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Research Article

Difficult-to-treat Spondyloarthritis: What Are the Associated Factors

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Abstract

Introduction: There have been significant advances in the treatment of spondylarthritis (SpA) in recent years. Despite these advances, there is still a proportion of patients who experience multiple changes in biologic, which may correspond to difficult-to-treat spondylarthritis (SPA DaT). Unlike rheumatoid arthritis, there is no consensus definition for this concept. The aim of our study is to determine the prevalence of multi-switchers with spondylarthritis, identify their characteristics, and analyse the number and reasons for switching in a Moroccan population. *Patients and methods:* This is a comparative cross-sectional study that included patients with SpA diagnosed according to the 2009 ASAS criteria admitted to our department for targeted treatment. Sociodemographic data, comorbidities, and clinical, paraclinical, and therapeutic characteristics were collected for each patient. Multi-switchers who had received at least two biologics were considered to be SpA DaT. Their prevalence was estimated, and a comparison was made with a control group of non-multi-switchers (SpA-non-DaT). *Results:* Two hundred and ten patients were included, 56.2% of whom were men, 63% with a long average disease duration. The prevalence of multi-switchers was 32.7%. Compared to the control group, patients in the DaT group were predominantly female (53.6% versus 39%, p=0.04), had more axial involvement (76.8% versus 91.5%, p=0.003) and peripheral joint involvement (88.4% versus 67.4%, p= 0.001) and associated fibromyalgia (33.3% versus 66.7%, p = 0.980), CsDMARD use (97.1% versus 31.9%, p= < 0.001), and corticosteroid use (34.8% versus 11.3%, p= < 0.001). Disease activity, BASDAI, ASDAS and CRP at the start of biotherapy were higher in the SPA DaT group (BASDAI: 21.8% versus 20.6%, p=0.08), (ASDAS: 46.4% versus 54.6%, p = 0.03), BASFI (27.5% versus 41.8% p=0.04) CRP (: 14.19 ±4.73 mg/l versus 13.7 ±2.1 mg/l, p = 0.01). Similarly, the time between diagnosis and use of the first biologic was longer (4 [2.25–6] years versus 3 [1–4] years, p = 0.03). All patients in the DaT group had received anti-TNFα, and 22.9% had received anti-IL17. Analysing switches between biologics in this difficult-to-treat group, the first switch was linked to primary failure in 59% of cases, secondary failure in 29% of cases, and an adverse effect in 12% of cases. In the second switch, primary and secondary failure were observed in 64% and 33% of cases, respectively, and adverse effects in 3%. Regarding the third switch, 83% had primary failure and 17% had secondary failure. *Conclusion:* This study reveals a significant prevalence of patients with multiple treatment changes in the Moroccan population, highlighting the need for a larger patient sample to better define this condition.

Keywords

Spondylarthritis, Targeted Treatment, Difficult to Treat, Definition, Associated Factors

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1. Introduction

There have been significant advances in the treatment of spondylarthritis (SpA) in recent years. Despite these advances in the management of spondylarthritis (SpA), there is still a proportion of patients with multiple biological changes, which may correspond to difficult-to-treat spondylarthritis (SPA DaT) [1], or a substantial proportion of patients with residual symptoms who do not achieve remission. These 'refractory' or 'difficult to treat' (DaT) forms are now characterised by an insufficient response to several lines of treatment with different mechanisms of action, a concept borrowed from that of DaT rheumatoid arthritis. However, this definition is insufficient. The concept of non-inflammatory refractory SpA and persistent inflammatory refractory SpA is more suited to clinical practice and allows therapeutic proposals to be adapted accordingly [2], or The development of new biotherapy treatments for patients with axial spondylarthritis (ax SpA) has resulted in low disease activity or prolonged remission in 1 in 3 patients. Despite current treatment options, only 40-50% of patients with axial spondylarthritis (ax SpA) achieve a relevant therapeutic response, and an even smaller proportion (approximately 10-20%) achieve remission or inactive disease status within 16-24 weeks of starting treatment, according to data from randomised controlled trials. In other cases, the disease remains active despite a change in specialty or mechanism of action. This study is the first to propose a definition of ax SpA DaT and a comparison of patients thus identified with non-DaT ax SpA patients [3]. Or The disease management strategy has evolved in recent years, with the introduction of new classes of targeted therapies and the development of concepts such as treat to target (T2T) and strict control, which may lead to more frequent treatment rotation and faster therapeutic escalation [4]. Unlike the definition of difficult-to-treat rheumatoid arthritis (DaT RA) [5], similar to the EULAR definition of D2T-RA, D2T-SpA has been defined as the failure of three synthetic biological/targeted DMARDs (b/tsDMARDs) or two b/tsDMARDs with different targets. Comorbidities and extra-musculoskeletal manifestations (EMMs) were identified using algorithms previously described in the literature. After comparing the characteristics between the D2T-SpA and non-D2T-SpA groups, a multivariate analysis adjusted for age and duration of exposure to b/tsDMARDs was performed using logistic regression [6]. When spondylarthritis is suspected, the diagnostic process begins with the identification of signs or symptoms that may suggest another condition with similar clinical or imaging characteristics. Identifying potential differential diagnosis is crucial in order to offer patients the most appropriate treatment [7]. There is no consensus definition for this concept. The aim of our study is to determine the prevalence of multi-switchers with spondylarthritis, identify their characteristics and associated factors, and analyse the number and reasons for multi-switching.

2. Patients and Methods

This is a comparative cross-sectional study that included patients with SpA diagnosed according to the ASAS 2009 criteria for axial SpA and the ASAS 2011 criteria for peripheral SpA [8], admitted to our department. Sociodemographic data, comorbidities, clinical, paraclinical and therapeutic characteristics were collected for each patient. Multi-switchers who had received at least two biologics were considered to be DaT SpA. Their prevalence was estimated, and a comparison was made with a control group of non-multi-switchers with "non-difficult-to-treat spondylarthritis (non-DaT SpA). The number and reasons for switching in the DaT SpA group were analysed. All other conditions [9] that could mimic SpA were excluded from our series.

3. Results

During our study, we collected data on 210 patients, 56.2% of whom were men, 63% with a long average disease duration. The prevalence of multi-switchers was 32.7%. Compared to the control group, patients in the difficult-to-treat (DaT) group were predominantly female (53.6% versus 39%, p= 0.04), had more axial involvement (76.8% versus 91.5%, p= 0.003) and peripheral joint involvement (88.4% versus 67.4%, p= 0.001) and associated fibromyalgia (33.3% versus 66.7%, p = 0.980), CsDMARD use (97.1% versus 31.9%, p= < 0.001), and corticosteroid use (34.8% versus 11.3%, p= < 0.001). Disease activity, BASDAI, ASDAS and CRP at the start of biotherapy were higher in the SPA DaT group (BASDAI: 21.8% versus 20.6%, p=0.08), (ASDAS: 46.4% versus 54.6%, p = 0.03), BASFI (27.5% versus 41.8% p=0.04) CRP (: 14.19 ±4.73 mg/l versus 13.7 ±2.1 mg/l, p = 0.01). Similarly, the time between diagnosis and use of the first biologic was longer, at 4 [2.25–6] years versus 3 [1–4] years, p = 0.03). All patients in the DaT group had received anti-TNFα, and 22.9% had received anti-IL17. Analysing switches between biologics in this difficult-to-treat group, the first switch was linked to primary failure in 59% of cases, secondary failure in 29% of cases, and an adverse effect in 12% of cases. In the second switch, primary and secondary failure were observed in 64% and 33% of cases, respectively, and adverse effects were found in 3%. Regarding the third switch, 83% had primary failure and 17% had secondary failure.

4. Discussion

When faced with a suspicious picture of SpA, the diagnostic approach is based on epidemiological, clinical and paraclinical arguments, in accordance with the classification criteria, and begins with the identification of signs or symptoms that may suggest another pathology with similar clinical or iconographic characteristics. Identifying potential differ-

ential diagnosis is crucial in order to offer patients the most appropriate treatment [9]. Managing spondylarthritis is difficult and has evolved in line with new concepts and treatments. The SFR recently issued new recommendations for the routine management of this condition. There is no recent-simplified text summarising these recommendations for patients. Rewrite the recommendations in language that is understandable to the general public for the practical management of patients with spondylarthritis (including psoriatic arthritis); rewrite based on the text of the recommendations of the French Society of Rheumatology published in January 2014. A working group was formed, comprising seven patients from national associations for patients with spondylarthritis (AFLAR and AFS), two rheumatologists and a reading group of 'patients' from patient associations (AFLAR, AFS and ACSAC Centre and Normandy). The working group rewrote the SFR recommendations in 'patient language' [10]. The management of immune-mediated inflammatory diseases (IMIDs) has been revolutionised, particularly by the advent of targeted treatments, including biologics and, more recently, Janus kinase inhibitors (JAKi). However, although their efficacy has been widely demonstrated, these treatments only achieve remission in 30 to 40% of rheumatoid arthritis cases, 50 to 60% of ankylosing spondylitis cases, 40% of psoriasis cases and 25 to 30% of inflammatory bowel disease cases. Chronic intestinal diseases (IBD) [7, 10, 11]. Spondylarthritis (SpA) has seen significant progress in its therapeutic management in recent years. However, there is a proportion of patients who remain in a situation of multiple switches between biologic for several reasons, which may correspond to spondylarthritis that is difficult to treat. Unlike rheumatoid arthritis, there is no consensus definition for this concept in spondylarthritis [12]. Multiple changes in targeted therapies are common in patients with spondylarthritis, according to a study of data from the National Health Data System (SNDS) [13], which found that first-line treatment was anti-TNFα in 87.3% of cases, which was higher than the result in our series (77.1%). The first switch was related to primary failure in 59% of cases, secondary failure in 29% of cases, and an adverse effect in 12% of cases, which is similar to the results of S. Zemrani et al, who found 57% of cases, secondary failure in 33% of cases, and an adverse effect in 10% of cases. Difficult-to-treat (DTT) patients reported a higher BASDAI at the initiation of biologic therapy (21.8% versus 20.6%, p=0.08) and a lower BASFI (27.5% versus 41.8%, p=0.044) and a lower ASDAS/CRP score (46.4% versus 54.6%, p=0.032) and more often presented with associated axial involvement, which differs from the results found by T. Delepine, is similar to the results of Jm K, Aa O, et al., and is higher than that found by Pham T, et al. Multiple changes in targeted therapies could be a sign of SpA DaT [14]. There have been major advances in the therapeutic management of SpA in recent years. When spondylarthritis is suspected, the diagnostic process begins with the identification of signs or symptoms that may suggest another condition with similar clinical or imaging characteristics. Identifying potential differential diagnosis is crucial in order to offer patients the most appropriate treatment [7]. However, there is a proportion of patients who continue to switch between multiple biologics for a variety of reasons, which may correspond to spondylarthritis that is difficult to treat. Unlike rheumatoid arthritis, there is no consensus definition of this concept in spondylarthritis [15]. The results were mixed, with some considering the disease difficult to treat if the ASDAS/CRP activity score was >2, others if two biological drugs had failed, if it was impossible to reduce the dose of corticosteroid therapy, and if there were extra-articular manifestations, comorbidities, or polypharmacy. Given this divergence of opinion, a consensus definition would be necessary in order to compare the results of different studies [3]. The exact prevalence of DaT-SPA is difficult to establish because it varies, there is no consensus definition, and it may depend on an ASDAS/CRP activity score >2, failure of two biological drugs, inability to reduce the dose of corticosteroid therapy, and the presence of extra-articular manifestations or comorbidities. According to our work, the prevalence of SpA DaT at the time of patient inclusion in the study was 32.7%, which is higher than the result of S. Zemrani et al., who found a prevalence of 23.7% [15]. Axial involvement in our study was found in 76.8% of patients, which is lower than the result reported by T. Délepine et al., who found 86% (3). Multiple changes in targeted therapies are common in patients with spondylarthritis, according to a study of data from the French National Health Data System (SNDS) [14], which found that first-line treatment was anti-TNFα in 87.3% of cases, which was higher than the result in our series (77.1%). The first switch was related to primary failure in 59% of cases, secondary failure in 29% of cases, and an adverse effect in 12% of cases, which is similar to the result of S. Zemrani et al., who found 57% of cases, secondary failure in 33% of cases, and an adverse effect in 10% of cases. Difficult-to-treat (DTT) patients reported a higher BASDAI at the initiation of biologic therapy (21.8% versus 20.6%, p=0.08) and a lower BASFI (27.5% versus 41.8%, p=0.044) and a lower ASDAS/CRP score (46.4% versus 54.6%, p=0.032) and more often presented with associated axial involvement, which differs from the results found by T. Delepine (3). These results highlight the need for a standardised definition of early SpA [16] and are similar to the results of Jm K, Aa O, et al. [16], and higher than those found by Pham T, et al. [16]. In multivariate analysis, among the factors associated with SPA DaT in our series, we found female gender 53.6% versus 39.0% with a 95% confidence interval (CI) = 0.55 [0.31-0.99], p=0.04, axial involvement 76.8% versus 91.5% with 95% CI= 3.25 [1.44 -7.32] p=0.003, peripheral joint involvement 88.4% versus 67.4% with 95% CI =0.271 [0.120-0.613] p=0.001, prolonged corticosteroid therapy 34.8% versus 11.3% with 95% CI=0.240 [0.12-0.49] p< 0.001, high disease activity with ASDAS/CRP=46.4% versus 54.6% p=0.03, moderate functional impact of the disease BASFI 27.5% versus 41.8%, 95% CI=1.89 [1.01–3.54]

p=0.04. None of the following factors are associated with SpA DaT, in particular mean age 36.0 ± 12.5 years p=0.19, HLA B27 genetic predisposition 75.4% versus 77.3% with 95% CI=1.11 [0.57–2.19] p=0.76, enthesitis 84.1% versus 87.9% with 95% CI=1.38 [0.609-3.14] p=0.44, anterior uveitis 31.9% versus 27.7% with 95% CI=0.817 [0.437-1.53] p=0.526, psoriasis-like skin involvement 29.0% versus 19.9% with 95% CI=0.607 [0.31-1.18] p=0.14, or presence of dactylitis 11.6% versus 5.0% with 95% CI=0.398 [0.138-1.15] p=0.08, IBD-type digestive involvement 34.8% versus 26.2% with 95% CI=0.67 [0.36 -1.24] p=0.20, presence of hypertension 7.2% versus 7.1% with 95% CI=0.977 [0.321–2.98] p=0.97, diabetes 7.2% versus 6.4% with 95% CI=0.873 [0.281 -2.71] p=0.81, smoking 8.7% versus 10.6% with 95% CI=1.25 [0.463–3.38] p=0.66, heart disease 0.0% versus 1.4% with 95% CI=2.49 [0.12 -52.6] p=0.320.

5. Conclusion

Despite significant therapeutic advances in the management of SpA, many patients do not complete remission and cycle through multiple biological (b) or targeted DMARDs. Patients with SpA that are difficult to treat due to repeated therapeutic failures are the most common in our daily practice. Here we describe the prescribing patterns and associated factors in patients with refractory SpA who have failed multiple b/tsDMARDs in our department. They report higher disease activity indices and more often present with associated peripheral involvement. Our study finds a high prevalence of multi-switchers in spondylarthritis. However, a larger patient sample is needed in order to establish a prerequisite for proposing an appropriate definition.

Table 1. *Demographic and clinical characteristics of all patients with SpA.*

	N=210	SpA DaT	SpA non DaT	P univarie	P multivarie
average (years)		38.8 ±12.5	39.9 ±13.8	<0.001	0.19
Sex (male)	118	27.1%	72.9%	0.04	0.57
HLA B27	161	32.3%	67.7%	0.9	0.76
CRP					
ASDAS/CRP	109	29.4%	70.6%	0.04%	0.03
BASDAI	44	34.1%	65.9%	0.84%	
BASFI	78	24.4%	75.6%	0.04%	p= 0.04
Axial damage Rx	165	29.1%	70.9%	0.003%	
Axial damage no Rx	15	33.3%	66.7%	0.97%	
Peripheral joint damage	156	39.1%	60.9%	0.001%	p=0.001
Peripheral enthesitis	182	31.9%	68.1%	0.44%	0.44
Coxite	13	49.0%			
Syndesmophytes	83	39.5%			
Dactylites	15	53.3%	46.7%	0.080	0.08
psoriasis lesions	48	41.7%	58.3%	0.14	0.14
IBD	61	39.3%	60.7%	0.200	0.20
Uveitis	61	36.1%	63.9%	0.53	0.5
Fibromyalgia	6	33.3%	66.7%	0.98%	
Depression	8	37.5%	62.5%	0.72%	
HTA	12	33.3%	66.7%	0.97%	0.97
Diabetes	14	35.7%	64.3%	0.81%	0.81
Heart disease	2	0.0%	100.0%	0.32%	0.32
IMC≥30	22	10.5%			
smoking	21	28.6%	71.4%	0.66%	0.66

	N=210	SpA DaT	SpA non DaT	P univarie	P multivarie
Osteoporosis	26	30.8%	69.2%	0.81%	
treated Osteoporosis	23	88.5%			
NSAIDs					
Corticosteroids	40	60.0%	40.0%	< 0.001%	< 0.001
CsDMARD	112	59.8%	40.2%	< 0.001%	
Biotherapy	117	55.5%	44.5%		p=0.08
SpA DaT	210	32.7%	67.3%		p=0.04

Abbreviations

SpA	Spondylarthritis
DaT SpA	Difficult-to-Treat Spondylarthritis
DTR	Difficult-to-Treat Rheumatoid Arthritis
non-DaT SpA	No Difficult-to-Treat Spondylarthritis
DaT	Difficult-to-Treat
CsDMARD	Conventionnels Disease-Modifying Antirheumatic Drugs
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
CRP	C-reactive Protein
BASFI	Bath Ankylosing Spondylitis Functional Index
ax SpA	Axial Spondylarthritis
TNFα	Tumor Necrosis Factor-Alpha
T2T	Treat to Target
JAKi	Janus Kinase Inhibitors
CI	Confidence Interval
EMMs	Extra-musculoskeletal Manifestations
b/tsDMARDs	Biologic/Targeted Synthetic Disease-Modifying Antirheumatic Drugs
DTT	Difficult-to-Treat
IBD	Chronic Intestinal Diseases
ASAS	Assessment of SpondyloArthritis International Society
HLA-B27	Human Leucocyte Antigen B27
SNDS	National Health Data System
AFS, AFLAR, ACSAS Center of Normandy	The working group AFS, ACSAC centre, ACSAC Normandy and the Internet Users with Spondyloarthritis
D2T-SpA	Difficult-to-Treat Spondylarthritis

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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