Retention Rates of Tumor Necrosis Factor Blockers in Daily Practice in 770 Rheumatic Patients

MURIEL DUCLOS, LAURE GOSSEC, ADELINE RUYSSEN-WITRAND, CARINE SALLIOT, MATHIEU LUC, SANDRA GUIGNARD, and MAXIME DOUGADOS

ABSTRACT. ***Objective***. Tumor necrosis factor (TNF) blockers are efficacious in clinical trials in rheumatic diseases. However, their efficacy in daily practice, depending on the specific diagnosis or the use of concomitant therapy, remains to be confirmed. Our objective was to evaluate TNF blocker retention rates and their predisposing factors in daily practice.

Methods. Retrospective evaluation of all TNF blocker therapies in one center. Retention rate was evaluated using a Kaplan-Meier survival data analysis technique in which the event was discontinuation of the drug due to inefficacy or toxicity with log-rank tests and a Cox proportional-hazards regression model.

Results. From 1997 to 2004, 770 patients with inflammatory rheumatism received at least one TNF blocker; 142 received more than one agent (975 treatment courses: 493 etanercept, 335 infliximab, 147 adalimumab). The underlying disease was mainly rheumatoid arthritis (RA), found in 57.1% of patients, and spondyloarthropathies (SpA) in 37.7%. The percentage of patients receiving the same treatment at Month 12, 24, and 36 was 64.0%, 50.3%, and 39.4%, respectively. No difference between the 3 TNF blockers was found ($p = 0.48$). The retention rate was longer for the first treatment course [hazard ratio (HR) 2.17, 95% confidence interval (95% CI) 1.82–2.58, $p < 0.0001$]; longer for patients with SpA (HR 1.60, 95% CI 1.20–2.13, $p = 0.001$); and longer without concomitant DMARD (HR 0.70, 95% CI 0.51–0.97, $p = 0.03$).

Conclusion. Our results indicate a lower retention rate of TNF blockers in daily practice compared with clinical trials, with no difference between the 3 currently available agents. Moreover, results suggest greater benefit in SpA. The role of concomitant DMARD remains to be confirmed. (First Release Oct 1 2006; J Rheumatol 2006;33:2433–9)

Key Indexing Terms:
INFLIXIMAB ETANERCEPT ADALIMUMAB RETENTION RATES

Treatment with tumor necrosis factor (TNF) blockers has changed the management of patients with inflammatory rheumatism, especially rheumatoid arthritis (RA) and spondyloarthropathies (SpA). Currently, 3 TNF blockers are available: infliximab, a chimeric monoclonal IgG antibody against TNF-α; etanercept, a recombinant TNF-α receptor fusion protein; and adalimumab, a human anti-TNF-α monoclonal antibody. Their efficaciousness has been evaluated in several large phase III trials in RA[1-6], ankylosing spondylitis (AS)[7-9], and psoriatic arthritis[10,11].

Retention rates have been considered a relevant tool to evaluate efficacy of TNF blocker therapy in daily practice[12,13]. A few studies based on retention rates (some reported as abstracts), conducted in cohorts of 200 to 400 patients with RA and in one larger Swedish cohort, have reported varying efficacy of TNF in daily practice: patients receiving the same treatment at 1 year ranged from 53% to more than 65%[12,14-17]. To our knowledge there is no study to date in patients with SpA.

Moreover, several issues in daily practice remain unresolved: Are the 3 available TNF blockers equivalent? To our knowledge, no prospective clinical trials have compared the TNF blockers head to head [a 2003 systematic review indicated 3 current TNF blockers had similar efficacy when added to methotrexate (MTX) in the treatment of RA[18]]. In daily practice, TNF blockers were indirectly compared in RA in a few studies and no differences between molecules were evidenced[12,14,19-21]. Another unresolved issue is whether prescription of concomitant MTX enhances efficacy. In clinical trials in patients with RA, the efficacy of TNF blockers is greater when associated with MTX[21,22]. In daily practice, several studies[19,23-25] showed that association of biologic agents and disease modifying antirheumatic drugs (DMARD) had higher retention rates in RA. In SpA, a study published in abstract form indicated comparable results in treatment of psoriatic arthritis by adalimumab[26] and in treatment of ankylosing spondylitis by infliximab[27], with or without MTX.

From René Descartes University, Faculty of Medicine; APHP Cochin Hospital, Department of Rheumatology B, Paris, France.

M. Duclos, MD; L. Gossec, MD; A. Ruyssen-Witrand, MD; C. Salliot, MD; M. Luc, MD; S. Guignard, MD; M. Dougados, MD.

Dr. Duclos and Dr. Gossec contributed equally to the conception, design, analysis, and interpretation of data, and to drafting the manuscript.

Address reprint requests to Prof. M. Dougados, Rheumatology B, Cochin Hospital, René Descartes University, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: maxime.dougados@cch.aphp.fr.

Accepted for publication May 30, 2006.

The influence of factors such as specific diagnosis or ranking of treatment on efficacy of TNF blocker therapy remains unclear. Recently, an observational study compared their effectiveness in patients with RA and AS, using evaluation of quality of life scores, and found a trend for a better efficacy in AS[28]. To our knowledge, the impact of the first prescription of a TNF blocker compared to the second or third prescription has never been formally evaluated, even though observational studies suggest that a switch to another drug agent because of inefficacy of the first might be of clinical benefit in some individual patients.

Thus, there are abundant data showing the efficacy of TNF blockers in randomized controlled trials, and there are some data suggesting that this efficacy is confirmed in daily practice. However, several issues, such as differences between the 3 TNF blockers and the role of concomitant MTX, especially in SpA, remain to be determined.

We retrospectively analyzed retention rates of the 3 available TNF blockers and sought to determine the elements explaining these rates, including type of TNF blocker, ranking of treatment course, underlying disease, and the role of concomitant MTX or other DMARD.

MATERIALS AND METHODS

Study design. Retrospective, observational study.

Setting. Monocenter French tertiary-referral rheumatology unit.

Selection of patient files. All patients from one department who received treatment with infliximab, etanercept, or adalimumab between 1997 and December 15, 2004, were selected through a full-text computer survey of patient files (using key words infliximab, etanercept, adalimumab, anti-TNF). With this exhaustive selection, we obtained 1571 patient files. We read all medical files to exclude patients who had not received a TNF blocker. Thus, all 770 patients with an inflammatory disorder treated with a TNF blocker were selected. Figure 1 shows the selection process.

Underlying disease was determined based on the American College of Rheumatology criteria for RA[29] and the Amor criteria for spondyloarthropathies[30]. Some patients had other diseases (e.g., Still's disease, juvenile arthritis, non-classified rheumatism, or idiopathic periosteitis).

In patients treated sequentially with several TNF blockers, each TNF treatment course was analyzed. Thus, a given patient may have been analyzed several times.

Data collection. A separate file was used for the purposes of this study. From December 2004 to April 2005, 5 residents (MD, CS, ML, AR, SG) collected data prospectively, based on the complete paper file or on face to face interviews (Figure 1) that included age, sex, underlying disease, disease duration, rheumatoid factor status (positive: IgG titer > 20 IU/l at any time, by nephelometry), presence of HLA-B27 allele, number of previous DMARD at introduction of first TNF blocker.

For each anti-TNF treatment course, data collected were: ranking of TNF blocker (i.e., the patient's first, second, or third TNF blocker), date of first prescription, prescription of concomitant DMARD/corticosteroid at initiation of the TNF blocker, and date of interruption or of last followup.

Causes of treatment interruption were classified as: inefficacy (according to the rheumatologist's opinion), adverse events, "administrative cause" (such as switches from infliximab to etanercept because of reimbursement differences), or other causes (e.g., wish to become pregnant, difficulty with intravenous infusion, patient initiative, etc.).

Double data entry was performed. All data were processed anonymously.

Statistical analysis. Descriptive statistics were used for patient characteristics, which were compared using t test or chi-square test for continuous and categorical variables with a level of significance set at 5% bilaterally. The primary outcome was retention rate, which was evaluated using Kaplan-Meier survival technique. The event for "global" retention rate was interruption of treatment due to inefficacy *or* toxicity; the event for "inefficacy" retention rate was interruption due to inefficacy; and the event for the "intolerance" retention rate was interruption due to intolerance. Other causes of interruption and loss to followup were considered as censored values. Potential factors explaining the retention rates were evaluated using log-rank tests. A Cox proportional hazards regression model was generated and all variables with a log-rank p value < 0.20 were entered in the model. The database was analyzed using SAS statistical software version 8.0.

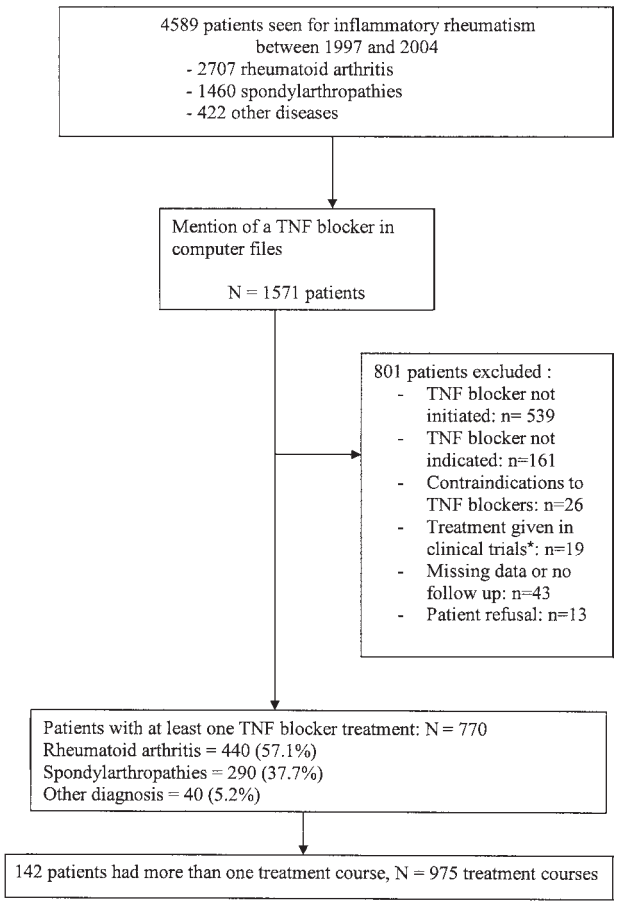

Figure 1. Patient selection: All patients with rheumatic disease who received TNF blockers between 1997 and December 2004 in one center. *Treatment allocation unknown between placebo and treatment groups.

RESULTS

Selection process. The selection process is shown in Figure 1. Seven hundred seventy patients received at least one course of treatment with a TNF blocker. Among the 770 patients, 244 (31.7%) received infliximab as first TNF blocker, 419 (54.4%) etanercept, and 107 (13.9%) adalimumab. Of the 770 patients, 142 received more than one TNF blocker, resulting in 975 treatment courses (493 etanercept, 50.5%; 335 infliximab, 34.5%; and 147 adalimumab, 15.0%).

Patient characteristics. Patient characteristics, according to

specific disease, are summarized in Table 1. Mean age of the population was 49.3 years, 60.4% were women, and the mean duration of disease before TNF blocker therapy was 13.4 years. Patients with RA were older (mean age at initiation of TNF blocker: 55.2 yrs) and were more often women (80.5%). Of the RA patients, 312 (80.0%) were rheumatoid factor-positive. Patients with SpA were younger (mean age 41.6 yrs) and more of them were men (70.3%); among them, 187 (81.2%) were HLA-B27-positive. Among the SpA patients, there were 166 with axial disease, 64 peripheral disease, and 60 with psoriatic arthritis. Among all patients, 216 patients received the TNF blocker in a clinical trial: 109 with RA and 107 with SpA.

Retention rates. Pooled retention rates of the 3 TNF blockers and according to reason for interruption are shown in Figure 2. In the global analysis, interruption of treatment was taken into account if it was due to inefficacy or intolerance. The percentage of patients who did not interrupt treatment due to inefficacy or intolerance was 82.5% ± 1.3 at 6 months, 64.0% ± 1.8 at 12 months, 50.3% ± 2.1 at 24 months, and 39.4% ± 2.4 at 36 months.

Retention rates according to interruption due to inefficacy. In this analysis, interruption of treatment was taken into account only if it was for inefficacy. Other causes of interruption (including due to intolerance) were censored. The percentage

Table 1. Characteristics of 770 patients receiving TNF blockers according to specific disease*.

	All Patients, N = 770	Rheumatoid Arthritis, N = 440	Spondyloarthropathies, N = 290
Women, no. (%)	465 (60.4)	354 (80.5)	86 (29.7)
Age, yrs	49.3 (15.0)	55.1 (13.9)	41.6 (12.2)
Disease duration, yrs	13.4 (9.7)	13.5 (9.5)	13.6 (10.0)
No. of previous DMARD	3.0 (2.1)	4.0 (1.9)	1.5 (1.5)
Cumulative corticosteroid intake, g†	16.1 (21.5)	23.3 (22.9)	4.8 (12.6)
Concomitant prescription of DMARD, no. (%)	405 (52.6)	281 (63.9)	103 (35.5)

* Except where indicated otherwise, values are the mean ± SD. DMARD: disease-modifying antirheumatic drugs. † Cumulative dose of corticosteroids given before TNF blocker therapy.

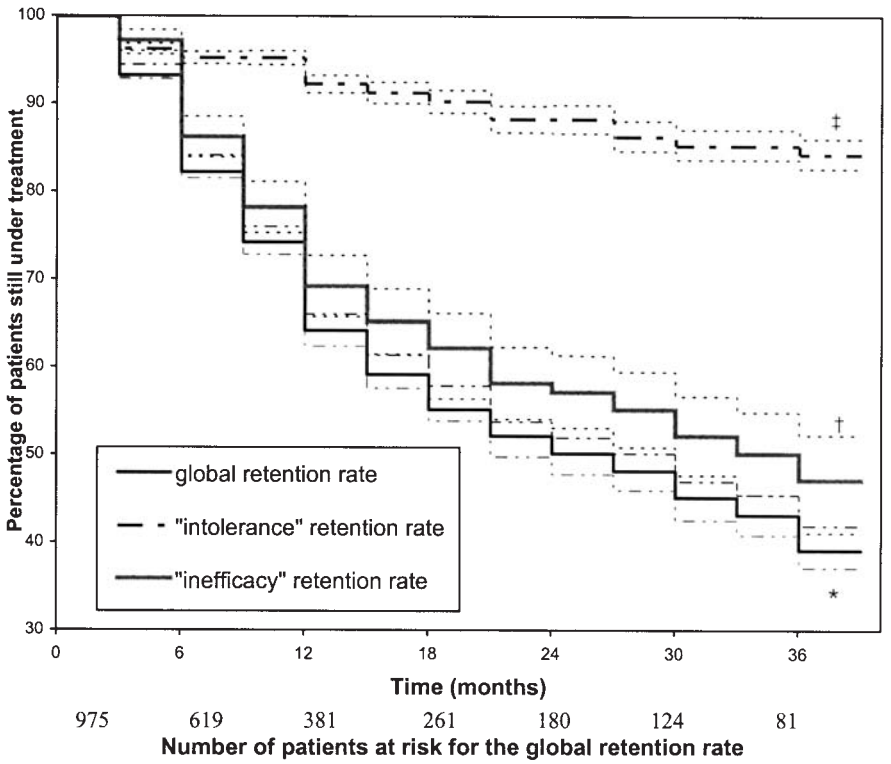

Figure 2. TNF retention rates for all TNF blocker treatment courses and all diagnoses (Kaplan-Meier survival technique). *Global retention rate: the event was defined as interruption due to inefficacy or intolerance. †Inefficacy retention rate: interruption for inefficacy. ‡Intolerance retention rate: interruption due to intolerance. Broken lines indicate the standard deviation for each curve.

of patients who did not interrupt treatment for inefficacy was 83.4% ± 1.2 at 6 months, 69.1% ± 1.8 at 12 months, 56.8% ± 2.1 at 24 months, and 46.5% ± 2.6 at 36 months.

Retention rates according to interruption due to intolerance. In this analysis, the percentage of patients who did not interrupt treatment due to intolerance was 95.4% ± 0.7 at 6 months, 92.4% ± 1.0 at 12 months, 87.8% ± 1.6 at 24 months, and 84.0% ± 2.2 at 36 months. Other causes such as pregnancy, moving to another region, and administrative causes were not included in these analyses, i.e., were considered as censored data.

Factors influencing retention rates in log-rank analysis are shown in Table 2.

Type of TNF blocker: Retention rates were similar for the 3 TNF blockers. At 1 year, rates were 63.2% ± 2.9, 63.9% ± 2.6, and 68.2% ± 4.6, and at 2 years, rates were 47.5% ± 3.2, 50.8% ± 3.0, and 60.2% ± 5.6 for infliximab, etanercept, and adalimumab, respectively (p = 0.48). Analyses according to reason for interruption did not find any difference in efficacy between the 3 agents (p = 0.33), but showed a trend for a better tolerance with etanercept and adalimumab versus with infliximab (p = 0.06) (Table 2).

Ranking of treatment: There was a longer retention rate for the first TNF blocker treatment course (p < 0.0001), with better efficacy (p < 0.0001) and tolerance (p = 0.0003) (Table 2).

Underlying diagnosis: Retention rates were longer in SpA than in other diseases (p < 0.0001), with better efficacy (p < 0.0001) and tolerance (p = 0.001) (Table 2).

Concomitant prescription of DMARD: The concomitant prescription of DMARD was linked in univariate analyses to a lower global retention rate (p < 0.0001). In the specific case of prescription of concomitant MTX, this was also the case (p = 0.003). These results were confirmed for cases of interruption due to inefficacy (p < 0.0001 and MTX p = 0.002) but not for those due to intolerance (concomitant DMARD: p = 0.55; MTX: p = 0.67) (Table 2).

Role of previous DMARD and corticosteroids: The global retention rate was higher when patients had not received previous DMARD (p = 0.04) or corticosteroids before introduction of the first TNF blocker (p = 0.002). Duration of disease before first prescription of a TNF blocker did not predict the retention rate (p = 0.17).

Cox model. Results are shown in Table 3. Three variables explaining the retention rate were picked up by the Cox proportional hazards model:

Rank of treatment: global retention rates were higher for the first TNF blocker treatment course than for the second or third [hazard ratio (HR) 2.17; 95% hazard confidence interval (95% CI) 1.82–2.58]. This was also the case in analyses of interruption for inefficacy (HR 2.17; 95% CI 1.79–2.64) and for intolerance (HR 2.12; 95% CI 1.43–3.15).

Underlying diagnosis: Global retention rates were higher for patients with SpA than for the other patients (HR 1.60; 95% CI 1.20–2.13), this was also the case in analyses of interruption for inefficacy (HR 1.44; 95% CI 1.06–1.95) and for intolerance (HR 1.97; 95% CI 1.10–3.53).

Concomitant DMARD: Retention rates were higher for patients without prescription of concomitant DMARD (DMARD: HR 0.70; 95% CI 0.51–0.97). These results were confirmed for interruption because of inefficacy (HR 0.65; 95% CI 0.46–0.93). The coprescription of MTX or other DMARD did not modify the tolerance of treatment by TNF blocker (Table 3).

Role of concomitant DMARD according to the specific disease. In separate Cox models evaluating the effect of concomitant DMARD in the 2 main disease types, concomitant

Table 2. Factors influencing retention rates by log-rank analysis*.

	Due to Inefficacy or Intolerance	Treatment interrupted Due to Inefficacy	Due to Intolerance
Nature of the TNF blocker	0.48	0.33	0.06
Rank of treatment: first prescription vs 2nd or 3rd	< 0.0001	< 0.0001	0.0003
Specific disease: SpA vs other	< 0.0001	< 0.0001	0.001
Concomitant DMARD: none vs any	< 0.0001	< 0.0001	0.55
Concomitant MTX: none vs any	0.0025	0.0021	0.67
No previous DMARD	0.04	0.20	0.15
No previous corticosteroids	0.002	0.003	0.83
If previous steroids: Cumulative steroid intake†	0.55	0.50	0.92
Disease duration†	0.17	0.16	0.96

* All results are p values after analysis of retention rates according to the event: Interruption of treatment because of inefficacy or toxicity (global analysis), due to inefficacy (inefficacy analysis), and due to intolerance (intolerance analysis). † Analyzed as categorical variables, above or below the median value (median cumulative steroid dose for patients treated with steroids = 14.2 g, median disease duration before TNF blocker initiation = 9.7 yrs).

Table 3. Factors influencing retention rates in Cox proportional-hazards model*.

	Retention Rates		
	Global	Inefficacy	Intolerance
First prescription	2.17 (1.82–2.58), p < 0.0001	2.17 (1.79–2.64), p < 0.0001	2.12 (1.43–3.15), p = 0.0002
SpA vs other disease	1.60 (1.20–2.13), p = 0.001	1.44 (1.06–1.95), p = 0.02	1.97 (1.10–3.53), p = 0.02
Concomitant DMARD, yes/no	0.70 (0.51–0.97), p = 0.03	0.65 (0.46–0.93), p = 0.02	NS
Infliximab vs other TNF blocker	NS	NS	0.67 (0.47–0.94), p = 0.02

* All results are the hazard ratio (HR) with (95% confidence interval) and p values. NS: nonsignificant. SpA: spondyloarthropathy.

DMARD was linked to lower retention rates in RA (DMARD: p = 0.04; HR 0.67; 95% CI 0.46–0.98), but when the analysis was restricted to concomitant MTX, retention rates were not significantly different with or without concomitant MTX (p = 0.59). In SpA, there was no statistically significant difference according to the use of concomitant DMARD (p = 0.13) or MTX (p = 0.90), and no difference between axial SpA forms and psoriatic arthritis (respectively, 38.6% and 35%), but with fewer prescriptions of concomitant DMARD in peripheral forms of SpA (15.6%).

DISCUSSION

In our study, in daily practice TNF blockers had a much lower retention rate than in clinical trials: at 1 year 64.0% of patients had not interrupted treatment for inefficacy or intolerance, and at 2 years 50.3%. There was no difference in retention rate according to the TNF blocker. First prescription of a TNF blocker, SpA as specific disease, and no concomitant DMARD were associated with higher retention rates.

To our knowledge, our study reports results from the largest cohort analyzed in a single center, and in terms of specific disease. We systematically analyzed all TNF blocker treatment courses in all patients, in order to reflect heterogeneity of daily practice. In RA, the only larger study is the analysis of Swedish databases[16,17]; no similar cohort has been analyzed in SpA.

High retention rates for TNF blockers were reported in clinical trials and in followup studies of clinical trials[2,3,7,31]. In daily practice, similar results were reported in small series[12,14], but lower retention rates, comparable to results reported here, were described in large cohorts, with retention rates of 70% at 1 year[15,16]. However, Van Vollenhoven, *et al* indicated that secondary loss of efficacy affects < 5% of patients for each year of treatment[17].

Compared with a reference treatment such as MTX[13,32,33], retention rates for TNF blockers reported here are lower. Thus according to these results, contrary to clinical trials, TNF blockers do not perform better than DMARD in daily practice — even in patients refractory to DMARD.

In our study, interruption of TNF blocker therapy was more often due to inefficacy than to intolerance. Our results are in contrast to previous studies: in fact in one study withdrawal was more often due to adverse events[16].

No difference between the 3 available TNF blockers was evidenced in this study, although there was a trend for a better tolerance with etanercept. No clinical trial has compared the 3 agents, but in daily practice, similar efficacy and adverse effects were described in the 3 agents. Our present results should be compared to Kristensen's study, in which etanercept had a longer retention rate than infliximab, because of a lower rate of withdrawal from therapy due to adverse events[16].

The ranking of prescription of the TNF blocker in our study predicted retention rate, including longer retention rate for the first TNF blocker course (vs the second or the third agent in the same patient). This result remained significant in the "inefficacy" and "intolerance" studies. To our knowledge, no study has compared influence of the ranking of prescription of the 3 agents, but studies of switches[21,34-41] have shown that lack of efficacy or intolerance to one TNF blocker does not predict response to another agent. An explanation for this result could be the existence of multi-resistant diseases; patients resistant to the first TNF blocker were still resistant to the second, and the third.

In our study, SpA had better retention rates than RA. This result is similar to that of daily practice. In a recent prospective study[28], efficacy of TNF blocker therapies evaluated by quality of life scores was greater in AS than in RA. Factors that could explain these longer retention rates include: (1) the influence of TNF in physiopathology of the disease could be more important in SpA than in RA. Population characteristics are probably important: a younger population with less corticosteroid and immunosuppressive therapy may tolerate TNF blocker therapy better than RA patients. This hypothesis is reinforced by the importance of the specific disease in the interruption due to intolerance but not in interruption due to inefficacy. Finally, it must be noted that in SpA, fewer therapeutic alternatives are available.

Our results indicate that patients who did not use concomi-

tant DMARD had a longer retention rate. This was the case for the global retention rate and for interruption due to inefficacy, but not for interruption due to intolerance. This surprising result is in contrast with previously published results in RA clinical trials[22,23] and in daily practice[16,19,24,25]. In SpA, the value of concomitant DMARD is unclear in the literature. Some recent abstracts suggest no benefit of coprescription of MTX[26,27]. Our results do not suggest any influence of concomitant treatment in SpA. In RA, however, coprescription of DMARD was significantly associated with lower retention rates. This result cannot be explained by more adverse events nor by particular infections, since the intolerance retention rate was not modified. These results may be explained by a bias we did not analyze. In particular, in daily practice, coprescription of DMARD could be more often associated to TNF blockers in cases of severe, resistant RA. Our multivariate analyses failed to demonstrate this hypothesis, since number of previous DMARD, cumulative dose of corticosteroids, and duration of disease, reflecting potential severity of disease, were not related to retention rates. However, the use of concomitant DMARD reflects physician behavior as well as patient status; this is another source of potential bias.

Limitations of our study include its retrospective, daily practice design. Our department is a tertiary referral center that treats a specific population, with potentially more severe cases. However, as TNF blockers are available in France only through hospitals, this selection bias was minimized. Further, all patients treated in our center were analyzed. However, it should be noted that most patients were only evaluated over relatively short periods, so that most of the conclusions about retention are limited to short-term use. Randomized controlled trials cannot evaluate daily efficacy of treatment, in particular when a population is heterogeneous with several differing diagnoses. The study design focusing on daily practice has the advantage, in comparison to controlled trials, of showing the effects of a new drug under typical everyday conditions, even if the result may be influenced by factors such as patient subjectivity in regard to a new drug, or physicians' prescription habits. Knowledge of side effects probably had an effect on duration of treatment. In clinical trials, the inclusion and exclusion criteria select a minority of patients, and evaluation of efficacy is dependent on standard quantitative measures or indices that are not systematically used in daily practice; efficacy is evaluated empirically by the physician's opinion, which translates into retention rates[13,42,43]. Thus, retention rate is considered a relevant tool to evaluate the utility of a therapy in rheumatic diseases in daily practice[13]. Our department is a tertiary referral center with a population that is specific and with potentially severe disease; however, as TNF blockers are available in France only through hospitals, this selection bias was minimized.

Some factors reported in our study, such as comparison between specific diseases[28] or the role of concomitant DMARD[16,19,22-26], were recently analyzed. Our study has the advantage of exploring all the factors likely to influence efficacy of TNF blocker therapy in a single large cohort in daily practice.

In conclusion, our large-scale daily practice study found a lower retention rate versus previous studies, but no difference in retention rates between the different TNF blockers. The role of concomitant DMARD remains to be confirmed in future studies.

REFERENCES

1. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;4:1552-63.
2. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving methotrexate: a randomised phase III trial. Lancet 1999;354:1932-9.
3. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.
4. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
5. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
6. Maini R, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004;50:1051-65.
7. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187-93.
8. Brandt J, Khariouzov A, Listing J, et al. Six-months results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48:1667-75.
9. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis. Results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.
10. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385–90.
11. Antoni C, Kavanaugh A, Kirkham B, et al. The infliximab multinational psoriatic arthritis controlled trial (IMPACT): substantial efficacy on synovitis and psoriatic lesions with or without concomitant DMARD therapy. Arthritis Rheum 2005;52:1227-36.
12. Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002;61:793-7.
13. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. J Rheumatol 1992;19:1885-94.
14. Flendrie M, Creemers MCW, Welsing PMJ, den Broeder AA, van Riel PLCM. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 2003;62

Suppl II:30-3.
15. Ostergaard M, Unkerskov J, Krogh NS, Friis M, Ravn T, Petri A. Poor remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept – results from the nationwide Danish "DANBIO" database [abstract]. Ann Rheum Dis 2005;64 Suppl III:59.
16. Kristensen L, Geborek P, Saxne T. Adherence to therapy of etanercept and infliximab during first anti-TNF treatment course in rheumatoid arthritis [abstract]. Ann Rheum Dis 2005;64 Suppl III:431.
17. Van Vollenhoven R, Cullinane Carli C, Bratt J, Klareskog L. Secondary loss of efficacy woth TNF alpha antagonists [abstract]. Arthritis Rheum 2005;52 Suppl:S136.
18. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor α blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003;62 Suppl II:13-16.
19. Zink A, Listing JD, Kary S, et al. Treatment continuation in patients receiving biological or conventional DMARD therapy. Ann Rheum Dis 2005;64:1274-9.
20. Van Vollenhoven RF, Harju A, Bratt J, et al. Etanercept and infliximab treatment in the Stockholm TNF alpha antagonist registry: a comparison of two TNF alpha antagonists [abstract]. Arthritis Rheum 2001;44 Suppl:S79.
21. Van Vollenhoven RF, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62:1195-8.
22. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
23. Breedveld F, Kavanaugh AF, Cohen SB, et al. Early treatment of rheumatoid arthritis with adalimumab plus methotrexate vs adalimumab alone or methotrexate alone: the PREMIER study [abstract]. American College of Rheumatology Annual Scientific Meeting, October 16-24, 2004; San Antonio, TX, USA. Abstract L5/520. [meeting abstracts on the Internet. Accessed July 25, 2006.] Available from: http://www.rheumatology.org/annual/abstracts/search.asp
24. Schrumpf M, Rodevand E, Mikkelsen K, et al. Adalimumab plus methotrexate is more effective than adalimumab alone in patients with rheumatoid arthritis (RA) – results from a longitudinal observational study [abstract]. Ann Rheum Dis 2005;64 Suppl III:184.
25. Kvien TK, Schrumpf M, Mowinckel P, et al. Comparison of remission and EULAR good response rates in 1677 patients with rheumatoid arthritis receiving methotrexate, leflunomide or TNF-blocking agents: results from a longitudinal observational study [abstract]. Ann Rheum Dis 2005;64 Suppl III:450.
26. Kavanaugh AF, Ritchlin CT, Malaise MG, Wordsworth P, Birbara CA, Weinberg MA. Adalimumab treatment with and without methotrexate in patients with moderate to severe psoriatic arthritis: results from ADEPT [abstract]. Ann Rheum Dis 2005;64 Suppl III:325.
27. Breban M, Ravaud P, Claudepierre P, Baron G, Hudry C, Euller-Ziegler L. No superiority of infliximab + methotrexate over infliximab alone in the treatment of ankylosing spondylitis: results of a one-year randomized prospective study [abstract]. Arthritis Rheum 2004;50 Suppl:S214.
28. Heiberg M, Nordvag B, Mikkelsen K, et al. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six month, longitudinal, observational, multicenter study. Arthritis Rheum 2005;52:2506-12.
29. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;3:315-24.
30. Amor B, Dougados M, Listrat V, et al. Are classification criteria for spondylarthropathy useful as diagnostic criteria? Rev Rhum Engl Ed 1995;62:10-5.
31. Keystone E, Kavanaugh A, Sharp J, et al. Radiographic, clinical and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. Arthritis Rheum 2004;5:1400-11.
32. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.
33. Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T. Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. Ann Rheum Dis 2005;64:207-11.
34. Shergy WJ, Philips RM Jr, Hunt RE, Hernandez J. Safety and efficacy of infliximab therapy after etanercept failure: a case series [abstract]. Arthritis Rheum 2001;44 Suppl:S81.
35. Brocq O, Plubel Y, Breuil V, et al. Switch etanercept-infliximab dans la polyarthrite rhumatoïde: 14 patients sur 131 traités par anti-TNF alpha. Presse Med 2002;3:1836-9.
36. Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. Joint Bone Spine 2004;71:601-3.
37. Ang HTS, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other TNF-alpha antagonists in patients with rheumatoid arthritis. J Rheumatol 2003;30:2315-8.
38. Hansen KE, Hildebrand JP, Genovese MC, et al. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol 2004;3:1098-102.
39. Van der Bijl AE, Breedveld FC, Antoni CE, et al. Adalimumab is effective in treating patients with rheumatoid arthritis who previously failed infliximab treatment [abstract]. Ann Rheum Dis 2005;64 Suppl III:428.
40. Furst D, Yocum D, Weisman M, et al. Infliximab provides additional clinical and radiographic benefits in RA patients who have an inadequate response to etanercept [abstract]. Ann Rheum Dis 2005;64 Suppl III:427.
41. Nikas SN, Voulgari PV, Papadopoulos CG, Venetsanopoulou A, Georgiadis AN, Drosos AA. The efficacy and safety of switching from infliximab to adalimumab. A prospective controlled study [abstract]. Ann Rheum Dis 2005;64 Suppl III:422.
42. Pincus T, Sokka T. Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? Ann Rheum Dis 2004;63 Suppl II:ii32-ii39.
43. Pincus T, Stein CM. Why randomised controlled clinical trials do not depict accurately long-term outcomes in rheumatoid arthritis: some explanations and suggestions for future studies. Clin Exp Rheumatol 1997;15 Suppl 17:S27-S38.