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CHARACTERISTICS OF DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: A REAL-LIFE STUDY

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ABSTRACT – *Objective:* Despite therapeutic advances and the "treat-to-target" strategy, 5-20% of Rheumatoid Arthritis (RA) patients fail to achieve treatment goals. The aim of this study was to identify the characteristics and risk factors associated with difficult-to-treat RA.

Patients and Methods: This is a real-life study of patients with RA according to the ACR/EULAR 2010 classification criteria. Sociodemographic, clinical, paraclinical and comorbidity data were collected, as well as the treatments used. Patients were divided into two groups: D2T RA and control group. The results were compared between the two groups. Logistic regression analysis was used to identify risk factors associated with D2T RA.

Results: We included 25 D2T RA patients and 62 non-D2T RA patients. Mean age of patients and disease duration were higher in D2T RA group. Rheumatoid factor seropositivity was higher in the D2T RA group (p = 0.04). They had more active disease (p = 0.001) and more severe functional impairment (p < 0.001). Among extra-articular manifestations, interstitial lung disease was more common in D2T RA patients (p = 0.018). Biologic disease-modifying antirheumatic drugs (bDMARDs) were prescribed more frequently in the D2T RA group and the glucocorticoid dose was higher in this group (p = 0.041). On multivariate analysis, disease activity, disease duration and lung involvement were identified as factors that were associated with D2T RA.

Conclusions: D2T RA can be classified in about one-third of our RA patients. We observed an association between longer disease duration, higher disease activity and rheumatoid factor seropositivity in D2T RA. In addition, lung involvement in the context of RA was more common in this group and may be a contributing factor to an inadequate response to treatment.

KEYWORDS: Rheumatoid arthritis, Difficult-to-treat rheumatoid arthritis, Disease activity, Treatment.

LIST OF ABBREVIATIONS: RA: Rheumatoid arthritis; T2T: Treat-to-target; EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; bDMARDS: Biologic disease-modifying antirheumatic drugs, biologic or target synthetic disease-modifying antirheumatic drugs (b/tsDMARDs); TNFi: Tumor necrosis factor inhibitors; D2T RA: difficult-to-treat RA; VAS: visual analogue scale; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: Anti–citrullinated protein antibody; DAS28: Disease Activity Score of 28 joints; HAQ: Health Assessment Questionnaire; cDMARDS: Synthetic disease-modifying antirheumatic drugs; RTX: Rituximab; Anti-IL6: Interleukin 6 inhibitors; SD: Standard deviation; IQR: Interquartile range.

INTRODUCTION

Rheumatoid Arthritis (RA) is the most prevalent chronic inflammatory rheumatic disease, aflicting 0.5 to 1% of the global population[1]. It is a chronic autoimmune disease involving genetic and environmental factors, with possible systemic manifestations[2].

The treatment of RA has evolved significantly in recent decades. The primary goal is to achieve remission or low disease activity. To attain this objective, a treat-to-target (T2T) approach has been taken to enhance the prognosis of patients with RA, according to the therapeutic recommendations of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Nevertheless, the disease persists as refractory in 20-75% of patients who receive their initial Biologic disease-modifying antirheumatic drugs (bDMARD) and in 40-55% of those who receive their second bDMARD[3-7].

Several causes of non-response to treatment are suggested. The study of Jani et al[8] found that patients who did not respond to the first Tumor Necrosis Factor inhibitors (TNFi) have a less favorable clinical response after switching to a second TNFi compared to secondary non-responders or those who discontinued treatment due to adverse events.

Also, immunogenicity might result in resistance or reduced effectiveness of the second TNFi, and as such, a change of mode of action is suggested for these patients[8].

Thus, in an Italian study, 8% of patients presented multiple bDMARDs failures. The main reasons for discontinuation were inefficacy (29%), intolerance (10%), acute adverse reactions (6.3%), and severe infections (1.5%)[9]. Despite current recommendations and therapeutic advances, a subset of patients continue to experience persistent symptoms after undergoing several lines of therapy[10]. Different definitions and nomenclatures have been associated with this patient group. To establish standardized terminology and proper management protocols, the EULAR Working Group recently established a consensus definition for this subgroup of difficult-to-treat RA (D2T RA)[11]. This definition is based on three criteria: a history of failure of two or more biologic or target synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) with different mechanisms of action, active disease, and clinical perception of the disease by the rheumatologist or the patient. The exact mechanisms that lead to D2T RA remain uncertain and diverse, and the management of this condition may require consideration of multiple contributing factors. Resistance to multiple drugs may arise from immune disorders linked to RA, in addition to lifestyle factors like smoking, alcohol consumption, obesity, and drug immunogenicity[12,13].

Similarly, drug-induced RA (D2T RA) may arise from therapeutic intensification problems, such as the development of adverse events or contraindications, which may be due to the presence of comorbidities and non-compliance. Identifying D2T RA in real-world scenarios would facilitate proper management and potentially diminish the socioeconomic burden of caring for this patient group. Given the lack of data on D2T RA in our context and the Middle East and North Africa region, our study aims to identify the characteristics and risk factors of patients with challenging-to-treat rheumatoid arthritis in our Moroccan population.

PATIENTS AND METHODS

Search strategy and selection criteria

This study is a cross-sectional study of patients diagnosed with RA according to the 2010 ACR/EULAR criteria[14], with at least six months of follow-up, recruited from the Rheumatology Department of El Ayachi University Hospital in Rabat. Recruitment took place between November 2021 and July 2022. Patients with inadequate data were excluded from the analysis.

RA patients were divided into two groups: those with D2T RA who met the EULAR definition criteria[11] and a control group for those who did not meet the criteria.

Clinical characteristics, paraclinical parameters, and comorbidities were collected and any changes in treatment were recorded during follow-up. A comparison was made between the two groups.

Data collection

Data collected included socio-demographic information such as age, sex, smoking habits, family history of RA, disease duration and comorbidities; clinical examination results including number of swollen

and painful joints, global visual analogue scale (VAS); and biological parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and Anti–citrullinated protein antibody (ACPA). Disease activity was assessed using the Disease Activity Score (DAS28), and functional impact was measured using the Health Assessment Questionnaire (HAQ). Rapid radiographic progression was not included due to the cross-sectional nature of the analysis. Comorbidities were evaluated through comprehensive questioning, clinical examination of other systems, and laboratory tests performed less than three months ago, including evaluations of liver and kidney function, an electrocardiogram, and a chest X-ray. Recent liver serologies were also included in the analysis.

Treatment

Information on past and current use of disease-modifying antirheumatic drugs (DMARDs) was collected. Reasons for discontinuation, such as adverse events, intolerance and comorbidities, were documented. DMARDs were categorized as TNFi, Rituximab (RTX), Interleukin 6 inhibitors (anti-IL6) drugs based on their respective modes of action. Usage of glucocorticoids was also recorded, specifying the current dosage.

Statistical analysis

Statistical analysis was conducted using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA). Qualitative data frequencies were presented as both numbers and percentages. The mean ± standard deviation (SD) was used for parameters with a normal distribution, and the median ± interquartile range (IQR) for those with an asymmetric distribution. T-student and Mann-Whitney tests were employed for quantitative variables, while Chi2 was used for qualitative variables to examine differences between the two groups. The level of significance was set at $p < 0.05$. It entailed the application of a logistic regression model to establish risk elements.

RESULTS

Patients

A total of eighty-seven patients were included in our study, of whom twenty-five (28.7%) were classified as RA D2T and sixty-two (71.3%) as non-D2T. The demographics and disease characteristics of the patients are presented in Table 1.

In our sample, 86.2% were female. The mean age was 44.94±12.3 years, and the duration of the disease was 9.2 ± 3.36 years. The seropositive character of rheumatoid arthritis was prominent (82.2%), and a family history of RA was present in 3.4% of the study population.

In the RA D2T cohort, patients tended to be older (50.32±11.08 *vs*. 42.77±12.23 years; p= 0.009) and had a longer disease duration (12.84± 5.66 *vs*. 4.68±2.75; p<0.001). While both groups consisted mainly of individuals who tested positive for seropositivity, the prevalence of rheumatoid factor positivity was markedly higher in the RA D2T group (70 *vs*. 48%; p=0.04). There were no notable differences between the two groups regarding a family history of RA or exposure to smoking.

The D2T RA group showed higher disease activity and functional impact scores [DAS28 VS: Gr-RA D2T: 3.6 [1.3-5.8], Gr-RA non D2T: 2.6 [1 - 5.5] (p=0.001)], [HAQ: Gr-RA D2T: 1.2 [0.6 - 2.9], Gr-RA non D2T: 0.45 [0.2 - 1.2] (p <0.001)].

Moreover, the non-D2T RAs group was 50% in remission compared to 16% in the D2T group (p = 0.03), and 61% of the non-D2T RAs group had a HAQ score of less than 0.5 compared to 4% in the D2T group (p< 0.001) (Figures 1 and 2).

Interstitial lung disease was observed more frequently in D2T RA patients compared to non-D2T RA patients as an extra-articular manifestation (with a significant difference of 20 *vs*. 1.6% p= 0.018 as per Table 2). Additionally, D2T patients showed a higher median number of comorbidities (96 *vs.* 25% p=0.032) and had higher prevalence rates of hypertension (44 *vs*. 14.5 %, p=0.03), diabetes (24 *vs.* 8 %, p=0.04) and osteoporosis (48 *vs.* 22 %, p=0.01) compared to non-D2T patients (Table 2).

Table 1. Sociodemographic, clinical and paraclinical characteristics of the study population.

	Total N=87	RA D2T N=25	RA no D2T N=62	*p*
Age (year)[1]	44.94 ± 12.3	50.32 ± 11.08	42.77 ± 12.23	0.009
Female[2]	75 (86.2)	23(92)	52(83)	0.32
Disease duration (year)[1]	9.2 ± 3.36	12.84± 5.66	4.68± 2.75	<0.001
Family history of RA[2]	3 (3.4)	1 (4)	2 (3.22)	0.8
Current smoking[2]:				
– Active[2]	5 (5.7)	9 (10.3)	1 (4)	4 (16)
– Passive[2]	4 (6.45)	5 (8)	0.7	0.063
Smoking cessation[2]	6 (6.9)	2 (8)	4 (6.45)	0.67
Seropositive (ACPA and/or RF)[2]	72 (82.8)	61 (70.1)	56 (64.4)	19(75)
ACPA positive[2]	19 (76)	17 (68)	53(85)	42 (67.75)
RF positive[2]	29 (46.77)	0.28	0.44	0.04
DAS28-ESR[3]	2.8 [1-5.8]	3.6 [1.3-5.8]	2.6 [1 – 5.5]	0.001
HAQ[3]	0.6 [0.2-2.9]	1.2 [0.6 – 2.9]	0.45 [0.2 – 1.2]	<0.001

Legend: [1]Mean ± SD; [2]Number and Percentage; [3]Median and IQR.
Abbreviations: RA: rheumatoid arthritis; D2T: difficult to treat; ACPA: anti–citrullinated protein antibody; RF: rheumatoid factor; DAS28: Disease Activity Score of 28 joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire.

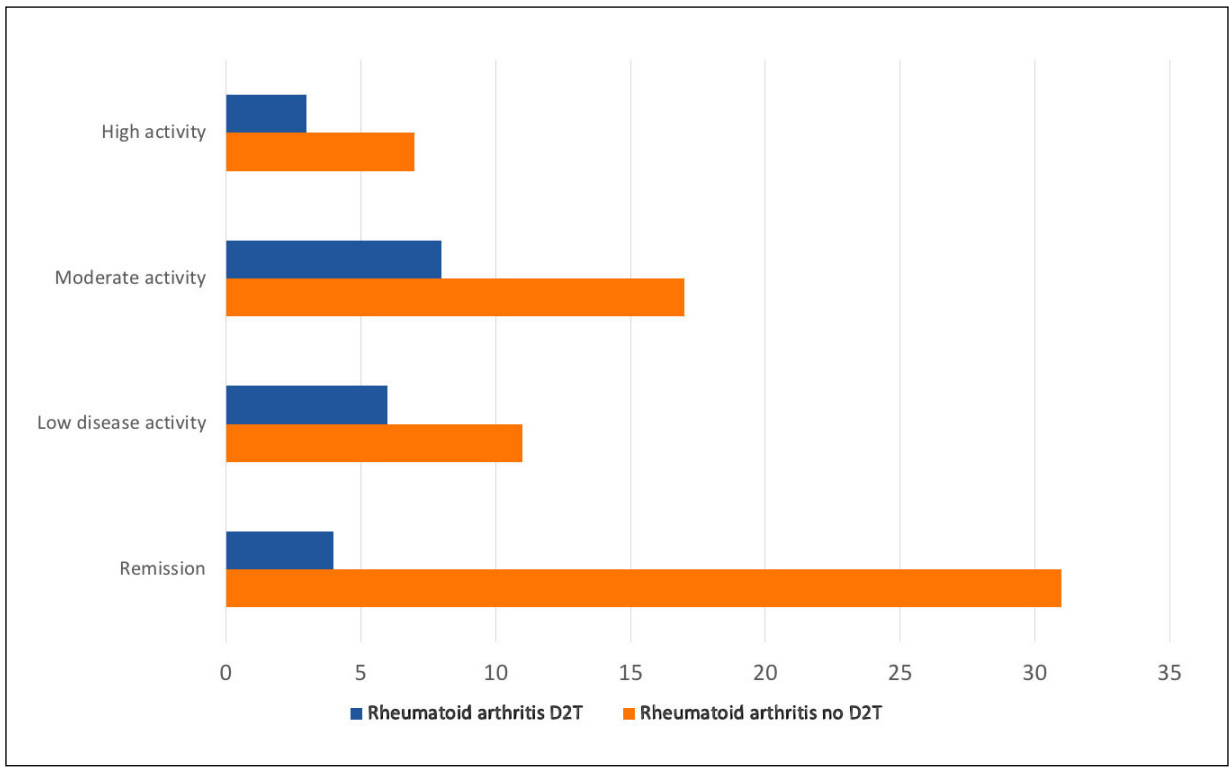

Figure 1. Disease activity based on DAS28 VS between D2T and no D2T group.

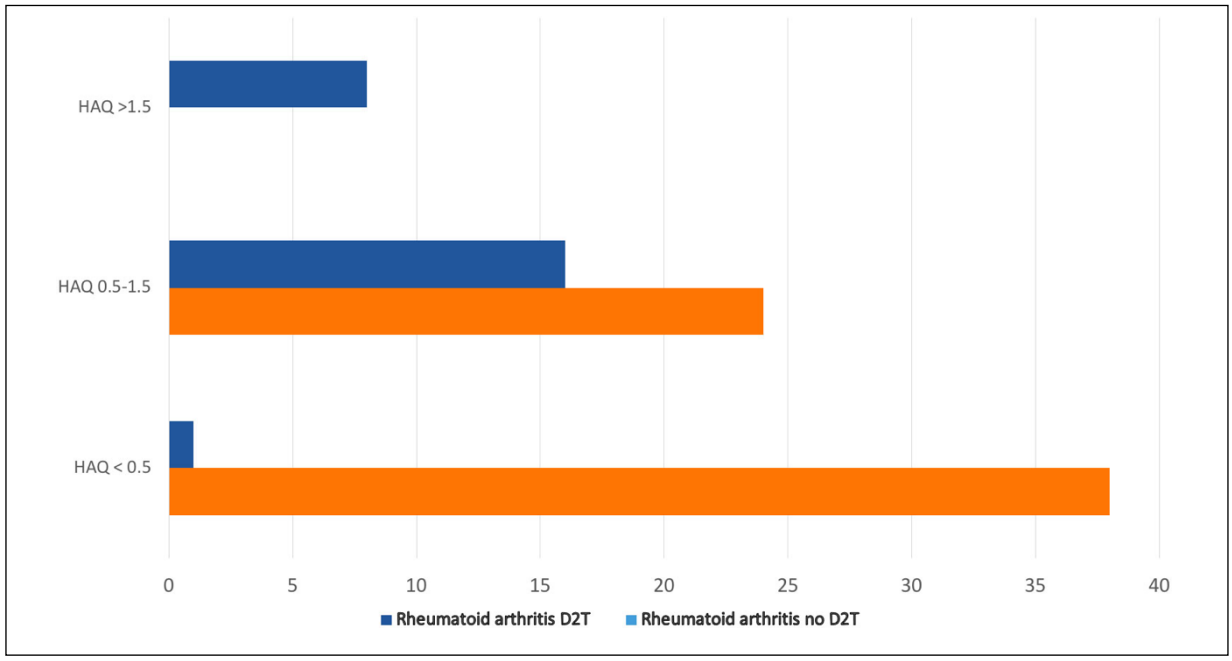

Figure 2. Function impact of disease using HAQ between D2T and no D2T group.

Table 2. Comorbidities and extra-articular manifestations in the study population.

	Total N=87	RA D2T N=25	RA no D2T N=62	*p*
Hypertension[1]	20 (22.9)	11 (44)	9 (14.5)	0.03
Ischemic heart disease[1]	1 (1.15)	1 (4)	0 (0)	0.07
Valvulopathy[1]	1 (1.15)	0 (0)	1 (1.6)	0.2
Hyperlipidemia[1]	16 (18.4)	5 (20)	11 (17.75)	0.36
Diabetes[1]	11 (36.78)	6 (24)	5 (8)	0.04
Renal failure[1]	3 (3.45)	1 (4)	2 (3.2)	0.14
Cancer[1]	0 (0)	0 (0)	0 (0)	-
Osteoporosis[1]	26 (29.88)	12 (48)	14 (22)	0.01
Hepatitis B and/or C[1]	0(0)	0(0)	0(0)	-
Hepatic Cirrhosis[1]	0(0)	0(0)	0(0)	-
Peptic ulcer disease[1]	1 (1.15)	1 (4)	0 (0)	0.07
Interstitial lung disease[1]	6 (6.9)	5 (20)	1 (1.6)	0.018
Recent or past tuberculosis[1]	2 (2.3)	0 (0)	2 (3.2)	0.09
Asthma[1]	1 (1.15)	1 (4)	0 (0)	0.07
Eye disease1[1]	11 (12.64)	4 (16)	7 (11.2)	0.17
Others[1]	3 (3.45)	1 (4)	2 (3.2)	0.13

Legend: [1]Number and percentage.

TREATMENTS

Current treatments

The study compared the treatment profile of two groups (Table 3). Of the non-D2T group, 45% were taking csDMARDs, with only 31% taking methotrexate. Glucocorticoids were commonly prescribed in both groups, with a higher mean dose in the D2T RA group than in the non-D2T patients (4.7± 2.8 vs. 3.5± 2.3; p=0.041). The D2T RA group was also more likely to be prescribed bDMARDs than the non-D2T RA group.

Table 3. Current treatment of D2T and non-D2T groups.

	RA D2T N=25	RA no D2T N=62	*p*
csDMARDs only[1]	0 (0)	28 (45)	<0.001
csDMARDs in association with b/tsDMARds	4 (16)	8 (12.9)	0.26
Corticotherapy[1]	25(100)	59(95)	0.2
Corticosteroid dose (mg/d)[2]	4.7± 2.8	3.5± 2.3	0.041
bDMARDs[1]	22 (88)	32 (51)	<0.001
– AntiCD20	3 (12)	21(33)	
– TNFi	9 (36)	11(17.5)	
1. Infliximab	4	2	
2. Etanercept	1	4	
3. Adaluminab	0	1	
4. Golimumab	4	2	
– Anti-IL6	10 (40)	2 (3.18)	
tsDMARDs[1]	3 (12)	2 (3.22)	0.11

Legend: [1]Number and Percentage; [2]Mean ± Sd.

Treatment history

Compared to the second group (Table 4), the number of failed DMARDs was significantly higher in the D2T RA patients. All D2T RA patients had failed ≥2 b/tsDMARDs utilizing distinct mechanisms of action, which is consistent with the definition of D2T RA. RA D2T patients were not successful with a median of 3 b/tsDMARDs utilizing distinct mechanisms of action.

Factors related to D2T RA

The multivariate regression analysis showed that disease activity, disease duration, and lung involvement were factors associated with D2T RA (Table 5).

DISCUSSION

Despite therapeutic advances having revolutionized RA management, some patients remain unresponsive to multiple drugs, presenting a challenge to clinicians. Previous studies on RA patients who could potentially have disease-to-treatment resistant RA have used dissimilar concepts to define this subgroup[15,16].

Table 4. D2T and non-D2T RA treatment history.

	RA D2T N=25	RA no D2T N=62	*p*
Number of csDMARD failure[1]	2 (2-4)	2 (1-3)	0.002
Number of b/tsDMARD failure[1]	4 (3-6)	1 (1-2)	<0.001
Number of modes of action used[1]	3 (2-4)	0 (0-0)	<0.001

Legend: [1]Median and IQR.

Table 5. Multivariate analysis of factors associated with D2T RA.

	OR	95% CI	*p*
Age	1.08	0.69–1.85	0.79
Gender	0.84	0.56-1.88	0.76
Current smoking	1.54	0.59-5.66	0.37
Disease duration	1.52	1.03-1.94	**<0.001**
FR	1.3	0.82-2.54	0.63
ACPA (IU/mL)	1.02	0.54-2.3	0.89
DAS28-ESR	1.52	1.12-3.1	**0.01**
Lung disease	2.29	1.32-4.05	**0.02**

Abbreviations – ACPA: anti–citrullinated protein antibody; RF: rheumatoid factor; DAS28: Disease Activity Score of 28 joints.

The estimated prevalence of disease-to-treatment resistant RA varies from 5% to 20%, which cannot be overlooked[17].

The EULAR team developed a definition of difficult-to-treat RA to provide appropriate recommendations for this patient group. The definition includes three criteria:

1. the first criterion considers the history of treatment failure. To meet the criterion, the person must have failed to respond to two or more b/tsDMARDs with different mechanisms of action, after failure or contraindication to csDMARDs. EULAR has included socio-economic factors as an additional criterion, unless treatment access is limited by socio-economic circumstances.
2. Disease activity is based on composite scores, the inability to discontinue corticosteroids, extra-articular manifestations, radiographic progression.
3. The patient's and/or rheumatologist's clinical assessment of the disease.

Our study suggests that approximately one-third of our patients with RA can be categorized as having D2T RA. This classification is in line with previous research. To be specific, out of a recent study's sample of 320 RA patients, 76 were identified as D2T, accounting for 23.75% of the total[18]. RA is a complex and multifactorial disease encountered frequently in clinical practice, making its management more challenging[19]. Our study indicates that long disease duration and activity, rheumatoid factor positivity and the presence of pulmonary involvement were significantly higher in the D2T RA group. These observations align with a real-life investigation that examined the traits of D2T RA patients, with longer disease duration being one of the hallmark features. The study also demonstrated an extended time lapse between symptom onset and treatment initiation within this group[12]. Furthermore, increased disease activity is a risk of D2T RA. The presence of persistent inflammation and activity, despite the use of conventional treatments, increases the difficulty of symptom management and the likelihood of joint destruction in people with D2T RA compared to those without[12]. The disease progresses rapidly and causes irreversible damage to the affected joints. This has a significant impact on quality of life. Our study shows that RF positivity is also a risk factor for D2T RA, regardless of the level which is in line with

other studies. Takanashi et al[12] revealed that the seropositivity was higher in the D2T RA group than in the non-D2T RA group. Also, the KURAMA cohort study demonstrated that a high level of rheumatoid factor is a risk factor for D2T RA after multivariate analysis of the results[20]. Furthermore, patients diagnosed with D2T RA often have increased rates of comorbidities which could complicate treatment[21]. Roodenrijs et al[13] found that the median number of comorbidities was higher in D2T RA patients than in non-D2T patients (2 *vs.* 1 p <0.001). Also, recurrent infections (54% *vs*. 15%), osteoporosis (37% *vs*. 17%) and gastrointestinal disease (19% *vs*. 7%) were statistically significantly more common in D2T RA patients. Additionally, interstitial lung disease is a common occurrence in patients with D2T RA and can potentially complicate RA management and may limit treatment options[12,21].

On another hand, low socioeconomic status at disease onset increases the risk of developing D2T RA[13], which may make it difficult to change treatment despite high disease activity. Access to certain treatments may also be challenging for these patients. The efficacy and safety of biosimilars allow affordable treatment for many patients, resulting in less financial pressure[23]. However, the need for frequent medical consultations, complex treatments, and the management of co-morbidities and overall wellbeing incurs extra costs to society.

The management of D2T RA requires a comprehensive, individualized strategy. Currently, there are no specific guidelines for this group of patients.

Nevertheless, the EULAR Working Group has devised guidelines for managing D2T RA that need to be considered[24].

These guidelines emphasize the importance of confirming the diagnosis of D2T RA by first ruling out diseases that may present with similar features. Subsequently, clinicians must ascertain disease activity while employing diagnostic ultrasound to detect subclinical synovitis if any uncertainty arises. Patient non-adherence to treatment must also be taken into account. When optimizing or switching treatment with DMARDs, the patient's comorbidities should be carefully considered[24]. There is no preference for b/tsDMARDs as a first-line therapy. However, using a b/tsDMARD with a different mode of action seems to be more effective after at least two b/tsDMARD failures[25]. Furthermore, Interleukin 6 inhibitors and JAKi (JAK inhibitors) data have shown efficacy above placebo in third- or fourth-line treatment[26].

Finally, the management plan should include non-pharmacological interventions and complementary therapies[27]. The disease's inflammation can be reduced through lifestyle changes, such as weight loss, smoking cessation, and exercise, which may have a favorable effect. Physical and occupational therapy might help improve joint function and quality of life. Patients with D2T RA could benefit from psychological support, and shared decision-making between the patient and rheumatologist may improve treatment adherence.

Effective management also entails therapeutic education. Non-adherence to treatment is more prevalent in this group, mostly due to concerns over treatment safety and efficacy resulting from side effects[27].

CONCLUSIONS

Patients with D2T RA continue to present a daily challenge and management issue despite intensive therapeutic interventions. Nevertheless, our study reveals that D2T RA encompasses a considerable number of patients displaying distinctive clinical features. Hence, a personalized approach involving early diagnosis, regular follow-up and timely intervention in collaboration with the patient is essential to enhance clinical outcomes and quality of life. Further research with a larger sample size and optimized therapeutic strategies is also necessary to decrease the proportion of D2T RA.

Authors' Contribution:

Chaimae Charoui and Nada Jaouad drafted this manuscript, collected the data and reviewed the literature. Bouchra Amine and Imane Elbinoune participated in article writing and reviewed critically the manuscript; Samira Rostom and Rachid Bahiri reviewed critically the manuscript. All authors read and approved the manuscript.

Availability of data and material:

Data and material are available from the corresponding author on reasonable request.

Conflict of interests:

The authors declare that they have no conflict of interest to disclose.

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This was a cross-sectional descriptive study, so the involvement of an Ethics Committee was not mandatory.

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