

## CONCISE REPORT

# Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0

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Received 15 June 2011  
Accepted 10 September 2011  
Published Online First  
13 October 2011

## ABSTRACT

**Objective** To investigate in rheumatoid arthritis (RA) the rate and reason of discontinuation of tumour necrosis factor (TNF) antagonists over the past decade.

**Methods** RA patients in BIOBADASER 2.0 were stratified according to the start date of their first TNF antagonist into 2000–3, 2004–6 and 2007–9 interval years. Cumulative incidence function of discontinuation for inefficacy or toxicity was estimated with the alternative reason as competing risk. Competing risks regression models were used to measure the association of study groups with covariates and reasons for discontinuation. Association is expressed as subhazard ratios (SHR).

**Results** 2907 RA patients were included in the study. Competing risk regression for inefficacy shows larger SHR for patients starting treatment in 2004–6 (SHR 2.57; 95% CI 1.55 to 4.25) and 2007–9 (SHR 3.4; 95% CI 2.08 to 5.55) than for those starting in 2000–3, after adjusting for TNF antagonists, clinical activity and concomitant treatment. Competing risk regression analysis for adverse events revealed no differences across the three time intervals.

**Conclusions** In RA, the discontinuation rate of TNF antagonists in the first year of treatment is higher more recently than a decade ago, inefficacy being the main reason for the increased rate. The rate of discontinuation for adverse events has remained stable.

The treatment of rheumatoid arthritis (RA) has improved over the past decade. Biological agents in combination with methotrexate appear to be the most effective therapeutic regimen for the treatment of RA patients who have failed on traditional disease-modifying antirheumatic drugs (DMARD).<sup>1</sup> Approximately one third of patients discontinue biological agents in the first year of treatment, although a recent review suggested that clinical effectiveness is reached before switching to another biological agent.<sup>2</sup> Adverse events (AE) and lack of efficacy are the most important reasons for the termination of biological and non-biological DMARD,<sup>3 4</sup> but other determinants that guide the choice of DMARD in individual patients may impact on the survival of the drug. These include intent to treat early, disease activity, patients' and doctors' preferences and expectations, and the availability of new drugs, among others.<sup>5</sup> Some changes have occurred over the past few years

in the scenario of RA treatment. A significant number of biological agents are now available, and expectations of patients and doctors are much higher than before.<sup>6</sup> These changes may have triggered the use of biological agents in patients with lower disease activity than in the past, the global admixture of patients treated with biological agents, and the criteria underlying the decision to discontinue the biological agent. Overall, a change in the pattern of discontinuation of biological agents would be expected compared with what happened in earlier times.

The aim of the present study was to investigate whether the rate of discontinuation of tumour necrosis factor (TNF) antagonists, by reason of discontinuation, has changed over the past decade in the nationwide registry BIOBADASER 2.0. The study is focused on TNF antagonists, because they are the only biological agents approved for patients failing traditional DMARD for the whole duration of the registry.

## PATIENTS AND METHODS

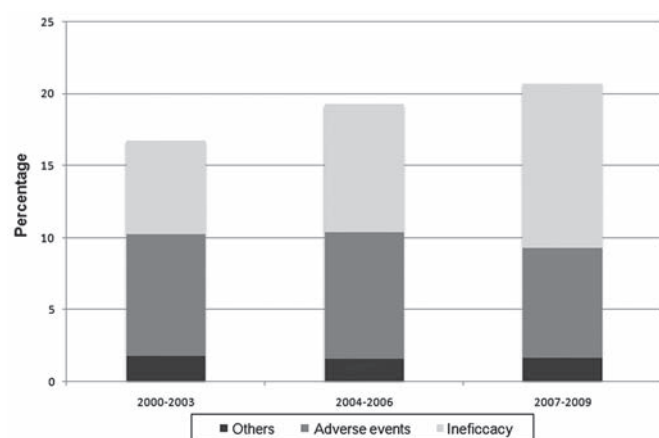
BIOBADASER 2.0 is a national drug registry of patients with rheumatic diseases starting treatment with any biological agent in 14 large public university hospitals in Spain. The registry was launched in February 2000. Patients entering the registry are followed prospectively and evaluated at the time when an AE or a change in the biological therapy (discontinuation, loss to follow-up, or start of another biological therapy) occurs. Data collected include: (1) data on patients including gender, date of birth, diagnosis and date of diagnosis, comorbidities and risk factors; (2) data on treatment including types of biological agents and dates of initiation and of discontinuation, concomitant treatment and tuberculosis prophylaxis; and (3) data on AE, including the date of occurrence, type and classification of AE according to the MedDRA. A full description has been published in detail elsewhere,<sup>7</sup> and the protocol is available at the register webpage (<http://biobadaser.ser.es/>). Procedures and materials comply with Declaration of Helsinki recommendations and with the Spanish regulations for data protection and research, and were approved by the Ethics Review Committee of the Hospital Ramon y Cajal (Madrid) acting as a reference committee.

In addition to the continuous online monitoring, a random sample of 280 patients was selected and audited annually in situ at all centres. Further validation of data includes direct consented contact with patients by the project managers to confirm whether patients are alive or have been admitted to a hospital for any reason in the preceding year.

For this study, we selected the first year of the first treatment of all RA patients in the registry. This particular selection was deemed convenient to make the groups comparable in the analysis. RA patients starting therapy were stratified by nearly equal periods of time: 2000–3, 2004–6 and 2007–9.

## STATISTICAL ANALYSES

The population is described using descriptive statistics as indicated by the distribution of variables. Continuous variables are expressed as means with SD, and categorical variables as



**Figure 1** Main reason for discontinuation during the first year of treatment. Each bar represents the percentage of discontinuation (inefficacy, adverse events or others) by period of treatment initiation (calendar year).

**Table 1** Baseline characteristics of RA patients by period of treatment initiation (calendar year)

	2000–3	2004–6	2007–9	p Value
No of patients	1170	955	782	
Women, n (%)	947 (81)	748 (78)	623 (80)	
Age at baseline, mean (SD)	54 (13)	54 (13)	55 (14)	
Disease duration at baseline (years), mean (SD)	11 (8)	10 (8)	9 (9)	***
DAS28, mean (SD)†	5.8 (1.2)	5.4 (1.2)	5.3 (1.3)	***
Diabetes, n (%)	69 (6)	56 (6)	52 (7)	
Hypercholesterolaemia, n (%)	132 (11)	124 (13)	112 (14)	
Hypertension, n (%)	245 (21)	164 (17)	173 (22)	*
Glucocorticoids, n (%)	541 (46)	501 (52)	502 (64)	***
Methotrexate, n (%)	574 (49)	510 (53)	509 (65)	***
Leflunomide, n (%)	149 (13)	177 (19)	188 (24)	***
Other DMARD, n (%)	66 (6)	97 (10)	74 (9)	***
TNF antagonists, n (%)				
Etanercept	257 (22)	287 (30)	329 (42)	***
Infliximab	778 (67)	312 (33)	183 (23)	***
Adalimumab	135 (12)	356 (37)	270 (35)	***

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

†Not available for all patients. Percentages of missing data are: 58%, 45% and 9%, respectively.

Baseline characteristics in the three time groups were compared using the  $\chi^2$  test or analysis of variance.

DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

totals with percentages. Baseline characteristics in the three time groups were compared using the  $\chi^2$  test or analysis of variance.

The cumulative incidence function of cause  $k$  of discontinuation (inefficacy or AE) defined by the probability,  $\text{Prob}(T=t, F=k)$ , of failing from cause  $k$  before time  $t$  was also estimated with the alternative reason as competing risk. We considered all other reasons for discontinuation (lost to follow-up, patient's decisions, planned or desired pregnancy, remission, surgery, etc.) as right censoring.

Competing risks regression models according to the method of Fine and Gray<sup>8</sup> were used to measure the association of study groups with covariates at baseline (clinical characteristics, comorbidities and concomitant treatment) and the reason for discontinuation. Main interactions between calendar year or molecule and RA profile (disease duration and activity) were investigated. All analyses were done with Stata 11.2, and a level of  $p < 0.05$  was considered statistically significant.

## RESULTS

A total of 2907 RA patients was included in the study: 1170 in the first period of treatment initiation (2000–3); 955 in the second period (2004–6) and 782 in the third period (2007–9). The baseline characteristics of patients by group are depicted in table 1. While sociodemographic characteristics and comorbidity were similar in all groups, disease activity and disease duration appeared to be lower in recent years. The first TNF antagonist was discontinued in the first year at a rate of 17%, 19% and 21% in 2000–3, 2004–6 and 2007–9, respectively (no statistical differences,  $p=0.074$ ). The proportion of reasons for discontinuation by study groups is shown in figure 1. In the early years of TNF antagonist use the main reason for discontinuation was AE, whereas in recent years the most common reason for discontinuation was inefficacy. Discontinuation due to other causes (mainly lost to follow-up, patient's decisions and planned or desired pregnancy) and to AE remained stable over time. Mean (SD) disease activity score in 28 joints (DAS28) at discontinuation due to inefficacy were 5.7 (1.3), 5.6 (1.4) and 5.2 (1.7) in each time interval, respectively, whereas mean DAS28 at discontinuation due to AE were 4.8 (2), 4.3 (1.4) and 3.9 (2.2) in 2000–3, 2004–6 and 2007–9, respectively.

Cumulative incidence curves in figure 2 show that it is more likely to discontinue the TNF antagonists due to inefficacy in recent years, whereas the probability of discontinuation due to an AE remained stable over the three time intervals.

Competing risk regression for inefficacy (table 2) showed larger subhazard ratios if treatment was started in 2007–9 compared with 2000–3, after adjusting for confounding. Competing risk regression for AE (right panel of table 2) showed no differences across the three time intervals. Main interactions were not significant.

## DISCUSSION

In the present study, we have investigated the discontinuation rate of TNF antagonists by the main reasons for discontinuation over the past decade in RA patients registered in BIOBADASER. The results show that discontinuation in the first year of treatment is in recent years higher than it was before, and that more patients discontinue biological agents due to lack or loss of efficacy than to AE. Interestingly, the rate of discontinuation due to AE has remained stable for years.

Our study aimed to substantiate the changing discontinuation patterns of TNF antagonists in RA patients using data collected over 10 years. Observational studies have reported a discontinuation rate of TNF antagonists in the first year for RA that ranges from 20% to 40%. In earlier studies, discontinuation due to AE was

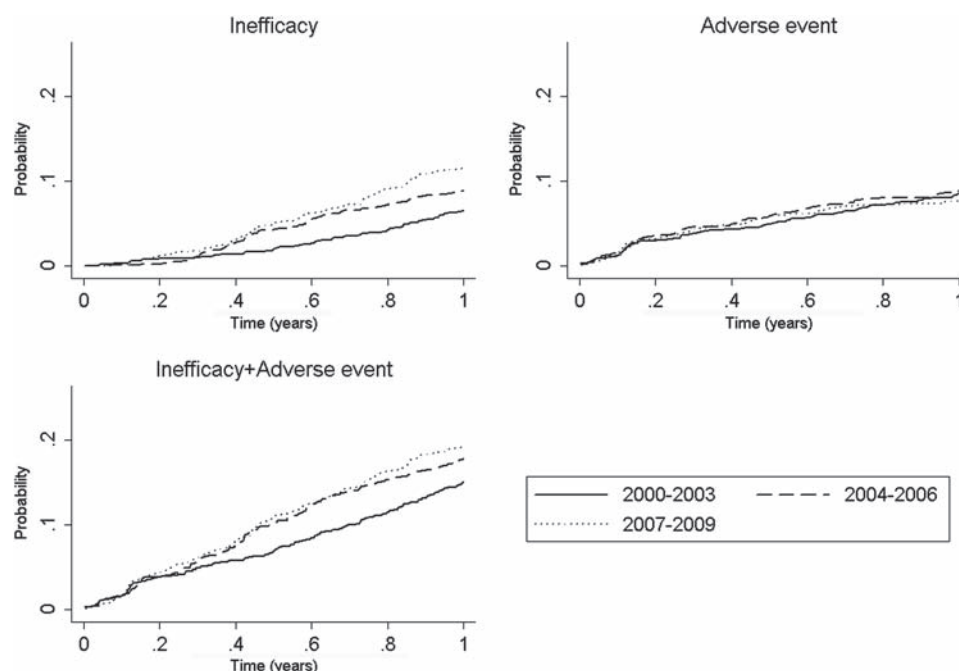
## Clinical and epidemiological research

more common than discontinuation due to inefficacy.<sup>3 4 9-18</sup> This disparity in the rate of discontinuation and the reason of discontinuation may reflect the constant revision of practice guidelines and consensus statements on the criteria of introduction, duration of treatment and of cessation of TNF antagonists. In this study, the characteristics of patients starting TNF antagonists differs from early to more recent years. Compared with earlier, patients starting biological agents more recently have lower disease activity, shorter disease duration and greater use of glucocorticoids, methotrexate and leflunomide. Also, DAS28 at discontinuation for inefficacy was lower in the most recent time interval. This trend towards a more intensive use of traditional therapies, less stringent criteria for the use of biological agents, and a higher expectation regarding response to therapy may have a significant impact on the use of biological agents, and perhaps on the long-term outcome of RA

patients. Large proportions of RA patients are likely to be treated with biological agents in the future. The cost of acquisition of biological agents is high, and demonstration of their cost effectiveness in real life within this changing scenario will be necessary.

The proportion of patients discontinuing TNF antagonists for AE remains stable across the observational study, with a trend to lower mean DAS28 at discontinuation in recent years. In the group of patients discontinuing for AE, the mean DAS28 at discontinuation was much lower than at discontinuation for inefficacy, indicating that AE were independently the major reason for discontinuation and not inefficacy or other reasons in the wake of mild AE.

In clinical trials of new biological agents in RA, many patients are selected on the basis that they are incomplete responders to TNF antagonists. This population may include patients failing on TNF antagonists for any reason. Our present work demonstrates



**Figure 2** Cumulative incidence curves of reason for discontinuation by period of treatment initiation (calendar year). Curves represent the probabilities of the occurrence of events (inefficacy, adverse events or both) in each period of treatment initiation (calendar year), during the first year of follow-up.

**Table 2** Competing risk regression models for reason of discontinuation (inefficacy or AE)

	Inefficacy		AE	
	Bivariate SHR (95% CI)	Multivariate SHR (95% CI)	Bivariate SHR (95% CI)	Multivariate SHR (95% CI)
Age at baseline (per 10 years)	0.87 (0.8 to 0.96)**	0.85 (0.75 to 0.97)*	0.93 (0.85 to 1.03)	0.89 (0.8 to 0.99)*
Disease duration (per 10 years)	0.77 (0.63 to 0.94)**	0.77 (0.59 to 1)*	1.11 (0.97 to 1.28)	1.19 (1.03 to 1.37)*
DAS28	1.15 (1.02 to 1.29)*	1.23 (1.08 to 1.41)**	-	-
Glucocorticoids	1.44 (1.11 to 1.85)**	1.78 (1.2 to 2.62)**	1.34 (1.03 to 1.72)*	1.35 (1.04 to 1.77)*
Methotrexate	0.9 (0.71 to 1.16)	0.65 (0.45 to 0.92)*	-	-
Leflunomide	-	-	1.55 (1.16 to 2.07)**	1.62 (1.19 to 2.2)**
TNF antagonist				
Etanercept	Reference	Reference	Reference	Reference
Infliximab	1.3 (0.96 to 1.77)	2.69 (1.7 to 4.25)***	1.03 (0.78 to 1.36)	1.05 (0.78 to 1.43)
Adalimumab	1.25 (0.88 to 1.76)	1.9 (1.18 to 3.07)**	0.47 (0.32 to 0.7)***	0.44 (0.3 to 0.66)***
Period of treatment initiation				
2000-3	Reference	Reference	Reference	Reference
2004-6	1.4 (1.03 to 1.91)*	2.57 (1.55 to 4.25)***	1.05 (0.78-1.4)	1.23 (0.89 to 1.7)
2007-9	1.82 (1.34 to 2.46)***	3.4 (2.08 to 5.55)***	0.91 (0.66 to 1.26)	1.08 (0.75 to 1.54)

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

Multivariate models were adjusted for gender, age, disease duration, comorbidities and concomitant DMARD treatment.

AE, adverse event; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; SHR, subhazard ratio; TNF, tumour necrosis factor.

that this population may be changing and the results of randomised controlled trials may not be comparable with earlier studies in RA patient incomplete responders to TNF antagonists. Our study has some limitations and strengths. The survival of a drug could be considered as a surrogate of drug effectiveness in the clinical setting. The decision to start or to stop treatment, although guided by recommendations, was based in our study on the physician's clinical opinion, and thus a possible influence of the physician on the results cannot be excluded. However, this does not have an impact on discontinuation for safety, as reflected by the constant rate of discontinuation for AE in all the time intervals. Other constraints could be the consistency of the information. Information in this article was gathered from the Spanish registry BIOBADASER 2.0 with a high data consistency as reported before.<sup>19</sup> Consistency of data was assured, and data were validated by calling and checking with the patients and by on-site audits. This consistency, valuable for data interpretation, strengthens the relevance of the present work.

Of note, the cumulative incidence of cause of discontinuation was estimated using a competing risks regression model. This regression analysis creates a model for the subhazard function of a failure event of interest. A standard analysis using Cox regression is appropriate only for a hypothetical universe in which competing events do not occur.<sup>8</sup>

In summary, the management and use of TNF antagonists in RA patients has changed in recent years. A trend towards the early use of TNF antagonists in patients with lower disease activity and more stringent response criteria for discontinuation is occurring. When interpreting new data from observational and experimental studies, this changing pattern should be borne in mind.

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**Acknowledgements** The authors would like to acknowledge the dedication to BIOBADASER of Angel Guillen, monitor, and Juan Manuel Barrio, technology assistant.

**Funding** BIOBADASER is supported by the Spanish Society and the Spanish Agency of Medicines and Healthcare Products. Grants in approximately equal amounts (all under €25 000/year) from Roche, Abbott, BMS, MSD and Pfizer contribute to the support of the registry. This work was partly supported by the RETICS Program, RD08/0075 (RIER) from Instituto de Salud Carlos III (ISCIII).

**Competing interests** JJGR is on the advisory boards of Schering-Plough, UCB, Wyeth, Pfizer, MSD, Bristol Meyers Squibb and Roche, and has received lecture fees

from Abbott Laboratories, Wyeth, MSD, Roche, Bristol Meyers Squibb and Schering-Plough. LC has received lecture fees from Abbott Laboratories and Pfizer. CRL has received lecture fees from Abbott, Bristol Myers Squibb and Wyeth. CCF, MM and MAD have no conflicts of interest.

**Patient consent** Obtained.

**Contributors** JJGR: Conception and study design, interpretation of data, drafting the article, revising it critically for important intellectual content. CRL, CCF and MM: Data collection, interpretation, revising it critically for important intellectual content. MAD: Statistical analysis, interpretation of data, revising it critically for important intellectual content. LC: Study design, interpretation of data, drafting the article, revising it critically for important intellectual content. All authors gave final approval of the version to be published.

**Ethics approval** This study was approved by the Ethics Review Committee of the Hospital Ramón y Cajal, Madrid, Spain.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Ann Rheum Dis* 2012 71: 382-385 originally published online October 13, 2011

doi: 10.1136/annrheumdis-2011-200302

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