Reumatología Clínica
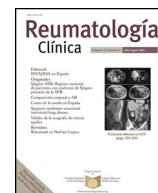
Original Article

Objectives and methodology of BIOBADASER phase III☆

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ABSTRACT

Objective: Describe the objectives, methods and results of the first year of the new version of the Spanish registry of adverse events involving biological therapies and synthetic drugs with an identifiable target in rheumatic diseases (BIOBADASER III).

Methodology: Multicenter prospective registry of patients with rheumatic inflammatory diseases being treated with biological drugs or synthetic drugs with an identifiable target in rheumatology departments in Spain. The main objective of BIOBADASER phase III is the registry and analysis of adverse events; moreover, a secondary objective was added consisting of assessing the effectiveness by means of the registry of activity indexes. Patients in the registry are evaluated at least once every year and whenever they experience an adverse event or a change in treatment. The collection of data for phase III began on 17 December 2015.

Results: During the first year, 35 centres participated. The number of patients included in this new phase in December 2016 was 2664. The mean age was 53.7 years and the median duration of treatment was 8.1 years. In all, 40.4% of the patients were diagnosed with rheumatoid arthritis. The most frequent adverse events were infections and infestations.

Conclusions: BIOBADASER phase III has been launched to adapt to a changing pharmacological environment, with the introduction of biosimilars and small molecules in the treatment of rheumatic diseases. This new stage is adapted to the changes in the reporting of adverse events and now includes information related to activity scores.

Objetivos y metodología de la fase III de BIOBADASER

R E S U M E N

Palabras clave:
Real World Data
Seguridad
Acontecimientos adversos
Metodología
Artritis reumatoide
Terapia biológica

Objetivo: Describir los objetivos, la metodología y los resultados del primer año de la nueva versión del registro español de acontecimientos adversos de terapias biológicas y fármacos sintéticos con diana identificable en enfermedades reumáticas (BIOBADASER III).

Metodología: Registro prospectivo multicéntrico de pacientes con enfermedades inflamatorias reumáticas en tratamiento con terapia biológica o fármacos sintéticos con diana identificable y atendidos en servicios de Reumatología en España. El objetivo principal de BIOBADASER Fase III es la recogida y análisis de acontecimientos adversos al que se ha añadido como objetivo secundario la evaluación de la efectividad mediante la recogida de índices de actividad. Los pacientes que entran en el registro son evaluados al menos una vez cada año y cada vez que presenten un acontecimiento adverso o se produzcan modificaciones en el tratamiento. La recogida de datos de la fase III se inició el 17 de diciembre del 2015.

Resultados: Durante el primer año han participado 35 centros. El número de pacientes incluidos en esta nueva fase en diciembre del 2016 era de 2.664. La edad media era de 53,7 años, con una mediana de duración de la enfermedad hasta el inicio de tratamiento de 8,1 años. Un 40,4% de los pacientes estaban diagnosticados de artritis reumatoide. Los acontecimientos adversos más frecuentes eran las infecciones e infestaciones.

Conclusiones: La fase III de BIOBADASER se ha puesto en marcha para responder a un entorno farmacológico cambiante con la aparición de los biosimilares y las pequeñas moléculas en el tratamiento de la patología reumática. Esta nueva etapa se adapta a los cambios normativos en la comunicación de acontecimientos adversos y amplía la información recogida incluyendo los índices de actividad.

Introduction

Inflammatory rheumatic diseases affect over 10% of the population at large.[1,2] According to data from the latest annual report of phase II of the Spanish registry of adverse events involving biological therapies in rheumatic diseases (BIOBADASER II), diagnoses of rheumatoid arthritis (RA), psoriatic arthritis (PA) and ankylosing spondylitis (AS) are the most prevalent among patients with rheumatic diseases included in the registry. According to data from December 2015, 50.5% of the patients included in this registry were diagnosed with RA; 16.6% with AS and 15.9% with PA.[3]

In Spain there are 14 approved drugs for the treatment of rheumatic diseases: 5 innovative tumour necrosis factor inhibitors (TNF)-α: infliximab, etanercept, adalimumab, certolizumab pegol and golimumab; one interleukin receptor antagonist recombinant protein (IL) 1: anakinra; one T-cell activation modulator fusion protein: abatacept; one monoclonal antibody against the IL 6 receptor: tocilizumab; one monoclonal antibody against CD20: rituximab; one monoclonal antibody against IL-1β: canakinumab, one monoclonal antibody targeted against the B-cell activating factor (BAFF): belimumab; one IgG1κ anti-IL-12/23 monoclonal antibody: ustekinumab; one anti-IL-17A antibody: secukinumab, and one monoclonal antibody which acts as an inhibitor of the ligand RANK (RANKL): denosumab. Information exists on safety and efficacy from randomised clinical trials which have assessed many of these drugs in the short term.[4–8] However, follow-up of these treatments long-term and information on safety and efficacy in clinical practice are still imited,[9] particularly in drugs which have been on the market for a shorter time. From February 2015 CT-P13 (Celltrion) has been made available. This is a biosimilar of infliximab which has been distributed in Mexico under 2 trade names,[10,11] and since the end of 2016 a second biosimilar to infliximab, SB2 (developed by Samsung Bioepis) and another biosimilar to etanercept, SB4 (Samsung Bioepis), are also available with the same indications as their innovative molecule.[12,13] Two oral inhibitor compounds of Janus Kinase inhibitor compounds (JAK), tofacitinib and baricitinib, will shortly be available for the management of RA, and will be combined with a phosphodiesterase 4 inhibitor, apremilast (already available), with an indication in PA. These will constitute a new group of synthetic drugs with an identifiable target.

BIOBADASER began its activity in the year 2000 and continued with phase II in 2006.[14] The goals of this project were to collect information on the safety and adverse events in patients who had begun biologic treatment. In different European, Latin American countries and in the United States other similar registries exist for patients being treated with biologic therapy.[15] The appearance of biosimilars and synthetic drugs with an identifiable target, and the need expressed by regulatory agencies in knowing direct data on the effectiveness and safety of these agents in daily clinical practice, together with changes in regulation and legislation in pharmacovigilance, has determined the launch of the BIOBADASER phase III.

BIOBADASER helped to establish the relationship between the anti-TNF therapy and the reactivation of latent tuberculosis in patients with rheumatic diseases.[16–18] These studies have led to an improvement in the usage safety of this type of treatment.

The Spanish Society of Rheumatology (SER), in collaboration with the Spanish Medicines and Health Products Agency (AEMPS), and support by finance from the pharmaceutical sector, has continued to drive BIOBADASER with the start-up of phase III of the project. This paper describes the objectives, design and methodology of BIOBADASER III, the results obtained in the first year and the strengths and weaknesses of the study.

Methodology

BIOBADASER is a prospective registry of follow-up of patients with rheumatic diseases who begin treatment with biologics, biosimilars and synthetic molecules with an identifiable target.

BIOBADASER phase III

The phase III objectives are as follows:

- Identify relevant adverse events which appear during the treatment of rheumatic diseases with biologic therapies and synthetic drugs with an identifiable target and estimate their frequency of presentation.
- Identify unexpected adverse events.

Table 1
Selection criteria of patients to participate in BIOBADASER Phase III.

Selection criteria
Patients with RA who are beginning treatment (or are being treated) with biologics (except infliximab, etanercept and adalimumab) or biosimilar in the participative centres, from the beginning of phase three.
Patients with any other diagnosis who are beginning treatment (or are being treated) with biologics or biosimilar in the participative centres, from the beginning of phase three.
Patients who are being treated with biologics or have had treatment suspended, for any reason, provided that no more than one year has passed since they received treatment for the last time and that all the necessary data are available for recording (concerning the patient, treatment and adverse events).
Patients who authorise the prospective collection of data in accordance with the formula indicated on the informed consent form.

The patient must meet with one of the 3 first criteria and without fail with the fourth criterion.

- Identify relevant adverse events which present after treatment has been suspended.
- Assess, under non experimental circumstances, time passing up to the suspension of biologic therapies in patients with rheumatic diseases, and the reasons for this withdrawal: side effect, loss of effectiveness, remission or death.
- Assess the effectiveness in clinical practice of the treatments included in the registry.

Centre selection

During the first year of phase III 35 centres participated. The selection of these centres was made through a public call for proposals advertised through the usual media available to SER members. All researchers interested in participating in the project had to fill in a document with the centre details and their commitment to study participation. A priori, there was no fixed minimum number of patients in treatment with biologic therapy for the centre selection. Final selection was made by the BIOBADASER Scientific Committee, based on the number of patients in treatment with biologic therapy in the Rheumatology Department of the interested hospitals until completion of the 35 centres who took part in the study the first year.

Patient selection

The population who were candidates for the study were those patients in treatment with biologic therapy or targeted synthetic drugs for any rheumatologic disease in the technical record or for compassionate usage, attended by the Rheumatology Services of the centres that participated in phase III and who gave their informed consent to take part in the study.

Study recruitment for the inclusion of new patients remains open indefinitely.

Selection criteria

Patients with any rheumatic disease were able to participate in the study provided they met with the criteria contained in Table 1. The patient had to meet one of the 3 first criteria and sign an informed consent form to participate in the study.

To enhance recruitment of new patient participants in the study, it was accepted that the patients could have initiated biology therapy in the 2 years prior to the start of BIOBADASER phase III. Information from the 2 previous years was collected from the clinical record.

Patients who had participated in phase II of the study could continue participating in phase III of BIOBADASER once the new informed consent form had been signed.

Data collection

Information recorded in BIOBADASER originated from the clinical record and visits from patients to the Rheumatology department. The information collected: (1) as baseline; (2) when an adverse event or change in treatment occurred (biologic therapy or with synthetic molecules with an identifiable target), for any other reason during this time period and (3) at least once a year (follow-up visit). Data were also recorded when death occurred for any reason and in the case of discontinuation of treatment due to remission or other causes.

Data recording and storage was conducted electronically, using an ad hoc designed IT application. An instruction manual was redacted to explain how it worked to the researchers. The IT application contained filters, ranges, menus and dialogues to help improve data reliability.

An annual online monitorisation of data recorded between the months of September and November of every year was made. The goal of this monitorisation was to filter out inconsistencies and possible data collection errors. From the second year onwards, apart from the continuous online monitorisation, an annual on-site monitorisation is to be made where all the participant centres in BIOBADASER phase III will be visited and 20 patients from each centre will be randomly selected to have their medical records monitored.

Variables

In the baseline visit the registry inclusion date was collected and sociodemographic variables such as gender and date of birth. The following clinical variables were also collected in this visit: diagnosis and date of diagnosis, weight and height on patient inclusion in the study, number of inflamed and painful joints, visual analogue scale of the disease activity, assessed by the patient, analytical values (ESR, CRP, rheumatoid factor, anti-CCP, HLB27 and antinuclear antibodies). Activity indices collected are the DAS28 for patients diagnosed with RA and PA, BASDAI and ASDAS-CRP in the case of AS and SLEDAI for patients diagnosed with SLE. This information was collected at the start of each new treatment and in the annual check-ups. Patient comorbidities were collected in the baseline visit through the components of the Charlson index.[19] In cases where the patient had previously received other biologic drugs, the initiation and termination dates of these treatments were also recorded.

From the moment the BIOBADASER phase III patient was included, the date of initiation and termination was recorded, as was the reason for treatment suspension. In this phase III the dose, periodicity and administration route of the biologic or synthetic drug with identifiable target treatment were also recorded. To avoid problems of traceability between innovators and biosimilars all the drugs were recorded with their trade name. Information was also collected relating to the screening for tuberculosis (previous

Table 2
Sociodemographic and diagnostic characteristics recorded in BIOBADASER phase III.

Number of patients	2664
Woman (%)	1.621 (60.9)
Current mean age (DE)	53.7 (14.4)
Mean age at treatment initiation (SD)	50.1 (13.9)
Median duration (P$_{50}$) of disease at the beginning of treatment (P$_{25}$−P$_{75}$)	8.1 (3.3–14.9)
Diagnoses (n [%])	
Rheumatoid arthritis	1077 (40.4)
Ankylosing spondylitis	552 (20.7)
Psoriatic arthritis SpA	522 (19.6)
Undifferentiated Sp	140 (5.3)
Juvenile idiopathic arthritis	74 (2.8)
Systemic lupus erythematosus	46 (1.7)
Enteropathic arthritis	41 (1.5)
Chronic seronegative polyarthritis	34 (1.3)
Uveitis without rheumatic disease	24 (0.9)
Osteoporosis	23 (0.9)
Non-radiographic axial ankylosing spondylitis	19 (.7)
Chronic seronegative oligoarthritis	18 (.7)
Vasculitis	15 (.6)
SAPHO syndrome	11 (.4)
Overlap	10 (,4)
Behçet's disease	8 (.3)
Still's disease	7 (.3)
Reactive arthritis	7 (.3)
Primary Sjögren syndrome	6 (.2)
Juvenile undifferentiated spondyloarthropathy	6 (.2)
Juvenile SA	6 (.2)
Polymyositis/dermatomyositis	5 (.2)
Sclerodermia	3 (0.1)
Rheumatic polymyalgia	3 (.1)
Sarcoidosis	2 (.1)
Undifferentiated connective tissue disease	2 (.1)
Autoinflammatory syndromes	2 (.1)
Relapsing polychondritis	1 (.0)
Total	2664 (100.0)

Table 3
Treatments registered in accordance with patient referral.

Variable	Patients phase II[a] No. (%)	Patients phase III[b] No. (%)	Total No. (%)
Anti-TNF	2248 (64.8)	632 (52.9)	2888 (61.7)
Biosimilars	46 (1.3)	86 (7.2)	132 (2.8)
Other groups	1177 (33.9)	477 (39.9)	1654 (35.5)

[a] Patients from phase II. Patients who were included in the study in phase II and who have now signed the informed consent form and have had their information updated in phase III.

[b] New patients, included in the study for the first time from the beginning of phase III.

Table 4
Frequency of adverse events communicated to BIOBADASER phase III.

AE	No.	% of total of AE
Infections and infestations	598	21.2
Skin disorders and subcutaneous tissue	384	13.6
Vascular disorders	174	6.2
Traumatic lesions, intoxications and complications from surgical procedures	172	6.1
Musculoskeletal and conjunctive tissue disorders	156	5.5
Medical and surgical procedures	151	5.3
Complementary examinations	126	4.5
Gastrointestinal disorders	119	4.2
Respiratory, thoracic and mediastinic disorders	116	4.1
Nervous system disorders	112	4
Metabolism and nutrition disorders	100	3.5
Immunological system disorders	80	2.8
Kidney and urinary disorders	68	2.4
Blood and lymphatic system disorders	61	2.2
General disorders and changes in administration	55	1.9
Ocular disorders	53	1.9
Cardiac disorders	46	1.6
Benign, malignant and non specified neoplasm's (including cysts and polyps)	45	1.6
Hepatobiliary disorders	44	1.6
Psychiatric disorders	39	1.4
Reproductive system and breast disorders	36	1.3
Pregnancy, puerperium and perinatal diseases	27	1
Ear and labyrinth disorders	27	1
Endocrinal disorders	25	.9
Congenital, family and genetic disorders	12	.4
Social circumstances	2	.1
Total	2828	100

AE: adverse events.

history, probability of contact, BCG vaccination, carrying out of diagnostic tests, chemoprophylaxis), vaccines and diagnostic tests for this disease, in addition to concomitant non biologic treatment. These variables had to be completed in each biologic treatment change.

The adverse event variable was collected in 2 ways, using an open-ended question and using a term based on the nomenclature of the Medical Dictionary for Drug Regulatory Activities (MedDRA). In this BIOBADASER phase III the updating of MedDRA to version 19.0. took place. In the event of adverse events, the product lot was also recorded in keeping with the pharmacovigilance regulation (Royal Decree 577/2013, of 26th July, with which the pharmacovigilance of drugs for human usage is regulated). In this new phase the Orange algorithm for assessing causality of adverse event with biologic treatment was recorded.[20]

Results

The number of patients included in BIOBADASER phase III in the first year of recruitment was 2664. Out of these patients, 1070 came from phase II of the registry (40.2% of patients), whilst 1594 patients (59.8%) were included for the first time in the study. Table 2 shows the sociodemographic characteristics and diagnoses of the patients included in the first year of the registry. The registry mainly comprises middle aged women over the age of 50 and with a median disease evolution of 8.1 years, with an interquartile range of 11.5 years, prior to beginning any of the treatments included in the study.

The total number of treatment recorded in BIOBADASER was 4666. 61.7% of treatment recorded in the study correspond to

anti-TNF. Table 3 shows the number of cycles administered, by treatment group, in all patients depending on their prior participation in phase II of the study.

Table 4 shows the frequency of adverse events recorded in BIOBADASER phase III. In total, 2828 adverse events were mentioned, including information from patients who had participated in phase II. 268.9 adverse events were recorded by 1000 patients-per year (Table 4). In total, there was mention of 4 adverse events which led to the patient's death. In total 268.9 serious adverse events per 1000 patients-per year were recorded. Infections and infestations were the group of which presented the highest incidence (Table 5).

Table 5
Incidence rates of groups of adverse events recorded in BIOBADASER.

Incidences (95% CI) × 1000 patients-per year	1st choice biologic	2nd choice biologic or posterior	Total
Total adverse events	226.1 (214.4–238.4)	326.5 (310.2–343.6)	268.9 (259.1–279.0)
Serious	40.6 (35.8–46.0)	66.0 (58.9–74.0)	51.4 (47.3–56.0)
Mortal	.2 (.0–1.2)	.7 (.2–2.1)	.4 (.1–1.0)
By organic systemic class			
Infections and infestations	47.6 (42.4–53.4)	69.4 (62.1–77.5)	56.9 (52.5–61.6)
Skin and subcutaneous tissue disorders	32.5 (28.2–37.4)	41.9 (36.3–48.4)	36.5 (33.0–40.4)
Vascular disorders	13.8 (11.1–17.1)	20.3 (16.5–24.9)	16.5 (14.3–19.2)
Trauma lesions, intoxications and complications of therapeutic procedures	13.6 (10.9–16.9)	20.1 (16.3–24.7)	16.4 (14.1–19.0)
Musculoskeletal and connective tissue disorders	11.8 (9.3–14.8)	19.0 (15.3–23.4)	14.8 (12.7–17.4)
Medical and surgical procedures	10.1 (7.9–13.0)	20.1 (16.3–24.7)	14.4 (12.2–16.8)
Complementary examinations	12.1 (9.6–15.2)	11.8 (9.0–15.5)	12.0 (10.1–14.3)
Gastrointestinal disorders	8.6 (6.6–11.3)	14.9 (11.8–19.0)	11.3 (9.5–13.5)
Respiratory, thoracic and mediastinal disorders	9.1 (7.0–11.9)	13.6 (10.6–17.5)	11.0 (9.2–13.2)
Disorders of the nervous system	8.9 (6.9–11.7)	12.9 (10.0–16.7)	10.6 (8.8–12.8)
Metabolism and nutrition disorders	9.1 (7.0–11.9)	10.0 (7.5–13.4)	9.5 (7.8–11.6)
Immunological system disorders	7.0 (5.1–9.4)	8.5 (6.2–11.6)	7.6 (6.1–9.5)
Kidney and urinary disorders	5.0 (3.5–7.1)	8.5 (6.2–11.6)	6.5 (5.1–8.2)
Disorders of the blood and lymphatic system	4.6 (3.2–6.7)	7.4 (5.2–10.4)	5.8 (4.5–7.5)
General disorders and changes in administration	5.0 (3.5–7.1)	5.6 (3.8–8.3)	5.2 (4.0–6.8)
Ocular disorders	3.3 (2.1–5.1)	7.4 (5.2–10.4)	5.0 (3.8–6.6)
Cardiac disorders	4.8 (3.3–6.9)	3.8 (2.4–6.1)	4.4 (3.3–5.8)
Benign, malignant and unspecified neoplasms (including cysts and polyps)	3.3 (2.1–5.1)	5.6 (3.8–8.3)	4.3 (3.2–5.7)
Hepatobiliary disorders	2.5 (1.5–4.1)	6.5 (4.5–9.3)	4.2 (3.1–5.6)
Psychiatric disorders	3.3 (2.1–5.1)	4.2 (2.7–6.6)	3.7 (2.7–5.1)
Disorders of the reproductive system and breasts	2.5 (1.5–4.1)	4.7 (3.1–7.2)	3.4 (2.5–4.7)
Disorders of the ear and labyrinth	2.8 (1.8–4.5)	2.2 (1.2–4.1)	2.6 (1.8–3.7)
Pregnancy, puerperium and perinatal disease	1.8 (1.0–3.3)	3.6 (2.2–5.8)	2.6 (1.8–3.7)
Endocrinal disorders	1.8 (1.0–3.3)	3.1 (1.8–5.3)	2.4 (1.6–3.5)
Congenital, family and genetic disorders	1.2 (.6–2.4)	1.1 (.5–2.7)	1.1 (.6–2.0)
Social circumstances	.0 (–)	.4 (.1–1.8)	.2 (.0–.8)

95% CI: 95% confidence interval.

Discussion

Phase III of the BIOBADASER registry has updated the project after 10 years, incorporating in this register data regarding biosimilars and synthetic drugs with identifiable target, dealing with new data protection laws and pharmacovigilence regulations and incorporating data on effectiveness using direct clinical activity assessment parameters. All of these changes are ample justification for the need for this new phase in the BIOBADASER registry, Table 5.

Despite all of these modifications, the main aim of BIOBADASER phase III continues to be data collection relating to the safety of these treatments in patients with rheumatic diseases. The limited scope in time and the strict inclusion and exclusion criteria of patients in clinical trials continues to be a justification for the existence of perspectives studies based on information collected through independent registers based on data from routine clinical practice. Since this is a prospective register based on clinical practice, BIOBADASER is able to become a tool for the detection and analysis of low incidence adverse events, which may be observed in the long term and in a larger patient population.

This new phase of BIOBADASER has strengthened the prospective nature of the study, following the trend of other national European and North American registries on biologics which establish periodical follow-up check-ups.[21] ARTIS, BSRBR, BRASS, CORRONA, RABBIT, SCQM and VARA are European and North American registries which collect information on effectiveness in routine clinical practice. One of the main changes introduced into this new BIOBADASER phase is the aim of assessing effectiveness in clinical practice. Up until the beginning of this new phase, BIOBADASER was able to assess effectiveness indirectly through the subrogated variable of survival of the biologic drug. In this new phase, in addition to information on survival of the drug, clinical activity indications for RA (DAS28 VSG and DAS28 CRP), PA (DAS28 ESR and DAS28 CRP), AS (BASDAI, ASDAS-CRP) and SLE (SLEDAI) are collected.

Since its initiation and in particular during phase II, BIOBADASER has participated in international collaborative projects, supplying data together with other registries.[22–25] On a national level, it has also carried out collaborations with the registries of other specialities.[26] In these multi-registry projects, and particularly in collaborative projects with other countries, a lack of alignment has been detected in the definitions and parameters included in the different platforms, which frequently limits the potential of these collaborative tasks.[15] The need has arisen to establish standardised definitions and a set of common variables to improve this situation. In the new BIOBADASER phase new variables have been introduced and the collection of others has been improved to foster collaborative projects with other databases. Changes introduced included the use of the Charslon index to record comorbidities, the administration route, dose, periodicity of administration of biologic drugs and dose of concomitant glucocorticoids.

With the intention of improving cooperation between registries, the BIOBADAMÉRICA Project was enhanced from SER. This is a collaborative project with scientific rheumatology societies from countries in Latin America which use the same platform and methodological design as BIOBADASER Phase III.[27,28] Recently, phase III of the study was initiated in the registries of Mexico, Argentina, Uruguay, Paraguay and Colombia.

One of BIOBADASER's main strengths continues to be its capacity to recruit and to collect information. In the new phase III 1594 new patients joined the study.[29] Participation from 35 centres throughout Spain has guaranteed extensive coverage of

the reality of dealing with biologic drugs. The number of patients included in the study is expected to continue increasing in the future.

Conclusions

BIOBADASER has become an international reference in the generation of information on safety in the use of biologic therapy in rheumatic diseases. Phase III of the project incorporates as its aim assessment of the effectiveness and it reinforces the prospective nature of the registry. BIOBADASER phase III complies with the new legislation in pharmacovigilance and communication of adverse events and includes the new biosimilars and synthetic drugs with an identifiable target with an indication in the rheumatic diseases.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have adhered to the protocols of their centre of work on the publication of patient data.

Right to privacy and informed consent. The authors obtained the informed consent from the patients and/or subjects referred to in this article. This document is held by the corresponding author.

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Conflict of interests

The authors have no conflict of interests to declare.

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Appendix 1. Centres and researchers involved in BIOBADASER phase III, 2016

Centre	Collaborators
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Hospital Universitario Miguel Servet	Javier Manero
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	Maria Victoria Irigoyen
	Inmaculada Ureña
Hospital General San Jorge	Rosa Roselló
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Hospital General Universitario de Valencia	Javier Calvo
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