

Adverse Reactions Related to the Administration of TNF Inhibitors. Analysis of a Registry of Biologic Therapy

Beatriz Pérez-Zafrilla, Miguel Ángel Descalzo, Loreto Carmona, and the BIOBADASER study group*

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

Objective: To estimate the frequency of administration related reactions (ARR), the risk window from the starting date, and finally if there are any differences between infliximab, etanercept, and adalimumab.

Patients and method: BIOBADASER is an adverse event registry established in 2001 for active long-term follow-up of safety of biological therapies in rheumatic patients. Data from patients, diagnosis, treatment, and adverse events are recorded.

Results: Four-hundred ninety-six relevant ARR were registered, 19.6% (496/2531) of all the adverse events communicated and 6.3% (496/2531) of all the patients registered. The incidence rate per 1000 patients-year with infliximab is 28 cases (95% CI, 25-31), with etanercept 0.2 (95% CI, 0.1-0.4), and with adalimumab 0.2 (95% CI, 0.07-0.7). Treatment was interrupted in more than 50% of all the ARR and 5% of all patients were hospitalized. More than 20% ARR happened after 15 months of treatment; in addition 2 appeared after 5 years of treatment. In delayed reactions the symptoms that most frequently were recorded were rash, fever, malaise, and myalgia.

Conclusions: ARR can appear in any moment of the treatment; they are among the most frequent causes of treatment interruption. Although with less frequency, ARR are also associated with etanercept and adalimumab with symptoms that cannot be identified as such.

Key words: Infliximab. Etanercept. Adalimumab. Toxicity. Adverse effects. Registry. Rheumatic diseases.

Reacciones adversas relacionadas con la administración de inhibidores del TNF. Análisis de un registro de terapias biológicas

Objetivo: Estimar la frecuencia de aparición de las reacciones relacionadas con la administración (RRA), los síntomas asociados a las graves o tardías, la ventana de exposición desde inicio de la terapia biológica y si hay diferencias entre infliximab, etanercept y adalimumab.

Pacientes y método: BIOBADASER es un registro de acontecimientos adversos establecido en 2001 para determinar la seguridad de las terapias biológicas en enfermedades reumáticas. Contiene datos de los pacientes, tratamiento y acontecimientos adversos relevantes.

Resultados: Se registró un total de 496 RRA relevantes en 442 pacientes, lo que representa un 19,6% (496/2.531) de todos los acontecimientos adversos comunicados y un 6,3% de los pacientes registrados (442/6.969). La tasa de incidencia de RRA por 1.000 años-paciente con infliximab es de 28 casos (intervalo de confianza [IC] del 95%, 25-31), con etanercept 0,2 (IC del 95%, 0,1-0,4) y con adalimumab 0,2 (IC del 95%, 0,07-0,7). En más de la mitad de las RRA, el acontecimiento adverso da lugar a la interrupción del fármaco relacionado y en el 5% de los casos el paciente requiere ser hospitalizado. Más del 20% de las RRA ocurren después de 15 meses de tratamiento, incluso aparecen después de 5 años. En las reacciones adversas tardías los síntomas comunicados con más frecuencia son erupciones, fiebre, malestar general y mialgias.

Conclusiones: Las RRA pueden aparecer en cualquier momento de la enfermedad, son una de las causas más frecuentes de interrupción de tratamiento con infliximab. Aunque con menor frecuencia, también se relacionan con etanercept y adalimumab en síntomas que pueden no identificarse como tales.

Palabras clave: Infliximab. Etanercept. Adalimumab. Toxicidad. Efectos adversos. Registro. Enfermedades reumáticas.

*The names of the BIOBADASER study group are shown at the end of the article.

Correspondence: Dra. L. Carmona.
Unidad de Investigación. Fundación Española de Reumatología.
Marqués del Duero, 5, 1.º. 28001 Madrid. España.

Manuscript received October 24, 2007; accepted for publication February 7, 2008.

Introduction

Pharmacologic inhibition of tumor necrosis factor (TNF), using infliximab, etanercept, or adalimumab, has demonstrated its efficacy in several inflammatory diseases. Among the expected adverse events of all therapies with a biotechnological origin, as is the case with these medications, administration related reactions (ARR) can be found. ARR of TNF inhibitors can be classified as acute or late.¹⁻⁴

Acute ARR are presented at the moment of administration or in the 24 hours that follow it and are usually manifestations such as itching, edema, urticaria, hypotension, hypertension, bradycardia, tachycardia, headache, or anaphylactic shock, among others. Late ARR are presented after 24 hours and up to 14 days after the administration of the drug and are often associated with symptoms such as joint pain, myalgias, urticaria, skin eruptions, fever, or headaches.

An isolated symptom of an ARR can be interpreted as an adverse event of some other kind because, except skin reactions, such as urticaria and itching, all of the symptoms usually described are non-specific. A better knowledge of the type and moment of appearance of adverse reactions can help the clinician when establishing a differential diagnosis upon the appearance of an adverse event in those patients taking TNF inhibitor treatment. Because of this, we decided to carry out an analysis in BIOBADASER, the Spanish Registry of Adverse Events of Biologic Therapies in Rheumatic Diseases, with the objective of estimating the frequency of appearance of ARR, as well as the accompanying symptoms or severe or late ARR, knowing the window of exposure since the beginning of biologic therapy and, finally, determining the differences in ARR that can exist between infliximab, etanercept, and adalimumab.

Patients and Method

BIOBADASER has been described in detail in previous publications.^{5,6} It is a registry of adverse events created in 2001 to determine the security of biologic therapy in rheumatic disease. In it, patient data (gender, age, diagnosis, date of the diagnosis), treatment data (type, date of initiation and end), and adverse events are registered. Patients included in BIOBADASER can have any illness treated by a rheumatologist for which a biotechnological treatment has been prescribed.

Only relevant adverse events are collected in BIOBADASER. To be relevant, an adverse event is considered to be any unfavorable occurrence that, independent of the dose, leads to death, endangers the life of the patient, merits hospitalization or prolongs persistent or important loss of capacity, or produces congenital malformations. Important medical events that

do not lead to an immediate endangerment of life or cause death, but that compromise the patient or require an intervention to prevent any of the results mentioned in the definition above are also considered relevant adverse events.

An ARR is defined as isolated manifestations or a syndrome that occurs in temporal relation to the administration of a drug or something that, due to its characteristics, (typical groups of symptoms) is considered as related with the administration even if its appearance is late. The physicians participating in BIOBADASER are the ones that defined whether or not it was or wasn't an ARR. All of the registered ARR are relevant by definition, but severe ARR were considered when they merited hospitalization or prolongation of it. Acute reactions were considered when presented up to 24 hours after the administration and those presented after 24 hours and up to 14 days later were considered as late.

Of all of the ARR collected in a systematic way through a checklist, all of the possible associated symptoms, such as skin eruptions, dyspnea, itching, thoracic pain, malaise, dizziness, hypotension, nausea, hypertension, fever, headache, facial edema, bronchospasm, lumbar pain, cough, oral pain, myalgia, paresthesias, abdominal pain, fatigue, supraventricular tachycardia, syncope, conjunctivitis, cyanosis, dyspepsia, peripheral edema, generalized edema, heart failure, respiratory, acidosis, and diplopia, including a blank space to add any other related symptom.

Participating centers are monitored both online, in a daily fashion, as in situ, annually, just before unloading the database for the annual report. Monitoring is done on a random sample of 20 patients per center, and the clinical histories are compared to the data loaded into BIOBADASER. Incomplete data and mistakes are corrected according to the monitor's instructions.

A descriptive analysis of ARR from the start of the registry to June 2006 was carried out. The ARR incidence rate was estimated with 95% confidence intervals (CI). The clinical characteristics of BIOBADASER patients with and without ARR were compared using appropriate tests to the variable distribution (χ^2 test for dichotomic or categorical variables, and Student's *t* for continual ones).

Results

Since its inception in February 2000 until January 2006, a total of 6969 patients from 100 Spanish centers have been registered in BIOBADASER. These patients have received up to 8321 biologic agent-treatments, of which 4525 (54%) have been with infliximab, 2595 (31%) with etanercept, 1081 (13%) with adalimumab, 107 (1%) with anakinra, and 13 (0.2%) with rituximab. Up to 1125 patients have been treated with more than 1 biologic agent in distinct moments of their progression. Given the small

TABLE 1. Characteristics of the Patients in BIOBADASER Who Presented ARR at Some Moment of the Follow-up Versus Patients Who Did Not Present Them^a

	Without ARR (n=6527)	With RRA (n=442)	P
Age, mean (SD)	54 (15)	52 (14)	.058
Women, n (%)	4206 (64)	310 (70)	.015
Time since onset of disease, mean (SD), y	10 (8)	10 (7)	.180
Most frequent diagnosis, n (%)			.001
Rheumatoid arthritis	4142 (66)	317 (76)	
Ankylosing spondylitis	853 (14)	43 (10)	
Psoriatic arthritis	787 (13)	35 (9)	
Other spondyloarthritis	236 (4)	9 (2)	
Idiopathic juvenile arthritis	223 (3)	11 (3)	

^aARR indicates administration related reactions; SD, standard deviation.

number of patients treated with anakinra or rituximab, they were excluded from the analysis.

A total of 496 ARR in 442 patients were registered, something that represented 19.6% (496/2531) of all of the adverse events recorded and 6.3% of the patients registered (442/6969). In 42 patients, 2 ARR were communicated; 3 ARR in 9 patients and 3 patients presented 4, 5, and 6 ARR, respectively.

When comparing patients who have presented ARR with the rest of the patients included in the registry, which have not presented an ARR, the percentage of patients with rheumatoid arthritis is larger among those not presenting ARR, while ankylosing spondylitis and psoriatic arthritis are less frequent as a diagnosis for which biologic treatment is indicated among patients with ARR. No significant differences were observed regarding age and disease duration, but there were noticed in the percentage of women, which is larger in patients presenting ARR (Table 1).

TABLE 2. Differences Between the ARR Produced by Infliximab, Etanercept, or Adalimumab^a

Reactions	Infliximab (n=472)	Etanercept (n=16)	Adalimumab (n=8)	P
ARR Rate per 1000 Patient- Years (95% CI)	28 (25-31)	0.2 (0.1-0.4)	0.2 (0.07-0.7)	
Severe, n (%)	24 (5.1)	1 (6.2)	0	.788
Late, n (%)	31 (6.6)	2 (12.5)	3 (37.5)	.484
ARR led to treatment interruption, n (%)	304 (64.4)	8 (50.0)	6 (75.0)	.471

^aARR indicates administration related reactions; CI, confidence interval.

The rate of appearance of ARR with TNF inhibitors is of 18 cases per 1000 patient-years (95% CI, 16-20). Regarding the frequency of appearance with respect to the type of biologic employed, it is larger with infliximab than with the rest of the TNF inhibitors TNF (Table 2). In 10.4% (472/4525) of all of the treatments with infliximab, there is the appearance of at least 1 ARR, in 0.5% (14/2595) with etanercept, and 0.7% (8/1081) with adalimumab.

Late ARR are more frequent with etanercept and adalimumab than with infliximab, though this is not statistically significant. In more than half the ARR, the adverse event leads to the interruption in the related treatment (Table 2). Symptoms registered with etanercept are itching (n=5), skin eruption (n=3), bronchospasm (n=2), and chest pain (n=2); in addition, headache, cyanosis, dyplopia, dyspnea, facial edema, oral edema, fever, malaise, dizziness, and paresthesias have been reported (in all, n=1). Symptoms related to adalimumab are skin eruption (n=4), fever (n=2), malaise (n=2), itching (n=2), and, in addition, polyarticular joint pain, bronchospasm, chest pain, and oral edema (all, n=1).

If we take into account the time from the start of treatment with a defined biologic until the moment in which the first ARR appears, one can observe that more than 20% of ARR occur after 15 months of treatment, even appearing, in 2 cases of ARR, after 5 years (Figure).

When studying the symptoms of the patients presenting any ARR, it must be considered that normally, in an ARR, there are associated symptoms. The symptoms that have been reported most frequently are: eruptions (n=195), dyspnea (n=115), itching (n=109), chest pain (n=65), malaise (n=64), dizziness (n=57), hypotension (n=57), and nausea (n=50). The mean (P₂₅₋₇₅) of symptoms that appeared due to a reaction was 2 (1-3).

Table 3 also shows the symptoms reported in late ARR; the most frequent ones were eruptions, fever, malaise, and myalgias. Of the 33 late ARR communicated, 5 required hospitalization and in 15, treatment was interrupted. The most commonly reported symptoms in the 25 severe ARRA have been: eruption (n=11), dyspnea (n=7), chest pain (n=7), fever (n=5), bronchospasm (n=4), headache (n=4), and hypotension (n=4). Of the 25 communicated reports, 6 were late and in 12, treatment was interrupted due to the ARR.

Discussion

In spite of the fact that ARR are a type of adverse reaction known to everyone who has used a drug of biotechnological origin, until now there had not been any studies evaluating all of the ARR associated to anti-TNF. All of the articles published up until the moment are centered on the infusion reactions related to infliximab^{1-4,7-10} and in case series or small sampling cohorts.

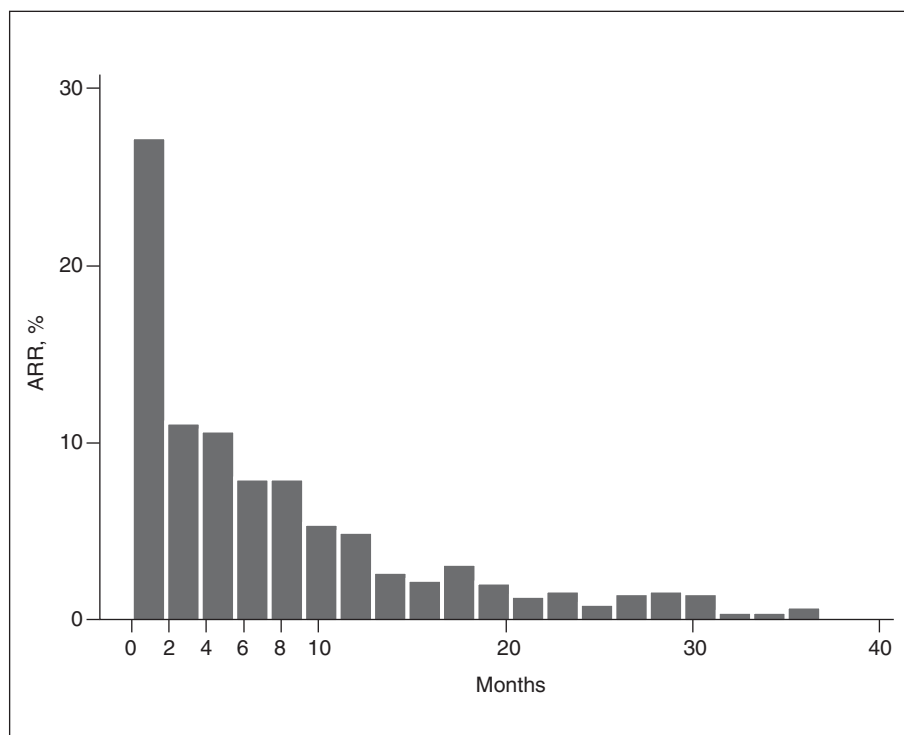


Figure. Time in months since the first administration of biologic to the appearance of any drug administration-related adverse event (ARR).

With respect to the factors that can predict the appearance of ARR, only an article by Kapenatovic et al,¹ coinciding with our results, mentions that patients with rheumatoid arthritis present infusion reactions with a greater frequency than those that use infliximab for ankylosing spondylitis (21% vs 13%), but the scarce number of patients (213 with arthritis and 76 with spondylitis) makes the detected difference non significant.

In relation to the percentage on the total of patients that presented at least one ARR there are some discrepancies because some studies show it is approximately 20%,^{1,4,7} and one of them even mentions that ARR appears in 53% of patients.⁸ Although our results coincide with those published by Cheifetz et al³ (10%), it is difficult to compare these results, because they study different populations, one analyzing only patients with rheumatoid arthritis, others with arthritis and spondylitis, and some patients with Crohn's disease.³ On this fact it is important to point out that BIOBADASER only notifies "relevant" adverse events, making it very likely that the total frequency of ARR is much higher.

One of the most important pieces of data coming from the present analysis is that the percentage of ARR in those anti-TNF's different from infliximab. It is very common to think that etanercept or adalimumab, both administered subcutaneously, only produce injection site reactions, but our results show that symptoms such as fever, chest pain, bronchospasm, nausea, dyplopia, paresthesias, and other

effects commonly related to infusion reactions might appear. In this respect, it would be useful to point out that the elevated number of ARR of infliximab versus etanercept or adalimumab can be increased, because when these occur during the infusion of infliximab, except in the late ones, the physician is always present, something that does not normally occur in the case of etanercept or adalimumab. In spite of the fact that these types of reactions are seldom severe and that they are controlled with medication that reduces sensitivity, such as antihistamines or steroids or by reducing the rate of infusion in the case of intravenous administration, up to 5% of patients have to be hospitalized. In most of the published literature, the percentage of severe ARR is very low, except in the case of Kugathasan et al,⁹ which mentions that 14% of ARR are severe. Also, ARR associated to infliximab are the most common cause for interrupting treatment and leads us to think that, although not severe enough to hospitalize the patient, 64% of them are sufficiently relevant as to merit treatment interruption. This data is different than that presented by Wasserman, Cheifetz, or Maini, in which the interruption of treatment occurred in 2% of cases and none merited patient hospitalization.

With respect to late reactions, although not very frequent (7%), it is noticeable that symptoms occur that are common in acute ARR, such as bronchospasm, edema, thoracic pain, nausea, or tachycardia. In addition, other types of symptoms such as myalgias, lumbar pain, fever,

TABLE 3. Symptoms of All Adverse Reactions Related With Medication and of the Late Ones by Order of Frequency

Total Symptoms	No. (%)	Late Symptoms	No. (%)
Skin eruption	195 (19.5)	Skin eruption	15 (25.4)
Dyspnea	115 (11.5)	Fever	9 (15.3)
Itching	109 (10.9)	Malaise	5 (8.5)
Chest pain	65 (6.5)	Myalgia	4 (6.8)
Malaise	64 (6.4)	Itching	4 (6.8)
Dizziness	57 (5.7)	Headache	3 (5.1)
Hypotension	57 (5.7)	Cough	3 (5.1)
Nausea	50 (5.0)	Bronchospasm	2 (3.4)
Hypertension	39 (3.9)	Oral edema	2 (3.4)
Fever	37 (3.7)	Facial edema	2 (3.4)
Headache	34 (3.4)	Paresthesias	2 (3.4)
Facial edema	31 (3.1)	Fatigue	1 (1.7)
Bronchospasm	19 (1.9)	Conjunctivitis	1 (1.7)
Lumbar pain	18 (1.8)	Dyplopia	1 (1.7)
Cough	17 (1.7)	Abdominal pain	1 (1.7)
Oral edema	16 (1.6)	Lumbar pain	1 (1.7)
Myalgia	11 (1.1)	Chest pain	1 (1.7)
Paresthesias	11 (1.1)	Nausea	1 (1.7)
Abdominal pain	9 (0.9)	Tachycardia	1 (1.7)
Fatigue	7 (0.7)	Total	59 (100)
Tachycardia	7 (0.7)		
Syncope	6 (0.6)		
Conjunctivitis	5 (0.5)		
Cyanosis	5 (0.5)		
Dyspepsia	5 (0.5)		
Peripheral edema	4 (0.4)		
Generalized edema	3 (0.3)		
Heart failure	2 (0.2)		
Respiratory acidosis	1 (0.1)		
Dyplopia	1 (0.1)		
Total	1000 (100)		

paresthesias, or dyplopia, by their characteristics cannot be identified as associated to late ARR and can be confused with concomitant diseases, making it important to always keep in mind late ARR.

As shown by other studies, the ARR is present in the first 3 infusions of infliximab in only 50% of cases, with a

greater frequency in the third infusion.^{3,10} It is important to point out that ARR have appeared even after 5 years after starting treatment and that more than 20% appear after 15 months of treatment.

In conclusion, it must be emphasized that while these types of reactions are associated to infliximab with a greater frequency, it must not be forgotten that they might appear with etanercept and adalimumab, with symptoms such as fever, chest pain, bronchospasm, or nausea. In addition, ARR are one of the most frequent causes of infliximab treatment interruption. It must be noted that one must be alert to the symptoms that might appear due to late ARR, because many times the relationship with the drug goes unnoticed. One must also remember that these reactions can occur at any moment of the disease, not only in the first administrations.

Thank You

We would like to thank everyone for his or her effort, past and present, done in every center that composes BIOBADASER.

Persons that Compose the BIOBADASER Study Group

Agustí Sellas, Basilio Rodríguez, Mireia Barceló (Ciudad Sanitaria Vall d'Hebron); Laura Cebrián, María Montoro (Hospital Gregorio Marañón); Dolores Montesinos (Hospital Universitario Virgen Macarena); Eva Pérez-Pampín (Hospital Clínico Universitario de Santiago); Paloma Vela (Hospital General Universitario de Alicante); Olga Maiz (Hospital Donostia-Edif. Guipúzcoa); Ana M. Ortiz (Hospital Universitario de La Princesa); Paloma Abreu, Isabel Granados (Hospital Ramón y Cajal); Francisco Javier Manero Ruiz, Chesús Beltrán, Eugenio Gimenez Úbeda, Fernando Jiménez Zorzo, Jesús Marzo, Marta Medrano, Ángela Pecondó (Hospital Universitario Miguel Servet); M. Victoria Hernández, Raimon Sanmartí, Juan D. Cañete (Hospital Clínic i Provincial); Carlos Rodríguez Lozano, Antonio Naranjo, Soledad Ojeda, Félix Francisco Hernández, Celia Erausquin, Íñigo Rúa (Hospital de Gran Canaria Dr. Negrín); Inmaculada Ureña, María Victoria Irigoyen, Laura Cano (Hospital General Carlos Haya); Ana Cruz Valenciano, Manuel Crespo Echeverría, Félix Cabero Del Pozo (Hospital Severo Ochoa); Luis Francisco Linares (Hospital Virgen de la Arrixaca); Rosa Roselló Pardo, Carlos Vázquez Galeano (Hospital General San Jorge); Juan Carlos Vesga, Eduardo Cuende (Hospital Txagorritxu); Carmen Idalgo Tenorio (Hospital Virgen de Las Nieves); Alexia de Juanes, Beatriz Joven, Javier García (Hospital 12 de Octubre); Delia Reina (Hospital de Bellvitge Princeps d'España); Manuel Fernández Prada (Hospital General Universitario de Guadalajara);

Joan Maymo Guarch (Ímas. Hospital de L'Esperança y Hospital del Mar); Javier Calvo, Cristina Campos (Hospital General Universitario de Valencia); Isabel Ibero Díaz, Vega Jovani Casado (Hospital General de Elda); Trinidad Pérez Sandoval (Hospital Virgen Blanca); Jose Raúl Noguera Pons (Hospital General Universitario de Elche); Eduardo Rejón (Hospital Universitario de Valme); Raquel Almodóvar (Hospital Fundación Alcorcón); Manuel Rodríguez Gómez (Complejo Hospitalario de Ourense); Eduardo Collantes Estevez, M. Carmen Castro Villegas (Hospital Universitario Reina Sofía); Jose Ángel Cabezas Lefler (Complejo Hospitalario San Millan-San Pedro); Marta Larrosa Padro, Jordi Gratacos Masmitja, Enrique Casado (Consorci Hospitalari del Parc Tauli); M. Teresa Ruiz Jimeno, Jaime Calvo Alen (Hospital Comarcal Sierrallana); M. Ángeles Mora (Hospital Universitario de Canarias); Jesús Ibáñez Ruan (Policlínico Vigo, S.A. Povisa); Juan Jose García Borrás, Rosa Negueroles, Luisa Muñoz, J.L. Valero, D. Ybáñez (Hospital La Fe); Eva Tomero Muriel (Hospital General de Segovia); Amalia Sánchez-Andrade Fernández (Hospital Xeral-Calde); Encarnación Saiz Cuenca (Hospital General Morales Meseguer); Montserrat Centellas (Hospital de Mataró); Jordi Fiter Aresté, Luis Espadaler Poch (Hospital Son Dureta); Lucia Pantoja, M. Valvanera Pinillos (Hospital del Bierzo); Julia García Consuegra, Rosa Merino (Hospital Infantil La Paz); Javier Rivera, Teresa González Hernández (Instituto Provincial de Rehabilitación); Vera Ortiz (Hospital Universitari Germans Trias i Pujol); Carmen Torres, Montserrat Corteguera (Hospital Nuestra Señora de Sonsoles); Javier Alegre (Hospital General Yagüe); Xavier Arasa (Hospital de Tortosa); Jordi del Blanco Barnusell (Hospital Sant Jaume de Calella); Anna Martínez Cristóbal (Hospital de La Ribera); Inmaculada Bañegil (Hospital de Mendaro); Ángel García Aparicio (Hospital Virgen de La Salud); Emilia Aznar (Hospital Reina Sofía); Maria Francisca Pina (Hospital Rafael Méndez); Miquel Ángel Belmonte, Juan Beltrán Fabregat (Hospital General de Castellón); Alberto Alonso Ruiz, Esther Uriarte Itzazelaia (Hospital de Cruces); Mauricio Minguez Vega, Gaspar Panadero Tendero (Hospital

San Juan de Alicante); Miguel Ángel Abad Hernández, María Torresano (Hospital Virgen del Puerto); Ana Urruticoechea (Hospital Can Misses de Ibiza); Jose Ivorra (Hospital General de Onteniente y Lluís Alcanyís de Xàtiva); Antonio Juan Mas, Jenaro Graña (Hospital Santa Teresa); Saúl Mario Gelman Aizen (Centre Hospitalari Manresa); Jose Carlos Rosas, Gregorio Santos, Raquel Martín (Hospital del S.V.S. de Villajoyosa); Cristina Hidalgo (Hospital de La Santísima Trinidad); Jaime Fernández Campillo, Víctor Eliseo Quevedo (Hospital Comarcal de Monforte); Isabel Rotes, Estefanía Moreno (Hospital de San Rafael).

References

1. Kapetanovic MC, Larsson L, Truedsson L, Sturfelt G, Saxne T, Geborek P. Predictors of infusion reactions during infliximab treatment in patients with arthritis. *Arthritis Res Ther*. 2006;8:R131.
2. Crandall WV, Mackner LM. Infusion reactions to infliximab in children and adolescents: frequency, outcome and a predictive model. *Aliment Pharmacol Ther*. 2003;17:75-84.
3. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol*. 2003;98:1315-24.
4. Lequerre T, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. *J Rheumatol*. 2006;33:1307-14.
5. Comité Científico de BIOBADASER. BIOBADASER: Registro español de acontecimientos adversos de terapias biológicas en enfermedades reumáticas. *Rev Esp Reumatol*. 2002;29:292-9.
6. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero MD, Pascual-Gómez E, Martín Mola E, et al. BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum*. 2005;52:1766-72.
7. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet*. 1999;354:1932-9.
8. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol*. 2004;31:1912-7.
9. Kugathasan S, Levy MB, Saecian K, Vasilopoulos S, Kim JP, Prajapati D, et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. *Am J Gastroenterol*. 2002;97:1408-14.
10. Buch MH, Lindsay S, Bryer D, Fairclough A, Rees-Evans B, Emery P. Incidence of infusion related reactions in patients receiving infliximab: recommendations for administration recommendations [abstract]. *Ann Rheum Dis*. 2004;63:285.