Effectiveness of a referral program for rheumatoid arthritis and axial spondyloarthritis diagnosis at primary care centers in Portugal – SIARA STUDY

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ABSTRACT

Objectives: Early diagnosis and treatment of rheumatoid arthritis (RA) and axial spondylarthritis (axSpA) can limit the impact of disease outcomes. This study evaluated the effectiveness of a referral program on the identification of patients with RA and axSpA.

Methods: This was an observational, prospective, randomized (by clusters) study conducted in Portugal to evaluate the impact of the implementation of a set of referral support actions (RSA). The study was divided in two sub-studies, the RA sub-study and the axSpA sub-study. 28 participating primary care units were randomly (by clusters) assigned to RSA or control group (with no intervention). Both RSA and control groups identified and referred patients with suspected RA or axSpA to the rheumatology unit of the reference hospital. The primary objective was to evaluate the correct diagnosis of RA or axSpA cases confirmed by the rheumatologist of the reference hospital.

Results: RA-Substudy: A total of 340 patients were recruited (144 in the RSA-exposed group; 196 in the control). RA diagnosis confirmation was 7.3% (95%CI, 2.1-12.5%) in RSA group versus 2.7% (95%CI, 0.0--5.7%) in control group. RSA effect was positive but moderate (4.6%) and not statistically significant (95% CI, 0.0%-11.8%; p=0.222, adjusted for clustering effect). Rate of confirmed arthritis of any type was 16.9% (n=14/83) in the RSA group and 6.0% (n=5/83) in the control group. This difference was statistically significant and favorable to RSA group (OR=3.2; 95% CI 1.1-9.2; p=0.028).

AxSpA-Substudy: A total of 231 patients were recruited (108 in the RSA-exposed group; 123 in the control). AxSpA diagnosis confirmation was 8.7% (95% CI, 2.1-15.4%) in RSA group versus 5.6% (95% CI, 0.0-11.73%) in control group. RSA effect was positive (3.1%) but not statistically significant (95% CI, -7.5--12.9%; p=0.568, adjusted for clustering effect).

Conclusions: This study showed a positive tendency for the RSA program, most relevantly on the diagnosis of patients with any type of arthritis in the RA substudy. It is possible that a referral program more comprehensive than the one herein tested might improve early diagnosis of RA and SpA.

Keywords: Referral program; Axial spondyloarthritis; Rheumatoid arthritis; Portugal.

INTRODUCTION

Rheumatic and musculoskeletal conditions are the second greatest cause of disability in the world[1], causing

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pain, impaired function, and diminished quality of life, imposing enormous healthcare expenditures and productivity losses.

Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are among the most common and impactful inflammatory rheumatic diseases in outpatient clinics.[2-4] In Portugal, the reported prevalence of RA is 0.7% and 1.6% for the whole group of SpA (0.3% for ankylosing spondylitis-AS)[5].

Many studies have shown that an early diagnosis of RA, allowing treatment initiation within 3 months of symptoms onset, is associated with improved clinical and radiographic outcomes[6-9]. However, the goal of early treatment in RA has so far been difficult to achieve due to a substantial delay between symptom onset and diagnosis by a rheumatologist[10-11]. This delay may occur at different levels: (1) patient delay – the time between symptom onset and first medical appointment (typically a general practitioner, GP); (2) GP delay – the time between the initial assessment by the GP and due referral to a rheumatologist; and (3) hospital delay – the time between the referral and the first rheumatologist visit[11-12]. Several studies show that the delay at these different levels vary markedly across Europe; for some countries patient delay was a key component, while in others GP referral to a rheumatologist was the most important contributor to the overall delay[10].

In Portugal, RA patient flow was analyzed in 2011 by interviewing different healthcare professionals at different organizational levels[13]. This study showed that the most important barriers conditioning access to treatment by RA Portuguese patients, were upstream of rheumatology practice and that efforts were needed at the primary care level to accelerate the referral process.

Although not formally evaluated, the situation regarding axSpA in Portugal is probably similar, with GPs acting as "gatekeepers" for specialty care. For axSpA, early diagnosis and referral are highly recommended, although the evidence that this will result in improved outcomes is still scarce[14-16]. Early diagnosis of SpA is hampered by the fact that the leading clinical symptom of AS/axSpA, back pain, is a problem that most people experience at some point in their lifetime[17-18]. AS/axSpA is difficult to identify, both by patients and primary care providers. As a consequence, the delay between symptoms onset and diagnosis has been reported to be between 5-10 years[19-20], although improving over the last years[21-23].

Overall, findings suggest that future actions to reduce diagnosis and treatment delay for both these conditions should be focused at the primary care level in order to improve referral to rheumatologists. In this study we conducted a cluster-randomized controlled trial to evaluate the impact of a set of referral support actions (RSA) performed in primary care centers, concerning the identification of individuals with possible RA and axSpA, compared with a control group not exposed to RSA.

METHODS

STUDY DESIGN AND STUDY POPULATION

This was an observational, prospective, randomized by clusters of primary care units (PCUs) study conducted in Portugal, from July-2012 until June-2015, to evaluate the impact of the implementation of a set of RSA for RA and axSpA as compared to standard of care (without RSA). The study was divided in two sub-studies, the RA sub-study and the axSpA sub-study. Figure 1 presents the study design and patients' disposition.

A total of 28 PCUs and 6 hospitals participated in this study. The participating sites were distributed across the 3 main regions (out of 5) of Portugal mainland, which account for more than 75% of the national population. Hospitals were selected by the following criteria: the highest referral population in their region; more than four PCUs covering 30.000-50.000 individuals in its referral area and at least 1 rheumatologist making outpatient consultations.

On their turn, selected PCUs served a population of 30.000-50.000 individuals, had at least 3 primary care physicians who agreed to participate in the study and were able to refer patients for rheumatology appointments to one of the hospitals included in the study.

The target study population included patients between 18 and 65 years old who had an appointment with their GP at a participating PCU during the study period. Investigators from participating PCUs were asked to recruit all patients who presented: i) peripheral joint symptoms (pain or swelling) lasting more than 4 weeks (RA sub-study) or ii) low back pain lasting at least 3 months with an onset before 45 years of age (axSpA sub-study). Patients who were already followed by a rheumatologist or had a previous diagnosis of inflammatory rheumatic disease were excluded from both sub-studies. The study protocol was approved by the Ethics Committee and Administration of the participating hospitals and by the corresponding regional

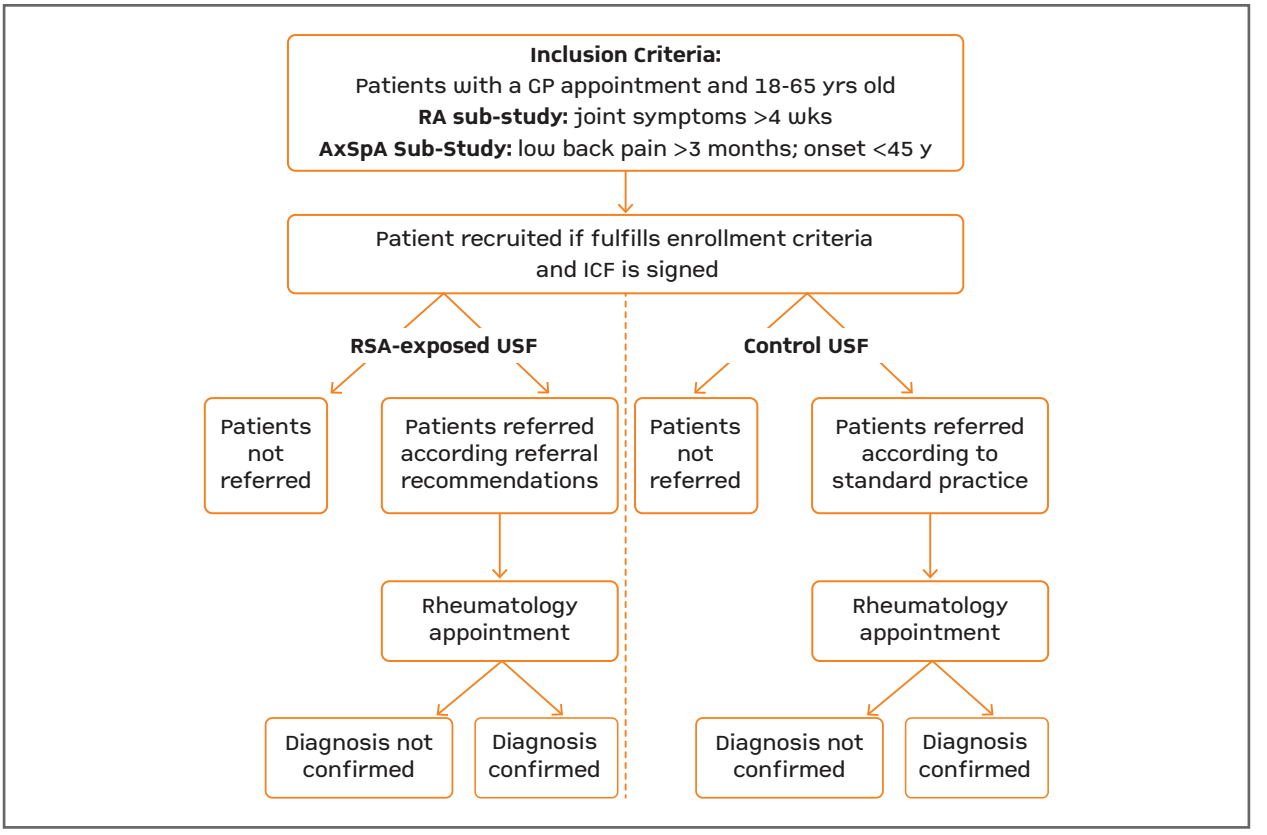

FIGURE 1. Diagram illustrating study design
GP: general practitioner; ICF: informed consent form; RA: rheumatoid arthritis; RSA: referral support actions; axSpA: axial spondyloarthritis; USF: family health unit; wks: weeks; y, yrs: years

health administrations responsible for the PCUs. Approval from the Portuguese Data Protection Authority (CNPD) was also obtained. All patients gave written informed consent. Each PCU had at least 1 year of recruitment and a maximum period of 9 months of follow-up per patient referred.

The participating PCUs from each referral hospital were randomly assigned (within clusters) to RSA or control group (with no intervention). Both RSA and control PCUs were asked to identify and refer patients, in their general population, with suspected inflammatory arthritis to the rheumatology unit of the reference hospital.

The final referral decision was left to the GP. If referral occurred, patients were followed-up until they had the first rheumatology appointment and a final diagnosis, for a maximum period of 9 months after referral. If a referred patient did not have a first rheumatology appointment or a final diagnosis after the maximum period of 9 months of follow-up, he was considered as having a non-confirmed diagnosis.

The primary endpoint of this study was the comparative (RSA-exposed group versus the control group) proportion of patients referred by the GP with a suspected RA (RA sub-study) or suspected axSpA (axSpA sub-study), who had their diagnosis confirmed by a rheumatologist. Patients included in the study from the 4th month through the end of recruitment at each PCU were considered for this analysis.

REFERRAL SUPPORT ACTIONS

A set of RSA was put in place for the RSA PCUs. All actions were previously validated by the Scientific Committee of the study, composed by five senior rheumatologists and one senior primary care physician:

1. Disease awareness campaign for RA and axial--SpA: Posters and leaflets increasing awareness about joint symptoms (RA sub-study) and inflammatory back pain (axSpA sub-study) were displayed in the PCUs surrounding areas and waiting rooms.

2. Referral criteria: Referral criteria were provided

to RSA PCUs. In the RA sub-study, recruited patients should have at least one of the following criteria to be referred: at least one swollen joint; metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints involvement as assessed by the squeeze test (tenderness on lateral compression of MCP or MTP joints); erythrocyte sedimentation rate (ESR) greater than 20mm/ /1st h; C-reactive protein (CRP) greater than 0.6 mg/dL.

In the axSpA sub-study, recruited patients had to have at least one of the following criteria to be referred[14,24]: inflammatory back pain (defined as morning stiffness greater than 30 minutes, pain at night or in the early morning and improvement with exercise); positive testing for HLA-B27 plus rachialgia of unknown cause; sacroiliitis detected by an imaging method.

3. Educational sessions for GPs: Two educational sessions of about 30 minutes each (one focusing on RA, another on axSpA) were performed by a rheumatologist from the corresponding referral hospital at each participating PCU. During these sessions the following topics were discussed: disease definition, main symptoms, how to identify swollen and tender joints/inflammatory back pain, referral criteria and disease management. After 3 months of study initiation, at each PCU, two additional educational sessions (one for RA and one for axSpA) were again performed by a rheumatologist to discuss practical cases of confirmed and non-confirmed diagnosis of referred patients.

4. Feedback from the Rheumatologist: a notification was sent by the rheumatologist back to the GP describing, for each patient whether the appropriate referral criteria were present and if the suspected diagnosis was confirmed or not. The rheumatologist was responsible for the diagnosis confirmation, according to the standard of care in each hospital and with national guidelines. For the RA sub-study, the rheumatologist also provided feedback if any other type of arthritis was found.

CONTROL GROUP

GPs from PCUs assigned to the control group were not exposed neither informed about any component of the RSA. The decision to refer the patient was made according to the standard of care. No educational sessions, referral recommendations, patient's disease awareness campaign or feedback from the rheumatologist was implemented at these PCUs.

DATA VARIABLES

For both sub-studies data collected included: demographic characteristics; date of symptoms onset; date of the first-ever appointment to the GP due to joint symptoms/low back pain, independently of the study start date; date of referral by the GP to the rheumatologist; date of rheumatology appointment; diagnosis by the rheumatologist; type of healthcare professionals consulted by the patients before GP appointment due to joint symptoms/low back pain. Referral criteria assessment by GPs and rheumatologists were also registered for the RSA-exposed PCUs.

SAMPLE SIZE CALCULATIONS

Sample size calculations were performed based on the expected difference in the proportion of patients referred to rheumatologists who would have their diagnosis confirmed between RSA-exposed and control group. For RA sub-study we estimated that 50% (expert opinion) of the patients referred by non-RSA-exposed units would have their diagnosis confirmed versus 80% using the referral matrix (a conservative approach when comparing with literature that suggests a value of 90%[25]). For axSpA study, we estimated that 14% of the patients referred by non-RSA-exposed units would have their diagnosis confirmed, versus 42% using the referral matrix[17,18] .

Since a cluster randomization was used, the sample size was adjusted by the design effect (DE), calculated as follows: DE=1+(nc-1)*ICC (where nc is the mean number of individuals in the cluster and ICC the theoretical intra-cluster correlation coefficient with a theoretical value of 0.05[26]). The cluster size was also calculated considering: (1) the estimated number of patients aged between 25-64 years seen by 3 GPs in one year – 1938 patients (based on regional health authorities reports); (2) the estimated percentage of patients with joint symptoms (10%)[27] (RA sub-study) and with low back pain (8%)27 (axSpA sub-study); (3) the estimated percentage of patients with joint symptoms for more than 4 weeks (17% – expert opinion) (RA sub-study) and with inflammatory back pain (14% – expert opinion) (axSpA sub-study); and (4) percentage of patients signing the Informed Consent Form – 90% (assumption). It was further assumed that 50% of the recruited patients would not be included for the primary endpoint analysis since this analysis only included referred patients between months 4-12 of the RSA program.

Assuming all the previous considerations, for an alpha of 0.05 and a power of 80% an estimated sample size of 422 patients (211 per arm) for RA sub-study and 350 patients (175 per arm) for axSpA sub-study was calculated.

STATISTICAL ANALYSIS

Statistical analysis was performed at the individual level considering the patient as the statistical unit. Analyses were based on the intention-to-treat principle (patients were analyzed according to the cluster that their PCU was allocated to). All statistical tests were two-tailed considering a significance level of 0.05. Statistical analysis was performed using IBM SPSS Statistics 19. Patients' demographics and the other variables were summarized for both RSA-exposed and control group using descriptive statistics namely absolute and relative frequencies for qualitative data and counts (n), mean, standard deviation, median, interquartile range, minimum and maximum for quantitative variables. For comparisons between groups the following tests were used: chi-square test for categorical data, t-test for continuous variables or Mann-Whiney test if normality was rejected.

The proportion of patients with confirmed diagnosis was calculated as the total number of patients with confirmed RA, arthritis or axSpA by the rheumatologist, divided by the total number of patients referred by the PCUs physicians with the corresponding suspicion, and presented in relative frequencies (%) and 95% confidence interval (CI).

The difference in proportions between groups was computed together with a corresponding 95% CI. This proportion was compared between RSA and control group using the chi-square test after adjustment for clustering effect. The chi-square test statistic was divided by the DE calculated as described above. Odds ratios (OR) and corresponding 95% CI were also calculated.

RESULTS

STUDY POPULATION

A total of 340 patients were recruited to the RA sub-study and 231 patients to the axSpA sub-study, in a total of 28 participating PCUs [14 exposed to the RSA program and 14 non-exposed (control group)]. The recruitment was stopped by sponsor's decision after achieving 80.5% and 66% of the sample size defined initially for the RA and the axSpA sub-study, respectively, due to low recruitment rate.

For the RA sub-study a total of 144 (42.4%) patients belonged to the RSA-exposed PCUs and 196 (57.6%) to the control group. For the axSpA sub-study 108 (46.8%) patients belonged to the RSA-exposed PCUs and 123 (53.2%) to the control group.

The characteristics of patients included in both sub-studies are described in Table I. In general, patients of

TABLE I. PATIENTS' CHARACTERISTICS, DURATION OF SYMPTOMS AND PREVIOUS VISITS TO OTHER HEALTHCARE PROFESSIONALS (HCP)

	RA sub-study			axSpA sub-study		
	RSA group (n=144)	Control (n=196)	P value	RSA group (n=108)	Control (n=123)	P value
Age (years), mean (SD)	49.8 (9.4)	47.0 (11.3)	0.059[b]	43.8 (9.7)	40.3 (10.3)	0.002[b]
Gender (female), n (%)	133 (92.4%)	163 (83.2%)	0.013[b]	87 (80.6%)	83 (67.5%)	0.024[b]
Duration of symptoms[a], (years), mean (SD)	5.38 (6.35)	4.7 (6.1)	0.379[c]	10.5 (10.3)	8.5 (8.3)	0.255[c]
	n=143	**n= 193**		**n =107**	**n = 118**	
Previous visits other HCP, n (%)						
no	99 (68.8%)	140 (71.8%)		67 (62.0%)	73 (59.3%)	0.677
yes	45 (31.3%)	55 (28.2%)	0.543	41 (38.0%)	50 (40.7%)	
Professionals, n(%)[d]						
Physiotherapist	27 (60.0%)	32 (59.3%)	0.940	20 (48.8%)	33 (67.3%)	0.075
Orthopedist	19 (42.2%)	29 (53.7%)	0.784	19 (46.3%)	27 (55.1%)	0.408
Others	9 (6.3%)	18 (9.2%)		18 (43.9%)	21 (42.0%)	

HCP: healthcare professional; RA: rheumatoid arthritis; RSA: referral support actions; axSpA: axial spondyloarthritis
a: time between first symptoms (pain/swollen joints) and study inclusion visit, calculated based on difference between these dates plus the addition of 1 year; b: chi-square unadjusted test; c: Mann-Whitney test; d: percentages calculated within patients with previous visits to other health professionals

the RSA and the control group were similar regarding the demographic characteristics and the duration of symptoms, in both sub-studies, even though, some statistically significant differences were found. For both groups, in both sub-studies, the majority of patients included were female. The axSpA sub-study showed that the median age of RSA patients was 5 years higher than the control group. On average, in the RA sub-study, patients had symptoms for 5.3 years in the RSA group and 4.7 years in the control group (p=0.379). AxSpA sub-study patients had, on average, symptoms for a longer time (RSA: 10.5 years; control: 8.5 years; p=0.255).

About one-third of the patients included in both sub-studies had had previous visits to other professionals (physiotherapist, orthopedist or others) due to the same symptoms that led the patient to a GP appointment. This percentage was similar between study groups in both sub-studies.

PROPORTION OF REFERRALS AND CONFIRMED DIAGNOSIS

Figures 2 and 3 describe patient's distribution by study group, referral and diagnosis outcome for RA and axSpA sub-studies, respectively.

- **RA sub-study**

In the RA sub-study the proportion of patients referred by the GP to a rheumatologist, was higher in the RSA group (66.7%) than in the control group (56.1%). This difference was statistically significant (p=0.049). On average, 7.3% (95%CI 2.1-12.5%) of the suspected diagnosis of RA were confirmed in RSA group versus 2.7% (95%CI 0.0-5.7%) in the control group. RSA effect was positive but moderate (4.6%) and not statistically significant (95%CI 0.0-11.8%; p=0.222) (Figure 2). Assuming the best case scenario (i.e., excluding the missing diagnosis from the sample), on average, 8.9% (95%CI 4.4-17.2%) of the suspected diagnosis of RA were confirmed in RSA group versus 3.8% (95%CI 1.0-10.7%) in the control group. RSA effect was slightly higher (5.0%) but still not statistically significant (95%CI -3.2-13.7.0%; p=0.301). Still for this scenario (i.e., excluding the missing diagnosis from the sample) the proportion of confirmed arthritis of any type by the rheumatologist, among the referred patients, was also assessed showing 17.7% (n=14/79) in the RSA group and 6.5% (n=5/77) in the control group. This difference was statistically significant (p=0.032).

In order to evaluate the global effectiveness of the RSA program, the proportion of patients with con-

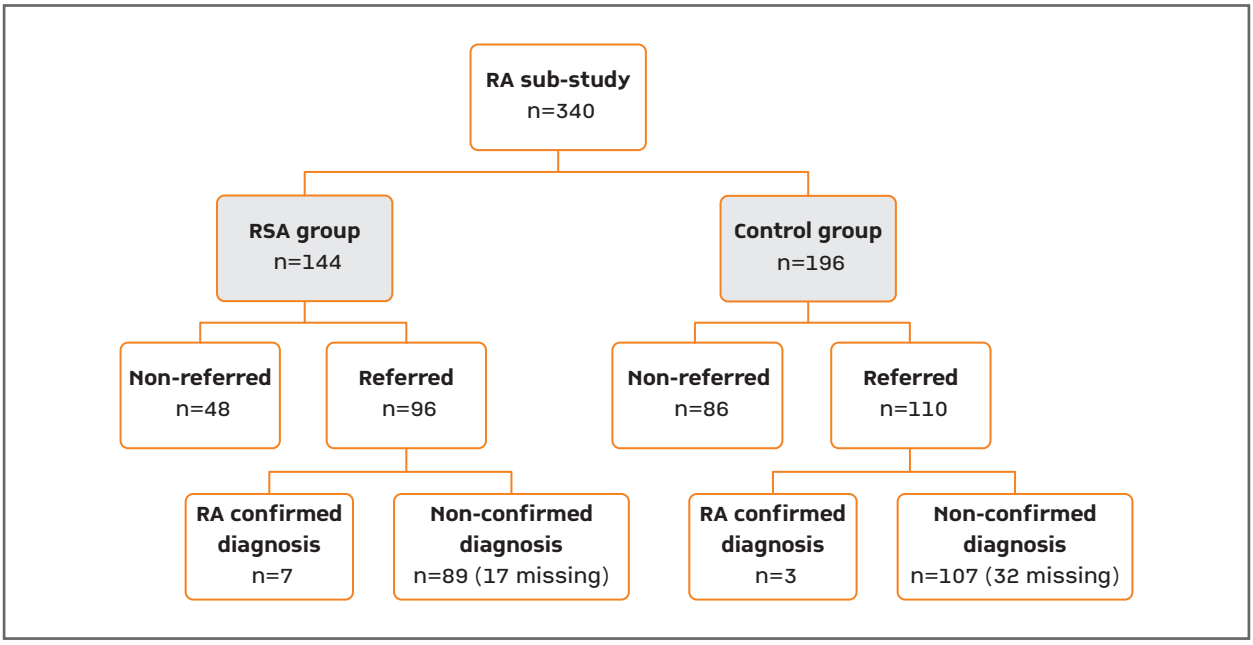

FIGURE 2. Patients' disposition in RA sub-study for the whole period of the RSA program, since the beginning until the end of study ("missing" refer to patients who, although referred by the GP, did not have a rheumatology appointment during the follow-up period of 9 months)
RA; rheumatoid arthritis; GP: general practitioner; RSA: referral support actions

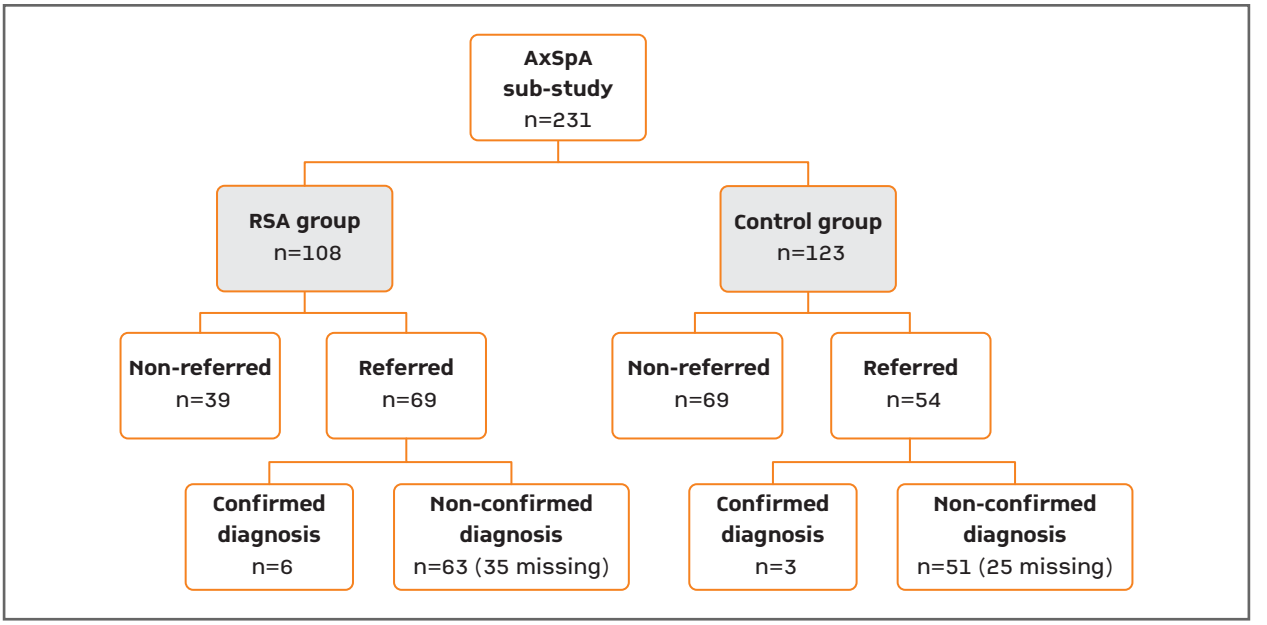

FIGURE 3. Patients' disposition in axSpA sub-study for the whole period of the RSA program, since the beginning until the end of study. "Missing" refer to patients who, although referred by the GP, did not have a rheumatology appointment during the follow-up period of 9 months.
axSpA: axial spondyloarthritis; GP: general practitioner; RSA: referral support actions

firmed diagnosis within the group of referred patients was calculated, including only referred patients enrolled from month-4 of the RSA program until the end of the program at each PCU. At month-4, all educational sessions had already taken place (at day 1 and month 3) and the RSA program training was completed. Under these conditions a value of 8.6% (95%CI 1.4-15.8%) in RSA-exposed group was obtained versus 2.6% (95%CI, 0.0-6.2%) in the control group. The RSA effect for this period was positive (6.0%) and higher when compared with the whole RSA program but still not statistically significant (95%CI 0.0-16.2%; *p*=0.184, adjusted for clustering effect).

A considerable proportion of patients referred to the rheumatologist didn't have a first appointment within the maximum period of 9 months (16% in RSA and 29% in the control group) and were considered as non–confirmed diagnoses unless otherwise stated.

- **AxSpA sub-study**

In the axSpA sub-study the proportion of patients referred by the GP to a rheumatologist was higher in the RSA (64.5%) than in the control group (43.9%; *p*=0.002). About 8.7% (95%CI, 2.1-15.4%) of the patients referred in the RSA group had the suspected axSpA diagnosis confirmed by the rheumatologist versus 5.6% (95%CI, 0.0-11.73%) in the control group. RSA effect was positive (3.1%) but not statistically significant (95%CI, -7.5-12.9%; p=0.568) (Figu-re 3). Assuming the best case scenario (i.e., excluding the missing diagnosis from the sample), on average, 17.6% (95%CI 10.2-39.5%) of the suspected diagnosis of RA were confirmed in RSA group versus 10.3% (95%CI 3.6-26.4%) in the control group. RSA effect was higher (6.1%) but still not statistically significant (95%CI -13.7-23.7%; *p*=0.477).

The proportion of referred patients with confirmed diagnosis included from month 4 of the RSA program to its end was 8.3% (95%CI, 0.0-17.3%) in the RSA-exposed group versus 5.7% (95%CI, 0.0-13.4%) in the control group. RSA effect was positive (2.6%) but not statistically significant (95%CI, -11.4-16.7%; p=0.694).

A considerable proportion of patients referred to the rheumatologist due to suspected axSpA didn't have a first appointment within the maximum period of 9 months (51% in RSA and 46% in the control group) and were considered as non–confirmed diagnoses unless otherwise stated.

ANALYSIS OF DELAY TIMES

Analysis of the delay times from patient initial sym-

ptoms until rheumatologist diagnosis was also evaluated for both groups in both sub-studies at 3 levels: patient delay, GP delay and hospital delay (Table II).

- **RA sub-study**

In the RA sub-study, patients went to a GP appointment (patient delay) 0.17 years (median time) after symptoms onset in the RSA group and 0.08 years in the control group. For the same sub-study the median time between first GP appointment and GP referral (GP delay) was 1.75 years in the RSA group versus 2.92 years in the control group. Lastly, the time between GP referral and first appointment with rheumatologist (hospital delay) resulted in a median time of 0.17 (IQR: 0.25) years in the RSA group and 0.25 (IQR: 0.17) years in the control group. Although delay times where higher for the control group, none of these differences were statistically significant (p=0.390; p=0.153; p=0.319, respectively Table II).

- **AxSpA sub-study**

In the axSpA sub-study patients went to a GP appointment due to rachialgia 1.42 years (median time) after symptoms onset in the RSA group and 0.42 years in the control group. The median time between first GP appointment and GP referral was 3.25 years in the RSA group versus 4.92 years in the control group. The median time between GP referral and first appointment with a rheumatologist was of 0.25 (IQR: 0.25) years for both RSA and control groups. The differences between groups for these delays showed p-values of 0.013, 0.017 and 0.336, respectively.

TABLE II. DELAY TIMES FROM PATIENT INITIAL SYMPTOMS UNTIL THE RHEUMATOLOGIST DIAGNOSIS, FOR RA SUB-STUDY AND axSpA SUB-STUDY AT 3 LEVELS: PATIENT DELAY, GP DELAY AND HOSPITAL DELAY

	RA sub-study		axSpA sub-study	
	RSA group (n=144)	Control group (n=196)	RSA group (n=108)	Control group (n=123)
	Time from symptoms onset to first GP appointment due to symptoms – Patient delay			
n	140	189	105	111
Mean, years	2.19	1.82	5.69	3.43
95% CI	1.47-2.92	1.12-2.52	4.05	2.38-4.49
Median, years	0.17	0.08	1.42	0.42
95% CI	0.12-0.21	0.04-0.12	0.47-2.37	0.11-0.72
Log-rank p-value	0.390		0.013	
	Time from first GP appointment to referral to rheumatologist – GP delay[a]			
n	134	186	93	100
Mean, years	4.38	5.56	6.17	12.10
95% CI	2.77-5.99	3.61-7.51	3.99-8.35	6.75-17.44
Median, years	1.75	2.92	3.25	4.92
95%CI	1.02-2.48	1.57-4.27	2.21-4.29	3.33-6.50
Log-rank p-value	0.153		0.017	
	Time from GP referral to first rheumatologist appointment – Hospital delay[b]			
	RSA group (n=96)	Control group (n=110)	RSA group (n=69)	Control group (n=54)
n	81	79	47	38
Mean, years	0.21	0.24	0.21	0.24
95% CI	0.18-0.24	0.22-0.27	0.16-0.25	0.20-0.29
Median, years	0.17	0.25	0.25	0.25
95%CI	0.13-0.21	0.23-0.27	0.19-0.31	0.20-0.30
Log-rank p-value	0.319		0.336	

CI: Confidence Interval; GP: General Practitioner; RA: Rheumatoid Arthritis; RSA: Referral Support Actions; axSpA: axial Spondyloarthritis
a) In patients not referred until the end of the study, the time was censored at one-year after study inclusion visit (end of the follow-up period); b) Referred patients that not had a first rheumatology appointment during the duration of the study were removed from the analysis

TABLE III. AGREEMENT BETWEEN REFERRAL CRITERIA EVALUATED BY THE GP VERSUS RHEUMATOLOGIST IN RSA GROUP FOR THE RA SUB-STUDY (N=96)

		Rheumatologist assessment					
		Yes		No		Kappa P-value	Observed agreement
GP assessment							
At least one swollen joint, n (%)	Yes	11	15.9%	52	75.4%	0.002	23.1%
	No	1	1.4%	5	7.2%	0.961	
Squeeze MCP test positive, n (%)	Yes	8	12.7%	40	63.5%	0.087	36.5%
	No	0	0.0%	15	23.8%	0.091	
Squeeze MTF test positive, n (%)	Yes	5	21.7%	4	17.4%	0.430	73.9%
	No	2	8.7%	12	52.2%	0.036	
ESR> 20mm/1st h, n (%)	Yes	16	32.0%	10	20.0%	0.566	78.0%
	No	1	2.0%	23	46.0%	<0.001	
CRP> 0.6 mg/dL, n (%)	Yes	11	34.4%	6	18.8%	0.632	81.3%
	No	0	0.0%	15	46.9%	<0.001	

CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; GP: general practitioner; MCP: metacarpophalangeal; MTP: metatarsophalangeal; RA: rheumatoid arthritis; RSA: referral support actions

AGREEMENT BETWEEN REFERRAL CRITERIA ASSESSED BY GP VERSUS RHEUMATOLOGIST IN THE RSA-EXPOSED GROUPS

The agreement between the GP and rheumatologist assessments of the referral criteria is described in Table III for the group of referred patients who had a final diagnosis (whether confirmed or not) from the RSA group in the RA sub-study.

For RA the highest agreement level was seen in CRP criteria where the two specialties were in accordance in 81.3% of the cases, followed by ESR criteria (78%). Squeeze MTF test had a moderate agreement (73.9%). The criteria with the lowest level of agreement were evaluation of swollen joints and squeeze MCP test (23.1% and 36.5%, respectively). Nevertheless, it should be highlighted that a considerable number of assessments were missing when compared to the number of referred patient in RSA-exposed group (n=96), mainly regarding squeeze MTF test and CRP.

For the axSpA sub-study these assessments were not available in more than half of the patients referred in the RSA-exposed patients (n=69). For rachialgia assessment (n=38), specialists were in accordance in only 36.8% of the cases. For sacroiliitis assessments values were only obtained for 17 patients and only 3 patients had assessments of HLA-B27.

DISCUSSION

This study showed that actions for supporting referral of patients with suspected RA or axSpA from GPs to rheumatologists can have a favorable effect as demonstrated by the higher number of confirmed diagnosis among referred patients. Although differences were not statistically significant when looking at definitive diagnosis (RA or axSpA), a statistically significant difference was verified in the RA sub-study when arthritis diagnosis was considered. Additionally, a higher number of patients were referred by GPs to rheumatologist in the RSA versus control group, which can be justified by increased confidence and awareness for referring this type of patients.

Our findings are consistent with previous reported increases in referral quality in similar intervention studies[28-29]. A dissemination of referral guidelines combined with education activities can indeed improve referral quality between primary and specialist health care, which is consistent with the conclusions of a Cochrane review[30].

The SIARA study also captured real data information about patient flow with RA and axSpA in Portugal. This analysis confirms our initial assumption that, in Portugal, the GP referral to the rheumatologist is a major contributor to the overall delay until final RA/axSpA diagnosis[13], reaching median values as high as almost 5 years in the axSpA sub-study, and 3 years in the RA sub-study. Patient's access to healthcare and treatment differs significantly among Europeans countries. Raza *et al.* published a report that showed different realities among RA patients across different Euro-

pean countries concluding that to reduce the overall delay, a detailed understanding of each component is required[10]. In this report[10], delay from the initial assessment by the GP to referral to a rheumatologist was an important contributor to overall delay, with a median value of at least 8 weeks for 7 of the 10 centers analyzed. This conclusion shows that in Portugal this delay is way more serious than in other countries across Europe, showing, again, the relevance of these education programs. Other studies conducted in Portugal also raised the importance of a better characterization of patients' access to healthcare system and to treatment by rheumatologists in order to improve the standard of care in RA[13,31]. By analyzing the delay times in both sub-studies, we may conclude that patients who had low back pain with an onset age before 45 years old took more time to seek medical advice from a GP when compared with patients with joint peripheral symptoms (RA sub-study). For RA patients, when compared with other European countries, this study shows that Portugal has again values of patient delay and hospital delay higher than the majority (median values between 2-22 weeks and 1-11 weeks, respectively)[10]. Additionally, since about a quarter of the patients in both substudies did not have a first rheumatologist appointment within the 9-month period considered, hospital delay is underestimated. Nevertheless, both patient delay and hospital delay have still lower values when compared to the GP delay, which accounts as the most important contributor for the overall delay.

Analysis of the agreement between referral criteria assessed by GP versus Rheumatologist in the RSA-exposed groups showed low agreement rates in the rheumatologic examination, particularly in MCP joint assessments. This highlights the need for continuous education of GPs on rheumatologic examination or, alternatively, not to expect GPs to refer patients based on these signs. Additionally, low agreement rates were verified for the lab test, which is justifiable by the lag time between the lab test requested by the GP and the one performed by the rheumatologist combined with the fluctuating character of inflammatory diseases and possible treatment interventions by the GP.

Limitations of this study include the small sample size obtained for both sub-studies due to low recruitment rate but also the considerable number of patients where the confirmation of the rheumatologist is missing since hospitals had a larger waiting time than initially expected. These limitations resulted in very low numbers of confirmed diagnoses which didn't allow for more complex analyses (e.g: logistic regression, generalized estimating equations). Another drawback was the referral criteria used that was broad and not specific, especially for RA. Additionally, a different procedure was created at PCUs for patients' referral to the rheumatologist in both groups in both sub-studies. This procedure was created to allow a quick signalization of the patients that were participating in the study at the hospitals but that may led to patients being referred more rapidly than they would as standard of care, conducting to an underestimation of the hospital delay time described above. Using a cluster randomization also has limitations. It is possible that participants within one cluster share certain characteristics, such as the same quality of care, which may result in a substantial loss of power. Therefore we choose to adjust the cluster effect in the sample size calculation and in the data analysis[32]. Clinical research in primary care is still a challenge. GPs have a high number of patients that are attended intermittently in visits with limited time and additional organizational issues leave them with limited time for research. The fact that clinical research has historically been conducted in secondary care settings can also explain the lower motivation of GPs to clinical research[33].

In conclusion, SIARA study showed that actions supporting patient's referral with suspected RA or axSpA can have a favorable effect, especially when evaluating the impact on the referral and diagnosis of patients with arthritis in the RA sub-study. This study also showed that primary care is the most relevant contributor to the overall delay between symptom onset and the diagnosis by a rheumatologist. Thus, GPs are acting as "gatekeepers" to the rheumatologist, therefore delaying treatment initiation to patients with RA and axSpA. We believe that this sort of referral programs, especially with more intensive schemes (e.g. more frequent training/educational sessions), should be further considered by healthcare deciders in order to improve early diagnosis of RA and SpA, and hopefully health outcomes of these patients.

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CONFLICT OF INTERESTS

Conflicts of interest: Raquel Dezerto and Rui Mesquita are employees of MSD Portugal. Pedro Laires was an employee of MSD Portugal at the time the study was conducted. João Eurico Fonseca has received unrestricted research grants or acted as a speaker for Abbvie, Ache, Amgen, Biogen, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB.

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