

## REUMA.PT – THE RHEUMATIC DISEASES PORTUGUESE REGISTER

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### Abstract

**Introduction:** Since June 2008, Portuguese rheumatologists have been collecting on a routine basis, data into the nationwide Reuma.pt, the Rheumatic Diseases Portuguese Register from the Portuguese Society of Rheumatology (SPR), which includes rheumatic patients (rheumatoid arthritis – RA, ankylosing spondylitis – AS, psoriatic arthritis – PsA and juvenile idiopathic arthritis – JIA) receiving biological therapies or patients receiving synthetic disease modifying anti-rheumatic drugs (DMARDs).

The aim of this publication is to describe the structure of Reuma.pt and the population registered since June 2008.

**Methods:** Demographic and anthropometric data, life style habits, work status, co-morbidities, disease activity and functional assessment scores, previous and current therapies, adverse events codified by the Medical Dictionary for Regulatory Activities (MedDRA), reasons for discontinuation and laboratory measurements are registered at each visit. The platform is based on a structured electro-

nic medical record linked to a SQL Server database. All Rheumatology Departments assigned to the Portuguese National Health Service (n=21), 2 Military Hospitals (Lisboa and Porto), 1 public-private Institution and 6 private centers adhered to the Register. Until now, 18 centers have entered data into Reuma.pt.

**Results:** By January 2011, 3438 patients and 16130 visits had been registered. 2162 (63%) were RA patients, 700 of them treated with biological agents and 1462 with synthetic DMARDs. From the 515 (15%) AS patients, 297 were medicated with biological and 218 with non-biological therapies. 293 (8%) were PsA patients, 151 treated with biological drugs and 142 with other treatment strategies. 368 (11%) had the diagnosis of JIA, 68 were under biological treatment and 300 were managed with other treatment options. The register also includes 100 (3%) patients with other rheumatic diseases, submitted to treatments that required hospital day care infusions including 18 exposed to biological therapies.

**Conclusions:** Registers are crucial to ensure correct clinical use, adequate assessment of post-marketing biological therapies' efficacy and safety, thus contributing for a better cost-benefit ratio. Reuma.pt, is a powerful and accurate tool to answer to these unmet needs. It presents a national coverage of the rheumatology centers and constitutes an invaluable resource for scientific research and to improve rheumatic patients care.

**Keywords:** Register; Biological therapies; Reuma.pt; Rheumatic diseases; Portuguese Society of Rheumatology

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## Introduction

The Rheumatic Diseases Portuguese Register (RNDR), Reuma.pt, developed by the Portuguese Society of Rheumatology (SPR), became active in June 2008 and includes patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). The ultimate goal is to register all patients in Portugal (Mainland, Madeira and Azores Islands) with rheumatic diseases, treated with biological treatments and to follow them up to determine treatment efficacy, safety and long-term co-morbidities. The Register is also recruiting comparison cohorts of patients with RA, AS, PsA and JIA treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) and other treatment strategies (such as non-steroidal anti-inflammatory drugs in AS). This will enable to weigh the relative contribution of disease factors and standard treatments, whenever biological treatment effects (beneficial and hazardous) are being evaluated. Reuma.pt also includes BioGeral, a register for additional rheumatic diseases treated at rheumatology day care units, such as systemic lupus erythematosus, systemic sclerosis, vasculitis, Behçet's disease, myositis, idiopathic, uveitis and osteoporosis.

During the last decade, many rheumatology national societies and rheumatology organizations have developed large registries (BSRBR<sup>1</sup>, DANBIO<sup>2</sup>, RABBIT<sup>3</sup>, BIOBADASER<sup>4</sup>, CORRONA database<sup>5</sup>, ARTIS<sup>6</sup>). In spite of differences regarding informatics platforms, designs, data collection, national coverage and inclusion criteria, they all have a common mission of collecting data and increasing knowledge fostering the improvement of medical care of rheumatic patients. Moreover commonly used cores of validated measures such as ACR response components, RA disease activity score (DAS28), health assessment questionnaire (HAQ), Bath ankylosing spondylitis disease activity index (BASDAI) and adverse events are being registered.

Reuma.pt was designed based on previously published standard observational protocols, which were in use for local printed registries<sup>7-9</sup> and on national recommendations for the use of biological agents<sup>10-13</sup>. Reuma.pt displays a user friendly clinical chart scenario and has been subdivided for the medical users in several slightly different disease specific applications: BioRePortAR (the database for RA patients treated with biological therapies),

BioRePortEA (for AS), BioRePortAP (for PsA) and BioRePortAIJ (for JIA). RegistAR is similar to BioRePortAR and was designed to collect information from RA patients who are not treated with biological therapy. RegistEA, RegistAP and RegistAIJ are the correspondent databases to the other diseases. BioGeral is the registry used for rheumatic patients not included on the previous interfaces. All databases share the same platform and are linked upon the global register, Reuma.pt.

The aim of this publication is to describe the structure of Reuma.pt and the population registered since June 2008.

## Methods

### Technical specifications

Reuma.pt is accessed through an electronic medical record (EMR) application developed using Visual Studio, an integrated development environment (IDE) from Microsoft. It was written in VB.NET for the .NET Framework. The .NET Framework provides generic functionalities for Windows applications. It includes a large set of software components, and it supports several programming languages that allow language interoperability (each language can use code written in other languages). Programs written for the .NET Framework execute in virtual machine, known as the Common Language Runtime (CLR). The CLR provides several important services such as security, memory management, and exception handling.

Data are collected in a standardized format, through almost a hundred classification lists, that include drugs, pathologies, etc. All dates and numeric fields are also validated. The only fields that can be freely typed, are the fields specifically assigned for notes.

All entered data is stored in a SQL Server database, a relational model database management system produced by Microsoft. The application communicates with an instance of SQL Server by sending Transact-SQL statements to the server. SQL Server ensures that any change to the data is compliant with a set of properties (atomicity, consistency, isolation, durability), which guarantees that the database will always revert to a known consistent state on failure.

Besides pre-formatted reports, Reuma.pt allows each center to export raw data to common data analysis packages, such as SAS, Stata, R and SPSS.

All entered data can be selected for exportation accordingly to each analysis needs. A model of data exportation can also be selected. This can be done by choosing a longitudinal model (one row per visit) and/or the data grid model (lists as the ones seen on most common application screens).

Nowadays, each center (hospital or medical office) has its own local installation of Reuma.pt. There is also a central server that stores data from all centers. However, this requires a regular data transfer from each center to the central server. Later this year, a Reuma.pt web version will be launched. This new version is a rich internet application (RIA) built on Microsoft Silverlight. Silverlight is a platform that enables to develop Web-based applications with a modern and efficient user interface, and also secure user interactions with desktop files, devices, data and applications such as Microsoft Office. This will leverage Reuma.pt to higher levels of accessibility. Additionally, all entered data will be stored in a single web server, suppressing data transfers from local installations to a central server. All databases are linked, i.e. if a patient is already registered in RegistAR and starts a biological agent, once that information is inserted in the database, the patient is automatically switched to BioRePortAR environment.

### Reuma.pt description and contents

Reuma.pt access is protected by username and password, which are unique to each rheumatologist. New users can be authorized by current users. In the first menu the physician can create a new patient or a new visit, or edit previous visits. On the left hand side, Reuma.pt screen displays a tree format table of contents (Figure 1A). Some screens are the same across all databases: identification data, demographic data, work status, life styles, body mass index, previous medical history, joint surgeries, co-morbidities, SF-36 questionnaire, laboratorial results form, past and current therapies, adverse events, tuberculosis screening, observations/notes and charts while others are disease-specific. For RA, disease activity assessments include 3 visual analogue scales (VAS) (patient and physician disease activity and patient reported pain), 3 homunculus (tender joints, swollen joints and non evaluable joints), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). When data needed for DAS28 (DAS 28 with 3 and 4 variables, and with ESR or CRP) is inserted the score is

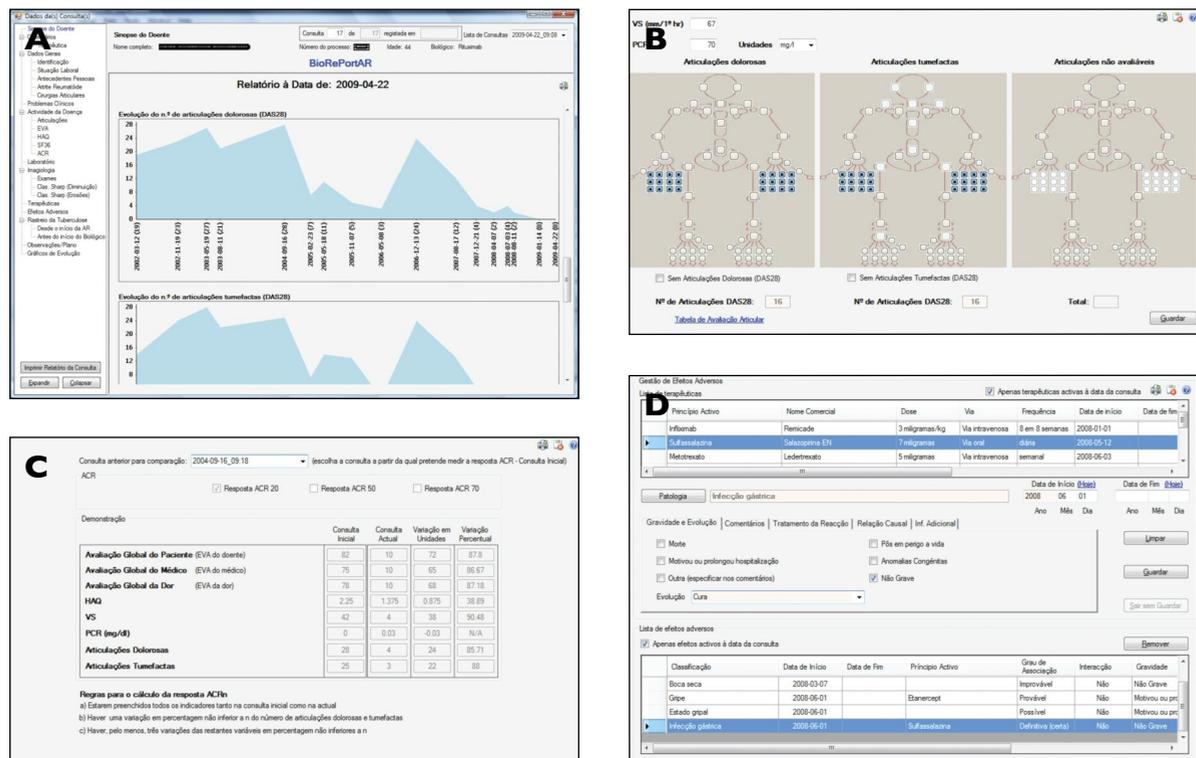
automatically computed (Figure 1B). ACR responses between 2 requested time points are also automatically displayed (Figure 1C). Other screens include health assessment questionnaire, hand and feet X-rays Sharp/van der Heijde score and RA features like extra-articular manifestations, rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Screens are user friendly and give assisted support to fill in the boxes (scroll options, clever writing, pre-written tables, classification systems, MedDRA), but without neglecting detailed data collection. For instance «therapy fields» include start and end dates, frequency, dose, route of administration, reasons for discontinuation and a link to the «adverse events window». «Adverse events» capture thorough information according to regulatory authorities demand (Figure 1D), including type, severity, causality, actions taken and evolution. Registers dedicated to ankylosing spondylitis include BASDAI, BASFI, BASMI, ASDAS, ASAS response, Stoke ankylosing spondylitis spine score, HLA B27 antigen and extra-articular manifestations. Psoriatic arthritis registers allow the patient disease classification in «AS-like» (axial disease) and/or «RA-like» (peripheral disease) and the choice of the best evaluation measures for a specific patient. In addition, PASI is also collected. JIA patients have also specific questionnaires like the child health assessment questionnaire (CHAQ) and validated assessments (active joints, joints with decreased mobility and ACR30 responses). In BioGeral instruments for SLE evaluation were included: SLE disease activity index (SLEDAI) and SLICC damage index.

All screens are printable (before and/or after filled). After data collection, Reuma.pt can generate a pre-formatted report, integrating all information.

### Reuma.pt Management

Reuma.pt was approved by National Data Protection Board and by the local Ethics Committees. Patients sign an informed consent for data research use and applications.

SPR owns the Register and controls data access, data analysis and its release. The Reuma.pt Coordination Board (CC RNDR) consisting of a Steering Committee with an Executive Coordinator from SPR Board (JEF), a National Coordinator (AF) responsible for Centers liaison, a Scientific Coordinator (HC) and a representative from each participating center, all appointed for a 2 years period



**Figure 1.** Reuma.pt screens for patient synopsis (A), joint involvement (B), automatically display of ACR responses (C) and adverse events (D)

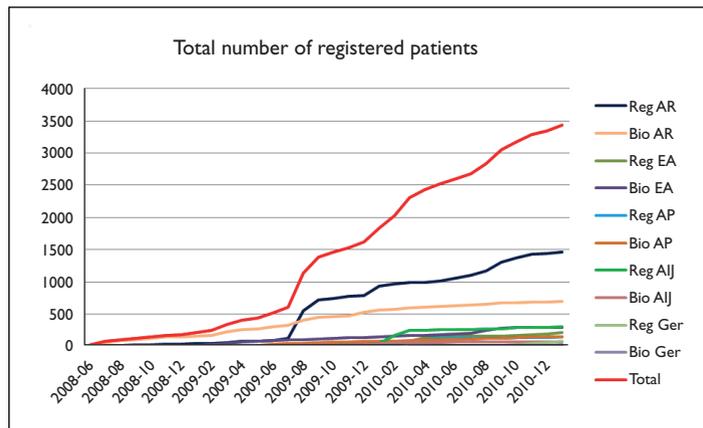
(the duration of a SPR electoral mandate). CC RNDR ordinary meetings are held every 6 months but extraordinary meetings can be scheduled whenever considered necessary. Regulations for data access, rules governing pharmaceuticals relationship, project application forms, data agreement utilization and regulations for payment for data insertion were approved by CC RNDR and are publicly available at [www.spreumatologia.pt](http://www.spreumatologia.pt). Individual research projects addressing specific questions can be submitted to CC RNDR by SPR members.

### Reuma.pt Implementation

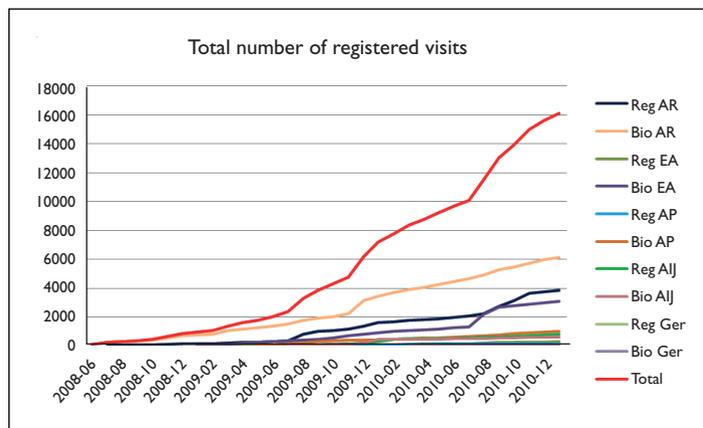
Reuma.pt's very early development was undertaken by SPR in a collaborative work with Instituto de Medicina Preventiva, Faculdade de Medicina de Lisboa.

Currently, Reuma.pt is widely established, encompassing all Portuguese rheumatology centers. Identifying the contributing factors for this generalized adherence could be of importance for countries trying to establish new registers. From the beginning, we have involved representatives from all centers who had an important role in the design of

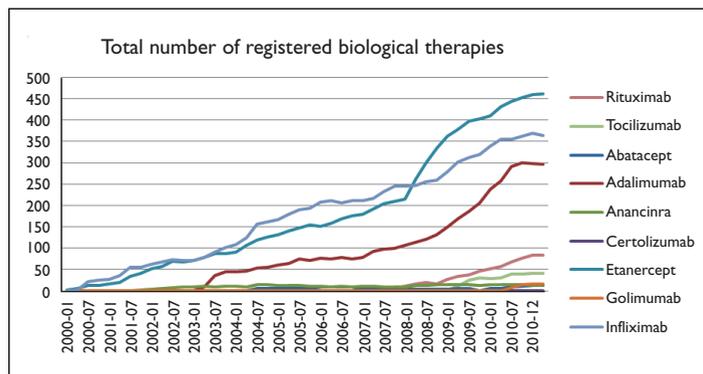
the interface and in the selection of the variables included in Reuma.pt. During the development, these representatives performed tests in their own centers and proposed changes. The database development process has taken those suggestions into consideration and has been shaped fitting general agreement. Moreover, advertisements and practical training sessions were done during the major SPR meetings. The steering committee has been periodically promoting local sessions with rheumatologists, informatics and hospital management staff, in order to facilitate Reuma.pt local implementation. For eligible cases a fee has been paid for data insertion. Reuma.pt applications allowed the link with the electronic system from the hospital, namely the electronic medical record, avoiding double-typing and record duplications. Some tools like the automated calculation of DAS and HAQ, patients' disease activity profile graphically displayed, easy search of therapies and co-morbidities history, adverse event report based on the same classification system used by regulatory authorities and analysis of data for each center have been other important facilitating factors for the success



**Figure 2.** Total number of patients registered in Reuma.pt



**Figure 3.** Total number of visits registered in Reuma.pt



**Figure 4.** Total number of biological therapies registered in Reuma.pt

of Reuma.pt.

The collaborative work with Direção Geral de Saúde (Portuguese Health Directorate) and also with international registers (such as the METEOR) has also been a priority. Reuma.pt has been funded by unrestricted grants from pharmaceutical com-

panies (Abbott, Bristol Myers Squibb, Merck Sharp and Dohme, Pfizer, Roche and UCB Pharma), which have not direct data access neither influence the research projects or data analysis. CC RNDR releases semiannual reports with detailed description of the data inserted. Every 2 months, a Newsletter including a FAQ section and news is sent for all SPR members and is posted on SPR website.

## Results

First BioRePortAR patients were registered in June 2008 and progressively centers have begun inserting patients and visits, with a steep increment since September 2009 (Figures 2 and 3). Data is prospectively inserted at each visit, but at the same time, rheumatologists have been inserting information recorded in paper forms before 2008, as part of the local printed registries that had been previously settled. Thus, Reuma.pt contains information on biological therapies since year 2000 (Figure 4).

On January 2011, 3438 patients and 16130 visits were registered. From this global number, 2162 (63%) were RA patients, 700 treated with biological agents and 1462 exposed to synthetic DMARDs. From the 515 (15%) AS patients, 297 were medicated with biological and 218 with non-biological therapies. 293 (8%) were PsA patients, 151 treated with biological drugs and 142 with standard non-biological therapy. Of the 368 (11%) patients with the diagnosis of JIA, 68 were under biological treatment and 300 were managed with other strategies. The register also includes 100 (3%) patients with other diagnosis, submitted to treatments that required hospital day care infusions, including 18 exposed to biological therapies. This register's environment includes diagnosis such as systemic lupus erythematosus, systemic sclerosis, myositis, idiopathic uveitis, vasculitis, Behçet's disease and osteoporosis. All Rheumatology De-

**Table I. Demographic features of patients registered in Reuma.pt, according to rheumatic disease.**

	<b>Rheumatoid arthritis</b>	<b>Ankylosing spondylitis</b>	<b>Psoriatic arthritis</b>	<b>Juvenile idiopathic arthritis</b>
Number of patients (total)	2162	515	293	368
with biological	700	297	151	68
non-biological	1462	218	142	300
Current age	59.7 ± 13.8	44.3 ± 12.7	53.3 ± 13	19.3 ± 11.1
Age at diagnosis	46.9 ± 14.4	31.9 ± 12.2	40.6 ± 12,9	6.6 ± 4.6
Age at biological onset	53.2 ± 12.6	40.6 ± 11.9	47.3 ± 11.1	20.6 ± 10.1
Mean disease duration at last observation	13.6 ± 9.9	17.7 ± 10.6	15.9 ± 9.5	13.3 ± 10.5
Mean disease duration at biological onset	10.6 ± 9.1	13.4 ± 10	12.5 ± 9.5	11.4 ± 9.6
Female	83.6%	38.2%	47.4%	68.2%
Biological	88.4%	35%	49%	73.5%
Non-biological	81.3%	42.7%	45.7%	67%

Biological – biological therapy group; Non-biological – Non-biological therapy group.

partments assigned to the Portuguese National Health Service (n=21), 2 Military Hospitals (Lisboa and Porto), 1 public-private Institution and 6 private centers adhered to the Register. Until now, 18 centers have entered data into Reuma.pt.

### **Rheumatoid arthritis (BioRePortAR and Registar)**

As previously referred 2162 RA patients (700 were treated with biological agents and 1462 with synthetic DMARDs), with a currently mean age of 59.7 ± 13.8 years old, are registered in Reuma.pt. RA patients treated with synthetic DMARDs had a mean age of 61.5 ± 14.2 years-old and those treated with biological agents were 56.1 ± 12.2 years old. Mean age at time of diagnosis was 46.9 ± 14.4 years old and at the beginning of biological treatment was of 53.2 ± 12.6 years old. Mean disease duration at last observation was of 13.6 ± 9.9 years and at the starting of the biological was of 10.6 ± 9.1 years. Females represent 83.6% of patients, 81.3% in the group treated with synthetic DMARDs and 88.4% in the group treated with biological therapies (Table I). Rheumatoid factor was found in 73.6% and anti-CCP in 70.9% of the cases. The disease was erosive in 72% of the patients. 35.7% of the patients treated with DMARDs and 35.6% treated with a biological agent presented extra-articular manifestations.

Forty five point five percent were exposed to at least one administration of etanercept, 35.3% to infliximab, 31.1% to adalimumab, 11.2% to ritu-

ximab, 6.3% to tocilizumab, 2.2% to abatacept, 2.1% to anakinra and 1.4% to golimumab. The total biological treatment's exposure was of 2869.4 years (Table II).

In the group of patients treated with synthetic DMARDs, current mean DAS28 (DAS 4 variables, with ESR) is 3.4 ± 1.5. 35.7% of patients with more than 6 months of follow-up were in remission defined by a DAS28 lower than 2.6 and 14.6% had a high disease activity (DAS28 above 5.1).

At the beginning of biological therapy, patients exhibited a mean DAS28 of 5.6 ± 1.7. Currently mean DAS28 is 3.6 ± 1.5 for patients under active treatment with a biological drug for more than 6 months and of 3.5 ± 1.4 for the group actively treated for at least 1 year. The proportion of patients with a DAS28 below 2.6 is inferior in the biological treated group: 26.4% of the patients treated for at least 6 months and 26.9% for those with more than 1 year of treatment.

Current mean HAQ is 1.07 ± 0.75 for patients on synthetic DMARDs. Baseline mean HAQ was of 1.47 ± 0.63 for patients starting biological agents, 1.13 ± 0.69 when patients were treated for more than 6 months and 1.1 ± 0.69 in patients who had been treated with biological therapies for at least 1 year.

From the 804 RA patients who did at least one administration of a biological drug, 495 (61.5%) remain on the first biological treatment registered into BioRePortAR, 108 (13.4%) definitely withdrew

**Table II. Proportion of patients exposed to at least one drug's administration and total amount of biological treatment's exposure in years**

<b>Proportion of patient's exposed to at least one administration of</b>	<b>Rheumatoid arthritis</b>	<b>Ankylosing spondylitis</b>	<b>Psoriatic arthritis</b>	<b>Juvenile idiopathic arthritis</b>
Abatacept	2.2%	–	–	8.1%
Adalimumab	31.1%	31.7%	36.3%	21.6%
Anakinra	2.1%	–	–	10.8%
Etanercept	45.5%	35.9%	50%	68.9%
Golimumab	1.4%	0.6%	2.5%	-
Infliximab	35.3%	53.8%	36.9%	9.5%
Rituximab	11.2%	–	–	1.3%
Tocilizumab	6.3%	–	–	2.7%
Total of biological treatment's exposure (years)	2869.4	987.6	512.3	275.3

from the biological therapy and 201 (25 %) have been switched to other biological agent. From the group of 201 patients who switched therapies, 138 (68.7%) of them have switched once, 43 (21.4%) twice and 20 (9.9%) patients switched three or more times (Table III).

Considering 1096 biological therapies prescribed in BioRePortAR, drug was discontinued in 398 cases (36.35%). As we saw before, in 108 (27.1%) patients the drug was not resumed, and it was replaced by another biological agent in 290 (72.9%) of the cases. The main reason for discontinuation was inefficacy (52.8%) and in a lesser degree, adverse events (21.1%) or other causes (22.7%) (Table IV).

#### **Ankylosing spondylitis (BioRePortEA and RegistEA)**

From the 515 (15% of the registered patients) AS patients, 297 were medicated with biological and 218 with non-biological therapies. The mean age at diagnosis was  $31.9 \pm 12.2$  years old. Current mean age is  $44.3 \pm 12.7$  years old. Mean age at biological treatment onset was of  $40.6 \pm 11.9$  years old. Mean disease duration at last observation was of  $17.7 \pm 10.6$  years and at the starting of the biological was of  $13.4 \pm 10$  years. Males were 61.8%, 57.3% in the group without biological therapy and 65% in the group exposed to biological therapy (Table I). In this AS sample 82.3% were HLAB27 positive and 44% had extra-articular manifestations.

Considering all AS patients exposed to biologi-

**Table III. Proportion of patients remaining on the first biological drug, withdrew biological therapy and switched between biological agents**

<b>Patients</b>	<b>Rheumatoid arthritis</b>	<b>Ankylosing spondylitis</b>	<b>Psoriatic arthritis</b>	<b>Juvenile idiopathic arthritis</b>
Remaining in the first biological therapy	495 61.5%	235 75.3%	118 73.7%	55 74.3%
Withdrew from biological	108 13.4%	15 4.8%	9 5.6%	6 8.1%
Switched	201 25%	62 19.9%	33 20.6%	13 17.6%
Once	68.7%	83.9%	72.7%	53.8%
Twice	21.4%	16.1%	27.3%	30.8%
3 or more	9.9%	–	–	15.4%

**Table IV. Reasons for biological therapy discontinuation**

<b>Therapies</b>	<b>Rheumatoid arthritis</b>	<b>Ankylosing spondylitis</b>	<b>Psoriatic arthritis</b>	<b>Juvenile idiopathic arthritis</b>
Drug discontinuation (number and %)	398 36.3%	89 23.2%	51 25.2%	29 30.8%
Adverse event	21.1%	38.2%	39.2%	10.3%
Inefficacy	52.8%	51.7%	43.1%	44.8%
Lost for follow-up	0.55%	1.1%	–	3.5%
No indication	1.25%	–	2%	–
Remission	0.25%	–	–	–
Patient's refusal	1%	2.2%	–	3.5%
Death	0.25%	–	–	–
Other causes	22.7%	6.8%	15.7%	37.9%

**Table V. Proportion of juvenile idiopathic arthritis (JIA) subtypes in patients treated with synthetic and biological therapies**

<b>JIA subtypes</b>	<b>Synthetic DMARDs</b>	<b>Biological Therapies</b>
Persistent oligoarthritis	42.6%	12.3%
Extended oligoarthritis	11.8%	12.3%
Poliarthritis with rheumatoid factor positive	8.8%	26.3%
Poliarthritis with rheumatoid factor negative	13.2%	19.3%
Systemic	10.3%	21.1%
Arthritis related with entesitis	11.8%	7%
Psoriatic arthritis	1.5%	1.7%

DMARDs – disease modifying anti-rheumatic drugs

cals, 53.8% of the patients received at least one administration of infliximab, 35.9% of etanercept, 31.7% of adalimumab and 0.64% of golimumab. The total amount of biological treatment's exposure was of 987.6 years (Table II).

The mean BASDAI was reduced from  $6 \pm 2$  at biological therapy onset to  $2.7 \pm 2.2$  in the group of patients treated for at least 6 months and  $2.5 \pm 2.1$  for those treated for at least 1 year.

The mean ASDAS improved from  $3.8 \pm 1$  at baseline visit to  $1.8 \pm 1.1$  in patients treated for 6 months or longer and to  $1.7 \pm 1$  for patients under at least 1 year of biological therapy.

The mean BASFI was of  $5.5 \pm 2.4$  at start and it is now of  $2.9 \pm 2.5$  and  $2.8 \pm 2.4$  for patients treated at least 6 months and 1 year with biological therapies, respectively.

At 6 months, the ASAS20 response was achieved by ~95% patients treated with biological therapies. Forty five per cent of AS patients treated with a biological agent for at least 6 months presented a BAS-

DAI lesser than 2, and if the treatment was maintained for a minimum of 1 year this proportion was of 47.2%.

From the 312 AS patients who did at least one administration of a biological drug, 235 (75.3%) remain on the first biological treatment registered into BioRePortEA, 15 (4.8%) definitely withdrew from the biological therapy and 62 (19.9%) have been switched to other biological therapies. From the group of 62 patients who switched therapies, 52 (83.9%) of them have switched once and 10 (16.1%) twice (Table III).

Considering the 384 biological therapies prescribed in BioRePortEA, the biological agent was discontinued in 89 cases (23.2%). As we have seen before, in 15 (16.8%) patients the drug was not resumed, and it was replaced by another biological agent in 74 (83.2%) of the cases. The reasons for discontinuation were inefficacy (51.7%) in most cases and in a lesser degree, adverse events (38.2%) (Table IV).

### Psoriatic arthritis (BioRePortAP and RegistAP)

Two hundred and ninety three patients had PsA and they accounted for 8% of the patients registered in Reuma.pt; 151 were treated with biological drugs and 142 with non-biological therapies. The total biological treatment's exposure was of 512.3 years.

Current mean age was of  $53.3 \pm 13$  years old,  $56.2 \pm 14.7$  years old for patients without biological therapies and  $50.6 \pm 10.5$  years old for patients treated with biological agents. The mean age of disease onset was of  $37.4 \pm 13.6$  years old, the diagnosis was made, on average, at  $40.6 \pm 12.9$  years old and the biological therapy initiated at a mean age of  $47.3 \pm 11.1$  years old. Mean disease duration at last observation was of  $15.9 \pm 9.5$  years and at the starting of the biological was of  $12.5 \pm 9.5$  years. Considering all PsA patients, 52.6% of the patients were males; 54.3% were medicated with conventional therapies and 51% with biological drugs (Table I).

From the group of patients treated with biological therapies 74.3% were classified as having «RA-like» psoriatic arthritis and 25.7% had an «AS-like» disease. 30.6% of PsA patients were HLAB27 positive. 50% of the patients were exposed to at least one administration of etanercept, 36.9% to infliximab, 36.3% to adalimumab and 2.5% to golimumab (Table II).

The number of tender joints was of  $13.1 \pm 11.2$  in the beginning of biological therapy and was  $3.4 \pm 6.1$  and  $3 \pm 5.7$  after 6 months and 1 year under therapy, respectively. The correspondent figures for swollen joints were  $6 \pm 7.6$ ,  $0.9 \pm 2.5$  and  $0.8 \pm 2.3$ .

«RA-like» PsA group presented an initial mean DAS28 of  $5.1 \pm 1.6$  and after at least 6 months and 1 year of biological therapy it was of  $2.7 \pm 1.4$  and  $2.6 \pm 1.3$ , respectively. Currently, 49.1% of the patients treated at least for 6 months and 51.1% in the group treated at least for 1 year present a DAS28 below 2.6. Mean DAS28 is currently of  $4 \pm 1.6$  in patients treated with synthetic DMARDs.

For the «AS-like» group, mean BASDAI was of  $6.5 \pm 1.8$  at the beginning of biological therapy, it was  $3.6 \pm 2.4$  after a minimum of 6 months of treatment and  $3.4 \pm 2.4$  after 1 year.

Functional assessment in the «RA-like» group revealed a mean HAQ of  $1.3 \pm 0.7$  when patients started biological therapy. It decreased to  $0.85 \pm 0.7$  in patients treated for 6 months and to  $0.82 \pm 0.71$  for treatments over 1 year. Current HAQ in the group of patients treated with standard treatments

was of  $0.81 \pm 0.65$ .

In spondylitis PsA patients, mean BASFI was of  $5.7 \pm 2.1$  at baseline, and is currently of  $3.5 \pm 2.4$  in patients treated for more than 6 months and of  $3.4 \pm 2.4$  in those treated for more than 1 year.

From the 160 PsA patients who did at least one administration of a biological drug, 118 (73.7%) remain on the first biological treatment registered into BioRePortAP, 9 (5.6%) definitely withdrew from the biological therapy regimen and 33 (20.6%) have been switched to other biological therapy. From the group of 33 patients who switched therapies, 24 (72.7%) of them have switched once and 9 (27.3%) twice (Table III).

Considering 202 biological therapies prescribed in BioRePortAP, drug was discontinued in 51 cases (25.2%). As we saw before, in 9 (17.6%) times the drug was not resumed, and it was replaced by another biological agent in 42 (82.4%) of the cases. The main reasons for discontinuation were inefficacy in 43.1% and adverse events in 39.2% of cases (Table IV).

### Juvenile idiopathic arthritis (BioRePortAIJ and RegistAIJ)

Three hundred sixty eight (11%) Reuma.pt patients had the diagnosis of JIA. 68 were currently medicated with biological agents while 300 were being managed with non-biological treatments. Mean age at disease onset was  $6.6 \pm 4.6$  years old. Mean age at beginning of biological therapy was of  $20.6 \pm 10.1$  years old. We clearly noticed two groups of JIA patients medicated with biological drugs. A group of JIA patients ( $n=32$ ) who started biological therapies during childhood and whose mean age was of  $12.8 \pm 4.1$  years old, and a group of JIA patients ( $n=38$ ) who started biological therapies already as young adults with a mean age of  $27.2 \pm 8.9$  years old at the beginning of biological treatment. The 300 JIA patients treated with synthetic DMARDs presented a mean age of  $18.3 \pm 11.1$  years old. Mean disease duration at last observation was of  $13.3 \pm 10.5$  years and at the starting of the biological treatment was of  $11.4 \pm 9.6$  years. Females account for 68.2% of patients; they were 67% in the synthetic treated group and represented 73.5% in the biological treated group (Table I).

The proportion of patients assigned to JIA subtypes differed in patients treated with non biological or biological therapies (Table V).

Antinuclear antibodies were positive in 35% of patients and 21.4% were HLAB27 positive.

Rheumatoid factor was found in 22.1% and anti-CCP in 31.2% of the patients. Extra-articular manifestations were reported in 35.2% of patients from the conventional DMARDs group and 55.4% in the biological treated group.

The total amount of biological treatment's exposure was of 275.3 years. Taking into account all JIA patients treated with biologics, 68.9% were exposed to at least one administration of etanercept, 21.6% to adalimumab, 10.8% to anakinra, 9.5% to infliximab, 8.1% to abatacept, 2.7% to tocilizumab and to 1.3% rituximab (Table II).

The mean active joint count reported at beginning of biological therapies was  $8.5 \pm 8.4$  and decreased to  $1.3 \pm 2.2$  and  $1.4 \pm 2.3$  after 6 months and one year of therapy, respectively. Limitation of passive motion (LOM) was observed at baseline in  $4.7 \pm 5$  joints and after 6 months and 1 year in, respectively,  $3.9 \pm 8.8$  and  $4.2 \pm 9.3$  joints. Mean ESR was of  $31.5 \pm 21.4$  mm/1<sup>st</sup> hour at biological treatment onset and of  $16.6 \pm 15.5$  and  $17.3 \pm 15.7$  after, respectively, 6 months and 1 year of treatment. Mean Child health assessment questionnaire (CHAQ) and for adult patients HAQ scores showed  $0.99 \pm 0.7$  at baseline,  $0.42 \pm 0.53$  after 6 months and  $0.45 \pm 0.55$  after at least 1 year of treatment.

From the 74 JIA patients who did at least one administration of a biological drug, 55 (74.3%) remain on the first biological treatment registered into BioRePortAIJ, 6 (8.1%) definitely withdrew from the biological therapy and 13 (17.6%) have been switched to other biological therapy. From the group of 13 patients who switched therapies, 7 (53.8%) of them have switched once, 4 (30.8%) twice and 2 (15.4%) patients switched three or more times (Table III).

Considering 94 biological therapies prescribed in BioRePortAIJ, the drug was discontinued in 29 cases (30.8%). As we have seen before, in 6 (20.7%) of the times, the drug was not resumed, and it was replaced by another biological agent in 23 (79.3%) cases. The reasons for discontinuation were inefficacy in 44.8% of the cases and other reasons in 37.9%. Interestingly adverse events only accounted for 10.3% of the reasons reported for discontinuing therapy in JIA patients (Table IV).

## Discussion

The aim of this work was to present the structure, organization, management and first available data

from Reuma.pt, the Rheumatic Diseases Portuguese Register from SPR, after 2.5 years of its launch.

In 2005, SPR published two nationwide analyses of 376 rheumatoid arthritis<sup>14</sup> and 113 ankylosing spondylitis<sup>15</sup> patients treated with biological therapies. Also, single center's analyses were performed<sup>16-17</sup>. At that time, observations were periodically registered using paper forms with a common core of measures. With Reuma.pt development and implementation a huge step has been made towards a more efficient and accurate data collection, storage and analysis.

In this work we have presented data that supports the important role performed by registers in the evaluation of rheumatic patients treated with conventional or biological therapies. Treatment's long term efficacy, drug's survival time and analysis of switches between biologics are accurately evaluated by our and other registers.

Short and long term safety of biological agents in clinical practice pose additional challenges to registers. Similarly with the regulatory health authority INFARMED, we have adopted MedDRA as our classification system for adverse events. However in clinical daily practice, reporting all adverse events is a difficult task for the overwhelmed physician and currently there are discrepancies between centers in the criteria for registering adverse events in Reuma.pt. The CC RNSR is developing recommendations for adverse events collection, prioritizing adverse events by clinical relevance and/or severity in order to guarantee an adequate and reliable reporting from all centers.

Safety data analyses from Reuma.pt have been previously presented, based on a single center data. In an evaluation in 136 RA patients registered in BioRePortAR<sup>18</sup>, with a mean follow-up of  $3.7 \pm 2.8$  years and an exposure to biological therapies of 510 patient-years, the authors have reported 311 adverse events, 242 of them classified by the rheumatologist as being related with the biological therapy. Twenty four (7.7%) were classified as serious adverse events which corresponded to an incidence rate of 5.8 serious adverse events/100 patients-year (2.2 infections /100 pt-years and 1.5 hypersensitivity reactions/ 100 pt-years).

Other analysis<sup>19</sup> of 42 BioRePortAP patients reported 56 adverse events. Only one has been assigned as a serious adverse event (incidence rate of 1.3 serious adverse events/100 patients year) and it was classified as unlikely related to anti-TNF

therapy. The remaining adverse events were not severe and 67% of them were due to infections.

Also, in a group of 24 BioRePortAIJ patients<sup>20</sup>, 3 serious adverse events (1 forearm fasciitis necrosans, 1 orchiepididymitis and 1 allergic reaction) were reported, none of them resulted in patient's death. There were no reports of opportunistic infections.

Latent tuberculosis infection (LTBI) is still a problem in Portugal. Due to that, SPR issued recommendations<sup>21</sup> for LTBI screening in patients starting biological therapies. In a previous nationwide study<sup>22</sup>, based on the paper registry forms prior to Reuma.pt launch, we have reported 13 cases of tuberculosis between 1999 and 2005 in patients treated with biological therapies. Nine patients had RA (in 639 RA exposed patients, 1.4%), 3 AS (in 200 AS exposed patients, 1.5%) and 1 had PsA (in 101 PsA exposed patients, 1%). Tuberculin skin test (TST) was performed in 9 out of the 13 patients. In 3 cases, the TST response was 0 mm. Also in 3 cases, the TST response was superior to 10 mm, and all of them were treated with isoniazid treatment 300 mg/d during 9 months. The time between first symptoms and TB diagnosis was 2.6 +/-2.9 months. One death was reported; all of the other cases had a good outcome after anti-TB treatment. Four cases have occurred before the widespread screening established for all patients in 2003. The 2006 and 2008 update<sup>21</sup> of the recommendations for tuberculosis screening and LTBI treatment were more stringent, with the decrease of TST positivity threshold to 5mm and the introduction of a TST retest 2 weeks apart. Reuma.pt comprehends specific questions to address the issue of tuberculosis and a report will be prepared specifically on this issue.

In conclusion, patient registries are an important source for longitudinal observational studies in rheumatic diseases, which in turn are an essential complement to data obtained from randomized clinical trials. In fact, registers are crucial to ensure correct clinical use, adequate assessment of post-marketing biological therapies' efficacy and safety, therefore contributing for a rational cost-benefit ratio. Several registers across Europe and North America have demonstrated to be excellent tools for monitoring quality of care and for conducting scientific research that deals with important daily clinical problems. Reuma.pt, the national register from SPR, is also a powerful and accurate tool that will be able to contribute to some of the

unmet needs in the field of clinical rheumatology. In the near future, we are planning to develop synergies with international registers and to present Reuma.pt data in major scientific meetings and major international peer-review journals.

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