BIOBADASER, BIOBADAMERICA, and BIOBADADERM: safety registers sharing commonalities across diseases and countries

L. Carmona[1], M. de la Vega[2], R. Ranza[3], G. Casado[2], D.C. Titton[4], M.Á. Descalzo[5], J. Gómez-Reino[6]

[1]*Instituto de Salud Musculoesquelética, Madrid, Spain;*
[2]*BiobadaSAR Coordinator, Sociedad Argentina de Reumatología, Buenos Aires, Argentina;*
[3]*Rheumatology Unit, Teaching Hospital, Universidade Federal de Uberlândia, MG, Brazil;*
[4]*Universidade Federal do Paraná, Brazil;*
[5]*Universidad del Valle de Guatemala, Guatemala;*
[6]*Departments of Rheumatology and Medicine, Hospital Clínico Universitario, Medical School, Universidad de Santiago de Compostela, Spain.*

Loreto Carmona, MD, PhD
María de la Vega, MD
Roberto Ranza, MD
Gustavo Casado, MD
David Cezar Titton, MD
Miguel Ángel Descalzo, BSc, PhD
Juan Gómez-Reino, MD, PhD

Please address correspondence to:
Loreto Carmona, MD, PhD,
Calle Ofelia Nieto, 10
28015 Madrid, Spain.
E-mail: loreto.carmona@inmusc.eu

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ABSTRACT

Registers facilitate the collection and communication of safety concerns. There are as many different register structures as registers, making the merging of rare data and comparison between registers difficult. BIOBADASER, the Safety Register of the Spanish Society of Rheumatology has served as template for other registers within the specialty, BIOBADAMERICA, and outside rheumatology, BIOBADADERM. Here we present the limitations and strengths of such template registers.

Registers facilitate the investigation of drug safety (1). In 2000, the Spanish Society of Rheumatology (SER) launched the BIOBADASER register. BIOBADASER is the result of a collaborative effort of the Spanish rheumatologists, the Research Unit of the Spanish Foundation for Rheumatology (FER), the Spanish Agency for Medicines and Medical Devices (AEMyPS) and the SER. The objectives of the register were to identify adverse events in daily practice conditions, to estimate the risk of adverse events, and to assess the retention of the biologics in the long term.

A distinct characteristic of BIOBADASER compared to other biologic registers (2) is that, from inception, it included patients who were treated with a biologic agent and had any rheumatic disease, not only rheumatoid arthritis. That implied that only safety could be measured, as collecting efficacy on all inflammatory diseases in one register was considered complicated, or at least no tool was agreed upon. On the other hand, this characteristic simplicity of BIOBADASER fact facilitates data collection enormously. BIOBADASER collects information actively on relevant adverse events (AE) occurring during the long-term treatment with biologic therapies.

The main outcome variable is thus relevant AE, defined as any untoward event that, regardless of dose (or drug relationship), results in death, endangers life, induces hospitalisation or prolongs a previous one, or produces a persistent or significant disability. Other events not posing immediate danger to life but compromising the patient or requiring intervention to prevent one of the outcomes listed in the definition above are also included. This is the definition of AE in clinical trials, and includes AE that are related to the drug, which is what most rheumatologists collect in "real life conditions", but also other events that are sometimes collected by rheumatologists as comorbidity, or not collected at all, as they seem totally unrelated. Those events reported by rheumatologists as related are subsequently notified to the pharmacovigillance system. Other variables collected in BIOBADASER are outcome and dates, concomitant DMARDs, age, sex, and comorbidities.

The structure and organisation has remained simple since the launching of the register, collecting data concerning any patient at the participant centres at any time a change occurred, whether a treatment change or an AE (the protocol is available in English at: https://biobadaser.ser.es/biobadaser/index.html). In 2006, BIOBADASER was re-designed into what was called BIOBADASER 2.0. Some of the improvements of BIOBADASER 2.0 were a new web-based platform that increased the navigation speed and thus improved the collection of data; in addition, the platform allowed continuous on-line monitoring, facilitated the interaction between monitor and centres, made centre data downloads available, enabled the connection to local databases, and implemented a button to notify the national pharmacovigillance system directly

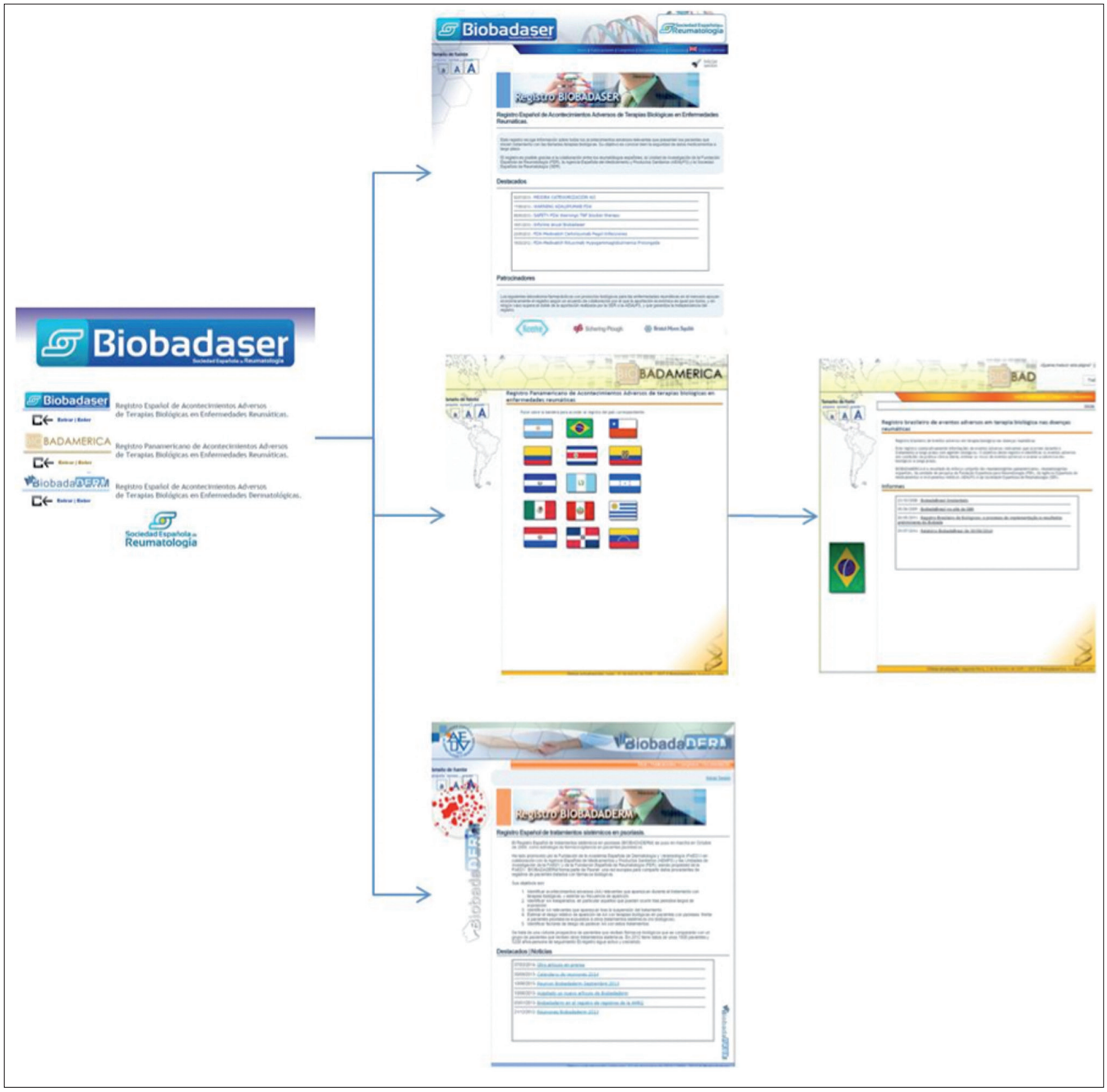

Fig. 1. The "mother" register BIOBADASER and the subsequent registers.

from the BIOBADASER program. All these measures improved dramatically the collection and reliability of data, as revealed by the subsequent yearly audit reports.

The type of data that BIOBADASER produces includes rates of specific adverse events in total, by drug, and by disease. Additional data for specific AE is recollected retrospectively. To analyse the risk of AE in rheumatoid arthritis, we filter rheumatoid arthritis patients only and compare their rates to a cohort specifically launched by the SER in 1998 to follow the incidence of comorbidity in rheumatoid arthritis during 5 years prior to the extensive marketing of biologic agents, the EMECAR cohort (3, 4). This cohort was created from a random sample of patients from 34 centres with any disease duration and activity, and followed at annual visits with a standardised form to assess the incidence of specific comorbidities including cancers, infections, and other complications. EMECAR was considered a good control group, as comorbidity – which is the same concept as adverse events – was actively followed-up and many patients had moderate to high levels of disease activity, something very rare in Spain nowadays.

BIOBADASER as a register of a Southern European country has had a significant impact, including 29 indexed publications, more than 75 presentations at congresses of rheumatology, public health or dermatology, and a mention in a key textbook (5); BIOBADASER is

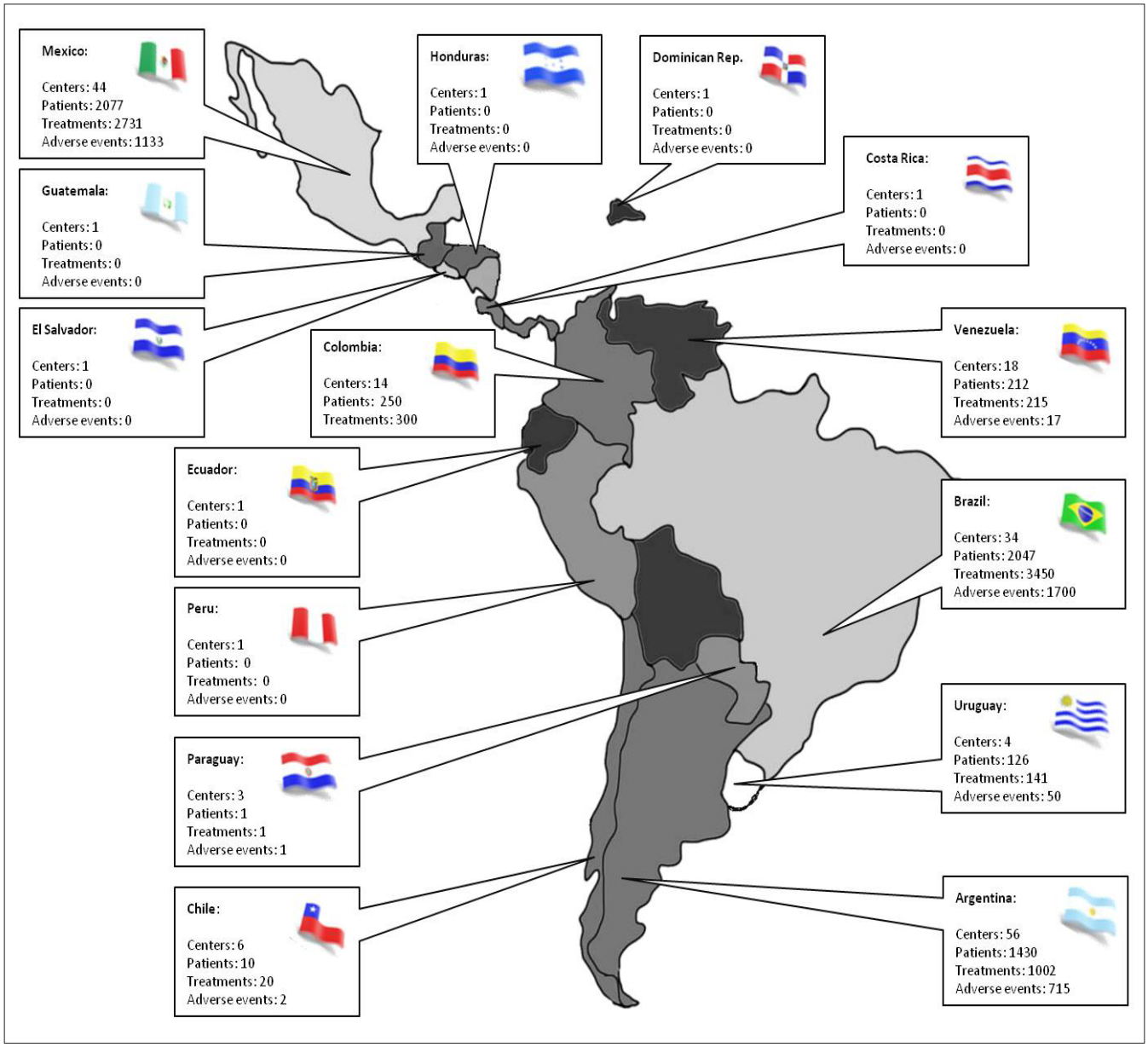

Fig. 2. Recruitment and monitoring status of the BIOBADAMERICA registers as of 2012.

regarded also as an important and reliable source of information by the health authorities. Some key achievements were 1) the identification of tuberculosis as a related adverse event, and its subsequent resolution by the issue of joint recommendations SER-Medicines Agency (6, 7), 2) the analysis of cardiovascular outcomes (8), and 3) the detailed analysis of infections that was reflected in specific recommendations by the SER on how to manage safety in patients with biologic therapies (9-12). But perhaps, BIOBADASER's largest achievement has been to become a template safety register for other countries, as well as for other specialties, namely dermatology (Fig. 1).

In 2007, several Latin American countries, under the auspices of PANLAR, signed three party agreements (SER, PANLAR, Rheumatology society) to replicate the register in their home countries. The collaboration is called BIOBADAMERICA. Each national society owns its register, and each register has its own governance and staff trained in how to collect, monitor, and analyse the register, as the databases are downloadable locally. SER provides access to the application providing that the design is not modified, and the code is not open (the platform code is owned by the SER). The SER trains the staff through an online course, and offers the possibility of rotating at the research unit to learn how to monitor and to analyse the register. The status of all American registers as of 2012 is illustrated in Figure 2. Participation is irregular among countries, as many face internal problems either with their societies or with regulators. The registers can share data but not access to others societies' data without a previous agreement. In addition, each country has embedded a control group in the register. This was not necessary, in principle, in Spain,

Table I. Comparative description of two BIOBADAMERICA databases and BIOBADASER and their national context.

Register	BIOBADASAR	BIOBADABRASIL	BIOBADASER2.0
Country	Argentina	Brazil	Spain
Patients registered	All new patients starting biologics as well as patients on current treatment that have started its use within a year from all centres.	All new patients starting biologics as well as patients on current treatment that have started its use within 6 months from 32 centres	All patients with rheumatic diseases treated with biologics from 14 centres
Control cohort	Yes, internal	Yes, internal	Yes, external
Monitoring	On line, 100%. Centralised review of randomly selected charts sent to the SAR for consistency. In situ review of selected charts.	On line, 100% checking error messages. By phone, contacting patients every 6 months In situ, 20% of charts of randomly selected patients for consistency.	On line 100% By phone, calling patients In situ, 20% of charts of randomly selected patients for consistency.
Recommendations for the use of biologics	Yes, national guidelines by SAR.	Yes, national guidelines by BSR.	Yes, national guidelines by SER.
Biologics financial coverage	100% coverage by law.	100% coverage by Public Health System.	100% coverage by Public Health System.
Recommendations for vaccination	Specific recommendation by the SAR.	Specific recommendations by BSR	Specific recommendations by the SER
Recommendations for tuberculosis	Yes, by SAR	Yes, by Brazilian Ministry of Health	Yes, by SER

BSR: Brazilian Society of Rheumatology; SAR: Argentinian Society of Rheumatology; SER: Spanish Society of Rheumatology.

given the existence of EMECAR. In addition, in Spain it is a challenge to create a control group nowadays; the vast majority of patients with high levels of disease activity are treated with biologic agents unlike what happens in countries with more stringent requirements for patients to be treated with biological agents, such as the UK (6), or without universal coverage, as it is the case in some Latin American countries.

Table I shows a side by side description of the Argentinean, Brazilian, and Spanish biological registers, as well as the national context for the use of biologics. These three countries are perhaps the most homogenous countries within BIOBADAMERICA and merging of data for the analysis of AE is underway. Table II shows a description of the rheumatoid arthritis patients in the three databases and their use of anti-TNF therapies as of 31st December, 2012.

In addition, in 2008, the Spanish Academy of Dermatology solicited SER for help in designing their register for drug safety. The decision was then to replicate BIOBADASER and to adapt it to psoriasis and other dermatological diseases, the Spanish Registry of systemic treatments in psoriasis (BIOBADADERM) (13, 14). It was promoted by the Foundation of the Spanish Academy of Dermatology and Venereology (FAEDV) in collaboration with the Spanish Agency for Medicines and Health Products (Competent Authority) and the Research Units of FAEDV and the Spanish Foundation of Rheumatology (FER). BIOBADADERM is part of Psonet: a European network for sharing data from psoriasis registers (15). A manuscript on the differential safety between rheumatoid arthritis and psoriasis is being prepared.

Table II. Comparative description of the rheumatoid arthritis patients on anti-TNFs included in three template-equal registers as of 31/12/2013 (BIOBADASER as of 2011).

	BIOBADASAR	BIOBADABRASIL	BIOBADASER
Number of patients	784	952	970
Women, n (%)	667 (85)	816 (86)	770 (79)
Age at baseline, m (SD)	53 (13)	50 (12)	55 (14)
Disease duration years, mean (SD)	9 (8)	10 (8)	8 (8)
DAS28, mean (SD)	5.5 (1.1)	5.3 (1.3)	5.1 (1.5)
Diabetes, n (%)	53 (7)	97 (10)	64 (7)
Hypercholesterolemia, n (%)	133 (17)	99 (10)	149 (15)
Hypertension, n (%)	200 (26)	319 (34)	224 (23)
Renal Insufficiency, n (%)	9 (1)	4 (0)	14 (1)
Interstitial lung disease, n (%)	29 (4)	28 (3)	25 (3)
Cancer, n (%)	11 (1)	5 (1)	19 (2)
Ischaemic heart disease, n (%)	10 (1)	8 (1)	22 (2)
Cardiac failure, n (%)	7 (1)	3 (0)	9 (1)
HBV, n (%)	8 (1)	3 (0)	27 (3)
HCV, n (%)	5 (1)	5 (1)	3 (0)
COPD, n (%)	19 (2)	12 (1)	23 (2)
Smokers, n (%)	88 (11)	125 (13)	147 (15)
Glucocorticoids, n (%)	438 (56)	727 (76)	614 (63)
Methotrexate, n (%)	612 (78)	680 (71)	620 (64)
Other DMARDs, n (%)	303 (39)	547 (57)	308 (32)
First TNF antagonists, n (%)			
Etanercept (ETA)	488 (62)	249 (26)	393 (41)
Infliximab (INF)	81 (10)	346 (36)	203 (21)
Adalimumab (ADA)	215 (28)	357 (38)	374 (39)

The clear advantage of using a common template register is that it facilitates merging data and to compare information across registers. In fact, the similarities among the databases in Spain and Latin America appears greater than between those of European countries (16). This information is regarded as critical to understand the safety of biological therapies in real life conditions across different health systems and environments, especially in the present context with increasing available treatments, and small samples for specific drugs (17). In addition, it provides a forum to share and to comment on the effects of different policies and perspectives concerning safety.

In summary, a template register provides a platform to merge, compare, discuss, understand, and empower the safety of biologics.

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