

Reuma.pt contribution to the knowledge of immune-mediated systemic rheumatic diseases

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ABSTRACT

Patient registries are key instruments aimed at a better understanding of the natural history of diseases, at assessing the effectiveness of therapeutic interventions, as well as identifying rare events or outcomes that are not captured in clinical trials. However, the potential of registries goes far beyond these aspects. For example, registries promote the standardization of clinical practice, can also provide information on domains that are not routinely collected in clinical practice and can support decision-making. Being aware of the importance of registries, the Portuguese Society of Rheumatology developed the Rheumatic Diseases Portuguese Register- Reuma.pt – which proved to be an innovative instrument essential to a better understanding of systemic immune-mediated rheumatic diseases.

Objective: To describe the contribution of Reuma.pt to the knowledge of systemic immune-mediated rheumatic diseases.

Results: Reuma.pt is widely implemented, with 77 centres actively contributing to the recruitment and follow-up of patients. Reuma.pt follows in a standardized way patients with the following systemic inflammatory rheumatic diseases: rheumatoid arthritis (n=6.218), psoriatic arthritis (n=1.498), spondyloarthritis (n=2.529), juvenile idiopathic arthritis (n=1.561), auto-inflammatory syndromes (n=122), systemic lupus erythematosus (n=1.718), systemic sclerosis (n=180) and vasculitis (n=221). This platform is intended for use as an electronic medical record, provides standardized assessment

of patients and support to the clinical decision, thereby contributing to a better quality of care of rheumatic patients.

The research based on Reuma.pt identified genetic determinants of susceptibility and response to therapy, characterized in detail systemic rheumatic diseases and their long-term impact, critically appraised the performance of instruments for monitoring the disease activity, established the effectiveness and safety of biologic therapies and identified predictors of response, and proactively engaged patients in the management of their disease.

Conclusion: Reuma.pt is an innovative tool, widely established in the country that contributes to a clinical practice of excellence and simultaneously to increase the knowledge of systemic immune-mediated rheumatic diseases. Additionally, Reuma.pt fosters patients' participation in the management of the disease.

Keywords: Rheumatic diseases; Portugal; Register; Reuma.pt

INTRODUCTION

Patient registries and databases can help understand the natural history of diseases, their outcomes and burden in a real life setting. As they provide information from a large number of patients on long-term follow-up, registries are chief instruments that can overcome some limitations of randomized clinical trials, and establish the effectiveness and safety of therapeutic interventions in daily clinical practice. Furthermore, registries can capture information on particular patient groups under-represented or not included in clinical trials, as well as on rare clinical events or outcomes.

Being aware of the importance of registries, one of the strategic objectives of the Portuguese Society of Rheumatology was the development of the Rheumatic

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Diseases Portuguese Register - Reuma.pt. The initial purpose of this registry, launched in 2008, was the monitoring of safety and efficacy of biological therapies, but soon the potential of Reuma.pt went far beyond this aim. A web-based online version is available since 2012 (www.reuma.pt). Currently, its overall goal is to prospectively record data on rheumatic patients, from all rheumatology departments, treated with biological therapies as well as with synthetic disease modifying anti-rheumatic drugs (DMARD) and other therapeutic strategies, as well as to determine the efficacy and safety of treatments and associated long-term comorbidities and outcomes.

Reuma.pt is intended for use as an electronic medical record, thereby contributing to the standardization of procedures among rheumatology departments. The regular use of validated instruments for monitoring disease activity in routine practice and embed patient-generated data into the flow of decision is a way of improving and maintaining the quality of care of rheumatic patients. The frequency of patients' assessments is entered according to local clinical practice. Patients can access their own area and complete the patient reported outcomes before the medical visit. Other available features of Reuma.pt facilitate follow-up and monitoring of the patient and support clinical decision. Reuma.pt covers publicly funded hospitals as well as private practice. The physicians' participation is voluntarily. The recruitment is ongoing with a growth rate of approximately 2000 new patients per year. A detailed description of the registry is available elsewhere^{1,2}.

The aim of this work is to ascertain the contribution of Reuma.pt for the knowledge of systemic immune-mediated rheumatic diseases.

METHODS

STUDY DESIGN

This is a review and summary of the generated evidence based on Reuma.pt. We searched Pubmed as well as the abstracts from the main rheumatology congresses (Portuguese Congress of Rheumatology, American College of Rheumatology and European League Against Rheumatism) since 2013. Studies published in peer-reviewed journals and abstracts presented at those congresses that analysed data from Reuma.pt were included. Papers resulting from international collaborations were also considered. Single centre

works were excluded. The addressed diseases were Rheumatoid Arthritis (RA), Spondyloarthritis (SpA), Psoriatic Arthritis (PsA), Juvenile Idiopathic Arthritis (JIA), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc) and vasculitis.

Reuma.pt is approved by the Portuguese Data Protection Authority and by the Ethics Committees of the participating centres. Patients provided written informed consent before enrolment.

RESULTS

There are currently 66 participating centres from Portugal Mainland, 1 from Madeira and 2 from Azores Islands. In addition, there is one affiliated centre from the United Kingdom and 7 from Brazil (Figure 1). More than 15.100 patients (RA=6.218, PsA=1.498, SpA=2.529, JIA=1.561, autoinflammatory syndromes=122, SLE=1.718, SSc=180 and vasculitis=221) and more than 111.000 visits were registered until the end of June 2016 (Table I). Several scientific projects based on the analysis of Reuma.pt data have resulted in presentations in major rheumatology meetings and publications in national and international peer-reviewed journals. A total of 24 full-length articles and 6 abstracts presented in national or international congresses were included in this review.

A KNOWLEDGE HUB FOR IMMUNE-MEDIATED SYSTEMIC RHEUMATIC DISEASES GENETICS AND PHARMACOGENOMICS

The aetiology of systemic rheumatic diseases remains unrevealed though an increasing body of evidence suggests that genetic variants within immune-related genes can influence the risk of developing the disease and affect drug response.

Rheumatoid arthritis (RA) is characterized by chronic inflammation of the synovial lining of the joint and if left untreated results in irreversible joint damage, disability and early death. According to the recent population based epidemiologic study Epireuma.pt, RA affects 0.7% of the adult Portuguese population. Genetic variants associated with RA susceptibility and severity includes the *HLA-DRB1* and polymorphisms in various genes outside the major histocompatibility complex. As part of an international collaboration, we participated in a detailed analysis of the 19p32/TYK2-*ICAM* locus to investigate the contribution of common and rare protein-coding variants to RA suscepti-



FIGURE 1. Geographic distribution of Reuma.pt centres

TABLE I. TOTAL NUMBER OF PATIENTS AND VISITS REGISTERED IN REUMA.PT ACCORDING TO THE DIAGNOSIS AND CURRENT THERAPY

Current date and time 2016-06-28 22:43	Current therapy with biological agents			Current therapy with classical immunomodulatory agents			Totals		
	Patients	Visits	Mean	Patients	Visits	Mean	Patients	Visits	Mean
Rheumatoid Arthritis	1940	34272	17.67	4278	22267	5.21	6218	56539	9.09
Spondyloarthritis	1018	15790	15.51	1511	5665	3.75	2529	21455	8.48
Psoriatic Arthritis	569	8304	14.59	929	4038	4.35	1498	12343	8.24
Juvenile Idiopathic Arthritis	366	5055	13.81	1195	6894	5.77	1561	11949	7.65
Systemic Lupus Erythematosus	54	956	17.7	1664	5915	3.55	1718	6871	4
Early Arthritis	2	18	9	133	621	4.67	135	639	4.73
Autoinflammatory syndromes	21	312	14.86	101	191	1.89	122	503	4.12
Vasculitis	22	329	14.95	308	487	1.58	330	816	2.47
Osteoarthroses	0	0		51	62	1.22	51	62	1.22
Scleroderma	4	32	8	176	1224	6.95	180	1256	6.98
Other juvenile diagnoses	7	126	18	214	354	1.65	221	480	2.17
Other diagnoses – adults	30	319	10.63	526	956	1.82	556	1275	2.29
TOTAL	4033	65513	16.24	11086	48674	4.39	15119	114187	7.55

77 centres with data are registered in Reuma.pt

lity and explore the pleiotropic effects of these same variants. This work provided compelling genetic data

demonstrating that *TYK2* alleles with partial loss-of-function protect against RA, SLE and potentially other

autoimmune diseases and provided supporting evidence for TYK2 as a promising drug target for the treatment of autoimmune diseases³.

Tumour necrosis factor inhibitors (TNFi) are widely used in the treatment of RA, but for unknown reasons, some patients fail to respond adequately. Importantly, the identification of genetic predictors of response to treatment might support a more precise therapy. Reuma.pt participated in a genome wide association study of 2,706 individuals of European ancestry that identified a SNP (rs6427528) at the *Iq23* locus associated with change in disease activity score in patients receiving etanercept ($p=8\times 10^{-8}$), but not with other TNFi ($p>0.05$). The allele associated with better response to etanercept was associated with higher *CD84* gene expression in peripheral blood mononuclear cells, and *CD84* expression correlates with disease activity, supporting a model in which *CD84* genotypes and/or expression may serve as a useful biomarker for response to etanercept treatment in RA patients of European ancestry⁴. Another study including Portuguese and Spanish RA population identified TRAF/C5 as a predictor of response to TNFi⁵. The analysis of 49 single nucleotide polymorphisms within or near 17 immune-related genes suggested that *IL4* and *IL8RB* loci may have a small-effect genetic impact on the risk of developing RA, whereas *IFNG* might be involved in modulating the response to anti-TNF drugs⁶.

Juvenile Idiopathic Arthritis (JIA) incorporates a heterogeneous group of chronic arthritides of unknown aetiology beginning before the age of 16. The rate of active JIA progressing into adulthood is still high as it is the risk for serious and lifelong complications. The study of 291 Portuguese patients with JIA and 300 matched controls provided additional evidence for an association between polymorphisms in genes *PTPN2* and *PTPN22*, and in the intergenic region rs7151781 of chromosome 14, and the risk of rheumatoid factor-positive polyarticular, extended oligoarticular and systemic JIA, respectively (AF Mourão *et al* submitted). Nevertheless, we could not confirm the association between a panel of selected single nucleotide polymorphisms and poor prognosis in Portuguese patients with JIA⁷.

CLINICAL ASSESSMENT AND APPRAISAL OF THE EXISTING INSTRUMENTS

Systemic sclerosis (SSc) is a rare disease and the assessment of these patients requires skills far beyond musculoskeletal examination. The extension of

Reuma.pt to include SSc patients occurred in September 2015 and this protocol includes variables such as modified Rodnan skin score, presence of digital ulcers, pulmonary and cardiac assessment and the DETECT algorithm for screening pulmonary hypertension. The analysis of the first patients registered showed a high predominance of females (87.5%) and of limited cutaneous disease (49.1%)⁸.

The vasculitides are a group of relatively uncommon and complex diseases.

The increased clinical trial activity and new therapeutic options for patients with vasculitis has led to the development and validation of several disease assessment tools, as well as long-term specific registries for vasculitis. In October 2014, Reuma.pt has launched a dedicated protocol to register patients with vasculitis. It allows the assessment of disease activity by using the Birmingham Vasculitis Activity Score - BVAS; of damage through the Vasculitis Damage Index - VDI; of prognosis with Five Factor Score FFS; and of quality of life by using the Short-Form 36 - SF36^{9,10}.

Systemic lupus erythematosus (SLE) diagnosis and classification may represent a great challenge due to its extremely heterogeneous multisystem manifestations. Classification criteria are of utmost importance to ensure a consistent case definition for clinical research. We conducted a cross-sectional observational study of patients with a clinical diagnosis of SLE registered in Portuguese and Spanish national registries to compare the sensitivity for SLE classification between the American College of Rheumatology (ACR) 1997 and the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria sets in a real-life population. We found the SLICC 2012 criteria more sensitive than the ACR 1997 criteria in real-life clinical practice, which may allow patients to be classified as having SLE earlier in the disease course¹¹.

Routine use of composite measures to assess disease activity has become standard practice in rheumatology. The 28-joint DAS (DAS28), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are frequently used to assess disease activity in RA. By analysing a total of 2795 patients and 14,440 visits selected from Reuma.pt, we found strong correlation between the three indices throughout the 14,440 visits: $r=0.874$ for DAS28/CDAI, $r=0.877$ for DAS28/SDAI and $r=0.984$ for CDAI/SDAI (all $p<0.0001$). However, when categorization in the different disease activity states was analysed, there was significant disagreement between the cut-offs of the three in-

dices. These differences may have considerable implications regarding the application of target-oriented RA treatment recommendations in practice¹².

The juvenile arthritis disease activity score (JADAS) based on erythrocyte sedimentation rate and on C-reactive protein performs similarly in the evaluation of disease activity in JIA patients registered in Reuma.pt. Moreover, the correlation of JADAS with and without sedimentation rate is high, suggesting that a tool using exclusively clinical parameters (the clinical JADAS) might be useful in the absence of laboratory measures¹³.

DISEASE FEATURES, COMORBIDITIES AND LONG-TERM OUTCOMES

As said before, SLE is a challenging immune-mediated multisystem disease and the phenotypic characterization as well as the understanding of disease burden and long-term outcomes will contribute to a better health care of these patients. Unlike other rheumatic diseases, there are few registries of SLE populations. Lupus affects predominantly women of reproductive age, and the disease phenotype may be distinct in male patients and in other age groups. Physicians must be aware of these differences, which may have impact on SLE diagnosis and disease management.

In fact, gender and age at disease onset influence clinical and serological findings, as well as the occurrence of damage. The analysis of 1510 SLE patients from Reuma.pt revealed that male patients with SLE are older at disease onset and present less mucocutaneous and articular manifestations but have more major organ involvement. Despite the recognised global benefit of antimalarial drugs in all lupus patients, men are less likely to use these medications¹⁴. While childhood-onset SLE is a more severe disease, late-onset SLE has a more indolent course but patients have more comorbidities and acquire more damage¹⁵. After a mean disease duration of 14 years, 37.4% of the patients present irreversible damage. Musculoskeletal and neuropsychiatric domains are the most frequently affected. Age, disease duration, renal involvement, antiphospholipid antibodies positivity and current therapy with corticosteroids are independently associated with damage. Early retirement is significantly more prevalent in patients with severe damage¹⁶.

The global burden of JIA is not fully understood, as many patients are reclassified in adulthood using adult rheumatic diseases terminology. The analysis of JIA patients older than 18 years and with more than 5 years of disease registered in Reuma.pt offers the opportuni-

ty to understand how they fulfilled classification criteria of adult rheumatic diseases, how active is the disease in adulthood, what are the long-term functional, structural and social outcomes. Most of JIA patients followed in adult rheumatology clinics fulfil classification criteria for adult rheumatic diseases, maintain active disease and have functional impairment at long-term follow-up¹⁷.

TREATMENT EFFECTIVENESS AND SAFETY

Reuma.pt is becoming an increasingly important source of knowledge, as it provides valuable information to assess routine management of diseases and can be used to validate the results obtained during trials and generate epidemiological data. TNF inhibitors are the most frequent first line biologics in the treatment of RA, but no randomized trials are available comparing these agents. Like other registries, data from Reuma.pt showed comparable effectiveness of 3 TNFi (adalimumab, etanercept and infliximab) in RA patients. Smoking, positivity for anti-citrullinated peptide antibodies (ACPA), glucocorticoid therapy and higher physician global assessment of the disease negatively affected the response to anti-TNF, while higher education level was associated with better response¹⁸. Golimumab, another TNFi, was introduced in Portugal more recently. Data from Reuma.pt support a significant decrease in RA disease activity and a significant functional improvement over 52 weeks of treatment¹⁹. Golimumab persistence rate is 75.3% for individuals with follow-up time of at least 52 weeks. Furthermore, the vast majority of patients gained QALY²⁰.

We also analysed the comparative effectiveness of two classes of biologics in RA (TNFi and the IL-6 antagonist tocilizumab), according to different response criteria. Patients treated with tocilizumab were more likely to achieve DAS28, CDAI and SDAI remission/low disease activity, as well as good EULAR response at 6 months, when adjusting for confounding factors. On the other hand, the probability of Boolean remission did not differ between groups and neither did the likelihood of achieving a good/moderate EULAR response. We have also found that previous biologic therapy had an important effect on response to treatment. In fact, the biologic-naïve subgroup of patients achieved higher remission rates²¹.

Medication persistence is essential in order to maintain disease control and prevent damage. The effect of classic synthetic DMARDs comedication on TNFi retention was evaluated in 954 patients with spondy-

larthritis (SpA), starting first TNFi between 2001 and 2014. 30.3% discontinued their first TNFi after a median follow-up time of 2.5 years (range: 0.08-13 years), mostly due to inefficacy (55.7%). Comedication with classic synthetic DMARDs had no measurable effect on TNFi-retention²².

Reuma.pt also generated evidence on the sustained effectiveness and safety of TNF inhibitors in JIA patients. More than 80% of patients respond to biologics and the retention rate after 4 years of treatment is 68.1%²³.

FOSTERING COLLABORATION WITH OTHER REGISTRIES

Despite large patient numbers registered in Reuma.pt, it is likely that it lacks power to confidently rule out moderate yet clinically meaningful increases in risks of rare potential adverse events. Under the auspices of the European League Against Rheumatism (EULAR), a study group of investigators representing European bDMARD registers was convened to explore the feasibility of combined analyses. European RA biologic registers vary in design, recruitment and data items collected and this is an opportunity to work towards harmonization in methods of data collection across European rheumatology²⁴.

Under the auspices of the EULAR Registers and Observational Drug Studies (RODS) Study Group, representatives from 11 European biologic registers undertook a collaborative project to investigate the risk of developing invasive melanoma in patients who had RA treated with conventional synthetic or biologic DMARDs and to compare rates of invasive melanoma in different treatment groups of patients with RA to those in the general population. This large European collaborative project did not confirm an overall increased risk of melanoma following exposure to TNFi²⁵.

Moreover, Reuma.pt established collaborations with other European drug-based registers. As result of these partnership the effectiveness of other bDMARD (rituximab, tocilizumab and abatacept) was analysed. One of the important findings was that Rituximab lower or higher dose given as the first treatment course was equally effective at 6 months and this result may have some important cost implications in the treatment of patients with RA²⁶. Furthermore, in patients who discontinued rituximab, tocilizumab provided a better control of RA than abatacept or TNFi²⁷. Tocilizumab with or without concomitant sDMARDs results in comparable clinical response as assessed by CDAI change, but tocilizumab

retention is shorter under monotherapy²⁸.

Data from nine European observational RA cohorts, comprising 3961 patients treated with abatacept was also analysed. Patient characteristics at abatacept initiation vary across Europe, probably reflecting differences in eligibility criteria and prescription patterns²⁹.

In addition, Reuma.pt vasculitis registry is part of the European Vasculitis Study Group (EUVAS) initiative to have homogenous collection of data from patients with vasculitis across all European countries and to define a core-set of items present in all vasculitis registries¹⁰.

PATIENT PARTICIPATION

Integrating patient perspective in the clinical evaluation enhances the capture of the disease multiple faces and promotes shared decision. Patient reported outcomes (PRO) are one of the components routinely evaluated in Reuma.pt. PROs play an increasingly important role in the evaluation of distinct domains such as symptoms, function, health-related quality of life, productivity or compliance with medication. However, the use of paper-based questionnaires is time consuming and a source of potential errors. The benefits of computerized collection of questionnaire data have been emphasized and in the case of Reuma.pt patents can fill questionnaires online. This type of innovation clearly benefits patients and clinicians, minimizing the time required to complete comprehensive assessments and improving documentation. The validity and usability of computer touch screen questionnaires was established for RA and SpA Portuguese patients³⁰.

CONCLUSION

After eight years of existence we can conclude that Reuma.pt is an example of success not only as a scientific and clinical tool, but most importantly as a unifying project of the Portuguese rheumatologists. Reuma.pt became an invaluable resource for clinical research in the field of immune-mediated systemic rheumatic diseases. Moreover, it can provide paramount information to support decision-making. Nevertheless, as Reuma.pt growth, the responsibilities and challenges increase. The quality and accuracy of data must be continuously controlled, and strategies to avoid missing data and to assure patient retention developed, all while ensuring funding and sustainability of this project.

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