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ORIGINAL ARTICLE

Journey of rheumatoid arthritis patients in Tunisia: From symptoms to treatment

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ABSTRACT

Objectives: This study aims to assess the different delays of rheumatoid arthritis (RA) patients' journey from disease onset to treatment initiation and to identify possible influencing factors.

Patients and methods: This cross-sectional study included a total of 100 patients (14 males, 86 females; mean age: 56.5±12.4 years; range, 26 to 82 years) who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA between January 2019 and January 2020. Demographic and clinical data and disease characteristics were collected from the patient interviews and medical files. Five different intervals were defined from symptom onset until the initiation of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

Results: The mean age at RA onset was 46.6±12.4 years. Median delays from onset of symptoms until general practitioner (GP) and rheumatologist consultations were six (range, 0.25 to 240) months and 12 (range, 0 to 242) months, respectively. Median delays from onset of symptoms to RA diagnosis and treatment with csDMARDs were 15.7 (range, 2 to 252) months and 18 (range, 2 to 270) months, respectively. The mean number of consultations was 7.3±4.2 and the median number of physicians visited before the diagnosis was three (range, 1 to 8). The RA diagnosis delay was associated with rural geographic environment (p=0.02), lack of social insurance (p=0.027), progressive symptoms onset (p=0.006), morning stiffness (p=0.023), being initially examined by a GP (p=0.02), number of consultations (p<0.001; r=0.49), and number of physicians consulted before diagnosis (p=0.001; r=0.33) respectively. Based on the patients' self-perception, the main causes of this long delay were lack of financial means (33%), wait times until exploration results (31%), wait times until the first GP or rheumatologist visit (26%), and geographical difficulty in accessing healthcare services (18%).

Conclusion: Our study results suggest that patients with RA experience a significant delay until diagnosis and initiation of treatment. Healthcare providers should urgently consider factors related to diagnosis delay to shorten RA patients' journey.

Keywords: Diagnosis delay; disease management; rheumatoid arthritis; therapeutics.

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatism affecting 1% of the worldwide population.[1] It may lead to loss of functional capacity, significant morbidity and mortality, and increased rate of absenteeism.[2-4]

During the past decade, early intensive intervention with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and "Treat-to-Target" strategies have been emphasized to reduce structural damage and functional impairment.[5-8] First mentioned

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in 1992 by Dawes and Symmons,[9] the so-called "therapeutic window of opportunity" was not uniform until 2004, where Nell et al.[10] defined it as the first three months of RA onset and during which the early initiation of proper and opportune therapies can favorably affect disease activity, functional capacity, and radiographic progression.[11]

Previous studies have shown a wide variation in lag times to RA diagnosis, ranging from one month to 10 years.[10-13] However, to the best of our knowledge, there are few data in the literature concerning RA patient's journey in the North Africa.[12] In this study, we aimed to establish different intervals occurring between the onset of symptoms and csDMARDs initiation and examine different parameters associated with RA diagnosis delay in a sample of RA patients in a hospital-based population.

PATIENTS AND METHODS

This single-center, cross-sectional, hospital-based study was conducted at Mongi Slim University Hospital Center, Rheumatology Daycare Clinic between January 2019 and January 2020. A total of 100 patients (14 males, 86 females; mean age: 56.5±12.4 years; range, 26 to 82 years) who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA were included. Patients who refused to participate or had incomplete data in their medical files were excluded. The study flow chart is shown in Figure 1. A written informed consent was obtained from each patient. The study protocol was approved by Mongi Slim Ethics Committee (37/21). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

The data were collected by the patient interviews and medical files. The following variables were documented for each patient: demographic characteristics (age, sex, marital status, level of education, professional status, living environment and social security affiliation), age at onset of illness, mode of onset (sudden or progressive), year of RA diagnosis, disease duration, and first RA symptoms (type of joint involvement, location of joint involvement, presence of fatigue, presence of morning stiffness or nocturnal awakening).

At baseline (RA diagnosis), the following data were assessed: immunological status (rheumatoid factor [RF], anti-cyclic citrullinated peptide [ACPA]), extra-articular manifestations, disease activity, functional disability, and structural damage.

Disease activity was evaluated using the global pain intensity Visual Analog Scale (VASp), Patient Global Assessment (PGA), tender joint counts (TJCs), swollen joint counts (SJCs), erythrocyte sedimentation rate (ESR), and Disease Activity Score 28 (DAS28)-ESR. Functional disability was assessed using the Health Assessment Questionnaire (HAQ). The RA treatment with csDMARDs was noted.

Rheumatoid arthritis patient's journey

By patient interviewing, we determined for each patient the following data: healthcare service first attended (public/private), first physician consulted (general practitioner [GP], rheumatologist specialist, non-rheumatologist specialist), number of consultations before RA diagnosis, number of physicians visited before RA diagnosis, and different delays.

Accordingly, five intervals were recorded:

- Interval 1: Time between onset of symptoms and the first GP consultation
- Interval 2: Time between onset of symptoms and the first rheumatologist consultation
- Interval 3: Time between onset of symptoms and RA diagnosis
- Interval 4: Time between RA diagnosis and initiation of the first csDMARD
- Interval 5: Time between onset of symptoms and initiation of the first csDMARD

The different intervals were compared to patients' medical files to confirm the different delays.

Based on the 2016 update of the EULAR recommendations for the RA management[13] and on the 2018 update of French Society for Rheumatology (SFR) recommendations about the management of patients with RA,[14] we defined two variables:

Table 1. Demographic and disease characteristics of RA patients

Features	%	Mean±SD
Age (year)		56.5±12.4
Age at RA onset (year)		46.6±1
Sex		
Female	86	
Male	14	
Marital status		
Married	75	
Single	18	
Widow	5	
Divorced	2	
Level of education		
Illiterate	35	
Primary	35	
Secondary	16	
University	14	
Professional status		
Active	48	
Unemployed	6	
Retired	6	
Housewives	38	
Student	2	
Living environment		
Urban	76	
Rural	24	
Social security affiliation		
Yes	73	
No	27	
Year of RA diagnosis		
1990-1999	3	
2000-2009	46	
≥2010	51	

RA: Rheumatoid arthritis; SD: Standard deviation.

- Delayed diagnosis: if time between onset of symptoms and RA diagnosis (interval 3) was longer than six weeks.
- Delayed treatment initiation: if time between onset of symptoms and initiation of the first csDMARD (interval 5) was longer than three months (12 weeks).

Evaluation of the self-perception of RA patient's journey

The self-perception of RA patient's journey was assessed by asking these following questions:

Question 1 (Q1): "In your opinion, did the lag time separating the onset of symptoms and RA diagnosis seem to be long?"

If the answer was "Yes'', a second question, referring to the possible causes of this delay was asked:

Question 2 (Q2): "In your opinion, what was the cause of the delay between the onset of your symptoms and RA diagnosis? (Lack of financial means, wait time until the first GP or rheumatologist visit, wait time until exploration results, geographical difficulty in accessing healthcare services, other causes; i.e., to be specified).

Statistical analysis

Statistical analysis was performed using the SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The comparison of two independent series was made using the Mann-Whitney U test. The independent series were compared using the Pearson chi-square test. If the assumptions of the chi-square test were unmet, the Fisher exact test was used. A p value of <0.05 was considered statistically significant.

Table 2. Rheumatoid arthritis intervals

		Months	
Interval		Median	Min-Max
1	Time between onset of symptoms and first GP consultation	6	0.25-240
2	Time between onset of symptoms and rheumatologist consultation	12	0-242
3	Time between onset of symptoms and RA diagnosis	15.7	2-252
4	Time between RA diagnosis and initiation of first csDMARDs	0.5	0-18
5	Time between onset of symptoms and initiation of first csDMARDs	18	2-270

GP: General practitioner; RA: Rheumatoid arthritis; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs.

Table 3. Study of the association between RA diagnosis delay (interval 3) and demographic and disease characteristics in univariate analysis

Features	Lag time 3 in months		
	Median	IQR	*p*
Demographic parameters			
Sex			0.15
Female	7.5	2-121	
Male	17.5	2-252	
Marital status			0.13
Married	14	2-252	
Non married (single, widow, divorced)	25	2-24	
Level of education			0.12
Illiterate	24	2-247	
Primary	18	2-109	
Secondary	17.5	4-252	
University	8.5	2-12	
Professional status			0.6
Active	16.5	2-193	
Inactive (unemployed, retired, housewives)	15.7	2-252	
Living environment			**0.02**
Urban	14.5	2-252	
Rural	31	2-194	
Social security affiliation			**0.027**
Yes	14	2-252	
No	24.5	2-247	
Year of RA diagnosis			0.79
<2010	17.5	2-252	
≥2010	14.5	2-193	
Disease characteristics at RA onset			
Symptoms onset			**<0.001**
Progressive	18.5	2.2-252	
Brutal	6	2-73	
First RA symptoms			
Type of joint involvement			0.5
Arthralgia	14	2-252	
Arthritis + Arthralgia	19	2-194	
Location of joint involvement			0.42
Upper extremity	13.5	2.5-193	
Lower extremity	12	2.25-99	
Both	20	2-252	
Fatigue			0.61
Yes	16.25	2-252	
No	15.5	2-247	
Morning stiffness			0.02
Yes	18.5	2-252	
No	10.5	2-54	
Multiple nocturnal awakening			0.85
Yes	15	2-252	
No	15	2-252	
Positive RF			0.6
Yes	17	2-247	
No	15	2-252	
Positive ACPA			0.15
Yes	14	2-193	
No	24.5	2-109	

IQR: Inter quartile range; RA: Rheumatoid arthritis; RF: Rheumatoid factor; ACPA: Anti-cyclic citrullinated peptide.

Table 4. Study of the association between RA diagnosis delay (interval 3) and disease journey characteristics in univariate analysis

Features	Interval 3 in months			
	Median	IQR	*p*	r
Health care service first attended			0.08	-
Public	19	2-247		
Private	13	2-252		
First physician consulted			**0.02**	-
General practitioner	21	2-252		
Specialist	11	2-252		
Age at RA onset (years)	-	-	0.92	0.009
Number of consultations to final diagnosis	-	-	<0.001	0.49
Number of doctors visited to final diagnosis	-	-	0.001	0.33

RA: Rheumatoid arthritis; IQR: Inter quartile range; r: Spearman correlation test.

RESULTS

Of a total of 100 patients included in the study, the mean disease duration was 144±89.4 months. Baseline demographic and disease characteristics are shown in Table 1.

At RA onset, symptoms started progressively in 82% patients. Both upper and lower extremities were involved in 61% patients. In total, 58% patients experienced fatigue. Morning stiffness and multiple nocturnal awakening were reported in 76% and 82% of the patients, respectively.

At the time of diagnosis, RA was immunopositive in 70% patients. Extra-articular manifestations were found in 26% patients: ocular dryness (96.2%), subcutaneous rheumatoid nodules (3.8%), and diffuse parenchymal lung disease (3.8%). The median VASP and PGA were 80 (range, 20 to 100) and 80 (range, 30 to 100), respectively. The median TJCs and SJCs were 10 (range, 0 to 28) and 5 (range, 0 to 17), respectively. The median ESR was 43 (range, 6 to 133) mm/h. The median DAS28-ESR was 5.2 (range, 2 to 7.5). More than half of patients (57%) had a high disease activity (DAS28 >5.1). The median HAQ was 2 (range, 0 to 3). Erosions were present in 36% of the patients. Five (5%) patients had coxitis and one (1%) patient had an atlantoaxial subluxation. A total of 58% of the patients were on corticosteroid therapy with a mean dose of 9.7±3.7 mg/day. All patients were on csDMARDs. Methotrexate was the most prescribed csDMARDs in 86% of the patients. Different RA lag times are listed in Table 2.

According to 2016 update of the EULAR and to 2018 update of the SFR recommendations for the RA management, all patients had a delayed diagnosis and, in 95% of them, more than 12 weeks elapsed to initiate csDMARDs.

The healthcare service first attended was public health system (71%). Most of the patients (67%) were first seen by a GP. Only 19% of the patients were initially seen by a rheumatologist. In total, 7% and 5% of the patients first sought the opinion of orthopedic surgeon and internist, respectively. The mean number of consultations before diagnosis was 7.3±4.2. Patients consulted a median of three (range, 1 to 8) physicians before their final diagnosis.

A significant association was found between RA diagnosis delay (lag time 3) and the following parameters: rural living environment (p=0.02), absence of social security affiliation (p=0.027), progressive symptoms onset (p=0.006), presence of morning stiffness at the disease onset (p=0.023), and being initially seen by a GP (p=0.02). There were positive correlations between RA diagnosis delay and the number of consultations (p<0.001; r=0.49) and the number of physicians consulted (p=0.001; r=0.33) respectively. The correlation between RA diagnosis delay and demographic and disease characteristics is shown in Table 3. The correlation between RA diagnosis delay and disease journey characteristics is shown in Table 4.

Based on the patients' self-perception, 84% thought that the delay between the onset of

symptoms and RA diagnosis was long. The main causes were a lack of financial means (33%), a long wait time until exploration results (31%), a long wait time until the first GP or rheumatologist visit (26%), and geographical difficulty in accessing healthcare services (18%).

DISCUSSION

Over the last two decades, the management of patients with RA has considerably changed. The "Treat-to-target" strategies and initiating csDMARDs as soon as possible have become primary objectives for every rheumatologist.[15,16] Nevertheless, several patients are diagnosed at advanced-stage disease. In this study, we evaluated RA patients' journey to better identify the challenges of early RA diagnosis in our country.

In the current study, the majority of the patients (71%) initially sought care in the public health services, consistent with previous reports where the prevalence of public healthcare system was 81.2% in Venezuela[17] and 69.2% in Belgium.[18] Furthermore, the patients in our study required at least 7.3±4.2 visits and asked an average of three physicians before their final diagnosis. These findings are also consistent with previous studies where the average number of consultations before RA diagnosis varies between 1 and 16.[17-20]

Given the relatively high prevalence of RA, most patients are likely to be first seen by a GP.[21] As expected, the GP was the first contacted physician (67%), followed by the rheumatologist (19%) and the orthopedic surgeon (7%). These results are consistent with those reported by Feldman et al.[22] and by Rodríguez-Polanco et al.,[17] showing a prevalence of GP consultation of 60% and 63%, respectively.[4] Nevertheless, in a recent study published in Saudi Arabia by Hussain et al.,[23] the orthopedic surgeon was the first consulted physician (67%), followed by the GP (23.6%). Interestingly, in this study, very few patients (3.2%) initially sought a consultation with a rheumatologist.

In recent years, several studies from worldwide established the distinct delays separating disease first symptoms from RA diagnosis and treatment initiation. We found that patients spent a median of six months to the first consult a GP (interval 1) and waited up to 12 months to access to rheumatologist's consultation (interval 2). The wait time until the first rheumatologist encounter (interval 2) was similar to those found in Spain (10.2±12.7 months)[24] and Canada (10.9 months).[25] However, shorter delays in rheumatologist consultation were reported in other countries as follows: three (range, 1.2 to 7) months in Argentina,[26] 3.26 (range, 1.8 to 7.9) months in Australia,[27] and 3.4 (range, 1.4 to 71) months in the Netherlands.[28] This delay could be partly due to the large influx of patients to our center. The rheumatology department of the Mongi Slim University Hospital Center is one of the four main rheumatology centers located in the Northern Tunisia. Indeed, our center recruits patients from all socioeconomic backgrounds without geographical selection criteria through outpatient or emergency departments. The service has a capacity of 16 beds, with an average annual number of hospitalizations of 244 patients and an average number of consultations of 10,500 patients per year. Nine percent of all Tunisian RA patients (about 1,000 patients) are followed in our department, considering a total number of RA patients of 11,000 in Tunisia.

In the 2016 EULAR and 2018 SFR updates for the RA management, early diagnosis (<6 weeks after the onset of symptoms) and early csDMARDs therapy (<3 months after the onset of symptoms) are recommended.[13,14] According to these recommendations, all our patients had a delayed RA diagnosis and, in 95% of them, more than three months elapsed to initiate treatment. In two recent studies published in Spain[24] and Argentina,[29] diagnosis delays were similar to our findings with mean lag times of 11.3±13.2 months and 14.2±24 months, respectively. Compared to the published data in Arabic countries, it should be noted that some countries display even longer wait times until RA diagnosis such as Egypt (24.1 months)[12] and the United Arab Emirates (30.2±16 months).[23] Nevertheless, shorter delays between the first symptoms and final diagnosis were found in Europe: 3.17 months in Slovenia,[30] 5.25 months in Belgium,[18] and four months in Denmark.[31]

In our study, the demographic covariates associated with a longer RA diagnosis delay were

the rural living environment and the absence of social security affiliation. Similarly, Hussain et al.[23] found that rural geographic region was one of the major factors for delayed diagnosis. Consistent with the data in the literature, neither age at the time of RA onset nor sex was associated with increased RA diagnosis delays in our patients.[17-19,21,23]

On the other hand, we observed that longer RA diagnosis delays were significantly associated with progressive disease onset and prolonged morning stiffness. In 2010, in a study carried out in the Netherlands, van der Linden et al.[28] found that time delay to rheumatology consultation was considerably important in patients with progressive disease onset. In contrast, in a Korean study[19] and a Belgian study,[18] having progressive symptoms installation or morning stiffness (>1 h) were significantly related to shorter rheumatologist delays.

The impact of healthcare system on delay to diagnosis merits consideration. In our study, no correlation between RA patient's journey and the first health service attended was found. Although, as expected, being first examined by a GP was associated with longer diagnosis delay. Indeed, as demonstrated in a previous research, the complexity of different initial symptoms attributed to RA may mislead GP diagnosis.[20] Referral to rheumatologist consultation is, therefore, sometimes postponed.[23]

In a study, Rodríguez-Polanco et al.[17] reported that diagnosis delay was longer in patients who initially consult public health center or sought a GP or an orthopedic surgeon. These delays were mainly due to the difficulties encountered by the GP to recognize early RA symptoms.[17,20,23] In a recent Belgian study, De Cock et al.[20] compared the degree of agreement of RA diagnosis between the GP and the rheumatologist and found that only half of GPs could accurately identify RA.

Furthermore, in our study, RA diagnosis delay was significantly correlated with the number of consultations and number of physicians visited. Similar to our study, Hussain et al.[23] found that diagnosis delay in Saudi Arabia was longer in patients with a higher number of physicians visited.

The assessment of self-perception is a new concept during chronic rheumatic diseases. However, few studies have investigated the self-perception of RA patient's journey. In the Polish study of Raciborski et al.,[32] 36% of patients with rheumatic diseases spent an average of four months or longer to first consult a rheumatologist. Limited geographic access to physicians and the belief that symptoms would resolve spontaneously were the main causes of this wait time. Nevertheless, Belkhou et al.[33] found that 71% of rheumatic patients in Morocco were latecomers to the rheumatologist consultation. According to the authors, GP delay to refer the patient to a rheumatologist and poverty were the major determinants of this delay.

Consistent with previous studies, 84% of our patients thought that their diagnosis delay was long. The main causes of this delay were the lack of financial means, wait time until exploration results or until physician appointment, and limited geographic access to healthcare centers.

The present study has some limitations. First, the small size of the sample may have affected the statistical analysis results. Second, it is a single-center study and, therefore, the results cannot be generalized to the general population. Third, as in observational studies, patients may have inaccurately forgotten some exact dates of their journeys, which could have generated a recall bias and influenced our outcomes. Nonetheless, we reviewed the medical files of the patients to minimize this bias.

In conclusion, our study results suggest that delays from RA symptom onset to treatment initiation are still too long, exceeding the established benchmarks. Most of the wait times occur before the rheumatologist consultation. Furthermore, some demographic features appear to be the trigger for diagnosis delay such as rural environment, lack of security insurance, and GP delay. Based on these findings, targeted interventions are urgently required to shorten these delays and to better improve structural outcomes in early RA.

Declaration of conflicting interests

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