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Study of the Frequency and Characteristics of Difficult-To-Treat Rheumatoid Arthritis: Results of a Retrospective Cross-Sectional Study

Séiny Kanta[1*], Hajar Elhani[1], Najlae El Ouardi[1], Mahamadou Sagara[1], Houda El Assad[1], El Kacem El Marbouh[1], Hajar Zouaki[1], Alassane Alidou Garba[1], Abdellah Ould Mohamed[1], Laila Taoubane[1], Abderrahim Majjad[1], Hamza Toufik[1], Ahmed Bezza[1]

[1]University Mohammed V de Rabat, Faculté de Médecine et de Pharmacie, BP 6203 Rabat institut, Hospital Military d'instruction Mohammed V - BP: 1018, Service de Rhumatologie Rabat, Morocco

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***Corresponding author:** Séiny Kanta
University Mohammed V de Rabat, Faculté de Médecine et de Pharmacie, BP 6203 Rabat institut, Hospital Military d'instruction Mohammed V - BP: 1018, Service de Rhumatologie Rabat, Morocco

Abstract **Original Research Article**

Introduction*:** The new concept of difficult-to-treat rheumatoid arthritis (DaT RA) refers to the recent EULAR definition which describes it by the following three criteria agreed by all members of the working group as mandatory elements of the DaT RA definition: (1) Treatment according to the European League Against Rheumatism (EULAR) recommendation and failure of ≥ 2 biologic disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs (with different mechanisms of action) after failure of conventional synthetic DMARD treatment (unless contraindicated); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid therapy; rapid radiographic progression ; RA symptoms leading to reduced quality of life; and (3) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient. Our study aims to explore the frequency of this particular entity and to characterise its clinical aspects in a Moroccan population. ***Patients and Methods: This was a cross-sectional study with retrospective data collection, including all patients with rheumatoid arthritis (RA), meeting the 2010 ACR/EULAR classification criteria for at least one year (from January 2022 to January 2023) in the Rheumatology Department. To analyse the factors associated with RA DaT, we divided our population into two groups: a group designated as RA DaT and a 'control' group. ***Results*:** Our study included 240 patients, 78 (32.5%) of whom met the 'EULAR' definition of RA DaT, with a mean age of 54.6 ± 9.94 years, compared with 56.5 ± 11.5 years, p=0.05 for controls. Rituximab was used in 25.6% of the RA DaT patients in our sample. 45.42% of the PR DaT group received one anti-TNF alpha, 25% of PR DaT received two anti-TNF alpha and 10% of PR DaT received Tocilizumab. Our results showed that age (OR: 2.24, 95% CI: 1.04-4.02), p: 0.023), disease duration (OR = 2.15, 95% CI: 1.15-3.98), p = 0.05, and BMI (OR = 1.78, 95% CI: 1.09-3.08), p = 0.048), were significantly associated with 'RA DaT'. Furthermore, patients with intolerance or contraindication to csDMARDs were 1.5 times more likely to develop RA DaT (OR: 1.49, 95% CI: 1.02-2.17), p < 0.05. However, there was no significant association between RA DaT and gender, smoking or the presence of co-morbidities. ***Conclusion***: RA DaT remains a major challenge for rheumatologists. The findings of our study highlight the need for early management of RA and an individualised therapeutic approach.

Keywords: Rheumatoid Arthritis, RA DaT, Associated Factors, Management.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammation of the joints, leading to pain, stiffness and loss of joint function. Although advances in treatment have led to better control of disease activity in a large percentage of patients [1,2], there are still 5-20% of patients for whom targeted therapies do not work optimally [3,4,5]. This phenomenon is known as PR DaT. EULAR defines it as [6]:

1. A disease treated according to EULAR recommendations with failure of ≥ 2 biological or alternatively synthetic drugs (b/tsDMARDs) with different mechanisms of action after failure of conventional disease-modifying therapy (csDMARDs).

2. Presence of at least one sign suggestive of active/evolving disease which are : moderate or high disease activity (DAS28-ESR>3.2 or CDAI>10), inability to reduce glucocorticoid dose below 7.5 mg/ prednisone day or equivalent, rapid radiographic progression (with or without signs of active disease), disease well controlled according to the above standards, but still presenting with RA symptoms resulting in reduced quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

EULAR has recently defined DaT RA as RA that has failed at least two targeted biological and/or synthetic therapies with different mechanisms of action after failure of conventional disease-modifying therapy.

Recent studies [7, 8], have revealed that factors associated with difficult-to-treat RA include advanced age, duration of disease and the presence of co-morbidities. However, despite these findings, the mechanisms underlying RA DaT are still largely misunderstood.

The aim of this article is to study the prevalence and characteristics of difficult-to-treat rheumatoid arthritis (RA DaT) in a population of Moroccan patients, to identify the factors associated with this refractory nature of the disease, and to discuss future prospects for improving the treatment of this debilitating condition while awaiting the appearance of new recommendations concerning the management (ECP) of this sub-group of patients.

PATIENTS AND METHODS

We conducted a comparative cross-sectional study with retrospective data collection, including all patients with RA followed for at least 1 year. Patients were recruited from the rheumatology department of the Mohamed V military training hospital.

Inclusion criteria were as follows:

1. Age ≥ 18 years
2. Diagnosis of RA according to the criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) 2010.
3. Treatment with conventional synthetic antirheumatic drugs (csDMARDs) or biologic DMARDs (bDMARDs) for at least 6 months.

Medical records collected information on various patient characteristics, such as age, gender, marital status, education level, smoking habits, ethnicity, alcohol consumption, duration of symptoms, body mass index (BMI), medical history and previous use of RA medications. This included details of current and previous treatment with steroids, NSAIDs and/or DMARDs, including dosage, frequency and start date. To ensure accuracy; data obtained from medical records was verified through interviews with physicians.

Throughout the interviews, patients were assessed using the disease activity score based on the disease activity score, C-reactive protein level (DAS28-CRP) and visual analogue scale (VAS). Laboratory test results included a complete blood count, CRP, ACPA and rheumatoid factor. In addition, a count of painful and swollen joints (28) was performed. RA patients were classified as having RA DaT if they met all the criteria of the EULAR definition. RA patients who did not meet all three criteria were used as a control group. Patient characteristics and factors potentially contributing to the development of RA DaT were summarised using descriptive statistics and compared between the 2 groups. To this end, the independent t-test or one-way analysis of variance was used for continuous parameters, and the Mann-Whitney U test for distribution-free alternatives. Fisher's exact test was used to compare binary parameters. Multivariate logistic regression was also used.

RESULTS

Our study included 240 patients, 69% of whom were women, 57% of whom were DaT RA patients with a mean duration of disease of 61.5%≥ 6 years. 65% of patients were immunopositive, 51.5% of whom were DaT RA patients. Radiographic erosion was found in 172 patients, 71.8% of whom were DaT RA patients. Corticosteroid therapy was prescribed in 89.5% of patients, including 32.5% of DaT RAs, whose mean age was 54.6 ± 9.94 years, compared with 56.5 ± 11.5 years for controls, p=0.056. Rituximab was used in 25.6% of the RA DaT patients in our sample. 45.42% of the PR DaT group received one anti-TNF-alpha, 25% of PR DaT received two anti-TNF-alphas and 10% of PR DaT received Tocilizumab. In univariate analysis, our results showed that age (OR: 2.24, 95% CI: 1.04-4.02), p = 0.023), disease duration (OR = 2.15, 95% CI: 1.15-3.98), p = 0.05, and BMI (OR = 1.78, 95% CI: 1.09-3.08), p = 0.048), were significantly associated with DaT RA. Furthermore, patients with intolerance or contraindication to csDMARDs were 1.5 times more likely to develop RA DaT (OR = 1.49, 95% CI: 1.02-2.17), p < 0.05. In multivariate analysis, the presence of a low level of education and socio-economic status, the presence of fibromyalgia, a long duration of disease progression, a long delay in initiation of biotherapy, and the absence of conventional disease-modifying therapy were associated with RA DaT. On the other hand, no significant association was recorded between RA DaT and sex, smoking, or the presence of comorbidities as indicated in the table.

RESULTS

Table1: Demographic and clinical characteristics of all patients with RA

	All	PR Non-D2T	PRD2T	Univariate P	P multivariate
Age	240	162 ; 56,5[±11,5]	78 ; 54,6[±9,94]	0.056	0.399
Gender Female	166	108 (66.7 %)	58 ; (74.4 %)	0.23	0.159
Low level of education	166	114 ; (70.4 %)	52 ; (66.7 %)	0.023	0.039
BMI (mean± SD) ≥ 25 kg/m2	191	3,8%	96,2%	0,88	0.208
Active or weaned smokers (%)	21	16 ; (9,9 %)	5 ; (6,4 %)	0,37	0.557
Low socioeconomic level, n (%)	98	88,88%	46,09%	0,026	0.015
Hypertension, n (%)	76	49 ; (30,2 %)	27 ; (34,6%)	0.49	0.925
Dyslipidemia, n (%)	43	32 ; (19,9 %)	11 ; (14,1 %)	0.28	0.765
Diabetes, n (%)	79	53 ; (33.1 %)	26 ; (35.1 %)	0.76	0.645
Heart disease n (%)	27	20 ; (12,3 %)	7 ; (9 %)	0.44	0.445
Fracture n (%)	21	14 ; (8,6 %)	7 ; (9 %)	0.93	0.874
OPS history	64	41 ;(25.309 %)	23 ; (29.5 %)	0,49	0.561
Neoplasia n (%)	3	2 ; (1.2 %)	1 ; (1.3 %)	0.98	0.838
Fibromyalgia n (%)	30	1.56%	8.33%	0,222	0.045
Poor oral condition n (%)	114	80 ; (49,4 %)	34 ; (43,6 %)	0.400	0.193
DAS28-CRP, (average± ET)	240	3,4 ;(1,4%)	3,6 ; (1,6%)	<0 .001	0. 058
Anti-CCP positive, (%)	156	63.0 %	55.1 %	0.245	0.635
FR positive, n (%)	157	111 ; (68.5 %)	46 ; (59.0 %)	0.15	0.083
Erosion, n (%)	172	116 ; (71.6 %)	56 ; (71.8 %)	0.98	0.728
Interstitial lung disease, n (%)	32	21 ; (13%)	11 ; (14,1 %)	0.81	0.737
Corticosteroid use, n (%)	215	143 ; (88.3 %)	72 ; (92.3 %)	0.34	0.429
Antidepressant intake n (%)	45	26 ; (16%)	19 ; (24,4 %)	0.12	0.707
Rituximab n (%)	43	23 ; (14,2 %)	20 ; (25,6 %)	0.030	0.092
Methotrexate, n (%)	226	156 ; (96.3 %)	70 ; (89.7 %)	0.04	0.428
LFN, n (%)	63	36 ; (22.8 %)	27 ; (34.6 %)	0.05	0.049
SLP, n (%)	106	55 ; (34.8 %)	51 ; (65.4 %)	<0.001	< 0.001
PSA, n (%)	41	21 ; (13.4 %)	20 ; (26.0 %)	0.017	0.020
Duration of illness (in years) ≥ 6 years	137	89 ; (54.9 %)	48 ; (61.5 %)	0.333	0.028
Time to first biotherapy (months), (mean ± SD)	188	41 ± 63	33,6 ± 38,65	0,511	0.002

Table2: *Therapeutic lines and reasons for discontinuation in the EULAR-PR DaT group*

EULAR-PR DaT	Primary failure	Secondary exhaust	Side effects
Switch 1° to 2° line	23 %	68 %	3%
Switch 2nd to 3rd line	36 %	46 %	1%
Switch > 3rd line	51 %	21%	7%

DISCUSSIONS

The concept of RA DaT is a recent one. Practitioners have not agreed on a unanimous definition, according to an international survey [9], involving 420 healthcare professionals from different countries. The results were heterogeneous: some considered the disease difficult to treat if the DAS 28/CRP was greater than 3.2, others if 2 biological or synthetic drugs failed, if it was impossible to reduce the dose of corticosteroid therapy, and if there were extra-articular manifestations, co-morbidities or multiple medications. Faced with this divergence of opinions, an EULAR working group succeeded, after several meetings and discussions, in establishing a clear definition with uniform terminology based on an analysis of the literature [10]. The exact frequency of refractory RA is difficult to establish, as it varies according to the definition criteria and the populations studied. According to our work, the frequency of DaT RA refractory to biologic drugs at the

time of inclusion of patients in the study was 32.5%, which is higher than the result of Takanashi and al [11], who found a prevalence of 10.1% (173/1709). A recently published UK study [12], found approximately 6% (867/13502) of patients on the UK Biotherapeutics Society's Biotherapeutics Register with resistance to 2 biologics, with a numerical trend increasing over time. Another study [13], based on data from the Japanese FIRST registry found a lower percentage at 16.5% (353/2128) with the inclusion of rheumatoid arthritis patients on targeted therapies (biotherapies and JAK inhibitors). Another Japanese cohort [14], found 7.9% of patients to be refractory, which the authors explained by the fact that there is a high percentage of patients with moderate or high disease activity without recourse to biotherapy. The high percentage found in our study can be explained by the fact that a large percentage of patients were recruited from a tertiary university centre where patients with difficult disease management are referred.

Important future challenges include the identification of patients with RA DaT, and associated factors. One study [15], looked at the power of artificial intelligence to identify and predict this entity, with very promising results : ROC 0.88 (95% CI 0.82-0.94) for identification, and ROC 0.73 (95% CI 0.71-0.75) for prediction. The associated factors found in our study are in line with those in the literature. A recently published meta-analysis [16], which included data on 16934 patients from 21 scientific studies, found the following factors to be associated with RA DaT: female sex, age, obesity, smoking history, high disease activity, high sedimentation rate at diagnosis, and poor functional status. The results of the British study [17], cited above still identified female gender, obesity and smoking as risk factors, along with a high overall assessment by the patient and low socio-economic status, but this time it was young age that was associated with a poor response. Takanashi *et al*., [11], report female gender, RF and ACPA positivity, corticosteroid use and lung involvement. Roodenrijs *et al*., [18], report data from the Netherlands identifying comorbidities, fibromyalgia, high disease activity and obesity as risk factors. A Japanese cohort [19], identified RF positivity, lung involvement and high activity at diagnosis as factors favouring the development of RA DaT. In patients with RA resistant to at least 2 biologics, the EULAR Task Force [20] has proposed a number of steps in the management of these patients. Always starting with non-pharmacological measures (physical exercise, education, etc.), The diagnosis also needs to be discussed to rule out other pathologies or comorbidities mimicking RA, and to assess adherence to treatment. The treatment options that appear to be most effective are tocilizumab, tofacitinib, baricitinib, upadacitinib and filgotinib [21, 22], compared with placebo. However, this efficacy is lost over time, especially in patients who have received a high number of biologics [21-27]. This phenomenon is less significant for high doses of tocilizumab, tofacitinib and baricitinib. Before concluding, we would like to point out the limitations of our study, which are essentially represented by the retrospective nature of the data collection, the monocentric aspect and the recruitment of patients in a tertiary centre. However, it is a study with an interesting number of patients that can reflect real-life data.

CONCLUSION

In our series, 78 patients (32.5%) met the EULAR definition of RA DaT, a figure higher than that found in the literature and which may be explained by the fact that patients were recruited from a tertiary hospital centre.

Our results showed that age, duration of disease and BMI, and non-use of CsDMARDs were statistically significantly associated with RA DaT, as shown in the table. RA DaT remains a major challenge for rheumatologists. The findings of our study underline the imperative of early management of RA and an individualised therapeutic approach.

Conflict of Interest: The authors declare that they have no conflict of interest.

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