, (1.0)	0.77	0.62–0.90

tion in concomitant NSAID. Furthermore, we did not consider the 2 months' duration required by ACR criteria for remission since it was a cross-sectional study. The true remission rates might have been lower, but it would not alter the fact that TNF-α blockers were associated with more remissions.

The finding that progression of radiologic damage occurs in 15% of patients in clinical remission[13] supports the view that the definition of RA remission needs to be addressed and re-evaluated. The US Food and Drug Administration's guideline for complete clinical response for industry has taken radiological progression into consideration[14]. A consensus has yet to be reached on identification of integral factors in determining a remission.

If it is true that TNF-α inhibitors are associated with more clinical remissions, how long should we wait for traditional DMARD to work before we start treatment with costly TNF-α inhibitors, knowing that early intervention likely impacts remission rates more favorably? The apparent superiority of TNF-α inhibitors in inducing remission seems to have set a new standard of care. More studies are needed to assess the actual remission rates associated with these agents, currently available or on the horizon, as monotherapy or in combination. We are moving closer to inducing true remissions for patients with RA.

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