Longterm Retention of Tumor Necrosis Factor-α Inhibitor Therapy in a Large Italian Cohort of Patients with Rheumatoid Arthritis from the GISEA Registry: An Appraisal of Predictors

FLORENZO IANNONE, ELISA GREMESE, FABIOLA ATZENI, DOMENICO BIASI, COSTANTINO BOTSIOS, PAOLA CIPRIANI, CLODOVEO FERRI, VALENTINA FOSCHI, MAURO GALEAZZI, ROBERTO GERLI, ANNARITA GIARDINA, ANTONIO MARCHESONI, FAUSTO SALAFFI, TAMARA ZIGLIOLI, and GIOVANNI LAPADULA, and the Gruppo Italiano di Studio sulle Early Arthritides (GISEA)

ABSTRACT. **Objective.** To evaluate 4-year retention rates of tumor necrosis factor-α (TNF-α) inhibitors adalimumab, etanercept, and infliximab among patients with longstanding rheumatoid arthritis (RA), as derived from an Italian national registry.
Methods. The clinical records of 853 adult patients with RA in the GISEA (Gruppo Italiano Studio Early Arthritis) registry were prospectively analyzed to compare drug survival rates and the baseline factors that may predict adherence to therapy.
Results. In 2003 and 2004, 324 patients started treatment with adalimumab, 311 with etanercept, and 218 with infliximab. After 4 years, the global retention rate of anti-TNF-α therapy was 42%. Etanercept survival (51.4%) was significantly better than that of infliximab (37.6%) or adalimumab (36.4%; $p < 0.0001$). Accordingly, the mean duration of therapy was significantly longer for etanercept (3.1 ± 2 yrs) than for adalimumab (2.6 ± 2 yrs) or infliximab (2.7 ± 2 yrs; $p < 0.05$). The use of concomitant disease-modifying antirheumatic drugs, mainly methotrexate, and the presence of comorbidities significantly predicted drug continuation ($p < 0.01$), whereas a high Disease Activity Score did not.
Conclusion. The 4-year global drug survival of adalimumab, etanercept, and infliximab was lower than 50%, with etanercept having the best retention rate. The main positive predictor of adherence to anti-TNF-α therapy was the concomitant use of methotrexate. Our study provides further evidence that the real-life treatment of patients with RA may be different from that of randomized clinical trials. (First Release April 1 2012; J Rheumatol 2012;39:1179–84; doi:10.3899/jrheum.111125)

Key Indexing Terms:
ADALIMUMAB   ETANERCEPT   INFLIXIMAB   DRUG SURVIVAL

F. Iannone, MD, PhD, University of Bari; E. Gremese, MD, Università Cattolica del Sacro Cuore; F. Atzeni, MD, Ospedale Sacco; D. Biasi, MD, University of Verona; C. Botsios, MD, University of Padua; P. Cipriani, MD, University of Aquila; C. Ferri, MD, University of Modena and Reggio Emilia; V. Foschi, MD, University of Ferrara; M. Galeazzi, MD, University of Siena; R. Gerli, MD, University of Perugia; A. Giardina, MD, University of Palermo; A. Marchesoni, MD, Ospedale G. Pini; F. Salaffi, MD, Università Politecnica delle Marche; T. Ziglioli, MD, University of Brescia; G. Lapadula, MD, University of Bari.

Address correspondence to Dr. F. Iannone, DIMIMP-Rheumatology Unit, Policlinico, Piazza G. Cesare 11, 70124 Bari, Italy.
E-mail: f.iannone@reumbari.uniba.it

Tumor necrosis factor-α (TNF-α) blockade is a widely established therapy for treating rheumatoid arthritis (RA) after failure of conventional disease-modifying antirheumatic drugs (DMARD). Adalimumab, etanercept, and infliximab were the first TNF-α blockers to become commercially available. Although TNF-α inhibitors share the same target, they have different structures and/or mechanisms of antagonism that affect their pharmacokinetics and possibly their safety and efficacy.

Adalimumab, etanercept, and infliximab have led to similarly high response rates in randomized controlled trials (RCT) in terms of clinical efficacy and the arrest of structural joint damage[1], but the nonselected patients encountered in everyday clinical practice often have more complex situations than those enrolled in RCT because of concomitant therapies, comorbidities, personal habits, and poor adherence, all of which may affect treatment success.

One further aspect of this setting is measurement of the response to longterm therapy. The standard clinimetric tools, such as the European League Against Rheumatism (EULAR) criteria, the American College of Rheumatology (ACR) response criteria, and the Health Assessment Questionnaire (HAQ), require careful and close patient monitoring to collect data properly, and this may be difficult in the context of longterm routine care. One alternative that may be helpful in assessing the longterm outcomes of TNF-α antagonists is treatment survival, because the drug retention rate can be considered a result of all the variables affecting treatment discontinuation, and may ultimately represent an indirect overall measure of the worth of a drug in clinical practice.

Only a few studies have compared longterm adalimumab, etanercept, and infliximab drug survival in patients with RA[2,3,4,5]. One study of a cohort of patients with RA in a single region of Northern Italy (the Lombardy Rheumatology Network or LOHREN registry) showed that the 3-year drug survival rate was significantly higher in the case of etanercept[3], and more recently, the results of the Danish DANBIO registry have confirmed that etanercept has the highest 2-year retention rate[2].

Our aim was to compare longterm (4-year) drug survival in patients with RA who were entered into an Italian national registry and treated with adalimumab, etanercept, or infliximab, and to identify possible predictors of treatment adherence.

MATERIALS AND METHODS

Patients. The nationwide Gruppo Italiano Studio Early Arthritis (GISEA) registry was launched in 2003 to record and monitor patients with rheumatic diseases who were being treated with biological drugs on the basis of the standard of clinical care. The registry involves hospital and community-based rheumatology units throughout Italy. Patients aged > 18 years are enrolled after giving their written informed consent, and the registry has been approved by the local Ethics Committee.

Patient data are recorded at baseline and every 6 months thereafter. RA is diagnosed on the basis of the 1987 ACR criteria[6]. The data collected include age, sex, disease duration, the time from diagnosis to beginning of treatment with a biological drug (latency), the intake of glucocorticoids and DMARD, smoking status, the 28-joint Disease Activity Score (DAS28), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR; mm/hour), rheumatoid factor (RF), pain as assessed by a visual analog scale (VAS; 0–100), HAQ scores, side effects, anti-TNF-α discontinuation and the reason for it, and any switch to another biological drug. Comorbidities are recorded by monitoring the following: anemia, anxiety/depression, cardiopathy, cerebrovascular diseases, diabetes, gastropathies, hypertension, liver diseases, lung diseases, neoplasia, nephropathy, and peripheral vasculopathy. Change in DAS28 is used to assess the clinical response (modified EULAR response criteria[7]) by considering the response "good" when DAS28 improvement from baseline is > 1.2, "moderate" when it is > 0.6 to < 1.2, and "none" when it is < 0.6. Disease remission is defined as DAS28 > 2.6[8].

For the purpose of our analysis, we included only patients with RA who began adalimumab, etanercept, or infliximab therapy in 2003 and 2004. At that time, the guidelines were those released in 2001 by the Servizio Sanitario Nazionale, which recommended the use of anti-TNF-α drugs in patients with RA having active disease, at least 5 swollen or tender joints,

DAS ≥ 3.7, and not responding to 2 conventional DMARD. Analogous guidelines were later released by the Italian Society of Rheumatology in 2006[9]. Recommended doses were adalimumab 40 mg subcutaneously every other week, etanercept 50 mg subcutaneously/week (or 25 mg twice a week), and infliximab 3 mg/kg intravenously in Weeks 0, 2, and 6, and every 8 weeks thereafter. We analyzed all the patients (including those who received a single dose) during the first 4 years of treatment or until the discontinuation of the first TNF-α antagonist. The patients lost to followup were included in the final analysis (intention-to-treat strategy).

Statistical analysis. The differences among infliximab, adalimumab, and etanercept were analyzed using the Kruskal-Wallis nonparametric test for the continuous variables (mean values and SD) and the chi-squared test for the categorical variables (absolute numbers and percentages) regarding baseline characteristics and assessment of clinical outcomes. The univariate and multivariate analyses were performed using logistic regression models. The response variable was defined as discontinued therapy (yes/no) after 4 years of treatment. The baseline variables taken into account were sex, disease duration, ESR, DAS28, the concurrent use of glucocorticoids and DMARD, and comorbidities. The patients contributed to the 4-year survival models until the time of first discontinuation or the last time of observation on treatment. Continuing on therapy was measured using the Kaplan-Meier life-table method, and the log-rank test was used to compare the discontinuation rates of the 3 anti-TNF-α agents. All analyses were made using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), and a p value ≤ 0.05 was considered statistically significant. The data are expressed as percentages or mean values ± 1 SD or medians and interquartile range, unless otherwise indicated.

RESULTS

Patients and disease characteristics. Of the 853 patients with RA treated with TNF-α inhibitors and monitored for up to 4 years, 324 received adalimumab, 311 etanercept, and 218 infliximab. Table 1 shows their baseline demographic and disease characteristics. There was no significant difference between the groups in disease duration and VAS pain before starting the anti-TNF-α drug, but the patients on adalimumab had slightly lower DAS28 (p = 0.04) and HAQ (p = 0.03) scores than patients treated with infliximab or etanercept. Further, patients on infliximab had significantly fewer comorbidities (p = 0.01) and more frequently used DMARD (p = 0.01). Comorbidities were present in 45% of all patients, and cardiovascular diseases were the highest proportion (33%). Among DMARD, the most frequent was methotrexate (MTX; 77%), followed by hydroxychloroquine (10.6%) and leflunomide (7%). The mean dose of MTX was 11 mg/week. Glucocorticoid intake did not differ among the groups and the mean dose (prednisone or equivalent) was 6.2 mg/day (range 2.5–30). RF was detected in 71% of patients, without significant difference among the treatments.

Clinical outcomes. During the 4 years of the survey, 360 patients (42.2%) continued the treatment and 493 (57.8%) stopped it: 161 (32.6%) because of inefficacy, 120 (24.3%) because of adverse events, and 53 (10.7%) for other reasons, and 159 (32.2%) were lost to followup (these were not excluded from the statistical evaluation but considered as stopping treatment). In terms of the individual TNF-α antagonist, 206 patients stopped adalimumab (64%), 151 etaner-

Table 1. Demographic and disease characteristics of the patients at baseline. Kruskal-Wallis nonparametric test was used for continuous variables and the chi-squared test for categorical variables.

Characteristic	Adalimumab, n = 324, F: 273, M: 51		Etanercept, n = 311, F: 268, M: 43		Infliximab, n = 218, F: 172, M: 46		p
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Age, yrs	54.5 (12)	55.4 (19)	53.5 (14)	54.4 (19)	51.9 (13)	52.5 (19)	0.06
Latency, mo	9.6 (9.0)	7.7 (12)	10.0 (8.6)	7.9 (11)	8.8 (7.8)	6.8 (12)	0.19
Disease duration, yrs	11.5 (8.8)	9.9 (11)	10.7 (8.6)	8.7 (10)	9.9 (7.7)	8.3 (12)	0.17
VAS pain, 0–100	66.8 (19)	70 (24)	70.7 (22)	71 (38)	67.1 (24)	70 (35)	0.23
ESR, mm/h	35.7 (22)	30 (27)	40.3 (22)	38 (33)	40.2 (24)	35 (31)	0.06
RF, %	68		70		76		0.08
HAQ	1.28 (0.5)	1.2 (0.7)	1.6 (0.7)	1.6 (1.0)	1.5 (0.6)	1.4 (1.0)	0.03
DAS28	5.37 (1.5)	5.65 (1.8)	5.71 (1.5)	5.98 (1.8)	5.6 (1.4)	5.8 (1.4)	0.04
Glucocorticoid, baseline, %	29		44		30		0.06
DMARD before, %	97		99		96		0.19
DMARD baseline, %	25		31		44		0.01
MTX	78		78		81		
HCQ	11		11		7		
Leflunomide	8		8		5		
Sulfasalazine	1		1		4		
Cyclosporine	1		4		1		
Comorbidities, %	33		46		21		0.01

VAS: visual analog scale; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; HAQ: health assessment questionnaire; DAS28: Disease Activity Score based on 28 joints; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; HCQ: hydroxychloroquine; IQR: interquartile range.

cept (49%), and 136 infliximab (62%). Clinical response was considered at last visit before drug discontinuation or at 4 years (the end of the survey). Modified EULAR response criteria were used to assess the efficacy of each anti-TNF-α drug (Table 2). The proportion of patients achieving DAS28-driven remission (DAS28 < 2.6) at 4 years was significantly higher among those taking etanercept (43.6%) than those taking adalimumab (25.4%) or infliximab (29.6%; p < 0.01).

Survival analysis and predictors. Figure 1 shows the probability of the 4-year survival of each TNF-α antagonist. The retention rate of etanercept (51%) was significantly greater than that of infliximab (37.6%) or adalimumab (36.4%; p < 0.0001), which were not significantly different between them. Accordingly, the mean duration of therapy was significantly longer for etanercept (3.1 ± 2 years) than for adalimumab (2.6 ± 2 years) or infliximab (2.7 ± 2 years; p < 0.05). The overall drug survival was also stratified by inefficacy or occurrence of adverse events (Figure 2). The probability at 4 years of survival of anti-TNF-α therapy was significantly lower in patients with adverse events (9.7%) or with inadequate response (17.4%) than in other patients (50.7%; p < 0.0001).

Univariate logistic regression analysis of possible predictors of drug continuation showed that neither disease activity (DAS28) nor the biological measures (ESR) correlated with drug survival (Table 3). The best predictor of drug adherence was the baseline use of DMARD (OR 0.51, p < 0.001), of which only MTX was significant (OR 0.61, p <

0.001). The use of MTX significantly predicted drug survival only in the patients treated with infliximab (OR 0.24, p < 0.001). Surprisingly, concomitant diseases positively predicted drug continuation (OR 0.6, p < 0.01), even though no significant correlation with a single comorbidity was found. However, when multiple regression analysis was applied, the only baseline variable that significantly predicted drug survival at 4 years was DMARD intake (OR 0.64, p < 0.05), with MTX having the highest significance (OR 0.58, p < 0.01). Also, disease duration before starting anti-TNF-α therapy predicted drug retention, but the correlation was weak (OR 0.98, p < 0.05).
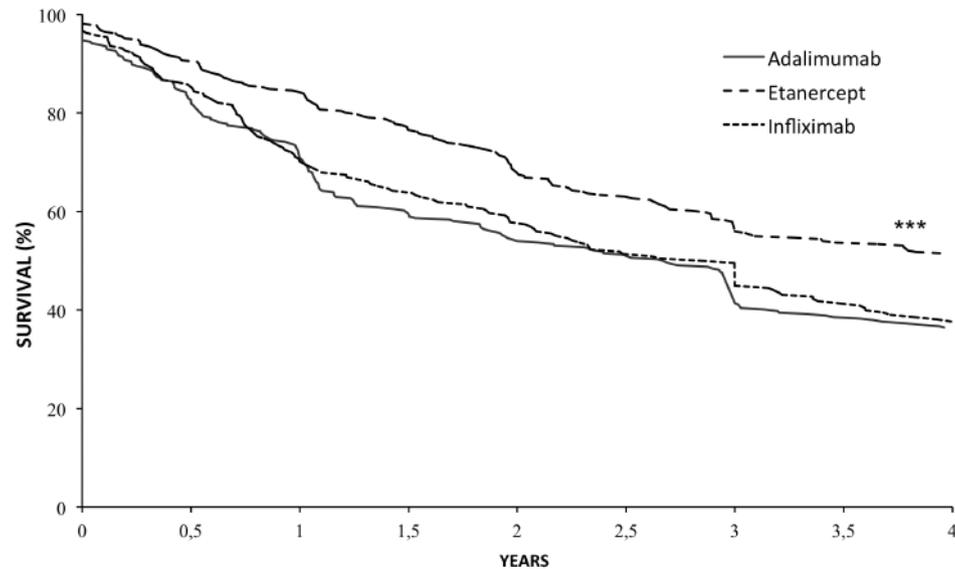
DISCUSSION

We compared real-life 4-year drug survival in patients with RA receiving 1 of the more commonly used TNF-α inhibitors (adalimumab, etanercept, or infliximab). Patients enrolled in RCT, including those in extended open-label phases, are quite different from those receiving routine standard of care in terms of comorbidities, associated therapies, and compliance. Together with drug safety and efficacy, all of these factors may affect the global retention rate of TNF-α blockers. Further, it may be difficult to measure the longterm clinical outcomes of a therapy in patients receiving standard care because of poor patient or even physician compliance. One alternative is to evaluate drug survival, the final result of the different variables affecting adherence to therapy.

The primary endpoint of our study was the analysis of the

Table 2. EULAR responses observed with etanercept (ETA), adalimumab (ADA), and infliximab (INF) at 1, 2, 3, and 4 years.

EULAR Responses	Adalimumab N	(%)	Etanercept N	(%)	Infliximab N	(%)	p (chi-square test)
1 year							
None	52	(25.7)	31	(16.6)	33	(20.2)	< 0.01 ETA vs ADA
Moderate	89	(44.0)	73	(37.8)	75	(46.0)	< 0.01 ETA vs INF
Good	61	(30.2)	89	(46.1)	55	(33.7)	< 0.01 ETA vs ADA
2 years							
None	31	(20.8)	26	(16.9)	18	(14.5)	NS
Moderate	50	(33.5)	49	(32.0)	52	(41.9)	< 0.01 ETA vs INF
Good	68	(45.6)	78	(50.9)	54	(43.5)	NS
3 years							
None	25	(19.5)	12	(9.1)	14	(14.1)	< 0.01 ETA vs ADA
Moderate	46	(35.9)	43	(32.8)	38	(38.3)	NS
Good	57	(44.5)	76	(58.0)	47	(47.4)	NS
4 years							
None	80	(39.6)	49	(23.2)	56	(33.1)	< 0.01 ETA vs ADA or INF
Moderate	62	(30.6)	54	(25.5)	54	(31.9)	NS
Good	60	(29.7)	108	(51.1)	59	(34.9)	< 0.01 ETA vs ADA or INF

EULAR: European League Against Rheumatism; NS: not significant.

Figure 1. Four-year drug survival rates of each tumor necrosis factor drug. The number of patients taking the therapy (patients at risk) and the number of withdrawals (events) at each year are shown. ***p < 0.0001.

longterm survival of adalimumab, etanercept, and inflix-imab in 853 patients with RA included in an Italian national registry. We chose 2003 and 2004 as the starting period of our analysis because that was when adalimumab became commercially available, and followed the patients for 4 years or until they discontinued the initial drug. The likeli-
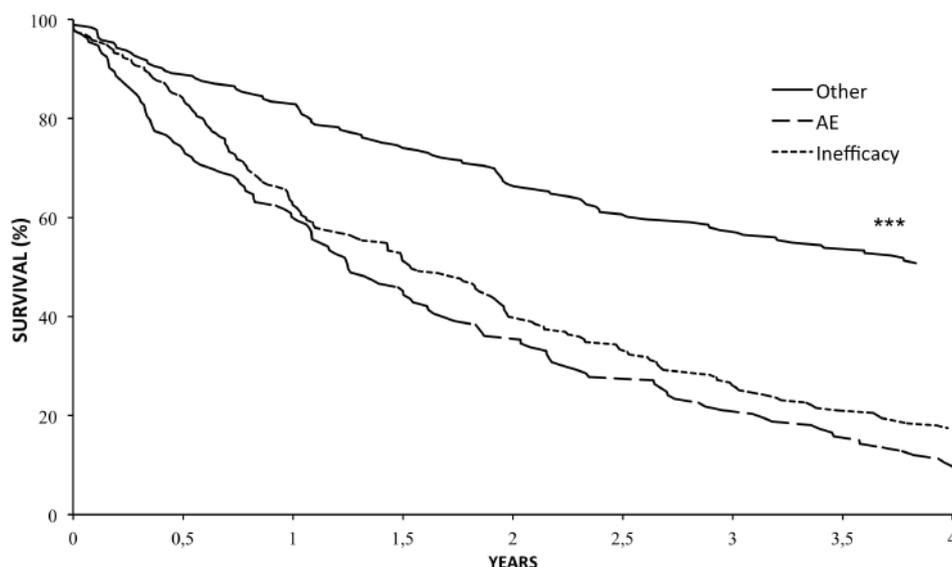
Figure 2. Four-year drug survival rates of anti-tumor necrosis factor drugs by main reasons of discontinuation. AE: adverse events. ***p < 0.0001.

Table 3. Odds ratios of anti-TNF-α therapy survival at 4 years. Results of various univariate and multivariate logistic regression analyses. Final multivariate models were found by stepwise regression.

Baseline Variables	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Sex: female vs male	1.15 (0.79–1.65)	0.46	1.3 (0.85–1.97)	0.22
Disease duration, yrs	0.99 (0.69–1.00)	0.054	0.98 (0.96–0.99)	0.02
ESR	1.00 (0.99–1.00)	0.69	1.01 (0.99–1.02)	0.14
DAS28	0.99 (0.90–1.09)	0.85	0.95 (0.85–1.06)	0.37
Comorbidities: yes vs no	0.67 (0.50–0. 87)	0.003	0.77 (0.56–1.05)	0.10
Glucocorticoids: yes vs no	0.76 (0.57–1.00)	0.05	1.18 (0.83–1.67)	0.39
DMARD: yes vs no	0.51 (0.38–0.68)	0.0001	0.64 (0.43–0.93)	0.02
MTX: yes vs no	0.61 (0.46–0.81)	0.0007	0.58 (0.41–0.82)	0.02

TNF: tumor necrosis factor; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score based on 28 joints; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate.

hood of survival was significantly greater in the case of etanercept (51%) than in that of adalimumab (37%) or infliximab (36%). These findings are consistent with some studies comparing the 3 TNF-α inhibitors. Analysis of the Danish DANBIO registry showed that etanercept had the highest adherence rate after 2 years (about 52%)[2], and an Italian regional observational study showed that the likelihood of survival on etanercept after 3 years was even higher (62%)[3]. A Swedish study comparing 5-year adherence found a higher rate for etanercept (65%) than infliximab (39%) when combined with MTX, and lower rates when they were given as monotherapy or in combination with other DMARD[10]. On the other hand, a survey of 230 patients with RA did not find any significant differences in drug survival of adalimumab (73%), etanercept (74%), and infliximab (66%) after 1 year[5], and similar results were reported in a French study after 2 years[11]. As expected, extended RCT have shown a greater longterm likelihood of drug survival than observational surveys[12,13,14].

A longer adherence to therapy does not imply a better clinical response. Hetland, *et al* has shown that adalimumab was the most effective TNF inhibitor, although etanercept had the highest retention rate[2]. These data were not confirmed in our analysis because we found that patients taking etanercept remained on therapy longer and achieved a higher rate of disease remission, defined by a DAS28 < 2.6, than patients taking adalimumab or infliximab.

We also analyzed possible predictors of drug survival. The presence of associated diseases and the coadministration of DMARD (especially MTX) were the best predictors of drug continuation. A weaker correlation was also found with the disease duration before beginning anti-TNF-α therapy. Better survival when using MTX in combination has recently been reported in the British Society for

Rheumatology (BSR) registry[15]. The proportion of patients taking MTX was quite low, denoting a gap between clinical practice and the official guidelines. A possible explanation is that our survey started from 2003, when the international guidelines on combination therapy (TNF inhibitors plus DMARD) had not been released. Indeed, the combination of MTX with the anti-TNF drug has been recommended by the Italian Society of Rheumatology and the French Society of Rheumatology in 2006 and 2007, respectively, and at that time the German Society of Rheumatology did not give any recommendation[16]. Further, in a recent appraisal of the BSR registry, the percentage of patients taking MTX in combination with TNF antagonists was only 59%[15]. The finding that comorbidities predict drug survival was unexpected but has also been reported by Marchesoni, et al[3]; however, it may be biased by the fact that the patients lost to followup had a lower frequency of comorbidities than those continuing therapy (data not shown). Further, this correlation was detected by univariate analysis but not by multiple regression analysis.

The data from different registries cannot be easily compared because of the different methods of collection and analysis, and because they are observational studies of unselected patients.

Further weaknesses in our analysis, which are shared by all the observational studies, must be considered. The absence of randomization or double-blinding, typical of RCT, may have unbalanced the 3 groups. There was a higher percentage of patients taking MTX in combination with infliximab than with adalimumab or etanercept. Further, we cannot be sure that the dose of infliximab was always kept unchanged throughout the survey. Nevertheless, our findings reconfirm that taking care of patients with RA in real life is more complex than in clinical trials, and that registries are valuable means of analysis of the behavior of large cohorts of patients over time.

APPENDIX

List of study collaborators. Gruppo Italiano di Studio sulle Early Arthritides (GISEA): Maria Lisa Bambara (Verona), Fabrizio Cantini (Prato), Gianfranco Ferraccioli (Rome), Rosario Foti (Catania), Roberto Giacomelli (L'Aquila), Roberto Gorla (Brescia), Walter Grassi (Jesi), Alessandro Mathieu (Cagliari), Ignazio Olivieri (Potenza), Giuseppe Passiu (Sassari), Leonardo Punzi (Padua), Carlo Salvarani (Reggio Emilia), Piercarlo Sarzi-Puttini (Milan), Raffaele Scarpa (Naples), Giovanni Triolo (Palermo), Francesco Trotta (Ferrara).

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