

# The lag time from symptoms onset of rheumatoid arthritis to initiation of Methotrexate: Data from the Moroccan register of biotherapies

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## Abstract

**Objective:** The purpose of this study is to determine the time between the onset of rheumatoid arthritis (RA) symptoms and the introduction of methotrexate, as well as the associated factors.

**Methods:** A multicenter cross-sectional study that included data from the Moroccan register of biologic patients with rheumatoid arthritis. Sociodemographic, economic patient data and disease data were collected. A logistic regression was performed to determine the factors that are associated with the change in the delay between the onset of symptoms and the initiation of cDMARD.

**Results:** A total of 225 RA patients were included. The mean age was  $51 \pm 11$  years, with a female predominance of 88% (n=197). The diagnosis lag time was 12 months (12-48). Seventy-three percent of the cases were housewives. Seventy-nine percent of patients received Methotrexate as the first CDMARDS. Salazopyrine was the second prescribed CDMARDS with 7%. Hydroxychloroquine was the third prescribed cDMARDs which 2.2%. The median lag time from symptoms onset to initiation of Methotrexate was 24 months (0.16-71). The factors, associated with the change in the delay between the onset of symptoms and the introduction of methotrexate in univariate analysis, were delay in diagnosis and corticosteroids Taking ( $p < 0.05$ ), only the delay of diagnosis in multivariate analysis persists  $p = 0.0001$ .

**Conclusions:** Our study suggests that there is a significant delay between diagnosis and the introduction of methotrexate as a first line cDMARDs. In multivariate analysis only the time to diagnosis was associated with the time to start methotrexate.

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that affects large and small joints causing bone erosions, joint deformities, and comorbidities [1-3].

Early initiation of the Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARDs) within 2 months from the onset of symptoms provides better control over the disease activity and prevents irreversible cartilage damage in the long term [1,4-6]. Conversely, the increase of the lag time between the onset of symptoms and the introduction of cDMARDs is associated with a risk of joint destruction and permanent disability [1].

Guidelines recommend the early referral of the general practitioner to the rheumatologist in order to confirm the diagnosis of RA and the early initiation of treatment [7,8], and also to ensure the monitoring and evaluation of patients and the response to treatment [9].

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The literature review shows that there are several factors associated with the initiation delay of cDMARDs [5]. In the Moroccan context, few data are available about the factors that influence the instauration delay of cDMARDs.

The aim of our study was to assess the lag time from symptoms onset to initiation of conventional DMARDs and to explore the factors associated with lag time in a sample of Moroccan patients.

## Methods

### Study design

The details of the data collected have been published previously [10]. We included 225 patients followed for rheumatoid arthritis treated by bDMARDs in different university hospitals in Morocco and meeting the criteria ACR-EULAR 2010.

Demographic data related to the patients included age, sex, educational level, type of health assurance and date of symptom onset reported by the patient or from patient chart.

The clinical and biological data collected were sedimentation rate (ESR), protein-C-reactive (CRP), the Disease Activity Score (DAS28-ESR), rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) status, erosion presence.

We calculated the lag time from the symptom's onset of RA to the initiation of cDMARDs.

The factors considered in analysis included: age, sex, anti-CCP and RF positivity, serum ESR and CRP, DAS28, taking analgesics and taking corticosteroid, erosion presence and diagnosis delay.

### Statistical analysis

Descriptive statistics were presented as mean and standard deviation (SD) or as median and inter quartile range (IQR) according to the distribution, and qualitative variables were presented as a frequency and percentage.

We chose as to cut off the lag time initiation of Methotrexate 24 months (Methotrexate was chosen because it is the most prescribed treatment as the first cDMARDs).

We performed a univariate analysis using a comparison test, and multivariate analysis to determine the factors associated with the increase of the lag time of methotrexate initiation.

## Results

A total of 225 patients with rheumatoid arthritis were included from the RBSMR data. The mean age of patients was  $52 \pm 11.36$  years. The majority of patients were females  $N=197$  (87.60%). Ninety percent of patients were ACPA positive and displayed the rheumatoid factor (Table 1).

The first cDMARD that was initially used was methotrexate (79%), followed by salazopyrin 7% and leflunomide (1.3%) and others (12.7%). The mean of disease duration was  $14.14 \pm 9.05$  years. The median of diagnosis lag time was 12 months (12-48) (Table 2).

The lag time between the symptom's onset and the initiation of methotrexate was 24 months (0.16-71) and the lag time in initiating Salazopyrin was 36 months (14-95) (Table 2).

In univariate analysis, we found in the group, which had the lag time of Methotrexate initiation more than 24 months, a longer

**Table 1.** Demographics and clinical features of the patient sample

Features	N : 225
Age <sup>1</sup> (years)	51 ± 11,36
Female sex <sup>2</sup>	197 (87,60)
<b>Marital status</b>	
• Married <sup>2</sup>	162 (72)
• Single <sup>2</sup>	28 (12,4)
• Widowed <sup>2</sup>	18 (8)
• Divorced	16 (7,1)
<b>Level of education</b>	
• Illiterate <sup>2</sup>	99 (44)
• Primary studies <sup>2</sup>	42 (18,7)
• Secondary studies <sup>2</sup>	52 (23,1)
• Higher education <sup>2</sup>	22(9,8)
Sedimentation rate <sup>1</sup> (mm/1 <sup>st</sup> hour)	42 ± 24
C-reactive protein <sup>3</sup> (mg/l)	22(8 - 41,5)
DAS28 <sup>1</sup>	5,2 ± 1
Positive rheumatoid factor* <sup>2</sup>	192 (90,5)
Positive Anti-ccp* <sup>2</sup>	151 (88,8)

1: Mean and standard deviation; 2: Number and percentage; 3: Inter-quartile median; \* Data available

**Table 2.** The first cDMARDs initiation and the lag time of Methotrexate initiation

Features	N : 225
First cDMARDs:	
Methotrexate <sup>2</sup>	177 (79)
Salazopyrine <sup>2</sup>	15 (7)
Leflunomide <sup>2</sup>	3 (1,3)
Other <sup>2</sup>	30 (12,7)
Initiation Methotrexate lag time <sup>3</sup> (months)	24(0.16-71)
Duration of evolution <sup>1</sup> (years)	14,14 ± 9,05
Diagnosis lag time <sup>3</sup> (months)	12(12-48)

1: Mean and standard deviation; 2: Number and percentage; 3: Inter-quartile median

diagnostic delay ( $p=0.0001$ ). The use of corticosteroids was important in the group that had the methotrexate initiation lag time  $\leq 24$  months ( $p=0.02$ ). On the other hand, no difference in age, sex, seropositivity, erosive form of rheumatoid arthritis and analgesic intake was found. In multivariate analysis, only the diagnostic lag time was associated with the initiation delay of Methotrexate  $> 24$  months (Table 3).

## Discussion

This study suggested that there is a delay between onset of symptoms and diagnosis, and initiation of cDMARDs treatment in RA patients. The median diagnostic lag time was 12 months (12-48) and the median lag time between initial presentation of RA and methotrexate instauration was 24 months (0.16-71).

More than 75% of patients with rheumatoid arthritis have erosions in the first two years of illness [11,4]. The current consensus is the need for early diagnosis and rapid initiation of treatment with cDMARDs to prevent destruction and joint damage [4,12-16].

In an American study by Kimsey and al [1], the time between symptoms onset and initiation of cDMARDs was 4 months (SD 5.8), and in an Australian study was 6,6 months (18-52.1) [2].

In the Danish nationwide DANBIO registry including 10416 patients with rheumatoid arthritis, they studied the changes of the diagnosis delay from year 2000 to 2011. The mean duration from initial symptoms to diagnosis for RA declined from 29 months (year 2000) to 3-4 months (year 2011) [14].

**Table 3.** Factors Associated with the variation in the Time of Methotrexate initiation in RA

Features	Univariate analysis			Multivariate analysis		
	Methotrexate initiation time > 24 n=64/130	Methotrexate initiation time ≤ 24 n=66/130	p	OR	IC	p
Age <sup>1</sup> (years)	52 ± 11	52 ± 11	0,6	-	-	-
Female sex <sup>2</sup>	58 (90,6)	56 (84,8)	0,3	-	-	-
Sedimentation rate <sup>1</sup> (mm / 1st hour)	39,7 ± 25	43,5 ± 21	0,3	-	-	-
C-reactive protein <sup>3</sup> (mg/l)	15(6 - 35)	27(9 - 47)	0,2	-	-	-
DAS28 <sup>1</sup>	4,9 ± 1,1	5,4 ± 0,9	0,05	0,7	[0,47-1,28)	0,3
Diagnosis lag time <sup>3</sup> (months)	48(12 - 72)	5(1 - 12)	0,0001	1,06	[1,03-1,09)	0,0001
Positive rheumatoid factor <sup>2</sup>	58 (92,5)	54 (91,5)	0,9	-	-	-
Positive Anti-ccp <sup>2</sup>	36 (81,8)	54 (93,1)	0,08	0,7	[0,46-1,32)	0,3
Carpite / Erosions <sup>1</sup>	30 (46,9)	27 (40,9)	0,5	-	-	-
Taking corticosteroids <sup>1</sup>	59 (92,2)	66 (100)	0,02	-	-	-
Taking analgesic <sup>1</sup>	31 (48,4)	34 (51,5)	0,9	-	-	-

1: Mean and standard deviation; 2: Number and percentage; 3: inter-quartile median

In a French study, Fautrel et al. [17], including 813 patients from a national claims database, the lag time from the symptoms onset and the first physician visit (lag1) was 0.5 months and the time between initial visit to rheumatology referral (lag2) was 1 month. In a Spanish cohort, the median lag time between symptom onset and the first visit to a rheumatologist was 17 months and between onset of symptoms and initiation of treatment by DMARD was 19 months [18].

In the ESPOIR cohort, the lag time before referral was 103.1 ± 52.4 days [19]. In a study conducted in 10 centers in Europe, the median time between onset of symptoms and diagnosis by the rheumatologist ranges from 12 to 24 weeks [20].

In the study by Massardo et al. [21] in Chilean patients, the lag time between symptoms and initial consultation ranged from 3 to 6 years.

In the study of Polanco et al. [4] based on the Venezuelan population, the diagnostic lag time was 40.5 months (1-424). Riad M et al. [22] included 152 RA patients, 35% were Caucasian, 37% Black, 20% Hispanic and 8% others. The median time to first rheumatology visit was 22.7 months in the group Spanish and 6-8 months for other groups.

Our study has demonstrated that the lag time between the onset of symptoms and the initiation of Methotrexate was longer in comparison with other studies conducted in some developed countries (United States of America, France and Denmark).

Furthermore, other studies realized at the level of some middle- or low-income countries (Chile and Venezuela) have shown a relatively long delay compared to that observed by our study conducted in Morocco.

In our study, the factors associated with the change in Methotrexate initiation lag time were the diagnostic delay and corticosteroids taking. Patients who started Methotrexate after 24 months had a higher diagnosis delay, while taking corticosteroids was greater in the group of patients who received Methotrexate before 24 months.

On the other hand, we did not find any difference concerning the age, sex, the seropositivity, the erosive form and the taking of analgesic.

In multivariate analysis, only the diagnosis delay is identified as a factor associated with the Methotrexate initiation delay.

Our results are similar to those of a Spanish study [18] where the variable that is associated with a delay of initiation of treatment was the lag time from the onset of symptom to the first rheumatologist

consultation. Furthermore, this study had also mentioned the level of education as a factor associated with the DMARDs therapy delay.

In the study of Chan et al. [23], the factors associated with shorter delays were disease progression and rheumatoid factor seropositivity, but no correlation was found with age, sex, or co-morbidities.

In Kimsey et al. [1], opioids and no steroidal anti-inflammatory drugs were the factors associated with delayed initiation of cDMARDs treatment.

Polanco et al. [4] found that the first consultation with a general practitioner at a public health center as well as with an orthopedic surgeon were the main factors associated with the increasing of the delay of the diagnosis and the introduction of cDMARDs. In agreement with the results of Matthew et al. [2] who found that the factors that are associated with a delay in cDMARDs introduction were the presentation of the patient to the general practitioner, the delay of referral from the general practitioner to the rheumatologist as well as the socio-economic disadvantage, fatigue score and low DAS28.

In fact, the delay of referral from the general practitioner to the rheumatologist is an important factor influencing the delay of diagnosis. Studies have shown that there is poor agreement in the diagnosis of RA between rheumatologists and general practitioners [4,24,25].

The limitations of our study are its retrospective nature, the collection of the database from the medical records and therefore missing data like the referral lag time to the rheumatologist. Secondly, the recall bias may occur during the patient interrogatory regarding the date of symptoms onset which is based on the memory of the patient. But this study presents strong points. It is a multicentric study of the first Moroccan and African register of biotherapies.

In order to ensure an early diagnostic and an early treatment, it is necessary to sensitize general practitioners to refer patients to a rheumatologist and raise the awareness of patients who medicate themselves with corticosteroids.

## Conclusions

In conclusion, this study, which was based on data from the Moroccan register of biotherapy patients with RA, suggests that there is a significant delay from the diagnosis to the initiation of treatment with cDMARDs. The delay of diagnosis was the factor associated with the Methotrexate initiation delay. Further large-scale studies are needed to confirm these results.

## Declarations

**Ethics approval and consent to participate:** The protocol for the original RBSMR study was reviewed and approved by local institutional review boards and the national ethic committee: Ethics committee for biomedical research Mohammed V university- RABAT.

Faculty of medicine and pharmacy of RABAT. The committee's reference number: 117/17

**Consent to publish:** This project has been reviewed and accepted by the scientific committee of the RBSMR study. Moreover, this committee has reviewed this current manuscript and has agreed upon its submission to your journal.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article.

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**Authors' Contributions:** We declare that we participated at the study as following:

ME performed the statistical analysis and interpretation and prepared the manuscript. SR participated in article writing and critical review of the manuscript. IH reviewed and interpreted the statistical analysis. RB participated in critical review of the manuscript. All authors read and approved the final manuscript.

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