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Biobadaser 2.0: analysis and trends in 2009

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ABSTRACT

Objective: To update the information on long-term safety of biological therapies used for the treatment of rheumatic diseases.
Methods: BIOBADASER is a safety registry of biological therapies established by the Spanish Society of Rheumatology. A description of BIOBADASER 2.0, a cohort composed of 14 centres within BIOBADASER, is reported from 2000 until 2009.
Results: The 14 centres have registered 5,493 patients, who have received 8,081 cycles of treatment with biological therapies. 30% (1,666) has received treatment with more than one biologic agent during follow-up. There have been 3,784 treatment discontinuations, with inefficacy or loss of efficacy being the most frequent cause (1,453; 38%), followed by adverse events (1,297; 34%). Up to 7,289 adverse events (AE) have been reported, of which 80% (5,764) were considered as non-serious, nearly 19% (1,340) were notified as serious and about 2% (110) were fatal. The most frequent AE were infections (2,668; 37%), followed by general problems and administration related events (10%). Cardiovascular events and cancer amounted to 7% of the total AE.
Conclusions: There does not seem to be a trend regarding different risks in BIOBADASER 2.0 with respect to the general registry, or to previous years.

Biobadaser 2.0: análisis y tendencias en 2009

Palabras clave:
Terapias biológicas
Seguimiento
Acontecimientos adversos
Registro
Enfermedades reumáticas

RESUMEN

Objetivo: Actualizar la información sobre la seguridad a largo plazo de los agentes biológicos en el tratamiento de las enfermedades reumáticas.
Métodos: BIOBADASER es un registro de seguridad de terapias biológicas establecido por la Sociedad Española de Reumatología. Se presenta la descripción de BIOBADASER 2.0, una cohorte de 14 centros dentro de BIOBADASER, desde el año 2000 hasta el 2009.
Resultados: Hay registrados 5.493 pacientes y han recibido 8.081 ciclos de tratamiento con terapias biológicas. Un 30% (1.666) recibió más de un agente biológico durante el seguimiento. Se han producido 3.784 interrupciones. La ineficacia o pérdida de eficacia es la causa más frecuente de interrupción (1.453; 38%), seguido de los acontecimientos adversos (1.297; 34%). Se han comunicado 7.289 acontecimientos adversos (AA), un 80% (5.764) han sido considerados como acontecimientos no graves, un 19% (1.340) como graves y un 2% (110) han sido mortales. Los AA más frecuentes son las infecciones e infestaciones (2.668; 37%), seguidos de los trastornos generales y alteraciones en el lugar de administración (10%). Los trastornos cardiovasculares y las neoplasias en conjunto suponen un 7% del total de acontecimientos adversos.
Conclusiones: No se observan tendencias diferentes de riesgo en BIOBADASER 2.0 respecto al registro global y a años anteriores.

Introduction

Over the past two years numerous biological agents[1] have been introduced and added to the therapeutic arsenal[2] used to treat rheumatic diseases. This new scenario complicates drug safety monitoring,[3-5] since the molecular targets vary and different adverse events are consequently expected to occur. The burden on immunosuppression will also increase through patients who exposed to various different agents[6] over many years. In addition, the number of patients receiving each kind of treatment is decreasing.

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Moreover, the permanence of registries in time, including the "Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas" (Spanish Registry for Adverse Events of Biological Therapies in Rheumatic Diseases) (BIOBADASER), is a real challenge[7] for both updating and integrating new information, and for the integrity and reliability of collected data. Over 100 centres participated in the BIOBADASER registry when it was created in 2000. However, since June 2006, several changes have been introduced to the database to improve the quality of data obtained; BIOBADASER 2.0 was launched, with only 14 centres included in the registry. The fields that have shown the most improvement are data collecting methods and monitoring, which are now more constant and agile. The 14 centres were chosen based on 2 criteria: having at least 100 registered patients and having a percentage of errors in previous monitoring below 25%. In addition, patients included or monitored since June 2006 have given their informed consent for an external assessment of their vital signs and of any hospitalisations they may have undergone. This information is later compared with the data in the registry.

The aim of this report is to describe the population exposed to biological agents in our environment and to explore safety trends with the inclusion of new biological agents.

Methods

BIOBADASER 2.0 is a drug safety registry for patients starting treatment with biological therapies. It collects information from the 14 centres (see list in the appendix) that have been included in BIOBADASER since it was established in 2000, in 3 categories: 1) patient data (gender, date of birth, diagnosis and date of diagnosis, comorbidities and risk factors); 2) treatment data (type of biological agent, initiation and discontinuation dates, prophylaxis and disease-modifying drug (DMD) treatment for tuberculosis and DAS/BASDAI for rheumatoid arthritis/ankylosing spondylitis); and 3) adverse events (AE), including date, type and classification according to the Medical Dictionary of Adverse Events (MedDRA[8]), severity, outcome and concomitant treatments.

The BIOBADASER 2.0 protocol and materials are available on the registry website (http://www.biobadaser.ser.es/biobadaser/index.html) Participating specialists report data there directly if modifications are made to the treatment or an adverse event is detected in the patient.

A relevant AE is defined as any incident, related or not to the biological treatment, that results in death, puts the life of the patient in danger, requires hospitalisation or prolongs it, or produces a persistent or significant disability. This also includes any AEs leading to a therapeutic attitude aimed at preventing the aforementioned cases and are consequently considered important by the physician.

Monitoring is carried out by a person with experience in pharmacovigilance. The data reported are continuously monitored online. A more detailed monitoring is also done in situ once a year on a random selection of 20 records, in direct contact with those in charge. In addition, once a year, patients who have previously given their consent are contacted to check their health condition and whether they have been hospitalised during the last year. The software application also contains filters that restrict the entry of data outside the admitted range. The study has been approved by the Clinical Research Committee of the Hospital Ramón y Cajal, Madrid.

The BIOBADASER 2.0 cohort monitored in the registry is described using central tendency measurements. The frequencies of the various treatments, the reasons for discontinuation and general and fatal AE are also presented.

Results

Until 9 October 2009, BIOBADASER 2.0 included a total of 5,493 patients, 62% (3,406) of whom were women, with an average age at the start of treatment of 49 years (standard deviation, SD=15) and with a disease evolution of 10 years (SD=9). The most common diagnoses were rheumatoid arthritis in 53% (2,907), followed by ankylosing spondylitis in 16% (882) and psoriatic arthritis in 16% (858). The remaining diagnoses were below 5% (Table 1).

Information was compiled from 8,081 treatment cycles. Of the 5,493 registered patients, nearly 31% (1,666) had been treated with more than 1 biological agent during the monitoring period. The most commonly used drugs were infliximab (2,865; 35%), etanercept (2,621; 32%) and adalimumab (1,902; 24%). The remaining treatments, rituximab (518), abatacept (104), anakinra (59) and tocilizumab (12), did not constitute more than 8% of the total.

Treatment was discontinued in 3,784 cases. Among the reasons for discontinuing treatment (Table 2), inefficacy or loss of efficacy was the most common cause, both during the first course of treatment (41%) and during the second or subsequent ones (35%). The occurrence of an adverse event was the second most common cause of discontinuing the first course of treatment (39%), while this was due to "other causes" (34%) during the second and subsequent treatments.

The frequency and percentage of the different AEs registered, divided into large groups by organs and systems, are shown in Table 3. There have been 7,289 reported adverse events. The most frequent were infections, representing 37% of all registered AEs, the second most common were general disorders and alteration at the site of administration in 10%, and the third most frequent cause were skin and subcutaneous tissue disorders in 7%. Cardiovascular diseases and neoplasms accounted for 7% of all AEs. As far as the events with a fatal outcome (Table 4), these occurred primarily due to infections, 34% (37), followed by heart diseases in 23% (25). Neoplasms were responsible for 10% (11) of all fatal events.

Discussion

The registry reflects the current situation of rheumatology patients treated with biological agents. The patients included are increasingly

Table 1
Diagnoses of the patients included in BIOBADASER 2.0

Diagnosis	n (%)
Rheumatoid arthritis	2,907 (53)
Ankylosing spondylitis	882 (16)
Arthritis or psoriatic spondyloarthritis	858 (16)
Juvenile idiopathic arthritis	217 (4)
Undifferentiated spondyloarthropathy	210 (4)
Enteropathic arthritis	96 (2)
Behçet disease	42 (1)
Systemic lupus erythematosus	34 (1)
Chronic seronegative polyarthritis	34 (1)
Chronic seronegative oligoarthritis	28 (1)
Overlap	25 (<1)
Still disease	19 (<1)
Uveitis without rheumatic disease	18 (<1)
Vasculitis	18 (<1)
Juvenile undifferentiated spondyloarthropathy	15 (<1)
Juvenile ankylosing spondylitis	15 (<1)
Reactive arthritis	13 (<1)
SAPHO syndrome	12 (<1)
Primary Sjögren syndrome	11 (<1)
Polymyositis /dermatomyositis	8 (<1)
Relapsing polychondritis	8 (<1)
Sarcoidosis	8 (<1)
Psoriasis	6 (<1)
Scleroderma	3 (<1)
Gangrenous pyoderma	2 (<1)
Muckle-Wells syndrome	2 (<1)
Felty syndrome	1 (<1)
Epidermolysis bullosa	1 (<1)
Total	5,493

Table 2
Reasons for suspending biological treatments based on treatment order

Reasons for suspension	First treatment, n (%)	Second treatment and subsequent, n (%)	All, n (%)
Inefficacy or loss of efficacy	980 (41)	473 (35)	1,453 (38)
Adverse event	943 (39)	354 (26)	1,297 (34)
Pregnancy or gestational wish	72 (3)	31 (2)	103 (3)
Loss of patient	100 (4)	30 (2)	130 (3)
Remission	79 (3)	14 (1)	93 (2)
Others	239 (10)	469 (34)	708 (19)
Total	2,413 (100)	1,371 (100)	3,784 (100)

Table 3
Frequency of adverse events according to the preferential system or organ

Organs and systems	n (%)
Infections and infestations	2,668 (37)
General disorders and alterations at the site of administration	761 (10)
Skin and subcutaneous tissue disorders	540 (7)
Gastrointestinal disorders	321 (4)
Musculoskeletal and conjunctive tissue disorders	310 (4)
Nervous system disorders	269 (4)
Complementary explorations	266 (4)
Medical and surgical procedures	253 (3)
Trauma, intoxications and therapeutic procedure complications	235 (3)
Respiratory, thoracic and mediastinal disorders	192 (3)
Cardiac disorders	190 (3)
Ocular disorders	177 (2)
Benign, malignant and non-specified neoplasms (including cysts and polyps)	169 (2)
Vascular disorders	166 (2)
Blood and lymphatic system disorders	127 (2)
Renal and urinary disorders	121 (2)
Hepatobiliary disorders	116 (2)
Psychiatric disorders	107 (1)
Metabolic and nutritional disorders	72 (1)
Reproductive apparatus and mammary disorders	67 (1)
Pregnancy, postnatal and perinatal diseases	33 (<1)
Immunological system diseases	33 (<1)
Ear and labyrinthine diseases	32 (<1)
Endocrine diseases	29 (<1)
Congenital, inherited and genetic diseases	27 (<1)
Social circumstances	8 (<1)
Total	7,289

Table 4
Frequency of fatal adverse events according to the preferential system or organ

Organs and systems	n (%)
Infections and infestations	37 (34)
Cardiac diseases	25 (23)
Respiratory, thoracic and mediastinal diseases	13 (12)
Benign, malignant and non-specified neoplasms (including cysts and polyps)	11 (10)
General diseases and alterations at the site of administration	9 (8)
Gastrointestinal diseases	4 (4)
Nervous system diseases	3 (3)
Hepatobiliary diseases	3 (3)
Vascular diseases	2 (2)
Trauma, intoxications and complications of therapeutic procedures	1 (1)
Immunological system diseases	1 (1)
Renal and urinary diseases	1 (1)
Total	110

more heterogeneous, and a notable increase has taken place in the proportion of spondylitis cases compared to rheumatoid arthritis. Figure shows the number of new treatments administered each year and clearly shows 3 separate stages. During the first, which

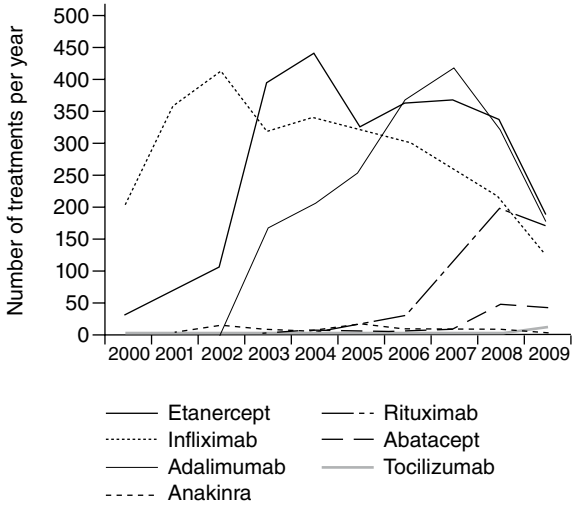

Figure. Evolution of the indication of biological therapies.

went from the beginning of the registry until 2003, the main active ingredient used was infliximab. During the second, which lasted until 2005, etanercept became the most commonly used active ingredient. In the third stage, during the period 2006-2007, adalimumab was the most common biological agent used, while the use of rituximab subsequently began to increase.

The reasons for discontinuing treatments with biological agents have changed slightly with respect to previous reports.[9] Both inefficacy and the occurrence of an adverse event continue to be the 2 main reasons; however, this new report shows the rise of a new category. The "other" category is linked to increased rituximab use and is partially due to the way in which treatments using this drug are administered and monitored. It mainly shows the completion of the cycles where no problems were encountered.

Survival functions and general incidents have not been included in this new report because it was considered that the molecular targets are varied and combining different active ingredients, rituximab in particular, adds a higher degree of complexity.

With regards to adverse events, we are limited by the fact that we can only make comparisons with reports elaborated since 2007, which is when MedDRA was introduced as the dictionary for classifying AEs. Previously,[10] classification had been carried out according to the WHO dictionary. In any case, it is evident in all of them[9,10] that infections, general disorders and alterations at the site of administration, and skin and subcutaneous tissue alterations are the 3 most common AEs, with infections being the most common of all. Infusion reactions are the second most common type of AE and are one of the main reasons behind treatment discontinuation.[11] In this context, it is important to pay close attention to symptoms that may appear, since reactions of this kind may occur at any stage of the disease, not just during the first administrations.[11]

There have not been any major variations in fatal AEs, although there has been a slight increase in the number of cardiac events

compared to the last report.[10] They still remain, together with infections and respiratory disorders, the most common fatal type of AE. The mortality rate for patients with rheumatoid arthritis and biological treatments does not appear to have increased,[12,13] except in the case of infections. The same is true for neoplasms.[14]

In summary, this report does not reflect different risk trends in BIOBADASER 2.0 with respect to the general registry or to previous years. This information can help to improve understanding of the safety profile of biological therapies.

Financing

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