Rheumatology Advance Access published July 7, 2010
RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/keq207

Safety and retention rate of off-label uses of TNF antagonists in rheumatic conditions: data from the Spanish registry BIOBADASER 2.0

Loreto Carmona[1], Miguel A. Descalzo[1], Dolores Ruiz-Montesinos[2], Francisco J. Manero-Ruiz[3], Eva Perez-Pampin[4] and Juan J. Gomez-Reino[4], on behalf of the BIOBADASER 2.0 Study Group*

Abstract

Objective. To compare the safety and retention rate of TNF antagonists used in approved indications (AIs) and non-AIs.

Methods. Analysis of the Spanish registry BIOBADASER 2.0 (February 2000 to October 2009). Patients were classified into AIs and off-label uses (OUs), according to the European Medicines Agency approval. Retention rates, incidence rates (IRs) and IR ratios (IRRs) of adverse events (AEs) with 95% CI were compared between uses, by log-rank test, cause-specific Cox regression models and generalized linear models with Poisson's distribution.

Results. First treatment with TNF antagonist was available in 5150 patients, of whom 4594 (89%) were AIs (2854 RA, 882 AS and 858 PsA) and 556 (11%) were OUs [437 chronic arthropathies in the spectrum of SpAs (CA) and 119 chronic immune-mediated diseases (CIDs)]. The IR of AE was largest in CID (649 events per 1000 patient-years) and lowest in PsA (250 events per 1000 patient-years). The occurrence of AEs was significantly associated with OU [IRR of CA *vs* RA 1.33 (95% CI 1.19, 1.49); IRR of CID *vs* RA 1.94 (95% CI 1.62, 2.31). The largest hazard ratio for discontinuation was for CID *vs* RA (1.33; 95% CI 1.02, 1.71) and especially *vs* AS (2.18; 95% CI 1.63, 2.90).

Conclusions. OUs of TNF antagonists need a very close ascertainment of risk/benefit. The safety and retention pattern for CID is similar to that for RA and the pattern for CA resembles that of AS. This study shows an additional value of a national registry.

Key words: Safety, Effectiveness, Registry, Off-label, Rheumatic diseases.

Introduction

TNFs have a role in the pathogenesis of immune-mediated inflammatory rheumatic conditions, and TNF antagonists have been approved by the European Medicines Agency (EMA) for the treatment of RA, AS, PsA and JIA. A growing number of published reports suggest that TNF antagonists may also be effective in the treatment of conditions outside their currently approved indication (AI) [1–6]. Concerns regarding off-label use (OU) include applicability, contraindications and precautions of drugs that were developed for a different use. Thus, recommendations have been made to analyse effectiveness and safety of OU drugs [7, 8].

Registries may pose a potential for analysing the safety of OUs. This is the case of the Spanish registry of adverse events (AEs) of biologic therapies in rheumatic diseases (BIOBADASER 2.0). In the present report, we describe the safety profile and retention rate of OUs of TNF antagonists in >500 patients suffering from a variety of rheumatic conditions. In addition, we

[1]Research Unit, Spanish Society of Rheumatology, Madrid, [2]Rheumatology Unit, Hospital Universitario Virgen de la Macarena, Sevilla, [3]Rheumatology Unit, Hospital Universitario Miguel Servet, Zaragoza and [4]Rheumatology Unit and Department of Medicine, Hospital Clínico Universitario, Medical School, Universidad de Santiago de Compostela, Santiago de Compostela, Santiago, Spain.

Submitted 30 March 2010; revised version accepted 4 June 2010.

Correspondence to: Juan J. Gomez-Reino, Rheumatology and Department of Medicine, Hospital Clínico Universitario, Medical School, Universidad de Santiago de Compostela, Santiago de Compostela, A Choupana s/n, 15706 Santiago, Spain.
E-mail: juan.gomez-reino.carnota@sergas.es

*See acknowledgements for a list of the members of the BIOBADASER 2.0 Study Group.

aimed to study their safety and retention rates in comparison with RA and AS.

Methods

BIOBADASER 2.0 is a national drug safety registry of patients with rheumatic diseases starting treatment with any biologic and followed thereafter. The original registry BIOBADASER was established in February 2000 with 100 centres [9]. BIOBADASER 2.0 is an adaptation of the former made in 2006, which includes all data, since February 2000, from 14 large public hospitals, as a way to reinforce quality and consistency, by facilitating monitoring. Patients entering the registry are followed prospectively and evaluated at the time an AE or a change in the biological therapy occurs; thus providing specific cohorts for specific analyses. The following data are collected online and systematically by participating physicians: (i) data of patients including gender, date of birth, diagnosis, date of diagnosis, comorbidities and risk factors; (ii) data on treatment including types of biologics and dates of initiation and of discontinuation, concomitant treatment for the rheumatic disease and tuberculosis prophylaxis preceding treatment; and (iii) data on AEs, including date of occurrence, type and classification of AE according to the Medical Dictionary for Regulatory Affairs [10], severity, outcome and concomitant treatments at the time of the AE.

For assessment of the consistency and quality, the database is constantly monitored online and once a year participating units are advised to update the information on all patients. Additionally, a random sample of patients is selected and audited *in situ* in all 14 centres annually. Starting from January 2008, additional validation of the data was also assured by yearly direct 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.

The registry protocol and materials of BIOBADASER 2.0 are available at http://biobadaser.ser.es/biobadaser/eng/index.html and were approved by the Ethics Review Committee of the Hospital Ramon y Cajal (Madrid, Spain) acting as reference committee. Starting from January 2008, all patients signed an informed consent that includes an agreement to be contacted by a member of the registry team to gather medical information, performed according to the principles of the latest Helsinki recommendations and complying with the Spanish regulations for data protection and research.

Study groups and definitions

AIs and OUs of biologics have been registered in BIOBADASER 2.0 since its launch. All adult patients with a diagnosis included in one of the study groups in whom a TNF antagonist was used were included in the analysis.

Patients were classified into AIs and OUs according to the present EMA AIs. AIs include RA, AS and PsA. JIA patients were not included in this analysis as age is a confounder for AEs and the total number of children with JIA followed in the participating hospitals in BIOBADASER 2.0 was low. OU was classified into: (i) chronic arthritis consisting of undifferentiated spondyloarthritis, enteropathic arthritis, seronegative chronic polyarthritis, seronegative chronic oligoarthritis, Still's disease, juvenile uSpA, ReA, Sapho's syndrome and juvenile AS; and (ii) chronic immune-mediated diseases (CIDs) including Behçet's disease, uveitis without rheumatic disease, vasculitis, SLE, PM/DM, sarcoidosis, relapsing polychondritis, SS and SSc.

Exposure

Time of exposure is considered from the beginning of therapy with a TNF antagonist to date of the last administration plus twice the half-life of the TNF antagonist (3 days for etanercept, 2 months for infliximab and 14 days for adalimumab). Observation spans from entry in the cohort (beginning of TNF antagonist date) to censor date (last visit in a lost-to-follow-up patient or discontinuation treatment date), death or 9 October 2009, whichever occurred first. Only the first treatment was considered in the analysis.

Statistical analyses

Continuous variables are expressed as mean (S.D.) and categorical variables are expressed as total with percentages. The population is described using descriptive statistics indicated by the distribution of variables.

The probability of discontinuation from any cause of interest was calculated using Kaplan–Meier survival curves, and a log-rank test was performed stratifying patients by study group for comparison. In patients discontinuing treatment, the cumulative incidence function [11] of cause k (inefficacy, AE or other cause) defined by the probability, Prob ($T \leqslant t$, $F = k$), of failing from cause k before time t, was also estimated, competing risks being the other reasons. Multivariate cause-specific Cox regression models adjusted by sex, age at treatment start and disease duration were used to measure the association between study groups, stratifying patients by reason for discontinuation. An analysis of correspondence with symmetric normalization was performed to examine whether the reason for discontinuation of TNF antagonists differed substantially in AIs and OUs.

Incidence rate (IR) of AE per 1000 patient-years of exposure with 95% CI was calculated in patients with RA, AS, PsA, CA and CID. IR ratios (IRRs) with 95% CI were obtained from generalized linear models with Poisson's distribution, and were adjusted by sex, age at treatment start and disease duration. As infliximab was the most widely used TNF antagonist, we performed separated estimations for infliximab. All analyses were done with Stata 10.1 (Stata Corp., College Station, TX, USA).

Results

Characteristics of the included patients are depicted in Table 1. Overall, 5150 patients were included, 4594 (89%) of whom were treated with TNF antagonists in AIs and 556 (11%) outside AIs. Among the patients with

TABLE 1 Characteristics of the patients and treatments by OUs and AIs

Disease	*n*	Female, *n* (%)	Age, mean (S.D.), years	Disease duration, mean (S.D.), years	Infliximab[a], *n* (%)	Etanercept[a], *n* (%)	Adalimumab[a], *n* (%)
RA[b]	2854	2277 (80)	54.0 (13.7)	10.1 (8.2)	1283 (45)	841 (29)	730 (26)
AS[b]	882	206 (23)	43.6 (12.2)	12.5 (10)	522 (59)	214 (24)	146 (17)
PsA[b]	858	405 (47)	47.1 (12.5)	9.5 (7.5)	316 (37)	346 (40)	196 (23)
uSpA[c]	210	99 (47)	42.1 (12.7)	7.4 (6)	119 (57)	63 (30)	28 (13)
Enteropathic arthritis[c]	96	46 (48)	40.5 (12.6)	8.5 (6.2)	78 (81)	2 (2)	16 (17)
Behçet's disease[d]	41	24 (59)	34.2 (10.7)	8.3 (5.5)	37 (90)	2 (5)	2 (5)
Seronegative chronic polyarthritis[c]	33	20 (61)	44.1 (12.2)	7.6 (9.6)	19 (58)	9 (27)	5 (15)
Seronegative chronic oligoarthritis[c]	28	14 (50)	40.8 (12.1)	4.9 (3.9)	12 (43)	12 (43)	4 (14)
Uveitis without rheumatic disease[d]	18	13 (72)	36.2 (13)	6.1 (6.5)	15 (83)	0 (0)	3 (17)
Vasculitis[d]	17	13 (76)	51.4 (22.5)	5.2 (4.1)	13 (76)	3 (18)	1 (6)
Juvenile AS[c]	15	3 (20)	27.5 (11.7)	14.2 (10.6)	5 (33)	4 (27)	6 (40)
Still's disease[c]	15	6 (40)	42.6 (11.9)	13.8 (10.5)	8 (53)	6 (40)	1 (7)
Juvenile uSpA[c]	15	4 (27)	29.7 (13.4)	16.3 (15.3)	11 (73)	3 (20)	1 (7)
ReA[c]	13	3 (23)	47.1 (15.1)	8.8 (6.8)	10 (77)	3 (23)	0 (0)
SLE[d]	12	11 (92)	38.2 (14.7)	8.6 (7.5)	3 (25)	7 (58)	2 (17)
Sapho's syndrome[c]	12	10 (83)	43.9 (12)	6.5 (3.9)	8 (67)	3 (25)	1 (8)
Relapsing polychondritis[d]	8	7 (88)	46.1 (11.3)	5.7 (6)	8 (100)	0 (0)	0 (0)
PM/DM[d]	8	4 (50)	38 (25.4)	11.4 (10.4)	5 (63)	2 (25)	1 (13)
Sarcoidosis[d]	8	6 (75)	42.7 (16.4)	8.2 (5.7)	7 (88)	1 (13)	0 (0)
SS[d]	4	4 (100)	50.4 (11.6)	9.5 (4.9)	3 (75)	0 (0)	1 (25)
Scleroderma[d]	3	3 (100)	50.6 (15.3)	15.1 (1.3)	3 (100)	0 (0)	0 (0)
CA	437	205 (47)	41.1 (13.1)	8.3 (7.5)	270 (62)	105 (24)	62 (14)
CIDs	119	85 (71)	39.9 (16.2)	8 (6.3)	94 (79)	15 (13)	10 (8)

[a]First treatment. [b]AI. [c]CA. [d]CID.

OUs, 437 suffer from CA and 119 from CID. Patients with CA and CID were younger and had shorter disease duration than the others. Gender distribution was uneven as expected. RA and CID patients were more commonly female, whereas CA, AS and PsA patients were more commonly male. Infliximab was the leading TNF antagonist used in AI and OU. Adalimumab was sparsely used off label. More than two-thirds of the patients in the CID group received CSs concomitant with the TNF antagonists, whereas only one-third of the patients in the CA group were treated with this drug (Table 2).

All AEs and specific events individually (Table 3) were more common in CID than in other groups, followed by CA and RA, with large and statistically significant IRR for both OU groups compared with RA or AS. This is mainly related to an excess of 'infections and infestations', and of 'general disorders and administration site conditions' in OU. AS patients have a significantly lower IRR of AEs compared with RA, crude and adjusted by gender, age and disease duration. As infliximab is the most widely used TNF antagonist in OU, we performed separated estimations for infliximab (Table 4) and similar results were achieved.

Retention rate curves (Fig. 1) were statistically different ($P < 0.0001$, log-rank test) between uses of TNF antagonists and demonstrated the highest survival in patients with AS and the lowest in CID. Cause-specific analysis for discontinuation (Table 5) showed a larger hazard ratio (HR) for CID compared with RA and AS in part due to a larger HR for discontinuation for AEs. The HR for discontinuation for CA was significantly larger than for AS but not for RA. The analysis by infliximab use demonstrated only a larger HR for discontinuation for both CA and CID compared with AS. CA has a lower HR for discontinuation compared with RA. Cumulative incidence curves (Fig. 2) show a similar pattern in RA to that in CID, and also similarity between AS and CA. The correspondence analysis (data not shown) had very low total inertia, and very low contribution of the specific categories, disease and reason for discontinuation, and therefore could not show a clear pattern of association between different reasons for discontinuation and AIs or OUs.

Discussion

This study is a description of the safety profile of the OU of TNF antagonists in patients included in a registry of rheumatic diseases. The spectrum of patients treated off label with TNF antagonists in our study seems to correspond to current practice, and is similar to the uses reported in other settings [12]. Overall, the safety profile of OU TNF antagonists in diseases characterized primarily by chronic inflammatory arthropathy was similar to that of SpA, whereas the profile in patients with chronic inflammatory conditions was in general comparable to that of RA.

Table 2 Use of most relevant concomitant medications by patients treated with TNF antagonists, by study group

n	RA 2854	AS 882	PsA 858	CA 437	CID 119
CSs, *n* (%)	1488 (52)	123 (14)	250 (29)	142 (32)	78 (66)
MTX, *n* (%)	1534 (54)	264 (30)	441 (51)	183 (42)	24 (20)
LEF, *n* (%)	498 (17)	17 (2)	82 (10)	20 (5)	2 (2)

Table 3 IR of AEs by OUs and AIs

All TNF antagonists	Number of events	Patient-years	IR (95% CI) × 1000	IRR (95% CI)[a]	
				vs RA	*vs* AS
All AEs					
RA	3087	8471	364 (352, 378)	1	1.07 (0.97, 1.18)
AS	714	2661	268 (249, 289)	0.93 (0.85, 1.03)	1
PsA	654	2613	250 (232, 270)	0.81 (0.74, 0.89)***	0.87 (0.77, 0.97)*
CA	441	1180	374 (340, 410)	1.33 (1.19, 1.49)***	1.43 (1.26, 1.63)***
CIDs	164	253	649 (557, 756)	1.94 (1.62, 2.31)***	2.08 (1.71, 2.52)***
Infections and infestations					
RA	1131	8471	134 (126, 142)	1	1.07 (0.91, 1.26)
AS	243	2661	91 (81, 104)	0.94 (0.79, 1.1)	1
PsA	241	2613	92 (81, 105)	0.82 (0.71, 0.96)*	0.88 (0.72, 1.06)
CA	157	1180	133 (114, 156)	1.36 (1.13, 1.64)**	1.45 (1.17, 1.8)***
CIDs	62	253	245 (191, 315)	1.89 (1.41, 2.55)***	2.02 (1.46, 2.79)***
General disorders and administration site conditions					
RA	348	8471	41 (37, 46)	1	1.23 (0.91, 1.67)
AS	64	2661	24 (19, 31)	0.81 (0.6, 1.1)	1
PsA	62	2613	24 (18, 30)	0.69 (0.52, 0.92)*	0.85 (0.59, 1.22)
CA	59	1180	50 (39, 65)	1.47 (1.08, 2.01)*	1.81 (1.25, 2.63)**
CIDs	24	253	95 (64, 142)	2.15 (1.34, 3.45)**	2.65 (1.56, 4.49)***
Skin and subcutaneous tissue disorders					
RA	235	8471	28 (24, 32)	1	1.03 (0.72, 1.46)
AS	55	2661	21 (16, 27)	0.97 (0.69, 1.38)	1
PsA	38	2613	15 (11, 20)	0.63 (0.44, 0.9)*	0.64 (0.42, 0.99)*
CA	27	1180	23 (16, 33)	1.01 (0.65, 1.57)	1.04 (0.63, 1.69)
CIDs	15	253	59 (36, 98)	2.09 (1.16, 3.77)*	2.14 (1.12, 4.1)*
Gastrointestinal disorders					
RA	120	8471	14 (12, 17)	1	1.02 (0.64, 1.63)
AS	32	2661	12 (9, 17)	0.98 (0.61, 1.56)	1
PsA	25	2613	10 (6, 14)	0.77 (0.49, 1.24)	0.79 (0.45, 1.38)
CA	29	1180	25 (17, 35)	1.94 (1.2, 3.16)**	1.99 (1.14, 3.46)*
CIDs	2	253	8 (2, 32)	0.78 (0.19, 3.19)	0.8 (0.19, 3.4)
Others					
RA	1253	8471	148 (140, 156)	1	1.05 (0.91, 1.22)
AS	320	2661	120 (108, 134)	0.95 (0.82, 1.1)	1
PsA	288	2613	110 (98, 124)	0.87 (0.76, 1)*	0.91 (0.77, 1.08)
CA	169	1180	143 (123, 166)	1.27 (1.07, 1.52)**	1.34 (1.1, 1.64)**
CIDs	61	253	241 (188, 310)	1.96 (1.48, 2.6)***	2.06 (1.52, 2.8)***

Adjusted IRR compared with RA or AS of all TNF antagonists combined. [a]Adjusted by gender, age at treatment start and disease duration. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

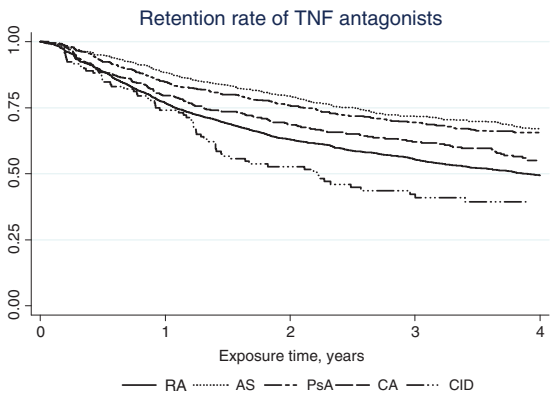
Patients may benefit from off-label prescribing supported by sound scientific and medical evidence. TNF may have a role in the pathogenesis of several chronic inflammatory conditions and inhibition of TNF outside the current AIs has been done in patients resistant to standard treatments in inflammatory myopathies [1], skin diseases [2, 3], multisystem sarcoidosis [4], ANCA-associated systemic vasculitis [6] and many other autoimmune disorders [5, 12]. Off-label prescribing presents a challenge as well as an opportunity involving

Table 4 IR of AEs, by OUs and AIs of infliximab

Infliximab	Number of events	Patient-years	IR (95% CI) × 1000	IRR (95% CI)[a]	
				vs RA	*vs* AS
All AEs					
RA	1712	4182	409 (390, 429)	1	1.02 (0.91, 1.14)
AS	564	1823	309 (285, 336)	0.98 (0.87, 1.10)	1
PsA	388	1134	342 (310, 378)	0.99 (0.88, 1.11)	1.00 (0.88, 1.15)
CA	371	863	430 (388, 476)	1.40 (1.23, 1.59)***	1.43 (1.24, 1.64)***
CIDs	138	198	697 (590, 823)	1.91 (1.57, 2.32)***	1.95 (1.57, 2.41)***
Infections and infestations					
RA	656	4182	157 (145, 169)	1	1.07 (0.88, 1.29)
AS	201	1823	110 (96, 127)	0.94 (0.77, 1.14)	1
PsA	147	1134	130 (110, 152)	0.97 (0.80, 1.17)	1.03 (0.83, 1.29)
CA	137	863	159 (134, 188)	1.38 (1.12, 1.69)**	1.47 (1.17, 1.85)**
CIDs	48	198	242 (183, 322)	1.63 (1.16, 2.28)**	1.74 (1.21, 2.5)**
General disorders and administration site conditions					
RA	237	4182	57 (50, 64)	1	1.39 (0.98, 1.96)
AS	53	1823	29 (22, 38)	0.72 (0.51, 1.02)	1
PsA	48	1134	42 (32, 56)	0.89 (0.64, 1.24)	1.24 (0.82, 1.85)
CA	53	863	61 (47, 80)	1.34 (0.95, 1.89)	1.86 (1.25, 2.78)**
CIDs	24	198	121 (81, 181)	2.08 (1.28, 3.36)**	2.88 (1.67, 4.97)***
Skin and subcutaneous tissue disorders					
RA	115	4182	28 (23, 33)	1	0.86 (0.56, 1.33)
AS	41	1823	22 (17, 31)	1.16 (0.75, 1.78)	1
PsA	25	1134	22 (15, 33)	0.95 (0.60, 1.51)	0.82 (0.49, 1.38)
CA	25	863	29 (20, 43)	1.28 (0.78, 2.10)	1.10 (0.65, 1.87)
CIDs	10	198	50 (27, 94)	1.78 (0.86, 3.72)	1.54 (0.7, 3.38)
Gastrointestinal disorders					
RA	56	4182	13 (10, 17)	1	1.09 (0.6, 1.95)
AS	24	1823	13 (9, 20)	0.92 (0.51, 1.66)	1
PsA	13	1134	11 (7, 20)	0.88 (0.47, 1.65)	0.95 (0.47, 1.91)
CA	20	863	23 (15, 36)	1.65 (0.89, 3.05)	1.79 (0.93, 3.43)
CIDs	2	198	10 (3, 40)	0.99 (0.24, 4.13)	1.08 (0.25, 4.71)
Others					
RA	648	4182	155 (143, 167)	1	0.91 (0.76, 1.1)
AS	245	1823	134 (119, 152)	1.10 (0.91, 1.31)	1
PsA	155	1134	137 (117, 160)	1.06 (0.87, 1.27)	0.96 (0.78, 1.19)
CA	136	863	158 (133, 186)	1.44 (1.16, 1.77)***	1.31 (1.05, 1.64)*
CIDs	54	198	273 (209, 356)	2.24 (1.64, 3.05)***	2.04 (1.46, 2.85)***

Adjusted IRR compared with RA or AS. [a]Adjusted by gender, age at treatment start and disease duration. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Fig. 1 Retention rate by OUs and AIs represented by means of a Kaplan–Meier curve.



effectiveness and safety. A review of OU of biologics in rheumatic diseases indicates that the best results have been observed with the use of rituximab for SS, lupus and cryoglobulinaemia; infliximab for sarcoidosis and adult-onset Still's disease; and etanercept for Behçet's disease, albeit not for uveitis [12]. Reference to safety was included in the review, but non-comparative data were presented.

The overall conclusion from our study is that patients treated with TNF antagonists for CID are at high risk of developing toxicity and the opposite for AS and related diseases. Also, the rate of discontinuation follows a similar pattern. In our study, most of the CA patients treated with TNF antagonists outside the AIs were within the spectrum of SpA. Thus, it is not surprising that their safety profile and discontinuation of TNF antagonists mimics that of AS

TABLE 5 Cause-specific Cox regression models by OUs and AIs of all TNF antagonists combined and infliximab individually

Disease	HR *vs* RA (multivariate)[a]			HR *vs* AS (multivariate)[a]		
	Inefficacy HR (95% CI)	AEs HR (95% CI)	All[b] HR (95% CI)	Inefficacy HR (95% CI)	AEs HR (95% CI)	All[b] HR (95% CI)
All TNF antagonists						
RA	1	1	1	1.79 (1.38, 2.32)***	1.90 (1.48, 2.43)***	1.64 (1.40, 1.92)***
AS	0.56 (0.43, 0.72)***	0.53 (0.41, 0.68)***	0.61 (0.52, 0.71)***	1	1	1
PsA	0.73 (0.59, 0.90)**	0.50 (0.39, 0.64)***	0.66 (0.57, 0.76)***	1.31 (0.98, 1.74)	0.95 (0.70, 1.28)	1.08 (0.90, 1.29)
CA	0.94 (0.70, 1.25)	0.74 (0.54, 1.01)	0.89 (0.74, 1.07)	1.68 (1.20, 2.34)**	1.40 (0.98, 2.00)	1.47 (1.18, 1.81)***
CIDs	0.93 (0.58, 1.49)	1.24 (0.80, 1.93)	1.33 (1.02, 1.71)*	1.66 (0.99, 2.80)	2.36 (1.45, 3.83)***	2.18 (1.63, 2.90)***
Infliximab						
RA	1	1	1	2.83 (1.99, 4.03)***	1.88 (1.39, 2.55)***	2.83 (1.99, 4.03)***
AS	0.35 (0.25, 0.50)***	0.53 (0.39, 0.72)***	0.35 (0.25, 0.50)***	1	1	1
PsA	0.60 (0.44, 0.83)**	0.63 (0.46, 0.87)**	0.60 (0.44, 0.83)**	1.71 (1.13, 2.57)*	1.19 (0.83, 1.72)	1.71 (1.13, 2.57)*
CA	0.56 (0.39, 0.82)**	0.70 (0.48, 1.02)	0.56 (0.39, 0.82)**	1.59 (1.02, 2.47)*	1.32 (0.87, 1.98)	1.59 (1.02, 2.47)*
CIDs	0.76 (0.45, 1.29)	1.08 (0.65, 1.80)	0.76 (0.45, 1.29)	2.16 (1.18, 3.95)*	2.03 (1.17, 3.54)*	2.16 (1.18, 3.95)*

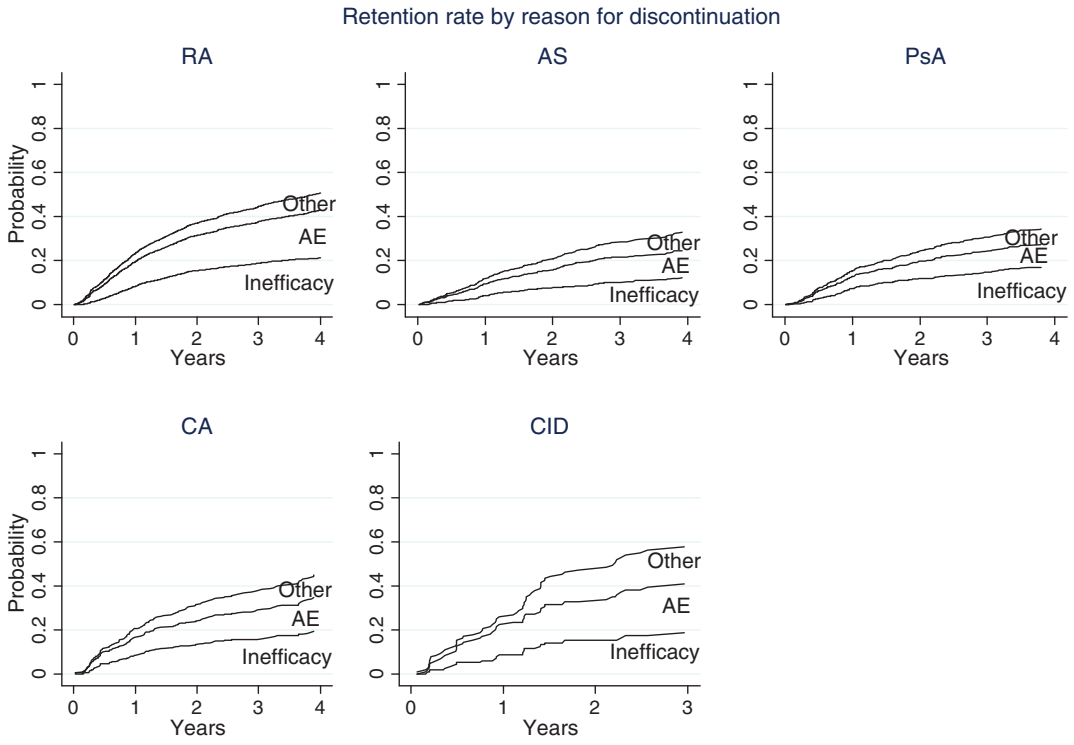
[a]Adjusted by gender, age at treatment start and disease duration. [b]All reason for discontinuation (inefficacy, AE and others). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

and of PsA. Furthermore, the majority of patients were treated with infliximab, suggesting that not only the safety but also the efficacy of this biologic in all forms of SpA may be alike. On the other hand, in CID, the pattern of discontinuation was somewhat similar to RA and characterized by a higher discontinuation rate and high infection rate. In RA, severity of disease, extra-articular manifestations, increasing age and CS therapy are independently associated with infection. In lupus, scleroderma and PM/DM, the risk of severe infections and opportunistic infections is increased and related to the use of CSs and/or immunosuppressors [13–17]. In our study, two-thirds of the CID patients treated with TNF antagonists were also receiving CSs, thus providing a clue for the high incidence of infections. Also, we found a significant risk of infection in RA patients treated with TNF antagonists. It is likely that CID patients with more severe disease were treated with TNF antagonists, confounding the effect of the disease severity itself and the treatment. Unfortunately, it is very difficult to measure horizontally the disease severity in all patients when diagnoses vary, one of the caveats of a universal drug registry, not a disease-related one. As a matter of fact, BIOBADASER 2.0 only includes a baseline measure of disease activity for RA (namely the DAS-28), AS (BASDAI) and now lupus (SLEDAI).

The rate of discontinuation of TNF antagonists in Still's disease was higher than in RA. Still's disease is nowadays viewed as a systemic autoinflammatory syndrome rather than an immune-mediated chronic inflammatory disease [18]. Rates of AEs and of medically serious infections in JIA including systemic JIA (Still's disease) treated with etanercept range between 6.0 and 7.1, and 1.8 and 2.1, respectively [19]. These numbers are smaller than that reported in Still's disease. However, our patients with Still's disease with a mean age of ~40 years represent a population of adult disease perhaps different from the juvenile form. Nevertheless, efficacy of blocking TNF in Still's disease is disputed, and furthermore recent publications show a significant improvement with IL1-Ra [20–23] or IL-6R antibody treatment [24, 25]. This indicates that the risk/benefit ratio of TNF antagonists in Still's disease does not support their use at the present time.

Our study has some limitations and strengths. Comparison of retention rates across AI and OU of TNF antagonists is troublesome. In RA, AS and PsA, long-term treatment is commonplace and retention rate mirrors effectiveness, whereas no indication regarding length for off-label treatments exists. A decision is based on physicians' opinion, restraining the comparison of effectiveness. This should not have an impact on the profiles of safety as described here. Other constraints could be the relevance and consistency of the information. Information in this article was gathered from the Spanish registry BIOBADASER 2.0, where the study cohort is large, with long-term follow-up, and representative of clinical practice in Spain [26, 27]. The quality and consistency of data were assured by a clear definition of its aim, an optimized number of variables and an easy method of data collection that allowed for consistency checks.

Fig. 2 Retention rate by reason for discontinuation represented by means of cumulative incidence curves in OUs and AIs. The cumulative incidence functions are stacked; the distances between curves represent the probabilities of the different events.



In addition, BIOBADASER 2.0 data were validated by calling and checking with the patients, and *in situ* audits. Information was found to be accurate in 92.6% of the cases, and all inconsistencies and missing data were amended. This consistency, valuable for data interpretation, strengthens the relevance of the present work.

In summary, our study shows an additional value of a national registry. Using data from the Spanish registry BIOBADASER 2.0, we were available to describe the safety profile of OUs of TNF antagonists in rheumatic conditions in comparison with other AIs. This information is critical for the evaluation of the risk/benefit ratio of medications used outside AIs.

Rheumatology key messages

- The safety profile of TNF antagonists used off-label in CIDs is similar to RA.
- The OUs of TNF antagonists must be closely followed to evaluate the risk/benefit ratio.

Acknowledgements

We gratefully acknowledge the invaluable aid of Beatriz Pérez and Juan Manuel Barrio with monitoring and computer programming, respectively.

The members of he BIOBADASER 2.0 Study Group include: Agustí Sellas, Basilio Rodríguez y Mireia Barceló (Ciudad Sanitaria Vall d'Hebron), Laura Cebrián, María Montoro (Hospital Gregorio Marañon), Dolores Montesinos (Hospital Universitario Virgen Macarena), Eva Pérez-Pampín (Hospital Clinico Universitario de Santiago), Ana M[a.] Ortiz, (Hospital Universitario de La Princesa), Fred Antón, Antonio Zea (Hospital Ramon y Cajal), Francisco Javier Manero Ruiz, Chesús Beltrán, Eugenio Gimenez Úbeda, Fernando Jimenez Zorzo, Jesús Marzo, Marta Medrano, Ángela Pecondón (Hospital Universitario Miguel Servet), M[a.] Victoria Hernández, Raimon Sanmartí, Juan D Cañete (Hospital Clinic I Provincial), Carlos Rodriguez Lozano, Antonio Naranjo, Soledad Ojeda, Félix Francisco Hernández, Celia Erausquin, Íñigo Rúa (Hospital de Gran Canaria Dr Negrin), Inmaculada Ureña, Maria Victoria Irigoyen, Laura Cano (Hospital General Carlos Haya), Rosa Roselló Pardo, Carlos Vazquez Galeano (Hospital General San Jorge), Alexia de Juanes, Beatriz Joven, Javier Garcia (Hospital 12 De Octubre), Javier Calvo, Cristina Campos (Hospital General Universitario de Valencia), Juan Jose Garcia Borras, Rosa Negueroles, Luisa Muñoz, J.L. Valero and D. Ybañez (Hospital La Fe).

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 per year) from Roche, Abbott, Bristol-Myers Squibb, Schering and Wyeth contribute to the support of the registry. This work was partially supported by the RETICS Program, RD08/0075 (RIER) from Instituto de Salud Carlos III (ISCIII).

Disclosure statement: J.J.G.-R. is on the Advisory Boards of Abbott, BMS, Pflzer, Roche, Schering-Plough and UCB SA, Belgium; has received lecture fees from Abbott, BMS, Roche, Schering-Plough and Wyeth; and has received research grants from Roche and Schering-Plough. L.C. has received a nominal grant from Abbott for an international research project. All other authors have declared no conflicts of interest.

References

1 Efthimiou P. Tumor necrosis factor-alpha in inflammatory myopathies: pathophysiology and therapeutic implications. Semin Arthritis Rheum 2006;36:168–72.

2 Alexis AF, Strober BE. Off-label dermatologic uses of anti-TNF-a therapies. J Cutan Med Surg 2005;9:296–302.

3 Graves JE, Nunley K, Heffernan MP. Off-label uses of biologics in dermatology: rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept (part 2 of 2). J Am Acad Dermatol 2007;56:e55–79.

4 Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med 2006;100:2053–9.

5 Atzeni F, Sarzi-Puttini P, Doria A, Iaccarino L, Capsoni F. Potential off-label use of infliximab in autoimmune and non-autoimmune diseases: a review. Autoimmun Rev 2005;4:144–52.

6 Booth A, Harper L, Hammad T *et al*. Prospective study of TNF alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004;15:717–21.

7 Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med 2006;166:1021–6.

8 Bennett WM. Off-label use of approved drugs: therapeutic opportunity and challenges. J Am Soc Nephrol 2004;15:830–1.

9 Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122–7.

10 Meddra maintenance and support services organization. http://www.Meddramsso.Org (21 March 2010, date last accessed).

11 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–430.

12 Ramos-Casals M, Brito-Zeron P, Munoz S, Soto MJ. A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. Medicine 2008;87:345–64.

13 Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martinez-Berriotxoa A, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther 2009;11:R109.

14 Marie I. [Infections in polymyositis and in dermatomyositis]. Presse Med 2009;38:303–16.

15 Marie I, Hachulla E, Cherin P *et al*. Opportunistic infections in polymyositis and dermatomyositis. Arthritis Rheum 2005;53:155–65.

16 Juarez M, Misischia R, Alarcon GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Rheum Dis Clin North Am 2003;29:163–84.

17 Alarcon GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Infect Dis Clin North Am 2006;20:849–75.

18 Vastert SJ, Kuis W, Grom AA. Systemic JIA: new developments in the understanding of the pathophysiology and therapy. Best Pract Res Clin Rheumatol 2009;23:655–64.

19 Giannini EH, Ilowite NT, Lovell DJ *et al*. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum 2009;60:2794–804.

20 Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31:2071–5.

21 Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V *et al*. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766–72.

22 Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum 2005;52:1794–803.

23 Lequerre T, Quartier P, Rosellini D *et al*. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis 2008;67:302–8.

24 Yokota S, Imagawa T, Mori M *et al*. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008;371:998–1006.

25 Mima T, Nishimoto N. Clinical value of blocking IL-6 receptor. Curr Opin Rheumatol 2009;21:224–30.

26 Carmona L, Hernandez-Garcia C, Vadillo C *et al*. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:1436–9.

27 Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 2007;57:756–61.