Loss to follow-up in registries of rheumatic patients treated with biologics: a potential information bias in assessing pharmacovigilance and efficacy outcomes

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ABSTRACT

Background: The information associated with loss to follow-up (LFU) patients may affect real-world data evaluation of the use of biologics that is not being adequately captured in registries.
Methods: We identified all patients (Pts) treated with biologics in our center who had no visits registered for more than 6 months, in the Rheumatic Diseases Portuguese Register, Reuma.pt. We retrieved baseline information from Reuma.pt and from the hospital electronic clinical record. We then performed a telephonic interview to characterize the reasons for LFU at our day care unit. For Pts unable to be contacted by telephone a letter of invitation to an appointment at the hospital was sent.
Results: From a total of 794 Pts registered in Reuma.pt at our center with active biologic therapy 227 did not have any information registered in the last 6 months. Of this, 36 Pts were on biologic therapy prescribed by other departments and maintained follow-up in these departments. 102 Pts had suspended biologic administration by medical indication and this information was registered in the hospital electronic clinical records but not updated in Reuma.pt. For 89 Pts no information could be retrieved from either the hospital electronic clinical record or Reuma.pt and we classified these Pts as true LFU.

26 of these LFU Pts were being followed up in another Rheumatology center. 26 of the LFU Pts died. 11 Pts had an adverse effect. 4 Pts of the LFU were considering to be in remission. We were not able to contact 15 of the LFU pts.
Conclusion: Identifying LFU Pts and clarifying the reason for the loss of data in a register contributes to a better knowledge on strategies to discontinue biologics in stable pts, to a better pharmacovigilance of adverse effects and to more efficiency in data capture by registries. Due to data protection reasons it was impossible to have access to the Pts's death certificates.

Keywords: Lost to follow-up; Biologics; Reuma.pt

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INTRODUCTION

Patients with inflammatory rheumatic diseases refractory to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have been treated with biologics for the last two decades, with a dramatic change in prognosis[1]. Biologic DMARDs (bDMARDs) are associated with a higher risk of serious infections than csDMARDs as well as other adverse effects that warrant the need for close monitoring[2]. A follow-up program is an integral aspect of high quality care of these patients and the failure to maintain regular follow-up is a major concern. Patients who are lost to follow-up (LFU) are more likely to experience considerable worsening of the disease, potentially leading to organ damage and increase in health care expenditure[3]. Thus, it is crucial that adequate and tight monitoring of efficacy and safety is organized to assure that patients on bDMARDs have an adequate balance between efficacy, risk of adverse events and costs. Ideally, no patient should be kept on a drug without clear benefit or if there are unacceptable adverse effects. Overlooking these aspects will translate into unnecessary risks for the patients and a significant burden to national health services.

When patients become LFU, there is missed information in their registries, which is crucial for a comprehensive evaluation of the real-world data on the efficacy and safety of bDMARDs[4]. Indeed, some patients stop treatment and thus escape the surveillance of re-

gistries and, on the other hand, some adverse effects might occur following the LFU and this information fails to be captured into the registry. In addition, patients who miss appointments, and ultimately their regular follow-up, might be more vulnerable to a poor long-term prognosis[3].

Our hypothesis is that identifying the reasons of LFU will contribute to improve pharmacovigilance and will eventually lead to an early identification of patients at risk of LFU and to a better knowledge on strategies of bDMARD tapering in stable patients. This will provide relevant information that will improve the quality of care of these patients.

To our knowledge, there have been no studies investigating the reasons for LFU in registries of rheumatic patients treated with bDMARDs. In this study, we aimed to identify the reasons for dropout from follow-up of patients with inflammatory rheumatic diseases treated with bDMARDs in our department and to determine these patients' characteristics.

METHODS

A close monitoring program is an integral aspect of high quality care of rheumatic patients treated with DMARDs in general, and bDMARDs in particular. At our department, all patients with inflammatory rheumatic diseases who are treated with bDMARDs are followed up in the day-care unit with at least 4 visits per year. These visits focus on ensuring the efficacy and safety of these drugs and the prescription is renewed for another 3 months (subcutaneous bDMARDs) or administered on the same day (intravenous bDMARDs) depending on this assessment. Furthermore, patients keep a regular contact (at least once a year) with their attending rheumatologist, who ensures an additional way of monitoring treatment efficacy, safety and adherence, as well as disease activity and damage.

Every appointment at the day-care unit is recorded with the assistance of the Rheumatic Diseases Portuguese Register (Reuma.pt), a nationwide clinical register established and managed by the Portuguese Society of Rheumatology, in which data from patients with various rheumatic diseases are recorded[5]. Reuma.pt serves as an electronic clinical record with real-time data, which is then copied into the local hospital electronic file. At the time of initial registration in Reuma.pt, all patients sign an informed consent, by which they allow their data to be used for research purposes. Reuma.pt is approved by the local ethics committee and by the national board for the protection of personal data. In addition, the ethics committee of our institution approved the design of this specific study.

As of May 2017, 790 patients were under active bDMARDs in our day-care unit. We included all patients with inflammatory rheumatic diseases with any exposure to bDMARDs prescribed and monitored in our department, who had the last visit registered in Reuma.pt more than 6 months before the starting date of the present study (May 1st, 2017). Information regarding diagnosis, age, gender, disease duration and date of first and last visits to the treating centre was retrieved from Reuma.pt. Clinical data collected at the last appointment was retrieved for the following variables: erythrocyte sedimentation rate [ESR], c-reactive protein [CRP]), patient and physician visual analogic scale (VAS), disease-specific activity scores (disease activity score-28 [DAS28], Ankylosing Spondylitis Disease Activity Score [ASDAS], Systemic Lupus Erythematosus Disease Activity Index [SLEDAI], Birmingham Vasculitis Activity Score [BVAS]) and functional scores (Health Assessment Questionnaire [HAQ]). Finally, we identified data on current and previous bDMARDs exposure and their safety, as assessed through adverse events and reasons for bDMARDs discontinuation registered in Reuma.pt. The local (hospital) and national (Health Data Platform) electronic clinical record was also revised to identify possible reasons for LFU that might have escaped Reuma.pt registration.

For patients without information in any of the electronic registers, a telephonic interview was performed to characterize the reasons associated with LFU. An appointment at our department was offered and further evaluation was pursued for patients who wanted to return to our care. For patients not reachable by telephone, a letter of invitation to a clinic appointment at our department was proposed.

Descriptive statistics were applied to characterize this cohort. Normally distributed variables are presented as mean and standard deviation and non-normal variables are presented as median and interquartile range. All the analyses were performed using Stata 14.2 for Mac.

RESULTS

From a total of 790 patients registered in Reuma.pt at our centre with active biologic therapy, 227 (28.7%)

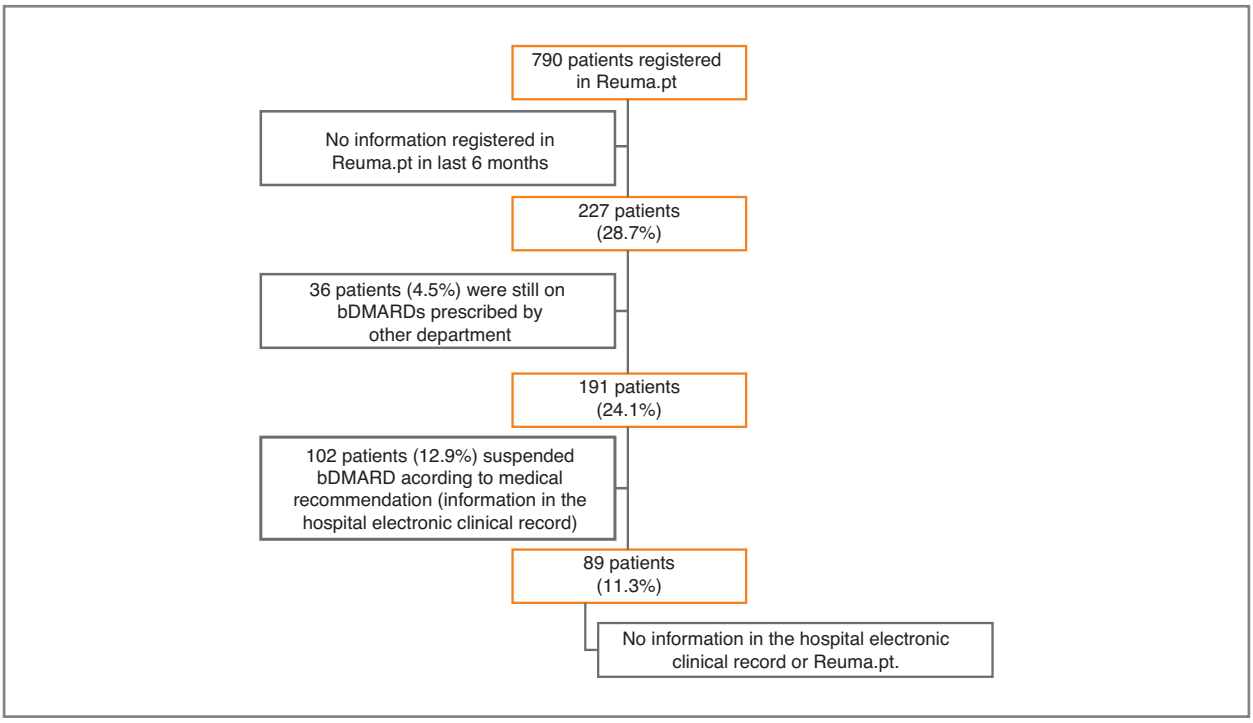

FIGURE 1. Process to reach the number of true loss to follow up
Reuma.pt: Rheumatic Diseases Portuguese Register; bDMARDs: biologic disease-modifying antirheumatic drugs

did not have any information registered in the previous 6 months (Figure 1). Of those, 36 patients (15.9%) were still on bDMARDs prescribed by other departments (dermatology and gastroenterology) in our hospital and maintained follow-up in these departments. One-hundred and two patients (44.9%) had suspended bDMARDs according to medical recommendation, and this information was registered in the hospital electronic clinical record but not updated in Reuma.pt. These patients maintained follow-up in our department and thus were not classified as true LFU. We have updated this information at Reuma.pt. Eighty-nine patients (39.2% of the 227 patients and 11.3% of the total of 790 patients) had no information in the hospital electronic clinical record or Reuma.pt and these patients were classified as true LFU patients. Here we present the description of these 89 patients LFU from our centre.

The demographic and clinic characteristics of these LFU patients are summarized in Table I. Twenty-nine of the total 89 LFU (32.6%) were male with a mean age of 51.3 (± 20.0) years. Mean disease duration was 15.7 ± 10.3 years and the mean duration of biologic therapy was 5.5 ± 3.5 years. The last biologic used was in the majority of the cases etanercept (24.7%) (Table I).

The reasons for LFU are represented in Figure 2. The most frequent causes of LFU were follow-up at another Rheumatology centre (n=26; 29.2%) and death (n=26; 29.2%). In 15 cases (16.9%) patients could not be contacted by telephone nor attended the appointment offered; therefore, no additional data could be retrieved.

Twenty-six (29.2%) of these LFU patients were being followed in other Rheumatology centres (Table I). The reasons for this change are represented in Figure 3. 15 patients (16.9%) had transferred their follow-up at a newly opened and closer Rheumatology Department; 6 (6.7%) had moved to another city and 5 patients (5.6%) had administrative problems related to our Department/Hospital.

Twenty-six (29.2%) patients died, at a mean age of 66.2 (± 14.7) years (Table I). The mean disease duration was 14.3 (± 10.5) years and the most common diagnosis was RA (n=21; 81.8%). The mean duration of bDMARDs therapy was 5.9 (± 3.5) years: 69.2% were on anti-TNF therapy, 15.4% on anti-CD20 therapy and 11.5% on anti-interleukin-6R therapy at the time of the last clinic appointment (Table I). The cause of death was identified in only 4 patients, through telephone interview with their relatives: myocardial infarction (n=1), lung cancer (n=1), peritonitis following hepatic

TABLE I. DEMOGRAPHIC CHARACTERISTICS, DIAGNOSIS AND BIOLOGIC THERAPY OF TRUE LOSS TO FOLLOW UP PATIENTS

	Total	Followed in Other Centres	Died	Adverse Effects	Remission	Other	Unknown
	N = 89	N = 26	N = 26	N = 11	N=4	N=7	N=15
Demographic characteristics							
Male gender (%)	29 (32.6%)	10 (38.5%)	7 (26.9%)	2 (18.8%)	1 (25%)	2 (28,6%)	5 (33.3%)
Age (Y), mean ± SD	51.3 ± 20.0	49.1 ± 15.6	66.2 ± 14.7	51.3 ± 14.8	30.0 ± 8.2	47.5 ± 31.8	36 ± 17.7
Disease duration (Y), mean ± SD	15.7 ± 10.3	8.6 ± 6.7	14.3 ± 10.5	15.42 ± 12.1	6.9 ± 5.4	4 ± 10.7	8.3 ± 11.4
Biologic therapy duration (Y), mean ± SD	5.5 ± 3.5	4.8 ± 3.4	5.9 ± 3.5	6.98 ±2.8	4.8 ± 3.0	7.7 ± 3.3	4.3 ± 2.9
Previous biologic therapy (N), mean (max-min)	0.59 (0-4)	0.56 (0-2)	0.72 (0-6)	0.56 (0-3)	1.0 (1-3)	0.5 (0-2)	0 (0-2)
Diagnosis, N (%)							
Rheumatoid arthritis	46 (51.7%)	11 (42.3%)	21 (80.8%)	5 (45.5%)	1 (25%)	2 (20%)	6 (40%)
Spondyloarthritis	21 (23.6%)	5 (17.9%)	2 (7.7%)	4 (36.4%)	2 (50%)	2 (40%)	6 (40%)
Psoriatic arthritis	11 (12.4%)	4 (15.4%)	1 (3.8%)	2 (18.2%)	–	3 (42.9%)	1 (6.7%)
Juvenile idiopathic arthritis	6 (6.7%)	4 (14.3%)	1 (3.8%)	–	–	–	1 (6.7%)
Autoinflammatory syndrome	2 (2.2%)	1 (3.6%)	–	–	1 (25%)	–	–
Systemic lupus erythematous	2 (2.2%)	–	1 (3.8%)	–	–	–	1 (6.7%)
Vasculitis	1 (1.1%)	1 (3.6%)	–	–	–	–	
Last Biologic, N (%)							
Etanercept	28 (32.4%)	7 (26.9%)	7 (26.9%)	2 (18.2%)	1 (25%)	6 (85.7%)	5 (33.3%)
Infliximab	20 (22.5%)	6 (21.4%)	3 (11.5%)	4 (36.4%)	1 (25%)	1 (10%)	5 (33.3%)
Adalimumab	12 (13.5%)	3 (10.7%)	6 (23.1%)	1 (9.1%)	–	–	2 (13.3%)
Rituximab	9 (10.1%)	2 (7.1%)	4 (15.4%)	2 (18.2%)	–	–	1 (6.7%)
Tocilizumab	9 (10.1%)	5 (17.9%)	3 (11.5%)	1 (9.1%)	–	–	–
Golimumab	8 (9.0%)	2 (7.1%)	2 (7.7%)	1 (9.1%)	2 (50%)	–	1 (6.7%)
Anacinra	1 (1.1%)	1 (3.6%)	-	–	–	–	–
Abatacept	1 (1.1%)	–	1 (3.8%)	–	–	–	–
Belimumab	1 (1.1%)	–	–	–	–	–	1 (6.7%)

N: Number; Y: years; SD: standard derivation.

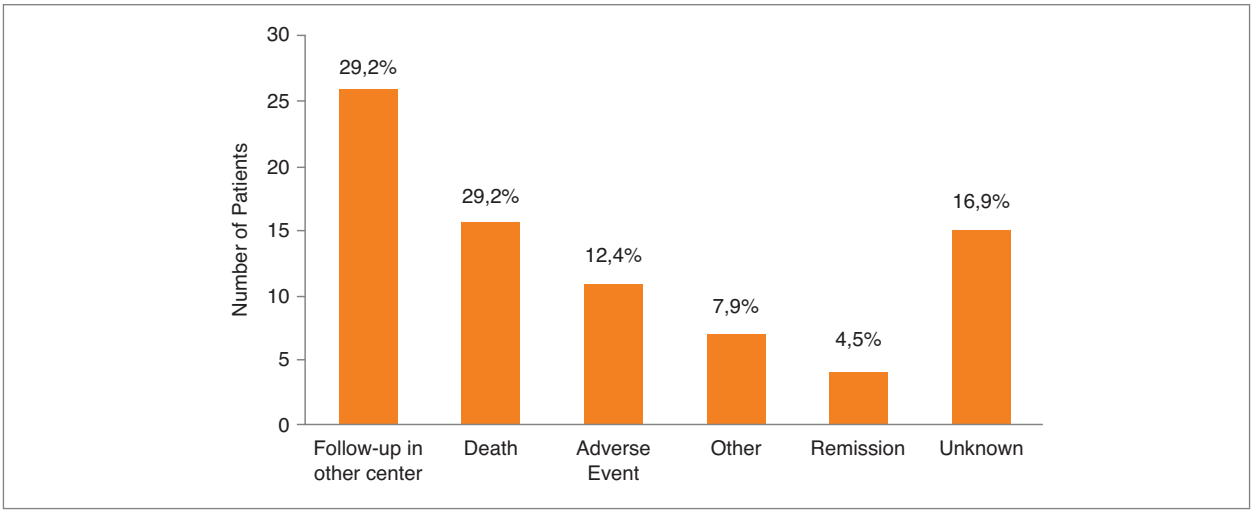

FIGURE 2. Causes of loss to follow up

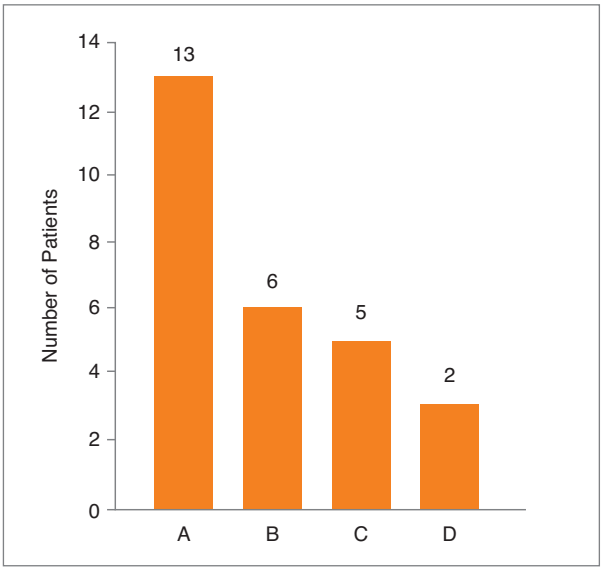

FIGURE 3. Reasons for follow up in others centres
A: follow-up at a newly open and closer Rheumatology Department; B: moved to another city; C: administrative problems related to our Department/Hospital; D: socio-economic reasons

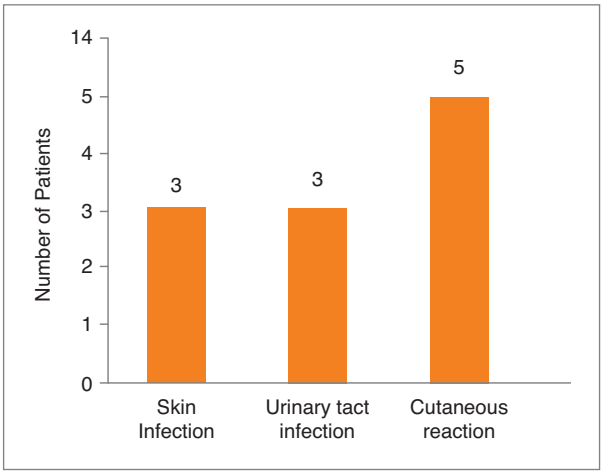

FIGURE 4. Reasons for follow up in others centres

cyst rupture (n=1) and acute pulmonary oedema after lower limb amputation surgery (n=1). None of these 4 patients were on bDMARD therapy at the moment of death. None of the patients were on active biologic treatment at the time of the death. However, we were not able to precisely determine how much time had passed since the last recorded appointment and the time of death; likewise, we could not retrieve the remaining 22 patients' causes of death, as we were not authorized to assess the death certificate.

Eleven patients (12.4%) had stopped biologic therapy and abandoned follow-up by their own decision after experiencing adverse effects attributed by the patient to the use of bDMARDs, although they were not reviewed by their assistant rheumatologist afterwards (Table I, Figure 4). Six patients (6.7%) had infectious complications, either of the skin (n=3, 3.4%) or the urinary tract (n=3, 3.4%). Of those, 2 patients had to be admitted to the hospital: one PsA patient treated with adalimumab who had an urosepsis and one RA patient treated with tocilizumab who acquired a pyelonephritis. Two out of the 3 patients classified as having a skin infection had an infection of a surgical

wound: one of them was an RA patient treated with etanercept who was submitted to an orthopaedic procedure of the foot and the other was a SpA patient treated with golimumab who had a laparoscopic cholecystectomy. The third patient had an infection of lower limbs' ulcers.

The remaining patients stopped the drug because of skin reactions (n=5, 5.6%). Those reactions were not observed by a physician or registered in Reuma.pt or electronic clinical record.

Four patients (4.5%) assumed that they were in remission and decided to stop the drug and medical follow-up by their own initiative. When contacted, all of them believed that the disease was inactive without the need for biological treatment.

Regarding the 7 other patients with miscellaneous reasons for LFU (Table I): 2 patients (2.3%) had socio economic issues and for these reasons were being followed-up only by their general practitioner, having stopped bDMARD therapy and were feeling that their disease was adequately controlled; one was currently in jail and decided not to continue medical therapy or medical follow-up because he was not feeling the need for active treatment; two patients preferred to replace the biologic with non-conventional therapies, believing that they would be sufficient to control their underlying disease and stated that their symptoms were adequately controlled; two patients quit medical follow-up because they missed their last appointment but they were experiencing worsening of their clinical condition and were interested in resuming follow-up at our centre.

As there were missing data regarding disease activity at the last appointment in Reuma.pt, we decided to describe the data referring only to RA and SpA patients (Table II). Furthermore, the number of patients was inadequate for a statistical analysis of these data.

Regarding patients who considered themselves to be in remission, we found that in the last clinical record, one of them had high disease activity (SpA patient with ASDAS 3.0), other had moderate disease activity (RA patient with DAS28-ESR 4.257) and two patients were in remission (a SpA patient with ASDAS <1.3 and a Still disease patient with no active joints or extra-articular symptoms and negative inflammatory markers).

DISCUSSION

To the best of our knowledge, this is the first study exploring the reasons for LFU in patients under biologic therapy.

LFU patients may represent a relevant bias that interferes with appropriate pharmacovigilance and assessment of efficacy outcomes in patients under bDMARDs[4].

TABLE II. DISEASE ACTIVITY AT THE LAST VISIT OF LFU PATIENTS WITH RA AND SPA

	Patients followed in other centres		Patients who died		Patients with adverse effects	
Disease activity, median (IQR)	RA (N=11)	SpA (N=5)	RA (N=21)	SpA (N=2)	RA (N=5)	SpA (N=4)
PhVAS	20 (10-30)	30 (20-40)	37 (27-44)	45 (32.5-57.5)	20 (20-25)	15 (7.5-22.5)
PtVAS	40 (30-50)	30 (20-40)	50 (30-70)	47.50 (33.8-61.3)	50 (45-52.5)	50 (45-60)
DAS28-ESR	3.17 (1.94-3.33)	–	3.39 (2.73-3.91)	–	2.44 (2.05-2.59)	–
ASDAS-CRP	–	2.55 (2.37-2.73)	–	2.29 (1.8-2.8)	–	1.69 (1.2-2.25)
ERS (mm/h)	32 (15-51)	8.49 (8.25-8.75)	31.49 (14-40.8)	16 (13-19)	29 (16-38.8)	8 (8.0-12.75)
CRP (mg/dl)	1.38 (0.04-1.95)	6.39 (5.1-7.7)	0.51 (0.16-2.04)	0.84 (0.65-1.02)	0.35 (0.19-0.56)	0.21 (0.19-0,38)

ASDAS CRP: Ankylosing Spondylitis Disease Activity Score, C-reactive protein; CRP: C-reactive protein; DAS28 ESR: Disease activity score-28, erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; IQ: Interquartile; PhGA: Physician global assessment; PtGA: Patient global assessment; RA: Rheumatoid arthritis; SpA: Spondyloarthritis.

Reuma.pt had missing data, namely patients who had already suspended bDMARDs for various reasons known to the attending physician (infectious cause, other adverse effects, change of residency, emigration, amongst others). However, this information had not been registered and although these were not true LFU to our care, this represented missing information, crucial to comprehensive pharmacovigilance.

Concerning the true LFU patients at our centre, most had a diagnosis of RA, mean age 51.3 (±20.0) years and there was a predominance of female gender. A study that evaluated the frequency of LFU from medical care of patients with rheumatic diseases also showed that LFU was higher in female gender3. The most common reason for LFU was moving to another Rheumatology centre in order to have continuous medical care at a newer and closer Rheumatology Department.

We identified 4 LFU patients who stopped treatment because they believed they were on remission and decided to abandon medical care and pharmacological therapy. However, when assessing disease activity at the last appointment, it was found that one patient had high disease activity, other moderate, and only two were in true remission.

When asked about returning to their consultations, most patients were willing to resume follow up, namely patients who had an adverse effect and patients who loss appointments and loss follow-up.

Of the 26 patients who died, we only identified the cause of death of 4. This is an important concern regarding pharmacological safety. This missing information is crucial for a comprehensive real-world data evaluation of the use of bDMARDs. Unfortunately, it was not possible to have access to the patient's death certificates, which is a major limitation of this analysis. Other relevant limitations were the lack of information on the education level and socio-economical background, missing data, sample size and the impossibility of having precise information available on the time interval between the last treatment administered and death.

CONCLUSION

The information hidden in these LFU patient's registries is crucial for a comprehensive real-world data evaluation of the use of biologics, regarding efficacy, safety and variables related to the social environment of rheumatic patients.

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