Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases (BIOBADASER): State Report, January 26th, 2006

Miguel Ángel Descalzo, BIOBADASER Scientific Committee,* and the BIOBADASER Study Group*

Unidad de Investigación, Fundación Española de Reumatología, Madrid, Spain

Objective: BIOBADASER is a prospective registry of rheumatic patients treated with biological therapies, which aim is the analysis of long-term survival and safety of these agents.
Patients and methods: As of January 26th 2006, 6969 patients from 100 centers were included in BIOBADASER. In total, 8321 treatments with biological therapies have been registered.
Results: Treatment was discontinued in 2351 (28%) occasions, mostly as a result of an adverse event (960; 41%) or inefficacy (942; 40%). A total of 2503 adverse events were notified. Of these, the most frequent ones were infections (909; 36%), followed by post-infusion reactions (500; 20%), skin lesions (255; 10%) and cardiovascular events (165; 7%).
Conclusions: The analysis reassures us in the increased rate of infections with biological therapies. Neither the rates of neoplasm nor of cardiac failure are significantly increased with these therapies. Specific measures have proved useful in preventing the occurrence of defined events.

Key words: Biological therapies. Follow-up. Adverse events. Registry.

Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas (BIOBADASER): informe de la situación, 26 de enero de 2006

Objetivo: BIOBADASER es un registro de pacientes reumatológicos en tratamiento con agentes biológicos, para el seguimiento de la supervivencia y la seguridad a largo plazo.
Pacientes y métodos: El 26 de enero de 2006, se ha registrado a 6.969 pacientes procedentes de 100 centros, que aportan información de 8.321 tratamientos con terapias biológicas.
Resultados: El tratamiento se suspendió en 2.351 ocasiones (28%), principalmente como resultado de un acontecimiento adverso (960; 41%), seguido de ineficacia (942; 40%). Se comunicaron 2.503 acontecimientos adversos, de los cuales el más frecuente fue la infección (909; 36%), seguido de las reacciones infusionales (500; 20%), y los trastornos cutáneos (255; 10%) y cardiovasculares (165; 7%).
Conclusiones: El análisis actual de BIOBADASER constata el aumento de las infecciones con el tratamiento, no así el de neoplasias o insuficiencia cardíaca. Las medidas específicas son útiles para la prevención de acontecimientos definidos.

Palabras clave: Terapias biológicas. Seguimiento. Acontecimientos adversos. Registro.

Introduction

BIOBADASER is the Spanish registry of adverse events when using biologic therapy for rheumatic disease. It was created in February of 2000 with the objective of identifying the relevant adverse events that could appear during the treatment of rheumatic disease with biologic therapy (to estimate the frequency of appearance), to identify the unexpected adverse events and to know the survival of the drug as an effectiveness measure. The existence of Rheumatoid Arthritis (RA) cohorts,[1,2] with a discreet time and space overlap with BIOBADASER, whose objective

*The listing of the members of BIOBADASER appears in the last page of the article.

BIOBADASER is carried out in collaboration with the Division of Pharmacoepidemiology and Pharmacovigilance of the Spanish Agency of Medications and Sanitary Products.

Correspondence: Dra. L. Carmona.
Unidad de Investigación. Fundación Española de Reumatología.
Marqués del Duero, 5, 1.º A. 28001 Madrid. España.
E-mail: lcarmona@ser.es

Manuscript received October 26, 2006; accepted for publication November 7, 2006.

is to estimate the incidence of co morbidity, also allows for the estimation of the relative risk of appearance of adverse events with biologic therapy in patients with RA versus patients that have not been exposed to these treatments.
These kind of registries are fundamental to establish the probability that a determined adverse event will happen in patients receiving a concrete drug. The estimation of risk is very difficult with other systems of pharmacovigilance in which the denominator is unknown nor is there an active search for the apparition of these adverse events. This report corresponds to the registry cut point done in January 2006 after 6 years of follow-up.

Patients and Methods

BIOBADASER has been described in detail in previous publications.[3,4] Basically, it is a registry of patients that have started treatment with biologic therapy in the participating centers and it collects information of the patient, of the treatment and of the adverse events.
A *relevant adverse event* is defined as any event, related or not to the treatment that, independent of dose, produces death, puts the life of the patient in danger, merits hospitalization or prolongs it, or causes persistent or important incapacity. Also included are the adverse events that the physician considered important because they oblige a preventive therapeutic attitude of the factors previously exposed.
The process of data entry is done directly on the internet (http://biobadaser.ser.es through a password), on the part of each of the participating centers every time that there is a change in the treatment of the registered patients or that adverse events appear. The participation of BIOBADASER is voluntary, there is no payment and it is open to all, of the center in Spain that prescribe treatment with biologics. Data is monitored on a weekly basis on-line and a more detailed review of the data is done randomly on 10% of the registered centers directly with the responsible personnel, be it in situ or on through a phone call, with the objective of identifying interruptions in treatment or relevant adverse effects that are not communicated. Occasionally, additional data is collected from patients who have had concrete adverse events and are undergoing a detailed study protocol.
For the description of the information collected by BIOBADASER, appropriate central tendency measures and dispersion for the descriptive variables are employed. Kaplan-Meier curves are obtained to describe the time of use of the therapies. Comparisons about duration of treatment among groups are done with logarithmic ranks, using a .05 significance level. To correct any under-notification on the part of the centers patient data is censored from the date of the last trustworthy input. On this cut-point, such a modification affects 128 patients (2%). To determine the relative risk of a concrete adverse event, the density of incidence is established (adjusting for multiple events) for such an event in BIOBADASER (cases/patients per year), using the density of incidence of such an event in the control EMECAR cohort of RA, as a denominator. The EMECAR cohort is a national RA cohort formed by 789 patients selected randomly from the registries of 34 centers. The mean duration since the onset of the disease at the beginning of the cohort is 10±8 years, and 72% of the patients are women.[2]
If an adverse event happened after the patient suspended treatment, even after he started another therapy with a biologic agent, the event was still being attributed to the initial treatment, unless it had been an infusion reaction or a digestive system effect, exanthema, allergic skin reaction or itching, syncope or dizziness and more than 30 days had passed since its suspension.

Results

Until the January 26, 2006 a total of 6969 patients had been registered in BIOBADASER, from 100 centers (see appendix list), with a total 8321 cycles of treatment (1125 patients had been treated with more than one biologic agent in different moments of their disease evolution, or with the same agent but the doses had more than 4 times the normal separation between doses).

Description of the Registered Patients

Sixty-five per cent of the patients registered are women (n=4516). Mean age at the start of treatment is 50±14 years, with a proportion of children (<16 years) at the beginning of therapy of 1% (n=81). In Table 1, the diagnosis of the patients that received biologic therapy and that are registered in BIOBADASER are shown. The patients started treatment with the first agent after a mean time since onset of disease of 10±8 years, 12±9 years in the case of Ankylosing Spondilytis (AS) and 10±8 year in the case of RA.

Description of the Treatment Cycles Registered

Biologic treatments registered up until this moment are infliximab (n=4525; 54%) etanercept (n=2595; 31%), adalimumab (n=1.081; 13%), anakinra (n=107; 1%), and rituximab (n=13; 0.2%). In Figure 1 the number of treatments initiated by semester and year of each one of the registered biologic treatments are shown.

TABLE 1. Diagnosis of the Patients Registered in BIOBADASER, by Order of Frequency

Diagnosis	No.	Percentage
Rheumatoid arthritis	4.459	64.0
Ankylosing spondylitis	896	12.9
Psoriasic arthritis	822	11.8
Undifferentiated polyarthritis	245	3.5
Juvenile idiopathic arthritis	212	3.0
Arthropathy associated to IBD	85	1.2
Seronegative chronic polyarthritis	43	0.6
Behçet´s disease	40	0.6
Still´s disease	26	0.4
Undifferentiated juvenle spondylitis	22	0.3
Seronegative chronic oligoarthritis	20	0.3
Reiter´s syndrome	14	0.2
Polymyositis	10	0.1
Vasculitis	10	0.1
Systemic lupus erythematosus	9	0.1
Idyopathic panuveitis	7	0.1
SAPHO syndrome	7	0.1
Scleroderma	6	0.09
Overlap RA-MCTD	6	0.09
Takayasu´s arteritis	5	0.07
Relapsing polychondritis	5	0.07
Wegener´s disease	4	0.06
Primary Sjögren´s syndrome	4	0.06
Sarcoidosis	3	0.04
Muckle-Wells disease	2	0.03
Panarteritis nodosa	2	0.03
Pyoderma gangrenosum	2	0.03
Epidermolysis bulosa	1	0.01
Eosynophilic fascitis with joint affectation	1	0.01
Felty´s syndrome	1	0.01
Total	6969	100

RA indicates rheumatoid arthritis; IBD, intestinal bowel disease; MCTD, mixed connective tissue disease.

Survival of the Drug

Two thousand fifty-one interruptions in treatment have been registered (28%), in the majority of cases as the result of an adverse event (n=960; 41%), followed by lack of efficacy (n=942; 40%). In 446 cases (19%) the motive of interruption was different: decision of the patient (166), improvement (38), and pregnancy (26), among others. In 1125 patients, as has been mentioned, interruption of treatment was followed by the start of treatment with another biologic agent or a different cycle of the same agent; a different cycle of the same agent refers to the last dose of the first cycle and the first of the second one are separated by a period of time that is 4 times greater than the interval approved for such a treatment. The mean time on treatment with biologic therapies in BIOBADASER is 2.4±1.6 years (median, 2.1; P_{25-75}=1.0-3.6). Figure 2 shows a global survival curve as first treatment registered in BIOBADASER. Drug survival for 1, 2, 3, 4, 5, and 6 years is, respectively, 83% (82-84), 73% (7274), 67% (66-68), 64% (62-65), 62% (60-63), and 60% (57-61). Four hundred ninety-eight patients have been treated for more than 4 years with etanercept or infliximab.

Drug survival was better for etanercept than for infliximab; differences between both are statistically significant. Survival of anakinra is significantly worse than with the other biologics ($P_{\text{log-rank}}$<.001). Drug survival is lesser in women than in men with a 5-year drug survival of 60% and 67%, respectively ($P_{\text{log-rank}}$<.001). Finally, there are significant differences regarding duration of treatment or drug survival in relation to the diagnosis, something that is largely seen in AS ($P_{\text{log-rank}}$<.001) (Figure 3).

Changes Between Biologic Agents

Eleven hundred twenty-five patients (16%) have been registered as receiving treatment with more than one biologic agent. The order combinations of the agents are varied, as can be seen in Table 2. The drug indicated as a first choice more frequently has been infliximab (4351) and as a second choice, etanercept (1818).

There is a great difference in the drug survival, according to the order of the treatment ($P_{\text{log-rank}}$<.001). The first agent certainly has a larger survival, 83% at 1 year, and this diminishes with successive treatments with other agents. The survival at 1 year of the second treatment is 80% and the third one is 72%.

The suspension motives vary depend on whether it´s the first time that biologics are employed or if it´s the second treatment option. Infliximab is suspended due to inefficacy more frequently in the second treatment than in the first, mainly because the first treatment is suspended more often due to "other causes," although the difference is not significant (*P*=.075). Agreement among the motives for suspension of the first and second treatments, independently of the drug, is low (kappa=0.30).

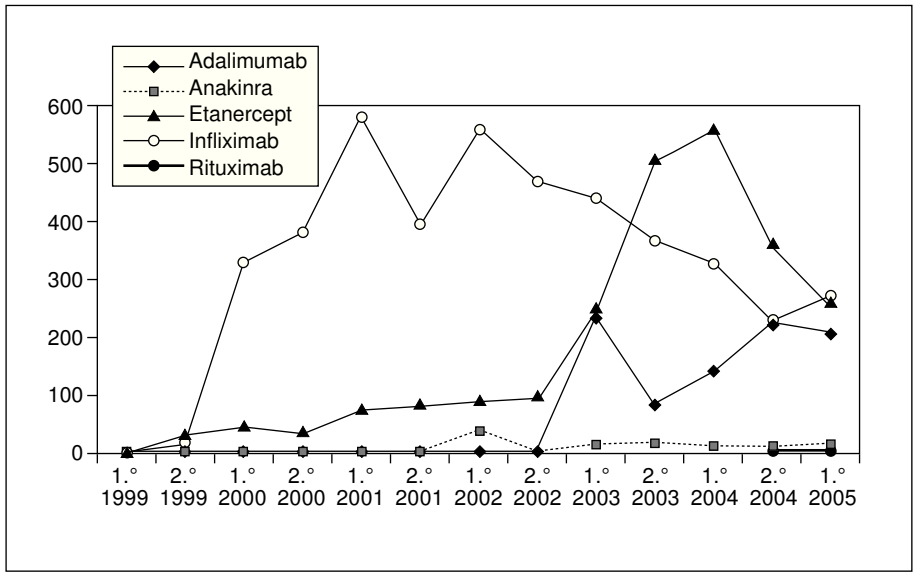

Figure 1. *Number of treatments started by semester and year in each one of the biologic agents registered in BIOBADASER.*

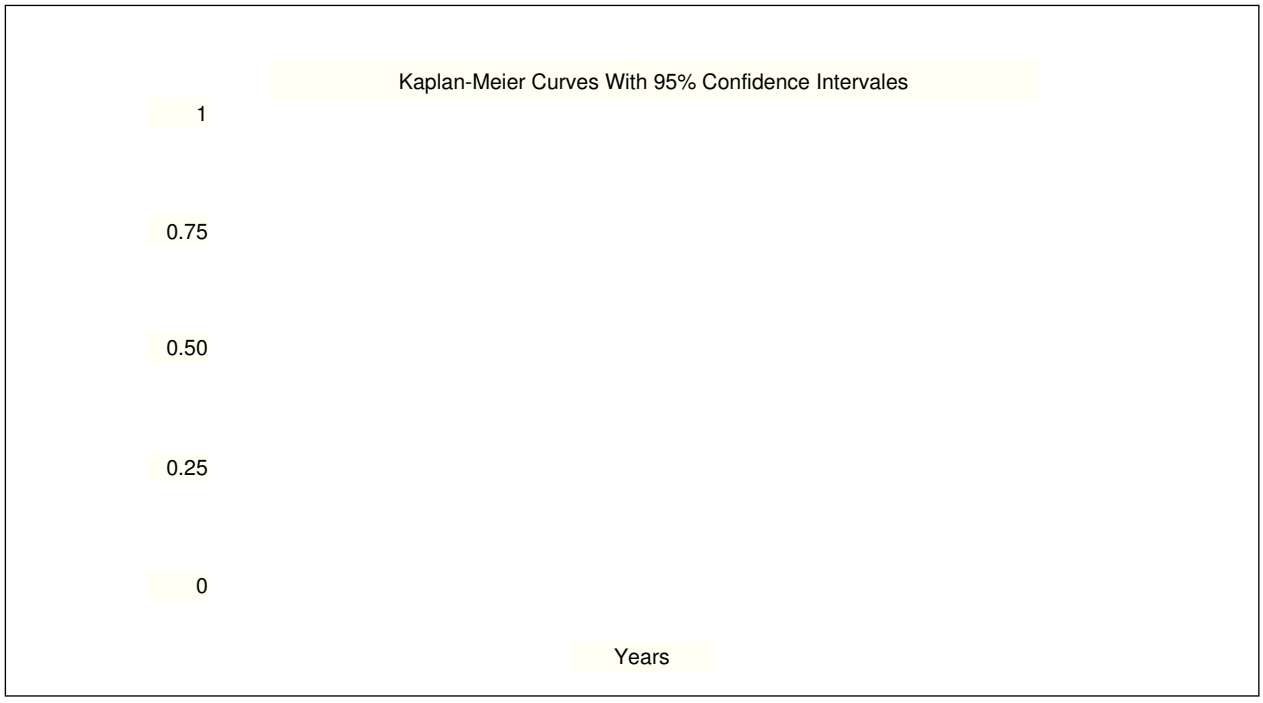

Figure 2. *Survival curve of biologic therapy of BIOBADASER.*

Detection of Latent Tuberculosis and Chemoprophylaxis

Since March 2002, BIOBADASER has collected chest x-ray data and Mantoux testing done before the start of biologic treatment.

At least 4972 patients (71%) have undergone a previous detection of latent tuberculosis (TB) with a chest x-ray and Mantoux, and that in the case of the other 391 (6%) at least 1 of the 2 tests were done. The fields that refer to TB testing were introduced into the database in March 2002.

A complete detection of latent TB was done in at least 4972 (87%) of the treatments started after the abovementioned date (Table 3), and the results are shown also.

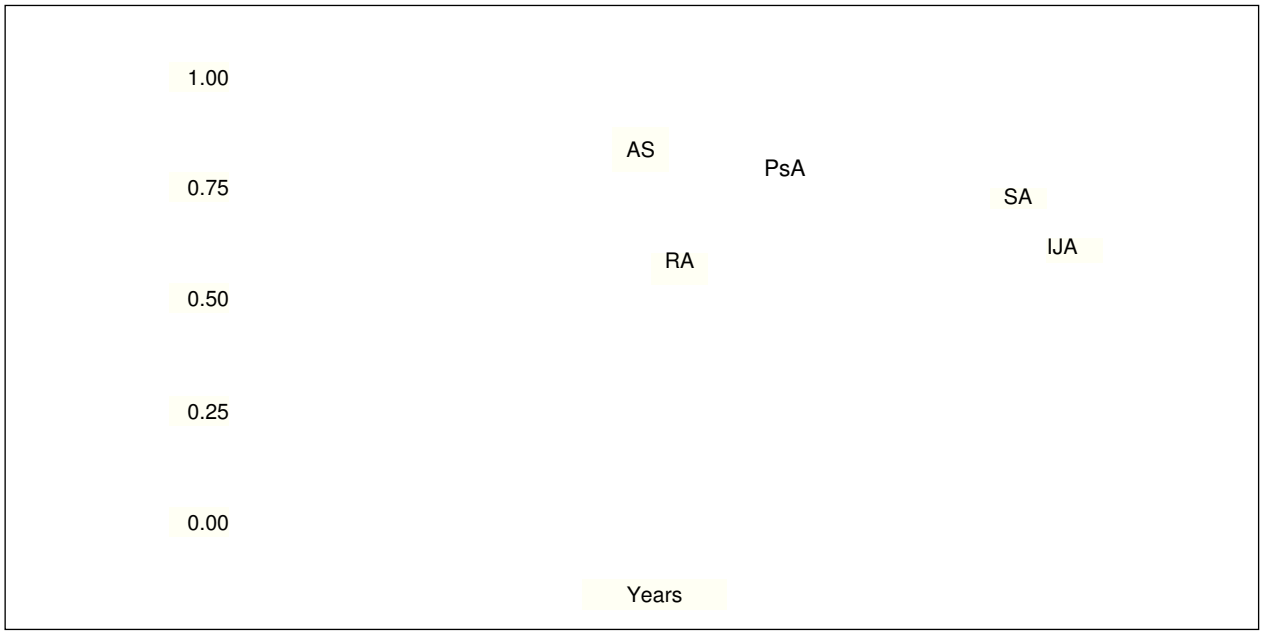

***Figure 3**. Survival curve of treatment in relation to diagnosis. IJA indicates idyopathic juvenile arthrtis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; SA, spondyloarthropathy.*

Pr*obable latent TB detected by x-ray* was defined as any of the following results: "calcified adenopathy," "possible bulla," "calcifications," "possible granulomas," "granulomas," "calcified granulomas," "pleural thickening," "fibro granular lesions," "previous TB," "scarring," or "apical lesions." We did not consider as a *probable TB* the following patterns: "non-specific alterations of the lung," "asbestosis," "atelectasia," "pleural effusion," "doubtful pleural thickening," "hilar thickening," "COPD," "stereotomy," "mediastinal enlargement," "pulmonary fibrosis," "infiltrate," "minimal pleural thickening," "nodules," "interstitial pattern," "sinus pinching," "volume loss," "no significant alterations," or "silicosis." According to this definition, 260 cases would have a compatible pattern (4%), 4034 wouldn´t (58%), and in 2675 (38%) the result is unknown.

Description of Adverse Events

Two thousand fifty-three adverse events have been reported in 1699 patients (24% of patients; Table 4 and Annex 1). In 319 patients there were 2; in 107 patients, 3; and in 69 patients, 4 or more. The type of adverse event most frequently seen was infection (n=909; 36%), followed by infusion reactions (n=500; 20%), and skin problems (n=255; 10%) and cardiovascular (n=165; 7%). Seven hundred eighty-three deaths have been reported and 587 hospitalizations as a consequence of adverse effects. In 1100 cases (44%) none of these occurred and the physician nonetheless reported the event as relevant. Deaths occurred in the majority of cases due to infection (n=28; 38%) or cardiovascular episodes (n=20; 27%). In Annex 2 the characteristics of patients that died during the follow up in BIOBADASER are shown.

Description of Infection

Nine hundred nine relevant infections were reported in 706 patients (114 patients with 2 infections and 37 patients with 3 or more infections). The 2 germs most frequently isolated were the herpes zoster virus and *Mycobacterium tuberculosis*, but the problem continues to be the lack of identification for most causes of infection.

Comparing the incidence of herpes zoster with the one of EMECAR, the risk of herpes zoster (measured as a relative risk of incidence) in patients with biologic therapy is 2.7 (confidence interval [CI] 95%, 0.7-22.9), and not conclusive.

Regarding the frequency of TB, compared both with the general population and EMECAR, is elevated, though in the second case in a non-significant manner (Table 5). Fifteen cases of newly diagnosed TB have been detected since the implementation of rules for the detection and prophylaxis, 8 with infliximab, 4 with adalimumab, and 3 with etanercept. In 9 cases, TB was detected in a period of 5 months or less after the start of treatment. In 4 there

TABLE 2. Changes in Biologic Agents in Patients Registered in BIOBADASER, by Order of Frequency

Changes Between Agents	Total Patients	Percentage of Patients
Only one agent		
Infliximab	3494	50.1
Etanercept	1615	23.2
Adalimumab	691	9.9
Anakinra	40	0.6
Rituximab	4	0.06
Two agents		
Infliximab-etanercept	569	8.2
Infliximab-adalimumab	118	1.7
Etanercept-adalimumab	82	1.2
Etanercept-infliximab	58	0.8
Infliximab-infliximab*	33	0.5
Adalimumab-etanercept	31	0.4
Adalimumab-infliximab	11	0.2
Etanercept-etanercept*	10	0.1
Anakinra-etanercept	6	0.09
Etanercept-anakinra	6	0.09
Infliximab-anakinra	6	0.09
Adalimumab-adalimumab*	5	0.07
Infliximab-rituximab	4	0.06
Anakinra-adalimumab	3	0.04
Anakinra-infliximab	2	0.03
Adalimumab-anakinra	1	0.01
Three agents		
Infliximab-etanercept-adalimumab	52	0.8
Infliximab-adalimumab-etanercept	15	0.2
Etanercept-infliximab-adalimumab	10	0.1
Etanercept-adalimumab-infliximab	8	0.1
Infliximab-etanercept-infliximab	8	0.1
Infliximab-etanercept-anakinra	7	0.1
Infliximab-etanercept-etanercept*	6	0.09
Etanercept-adalimumab-etanercept	5	0.07
Adalimumab-etanercept-infliximab	4	0.06
Etanercept-infliximab-etanercept	4	0.06
Infliximab-infliximab-etanercept*	4	0.06
Infliximab-anakinra-etanercept	3	0.04
Anakinra-infliximab-etanercept	3	0.04

(Continued)

TABLE 2. Changes in Biologic Agents in Patients Registered in BIOBADASER, by Order of Frequency

Changes Between Agents	Total Patients	Percentage of Patients
Infliximab-infliximab-adalimumab*	3	0.04
Etanercept-adalimumab-anakinra	2	0.03
Etanercept-infliximab-anakinra	2	0.03
Adalimumab-etanercept-adalimumab	1	0.01
Adalimumab-infliximab-etanercept	1	0.01
Etanercept-adalimumab-adalimumab*	1	0.01
Etanercept-anakinra-adalimumab	1	0.01
Etanercept-etanercept-infliximab*	1	0.01
Etanercept-infliximab-infliximab*	1	0.01
Infliximab-infliximab-infliximab*	1	0.01
Infliximab-anakinra-rituximab	1	0.01
Four or more agents		
Infliximab-etanercept-adalimumab-anakinra	3	0.04
Infliximab-etanercept-anakinra-adalimumab	3	0.04
Infliximab-etanercept-anakinra-etanercept	3	0.04
Etanercept-adalimumab-infliximab-etanercept	2	0.03
Infliximab-anakinra-etanercept-adalimumab	2	0.03
Infliximab-infliximab-etanercept-anakinra*	2	0.03
Infliximab-etanercept-adalimumab-infliximab	2	0.03
Infliximab-etanercept-anakinra-etanercept	2	0.03
Adalimumab-etanercept-infliximab-anakinra	1	0.01
Etanercept-adalimumab-anakinra-infliximab	1	0.01
Etanercept-etanercept-adalimumab-infliximab*	1	0.01
Etanercept-infliximab-adalimumab-anakinra	1	0.01
Etanercept-infliximab-adalimumab-anakinra	1	0.01
Etanercept-infliximab-adalimumab-infliximab	1	0.01
Etanercept-infliximab-anakinra-etanercept	1	0.01
Infliximab-adalimumab-anakinra-etanercept	1	0.01
Infliximab-adalimumab-etanercept-etanercept*	1	0.01
Infliximab-anakinra-anakinra-etanercept*	1	0.01
Infliximab-etanercept-adalimumab-adalimumab*	1	0.01
Infliximab-etanercept-adalimumab-anakinra	1	0.01
Infliximab-etanercept-anakinra-adalimumab	1	0.01
Infliximab-etanercept-etanercept-etanercept*	1	0.01
Infliximab-etanercept-infliximab-adalimumab	1	0.01
Infliximab-etanercept-infliximab-etanercept	1	0.01
Infliximab-infliximab-infliximab-etanercept*	1	0.01

*Two treatments with the same agent are considered different treatments because the interruption and the start of the next treatment are separated by more than 4 times the usual interdosis period.

TABLE 3. Detection of Latent TB in Patients Followed in BIOBADASER (n=6969)

Number of patients in which latent TB was detected	4972	71% from the total patients 87% that started after February 2002
Number of patients with positive Mantoux or retest	1282	In 173 Mantoux was negative and retest positive
Number of patients with negative Mantoux and chest x-ray suggestive of TB	142	
Number of patients treated for latent TB	1225	93% of the patients who should have been treated after February 2002

TB indicates tuberculosis.

had been a complete detection protocol (chest x-ray, Mantoux and booster), while in 8 no booster had been done due to a negative Mantoux. In 2 cases, treatment was started in spite of a positive Mantoux. One case had received chemoprophylaxis with isoniazide. In Table 5, the relative incidence with respect to the control population is shown, before and after the establishment of the abovementioned rules. The last incidence rates published for the Spanish population is of 25 per 100.00 cases according to the SEPAR.[5]

Heart Failure

Twenty-five cases of heart failure have been registered in BIOBADASER, almost all of them in patients older than 50 years (1 case in a patient younger than 50 years, 5 in the 50-60 year group, 9 in the 60-70 year range, 9 in the 70-80 year group and 1 in the older than 80 group). The incidence rate of heart failure per 100 000 patients/year is 145. If it is compared to EMECAR, a reduction in the number of cases is observed (relative incidence rate, 0.22; 95% CI, 0.1-0.51).

Infusion Reactions

A total 1006 symptoms and signs relating to 500 infusion reactions to infliximab have been described. The median time to onset with respect to the infusion is 0 h, with a range that goes from 0 to 336 h from infusion (P_{25-75}=0-0).

Neoplasia

Sixty-two cases of neoplasia have been described, 5 of which have caused the death of the patient. Compared to EMECAR, the incidence rate of neoplasia in BIOBADASER is inferior (relative incidence rate, 0.43; 95% CI, 0.22-0.9). Less conclusive is the comparison regarding the lymphoma rate (relative incidence rate, 0.39; 95% CI, 0.08-3.8).

TABLE 4. Adverse Events Communicated in BIOBADASER

No. Adverse Events	Total by Organ and System	Adverse Event, %
Infections/sepsis	909	36.32
Infusion reaction	500	19.98
Skin alterations	255	10.19
Cardiovascular alterations	165	6.59
Digestive alterations	136	5.43
Neoplasia	62	2.48
Hematologic alterations	59	2.36
Lung alterations	56	2.24
Neurologic alterations	51	2.04
Uro-renal alterations	26	1.04
Psychiatric alterations	21	0.84
Ophthalmologic alterations	21	0.84
Endocrine and metabolic alterations	10	0.4
Gynecologic alterations	8	0.32
Others	224	8.95
Total	2503	100

For a detailed description of the types of adverse events see Annex 1.

Demyelization Syndrome

Six cases of demyelization syndrome have been described, 5 with infliximab (incidence rate per 100 000 persons/year, 46; 95% CI, 19-109) and 1 with (incidence rate per 100 000 persons/year, 21; 95% CI, 3-149). In EMECAR there have not been any reports of demyelization syndromes, making it impossible to determine relative risk, tough it can be expected to be high.

TABLE 5. Incidence Rate Evolution of TB per 100 000 Persons/Year, in Treatments Initiated Before and After the Publication of the Detection and Prophylaxis Rules for Latent TB10, Versus General Population (Annual Incidence Rate 25 per 100 000) and Versus Control Population (EMECAR Cohort; Annual Incidence Rate of 90 per 100 000)

Start of Treatment	Persons-Year Exposed BIOBADASER	Cases	IR for TB per 100 000	RIR Versus General Population (95% CI)	RIR Versus EMECAR (95% CI)
Before the first trimester of 2002	8671	41	472 (384-642)	19 (11-32)	5.8 (2.5-15.4)
After the first trimester of 2002	8545	15	175 (105-291)	7 (3-13)	2.4 (0.8-7.2)

TB indicates tuberculosis; IR, incidence rate; RIR, relative incidence rate.

Hypertransaminasemia

Relevant hypertransaminasemia has been reported in 46 (0.7%) of the patients registered in BIOBADASER. Eight of the 46 were in treatment with isonizyde at the moment of the adverse event. One hospitalization was due to hypertransaminasemia in a patient taking leflunomide but not isoniazyde.

In Situ Follow-Up

Since December 2005 to January 2006, there has been a follow-up of randomly selected patients. Six hundred sixty-five patients were selected, from 82 centers, which at the time constituted 10% of all patients registered. The patient file could not be retrieved in 136 patients during monitorization, making it possible to review only 529 case files (80% of the compliance rate).
A *grave fault in the registry* was defined as the absence of communication at the end of treatment (detected in 49 patients; 9%) and no communication of adverse events (in 46 patients; 9%). One of the events was severe, a death due to high grade non-Hodgkin lymphoma. In total, 15% of the patients had some non-mild notification error. All of the errors in these patients have been corrected. If it is assumed that the rest of the 6440 registered patients maintain an error of 14%, the percentage existent in BIOBADASER is probably in the order of 13%.

Discussion

In its sixth year of follow-up, BIOBADASER is a world-renowned source of security information for biologic therapies and, indirectly, of their effectiveness in inflammatory arthropathies.
The events that have been registered more frequently have been, since the beginning of the registry, infections. This increase in the rate of infection in patients treated with biologics has been published in several series.[6-9] In concrete terms, an increment in the rate of TB[4] has been shown, but this has showed some lessening after the introduction of prophylactic measures in March 2002[10] down to the expected range (there are no differences when compared to EMECAR), which demonstrates its effectiveness,[11] though it is still elevated when compared with the rate in the general population. The compliance of these rules, it must be pointed out, is not complete: a very important percentage in patients who have still not received chemoprophylaxis with isoniazyde, in spite of a positive Mantoux, and a *booster* is not always done in patients with a negative Mantoux.[11]
Some personal communications lead us to think that there existed an increase in herpes zoster infections, but this has not been demonstrated in BIOBADASER. It is probable, though it cannot be demonstrated by the data of this registry, that the severity of infection is superior to the one reported in patients with no biologic therapy. Regarding other opportunistic agents, there has not been any comparison with EMECAR, due to their low frequency, though their existence is undeniable.
Heart failure is considered an adverse event of treatment with biologics. Nonetheless, the analysis from EMECAR and BIOBADASER has made evident that the opposite is true: there is a reduction in the rate of heart failure in patients receiving biologics. It may be premature, however, to state that biologics prevent heart failure because, due to it being a previously described, it is probable that these drugs are not being administered to patients with a risk of developing it.
Another group of controversial adverse events are lymphomas and all types of neoplasia. According to our experience, in general neoplasia did not increase its expected rate after 5 years of follow up, what´s more, evidence seems to point the other way, and in the case of lymphoma, there is no evidence that risk is either higher or lower.
In the case of de demyelization syndromes, the rate is too low and it cannot be known if it corresponds to what is expected because it cannot be compared to EMECAR, there having not been any such events described in that cohort.

Acknowledgement

We want to emphasize the effort, in some cases overwhelming, of persons of every center that are responsible of data capture and do it altruistically. We also want to bear witness to the professional manner in which Raquel Ruiz has monitored and lent support to the registry, both tasks of incalculable value.

Appendix

Participants in BIOBADASER (an asterisk denotes the members of the Scientific Committee): Dolores Montero* (División de Farmacoepidemiología y Farmacovigilancia, Agencia Española de Medicamentos y Productos Sanitarios); Alba Erra, Sara Marsal (Centre Sanitari Vall d´Hebron); Mónica Fernández Castro, Juan Mulero,* José Luis Andreu (Clínica Puerta de Hierro); Manuel Rodríguez Gómez (Centro Hospitalario de Ourense); Marta Larrosa Pardo, Enrique Casado (Centro Hospitalario del Parc Taulí); Elena Leonor Sirvent, Delia Reina, Carmen García Gómez (Hospital de Bellvitge); Beatriz Joven, Patricia Carreira (Hospital 12 de Octubre); M. Victoria Hernández (Hospital Clinic); Estíbaliz Loza (Hospital Clínico Universitario San Carlos); Alberto Alonso, Esther Uriarte (Hospital de Cruces); Lucía Pantoja, M. Valvanera Pinillos (Hospital del Bierzo); Teresa Mariné (Hospital de l´Esperit Sant); Rosario García de Vicuña, Ana M. Ortiz, Isidoro González Álvaro, Armando Laffón,* José M. Álvaro-Gracia* (Hospital Universitario de La Princesa); César Díaz López, Arturo Rodríguez de La Serna (Hospital de la Santa Creu i Sant Pau); Eduardo Loza (Hospital de Navarra); M. Victoria Irigoyen, Inmaculada Ureña, Virginia Coret (Hospital General Carlos Haya); Paloma Vela, Eliseo Pascual Gómez* (Hospital General Universitario de Alicante); Miquel Ángel Belmonte, Juan Beltrán, Juan José Lerma (Hospital General de Castellón); Myriam Liz (Hospital Clínico Universitario de Santiago); Saul Mario Gelman (Hospital General de Manresa); Elena Ciruelo, Eva Tomero, Olga Amengual (Hospital General de Segovia); Juan Carlos Cobeta (Hospital General de Teruel Obispo Polanco); Encarnación Saiz, José Gálvez (Hospital General Morales Meseguer); Gerardo Iglesias de La Torre (Hospital General Río Carrión); Rosa Roselló, Carlos Vázquez (Hospital General San Jorge); Juan Pablo Valdazo (Hospital General Virgen de La Concha); Xavier Tena,* Vera Ortiz (Hospital Universitario Germans Trias i Pujol); Manuel Fernández Prada, José Antonio Piqueras, Jesús Tornero Molina* (Hospital General Universitario de Guadalajara); Laura Cebrián, Luis Carreño* (Hospital Gregorio Marañón); Juan José García Borras (Hospital La Fe); Francisco Javier Manero (Hospital Universitario Miguel Servet); Manel Pujol, Josep Granados (Hospital Mútua Terrassa); José Luis Cuadra, F. Javier Paulino, Marcos Paulino (Hospital Nuestra Señora del Carmen); Olga Maiz, Estíbaliz Barastay, Manuel Figueroa* (Hospital Donosti); Carmen Torres, Montserrat Corteguera (Hospital Nuestra Señora de Sonsoles); Carlos Rodríguez Lozano, Félix Francisco Hernández, Íñigo Rua Figueroa (Hospital de Gran Canaria Dr. Negrín); Óscar Illera, Antonio C. Zea, Paloma García de La Peña, Marta Valero (Hospital Ramón y Cajal); Emilia Aznar, Ricado Gutiérrez (Hospital Reina Sofía); Ana Cruz Valenciano, Manuel Crespo, Félix Cabero (Hospital Severo Ochoa); M. Teresa Ruiz Jimeno (Hospital Comarcal Sierrallana); Jordi Fiter, Luis Espadaler (Hospital Son Dureta); Juan Carlos Vesga, Eduardo Cuende (Hospital Txagorritxu); Sagrario Sánchez Andrada, Vicente Rodríguez Valverde* (Hospital Universitario Marqués de Valdecilla); Iván Ferraz, Tomas González (Hospital Universitario de Canarias); José Luis Marenco,* Eduardo Rejón (Hospital Universitario de Valme); Eduardo Collantes, M. Carmen Castro (Hospital Universitario Reina Sofía); Blanca Hernández, José V. Montes de Oca, Federico Navarro, Francisco Javier Toyos (Hospital Universitario Virgen Macarena); Carlos Marras, Luis Francisco Linares, Juan Moreno (Hospital Virgen de La Arrixaca); Carmen González-Montagut (Hospital Virgen de La Luz); Ángel García Aparicio (Hospital Virgen de La Salud); Rafael Cáliz,* Carmen Idalgo (Hospital Virgen de Las Nieves); Amalia Sánchez-Andrade (Hospital Xeral-Calde); Emilio Martín Mola;*; Tatiana Cobo, Azucena Hernández (Hospital La Paz); Xavier Arasa (Hospital de Tortosa); José Raúl Noguera, Francisco J. Navarro Blasco, Juan Víctor Tovar (Hospital General Universitario de Elche); José Carlos Rosas Gómez de Salazar, Gregorio Santos (Hospital del Servicio Valenciano de Salud de Villajoyosa); Isabel Ibero, Vega Jovani, Raquel Martín (Hospital General de Elda); Jordi del Blanco Barnusell (Hospital Sant Jaume de Calella); Miguel Ángel Abad, Maria Torresano (Hospital Virgen del Puerto); Gaspar Pérez Lidon, Manuel Tenorio (Hospital del Insalud, Ceuta); Inmaculada Bañegil (Hospital de Mendaro); Jordi Carbonell;* Joan Maymo, Carolina Pérez García (IMAS. Hospital de l´Esperança y del Mar); Víctor Eliseo Quevedo (Hospital Comarcal de Monforte); Javier Rivera, Teresa González (Instituto Provincial de Rehabilitación); José Manuel Rodríguez Heredia, Ángel Gallegos Cid, Jesús García Arroba, Miguel Cantalejo (Hospital Universitario de Getafe); Raquel Almodóvar, Javier Quirós, Pedro Zarco, Ramón Mazzucchelli (Hospital Fundación Alcorcón); Alfonso Corrales (Hospital Comarcal de Laredo); Dolors Boquet (Hospital Arnau de Vilanova); Francisco Pérez Torres (Hospital General de Requena); José Ivorra (Hospital General de Onteniente); Xavier Suris (Hospital General

de Granollers); Trinidad Pérez Sandoval (Hospital Virgen Blanca); Javier Calvo Catalá, Cristina Campos (Hospital General Universitario de Valencia); María Francisca Pina (Hospital Rafael Méndez); Cristina Hidalgo (Hospital de La Santísima Trinidad); Julia García Consuegra, Rosa Merino (Hospital Infantil La Paz); Miquel Sala Gómez (Hospital de Figueres); Montserrat Centellas (Hospital de Mataró); José Miguel Ruiz Martín (Hospital de Viladecans); Antonio Juan, Inmaculada Ros (Fundación Hospital Son Llàtzer); Jaime Fernández Campillo, Rocío González Molina (Hospital del Servicio Valencianio de Salud Vega Baja); Mauricio Mínguez Vega, Gaspar Panadero (Hospital San Juan de Alicante); Jesús Ibáñez (Policlínico Vigo, S.A., Povisa); Anna Martínez Cristóbal, Pilar Trenor (Hospital de La Ribera); Jenaro Graña Gil (Hospital Santa Teresa); M. Teresa Bosque Peralta (Hospital Clínico Universitario Lozano Blesa); Ana Urruticoechea (Hospital Can Misses de Ibiza); José Román Ivorra, Inmaculada Chalmeta (Hospital Universitario Dr. Peset); Javier Alegre, Bonifacio Álvarez Lario, José Luis Alonso Valdivielso, Julia Fernández Melón (Hospital General Yagüe); M. Ángeles Belmonte (Clínica A. Belmonte).

References

1. Lipani JA, Strand V, Johnson K, Woodworth T, Furst D, Singh G, et al. A proposal for developing a large patient population cohort for longterm safety monitoring in rheumatoid artritis. J Rheumatol. 2001; 28:1170-3.
2. Carmona L, González I, Balsa A, Ángel Belmonte M, Tena X, Sanmartí R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis. 2003;62:897-900.
3. Comité Científico de BIOBADASER. BIOBADASER: registro español de acontecimientos adversos de terapias biológicas en enfermedades reumáticas. Rev Esp Reumatol. 2002;29:292-9.
4. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, Comité Científico de BIOBADASER. 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.
5. Caminero JA, Cayla JA, Lara N, Working Group on the Current Status of Tuberculosis in Spain. Evaluation of tuberculosis trends in Spain, 1991-1999. Int J Tuberc Lung Dis. 2003;7:236-42.
6. Bresnihan B, Cunnane G. Infection complications associated with the use of biologic agents. Rheum Dis Clin North Am. 2003;29:185-202.
7. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology. 2003;42:617-21.
8. Ellerin T, Rubin R, Weinblatt M. Infections and anti-tumor necrosis factor therapy. Arthritis Rheum. 2003;48:3013-22.
9. Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. J Rheumatol. 2002; Suppl 65:33-8.
10. Agencia del Medicamento y Productos Sanitarios. Nota informativa de la Agencia Española del Medicamento sobre riesgo de medicamentos. Ref: 2002/01. February 2002 [cited 13 Feb 2005]. Available from: www.agemed.es/documentos/notasPrensa/csmh/2002/cont_Infliximab_feb02_ps.htm
11. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, 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.

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System

	No.	Total, %
Infections/sepsis	909	36.32
Infusion reaction	500	19.98
Skin alterations	255	10.19
Rash-exanthema	62	2.48
Injection zone reaction	40	1.6
Urticaria	26	1.04
Dermatitis	19	0.76
Itching	19	0.76
Psoriasis	13	0.52
Alopecia	10	0.4
Skin vasculitis	9	0.36
Erithema multiforme	8	0.32
Skin ulcer	8	0.32
Angioedema	7	0.28
Lichenoid dermatitis	6	0.24
Lichenn planus	6	0.24
Face erithema	5	0.2
Erithema nodosus	3	0.12
Skin lupus	3	0.12
Lichen striatum	2	0.08
Acne	1	0.04
Dermatosclerosis	1	0.04
Ring granuloma	1	0.04
Hematoma	1	0.04
Hipertrycosis	1	0.04
Pyoderma gangrenosum	1	0.04
Keratoacantoma	1	0.04
Seborrhea	1	0.04
Vytiligo	1	0.04
Cardiovascular alterations	165	6.59
Heart failure	27	1.08
Myocardial infarction	22	0.88
Hypertension	20	0.8
Peripheral edema	18	0.72
Venous thrombosis	16	0.64
Cerebrovascular disease	15	0.6

(Continued)

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System *(Continuation)*

	No.	Total, %
Angina	12	0.48
Arrythmia	10	0.4
Pericarditis	7	0.28
Flebitis	6	0.24
Sudden death	6	0.24
Ruptured aortic aneurysm	2	0.08
Pulmonary thromboembolysm	2	0.08
Periphera ischemia	1	0.04
Valva disease	1	0.04
Digestive alterations	136	5.43
Hypertransaminasemia	46	1.84
Diarrhea	30	1.2
Biliary colic	9	0.36
Abdominal pain	8	0.32
Dyspepsia	6	0.24
Upper digestive hemorrhage	6	0.24
Appendicitis	5	0.2
Odynofagia	4	0.16
Gastritis	3	0.12
Intestinal occlusion	3	0.12
Diverticulitis	2	0.08
Crohn´s disease	2	0.08
Pancreatitis	2	0.08
Rectorrhagia	2	0.08
Ulcerative colitis	1	0.04
Duodenitis	1	0.04
Esofagitis	1	0.04
Anal fistula	1	0.04
Drug induced hepatitis	1	0.04
Bowel ischemia	1	0.04
Postpyloric perforation	1	0.04
Peptic ulcer	1	0.04
Neoplasia	62	2.48
Breast cancer	10	0.4
Lymphoma	9	0.36
Prostate cancer	5	0.2

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System *(Continuation)*

	No.	Total, %
Bladder cancer	5	0.2
Colon cancer	4	0.16
Lung cancer	3	0.12
Epidermoid carcinoma	3	0.12
Spynocelular carcinoma	3	0.12
Basocelular epitelioma	3	0.12
Monoclonal gammopathy	3	0.12
Basocelular carcinoma	2	0.08
Gastric cancer	2	0.08
Ovarian cancer	2	0.08
Pancreatic cancer	2	0.08
Peritoneal cancer	2	0.08
Melanoma	2	0.08
Glyoblastoma	1	0.04
Meningioma	1	0.04
Hematologic alterations	59	2.36
Leukopenia	26	1.04
Trombocytopenia	13	0.52
Anemia	12	0.48
Pancytopenia	5	0.2
Eosinophylia	3	0.12
Lung alterations	56	2.24
Neumonitis	13	0.52
Broncospasm	10	0.4
Pleural effusion	9	0.36
Dyspnea	4	0.16
Bronchiolitis obliterans	3	0.12
Hemoptysis	3	0.12
Pneumothorax	3	0.12
Worsening of lung fibrosis	2	0.08
Respiratory insufficiency	2	0.08
Abnormal chest x-ray	2	0.08
Neurologic alterations	51	2.04
Headache	26	1.04
Demyelization syndrome	6	0.24
Neurytis	5	0.2

(Continued)

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System *(Continuation)*

	No.	Total, %
Dementia	4	0.16
Epilepsy	2	0.08
Myastenia gravis	2	0.08
Amnesia	1	0.04
Trigeminal neuralgia	1	0.04
Polineuropathy	1	0.04
CNS vasculitis	1	0.04
Essential tremor	1	0.04
Amyotrophic lateral sclerosys	1	0.04
Uro-renal alterations	26	1.04
Acute renal failure	6	0.24
Nephrolithyasis	6	0.24
Altered renal function	5	0.2
Renal pain	4	0.16
Hematuria	3	0.12
Hemorrhagic cystitis	1	0.04
Dysuria	1	0.04
Psychiatric alterations	21	0.84
Depression	9	0.36
Impotence	4	0.16
Insomnia	2	0.08
Psycosis	2	0.08
Agorafobia	1	0.04
Libido loss	1	0.04
Hysteria	1	0.04
Acute confusional syndrome	1	0.04
Ophthalmologic alterations	21	0.84
Scleritis	3	0.12
Corneal ulcer	3	0.12
Uveitis	3	0.12
Visual acuity loss	2	0.08
Glaucoma	2	0.08
Iritis	2	0.08
Vitreous lesion	1	0.04
Diplopia	1	0.04
Eye pain	1	0.04
Eye hemorrhage	1	0.04
Myodesopsia	1	0.04
Ptosis	1	0.04
Endocrinometabolic alterations	10	0.4
Hyperthyroidism	4	0.16
Hypocalcemia	3	0.12
Diabetes	1	0.04
Hyperparathyroidism	1	0.04
Hypothyroidism	1	0.04
Gynecologic alterations	8	0.32
Menstrual abnormalities	5	0.2
Ectopic pregnancy	1	0.04
Endometriosis	1	0.04
Fybrocystic disease	1	0.04
Others	224	8.95
Pathologic fracture	44	1.76
Fever	25	1
Worsening rheumatoid arthritis	19	0.76
Lupus-like syndrome	15	0.6
Dizzyness	12	0.48
Fatigue	8	0.32
Complications of surgery	7	0.28
Compressive cervical myelopathy	7	0.28
Death due to unknown cause	7	0.28
Worsening. Ankylosing spondylitis	5	0.2
Avascular necrosis	5	0.2
Mechanical pain	4	0.16
Obesity	4	0.16
Rhinitis	4	0.16
Amyloidosis	3	0.12
Worsening Sjögren´s syndrome	3	0.12
Vertigo	3	0.12
Aphonia	2	0.08
Chest pain	2	0.08
Hernia	2	0.08
Hypercholesterolemia	2	0.08

(Continued)

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System *(Continuation)*

	No.	Total, %
Lypoma	2	0.08
Benign larynx neoplasia	2	0.08
Lowered drug concentrations	2	0.08
Weight loss	2	0.08
Anaphylactic shock	2	0.08
Syncope	2	0.08
Constitutional syndrome	2	0.08
Cough	2	0.08
Oral ulcer	2	0.08
Accident	1	0.04
Post-traumatic arthritis	1	0.04
Dyskitis	1	0.04
Dupuytren´s contracture	1	0.04
Worsening amyloidosis	1	0.04
Worsening Still´s disease	1	0.04

ANNEX 1. Adverse Events Registered in BIOBADASER, by Organ and System *(Continuation)*

	No.	Total, %
Worsening systemic lupus	1	0.04
Epystaxis	1	0.04
Gum hemorrhage	1	0.04
Hyperbilirrhubinemia	1	0.04
Delayed hypersensitivity to cobalt	1	0.04
Acute lumbocyatica	1	0.04
Atlanto-axial dyslocation	1	0.04
Benign colon polyp	1	0.04
Gum polyp	1	0.04
Prostate inflammation	1	0.04
Tendon rupture	1	0.04
Sarcoidosis	1	0.04
Xanthoma	1	0.04
Total	2.503	100

CNS indicates central nervous system.

ANNEX 2. Description of the Patients That Died During Follow-Up in BIOBADASER

Patient	Age	Diagnosis	Biologic Treatment	Treatment Start Date	Treatment End Date	Cause of Death	Date of Death
11	22	Juvenile idiopathic arthritis	Etanercept	26-11-2001	13-3-2002	Septic shock due to undetermined germ	13-3-2002
19	62	RA	Etanercept	18-8-1999	1-6-2002	Intracraneal hemorrhage	1-6-2002
170	62	RA	Infliximab	25-7-2000	1-10-2000	Pneumonia due to undetermined germ	1-10-2000
172	55	Spondyloarthritis	Infliximab	5-11-2003	22-12-2003	Death due to unknown cause	1-1-2004
180	57	RA with CRF undergoing hemodyalisis	Etanercept	20-6-2003	20-6-2003	Staphylococcus aureus Septic shock	2-7-2003
			Infliximab	30-4-2002	4-6-2003		
310	58	RA	Etanercept	11-10-1999	8-12-2003	Massive cerebral infarct	27-4-2004
		Infliximab	14-1-2004	14-4-2004			
353	69	RA	Infliximab	2-3-2000	1-9-2000	Massive cerebral thrombosis	2-11-2002
385	62	RA	Infliximab	9-3-2001	17-4-2003	Myocardial infarction	31-5-2003
394	46	PsA	Infliximab	3-1-2000	20-10-2002	Polymicrobian septic shock	1-2-2003

(Continued)

ANNEX 2. Description of the Patients That Died During Follow-Up in BIOBADASER *(Continuation)*

Patient	Age	Diagnosis	Biologic Treatment	Treatment Start Date	Treatment End Date	Cause of Death	Date of Death
409	64	RA	Infliximab	18-10-2000	22-10-2002	Lung cancer	1-4-2003
463	57	RA (interstitial pneumopathy mild	Infliximab	19-7-2000	4-9-2000	Disseminated TB	1-10-2000
641	62	RA	Infliximab	14-12-2001	31-10-2002	Sudden death	1-3-2005
		Etanercept	13-2-2003	23-8-2003			
773	53	RA(prosthesis, amyloidosis)	Infliximab	4-4-2000	18-6-2002	Endocarditis due to Staphylococcus epidermidis	11-5-2002
789	82	RA	Infliximab	10-5-2001	5-9-2001	Breast cancer	1-1-2004
930	51	RA	Infliximab	17-1-2002	12-6-2002	Septic shock due to undetermined germ	10-7-2002
967	66	RA	Infliximab	17-2-2000	1-7-2001	Septic shock due to S taphylococcus aureus	10-11-2001
1272	73	RA	Infliximab	8-3-2000	25-4-2003	Hemopthysis	19-1-2004
1475	67	RA	Infliximab	18-4-2001	19-12-2001	Sudden death	23-12-2001
1672	65	RA	Infliximab	30-4-2002	3-5-2004	Complicated diverticulitis	13-5-2004
1704	52	RA (secondary amyloidosis)	Infliximab	7-6-2000	25-1-2001	Sepic shock due to Pseudomonas aeruginosa	23-1-2001
2161	58	RA	Infliximab	15-3-2001	18-7-2001	Septic shock due to undefined germ	1-6-2001
2208	59	RA	Infliximab	29-3-2000	1-7-2003	Sudden death during cardiac surgery	24-12-2003
			Etanercept	1-7-2003	24-12-2003		
2336	76	RA (lung fibrosis secondary to AR)	Infliximab	3-10-2002	14-11-2002	Pneumonitis	22-12-2002
2354	62	RA	Etanercept	1-8-2000	20-12-2001	Pneumonia due to Pseudomonas aeruginosa	22-12-2001
2397	76	RA	Infliximab	11-9-2000	14-3-2003	Bowel ischemia	14-3-2003
2490	58	Sarcoidosis	Infliximab	16-4-2002	2-6-2004	Right heart failure due to cor pulmonale	4-6-2004
2501	70	RA	Infliximab	4-5-2001	15-7-2001	Pneumonia due to undetermined germ	20-7-2001
2595	38	RA	Infliximab	5-12-2001	15-1-2002	Aortic aneurysm rupture	1-2-2002
3199	54	SA	Infliximab	28-10-2003	23-12-2003	Death due to unknown cause	15-7-2005
		Infliximab	2-6-2004	1-6-2005			
3271	63	RA	Infliximab	26-6-2000	13-2-2001	Sudden death	21-9-2005
		Etanercept	16-5-2002	21-9-2005			
3402	61	PsA	Infliximab	3-3-2003	21-11-2004	Death due to unknown cause	21-11-2004
3415	66	RA	Infliximab	28-1-2000	7-9-2001	Sepsis due to perforated diverticulitis	6-5-2004
			Etanercept	24-3-2004	12-4-2004		
3605	65	RA	Infliximab	12-7-2001	23-10-2001	Sudden death	23-10-2001
3657	46	SA	Infliximab	3-7-2001	14-8-2001	Polymicrobian septic shock	21-9-2001
3717	77	RA	Infliximab	5-6-2001	23-6-2001	Pulmonary TB	20-8-2001

(Continued)

ANNEX 2. Description of the Patients That Died During Follow-Up in BIOBADASER *(Continuation)*

Patient	Age	Diagnosis	Biologic Treatment	Treatment Start Date	Treatment End Date	Cause of Death	Date of Death
3747	43	RA	Infliximab	4-12-2001	13-1-2003	Lymphoma	4-3-2004
3794	56	RA	Infliximab	24-7-2001	8-5-2002	Pneumonia due to undetermined germ	16-6-2002
4068	36	AS	Infliximab	16-7-2001	19-11-2004	Intracraneal hemmorrhage	13-11-2004
4185	83	RA	Infliximab	4-8-2003	15-9-2003	Brain infarction	15-9-2003
4.483	69	RA	Infliximab	17-7-2000	8-12-2000	Amyloidosis	4-12-2000
4525	78	RA	Etanercept	10-10-2002	18-3-2004	Skin ulcer resistant to treatment, complicated with thrombocytopenia, sepsis, and renal failure	1-6-2004
4536	67	RA (amyloidosis)	Infliximab	15-10-2002	16-1-2003	Myocardial infarction	20-1-2003
4584	55	RA (interstitial pneumopathy)	Infliximab	13-5-2002	3-7-2002	Cerebral infection due to undetermined germ	23-1-2003
4603	74	RA	Infliximab	24-8-2000	2-11-2001	Pneumopathy due to undetermined germ and pancytopenia	13-3-2002
4674	54	RA	Infliximab	24-5-2002	4-5-2003	Septic shock due to Legionella	
4689	67	RA (amyloidosis, terminal RF)	Infliximab	9-11-2000	1-12-2000	Sudden death, complications hemodyalisis	14-9-2004
			Etanercept	8-4-2002	6-5-2002		
4715	69	RA (AAN+, nodules)	Infliximab	31-10-2000	31-10-2000	Heart failure	31-10-2000
5161	76	RA	Infliximab	10-10-2001	18-1-2004	Death due to unknown cause	18-1-2004
5342	71	RA	Etanercept	28-6-2004	29-6-2005	Septic shock due to Streptococcus	29-6-2005
5370	75	RA (ALS)	Infliximab	29-5-2000	1-4-2003	Pneumonia due to undetermined germ	18-3-2004
			Etanercept	1-5-2003	18-3-2004		
5695	74	RA	Infliximab	2-8-2000	6-10-2000	Death due to unknown cause	1-5-2002
5726	69	RA (knee arthroplasty)	Infliximab	6-3-2000	27-1-2003	Endocarditis due to Salmonella	20-2-2003
5883	57	RA (lung fibrosis secondary to RA)	Infliximab	27-2-2002	27-2-2002	Worsening, lung fibrosis	27-2-2002
5889	63	RA	Infliximab	13-4-2000	1-4-2003	Myocardial infarction	8-4-2003
5898	81	RA	Infliximab	12-12-2000	9-2-2001	Aortic aneurysm rupture	14-5-2001
5899	66	RA	Infliximab	15-10-2001	14-2-2002	Lung TB	1-3-2002
6027	64	RA	Infliximab	10-12-2002	20-6-2004	Worsening, pulmonary fibrosis	27-8-2004
6484	64	RA	Infliximab	9-10-2000	5-11-2001	Bronchiolitis obliterans	11-11-2001
6642	70	RA	Infliximab	2-3-2000	8-11-2000	Lung TB	15-3-2004
			Etanercept	17-10-2001	1-3-2004		
6643	70	RA	Infliximab	8-4-2002	12-9-2002	Death due to unknown cause	12-9-2002
6797	62	RA	Infliximab	7-12-2000	14-9-2001	Pancreatic carcinoma	10-9-2001
6913	73	RA (seronegative)	Infliximab	27-8-2001	8-10-2001	Pneumonia due to undefined germ	1-12-2001
7322	71	RA	Infliximab	2-5-2001	18-12-2004	Upper digestive hemmorrhage	18-12-2004

(Continued)

ANNEX 2. Description of the Patients That Died During Follow-Up in BIOBADASER *(Continuation)*

Patient	Age	Diagnosis	Biologic Treatment	Treatment Start Date	Treatment End Date	Cause of Death	Date of Death
7397	66	RA	Infliximab Etanercept	1-6-2001 6-5-2002	2-4-2002	Spinocelular carcinoma 1-7-2003	19-8-2003
7.456	75	RA	Infliximab	27-2-2001	27-1-2004	Septic shock due to undefined germ	13-11-2004
7753	44	Scleroderma (lung fibrosis, GER, myocarditis)	Infliximab	1-10-2001	18-10-2001	Anaphylactic shock and pneumonitis	31-12-2001
7790	61	RA (CRF due to amyloidosis, prosthesis)	Infliximab	24-11-2000	24-11-2000	Brain infection, undefined germ	1-12-2000
7978	70	RA (amyloidosis, terminal RF, hemodyalisis)	Etanercept	28-1-2004	25-4-2004	Sudden death due to unknown cause	25-4-2004
8512	71	RA	Infliximab	18-3-2003	25-5-2003	Myocardial infarction	1-6-2003
9040	60	RA (lung fibrosis secondary to RA)	Infliximab	20-11-2001	2-1-2002	Pericardial effusion	11-2-2002
9386	72	RA	Infliximab	20-9-2004	14-11-2005	Septic shock due to undetermined germ	14-11-2005
9901	59	RA	Adalimumab	7-4-2003	28-10-2003	Pneumonitis	28-10-2003
10 658	73	SA	Infliximab	19-12-2003	1-2-2004	Respiratory insufficiency	1-1-2005
			Infliximab	19-10-2004	1-1-2005		

AAN indicates antinuclear antibodies; PsA, psoriatic arthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; RF, rheumatoid factor; HT, hypertension; CRF, chronic renal failure; GER, gastroesophageal reflux; ALS, amyotrophic lateral sclerosis; TB, tuberculosis.