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RESEARCH ARTICLE

FAILURE OF THE FIRST BIOLOGIC TREATMENT IN PATIENTS WITH SPONDYLOARTHRITIS: DATA FROM THE MOROCCAN REGISTRY OF BIOLOGICAL THERAPIES IN RHEUMATIC DISEASES (RBSMR)

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Abstract

Introduction: Spondyloarthritis is a group of chronic inflammatory rheumatic diseases that commonly affect young adults. The advent of biological background treatments has revolutionized the management of these conditions, although some patients may not respond adequately to these interventions.

Objectives: To assess the prevalence of first biological treatment failure in spondyloarthritis and identify the factors associated with this outcome.

Methods: Our study included patients with spondyloarthritis retained according to the ASAS criteria, aged over 18 years, treated with biological treatment, and providing written informed consent. The participants were sourced from the ten rheumatology departments in Morocco, utilizing data from the RBSMR registry, a multicenter historical-prospective registry. Primary failure was characterized by

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treatment inefficacy within the initial six months, while secondary failure concerns cases of ineffectivenessbeyond six months of treatment. Patients were assessed every six months with a scheduled follow-up period of three years. Inclusion began in June 2017 and ended in January 2019, when the database was first frozen.

Results: A total of 194 patients were included in the study. The mean age was 40.23 years with a standard deviation of 13.68. The gender ratio was 1.73 (M/F). The average disease duration was 615.9 weeks with a standard deviation of 349.12. HLA-B27 antigen was positive in 66% of patients. Peripheral involvement was observed in 70% of patients, axial involvement in 96.4%, and enthesic involvement in 61.5%. Radiographic sacroiliitis was identified in 87.6% of patients, radiographic coxitis in 40.7%, and sonographic coxitis in 19.8%. Regarding extra-articular manifestations, 14.5% of patients experienced anterior uveitis, 6.9% had cutaneous psoriasis, and 10.7% had concomitant chronic inflammatory bowel disease. The ASDAS CRP indicated high activity in 50.9% of patients, and the BASDAI (spondyloarthritis activity index) exceeded 4 in 79.2% of patients. During the initial visit, 22.5% of patients were undergoing corticosteroid therapy, and 53.8% were receiving csDMARDs. Etanercept was the most commonly prescribed biological, accounting for 33%. Over the three-year follow-up, five primary failures and 17 secondary failures to the first biological treatment were observed (eight failures at the 12th month, six at the 18th month, and three at the 24th month), resulting in a prevalence of 11,85% for the failure of the first biological. In bivariate analysis, no statistically significant factors were found to be associated with the failure of the first biological at the 6th, 12th, or 24th month visits. However, at the 18th-month visit, both the average BASDAI and C-reactive protein (CRP) levels were statistically higher in patients who experienced failure with the first biological.

Conclusion: The failure of the first biologicaltreatment is a rather rare situation in our study. Specific factors were notably linked to this failure and should be considered in patient management, particularly elevated BASDAI and CRP values. These factors have also been reported in the literature to be associated with first biological treatment failure, along with additional factors.

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Introduction:-

Spondyloarthritis (SpA) is a set of inflammatory rheumatic diseases that affect most frequently the sites where ligaments and tendons attach to bones referred to as “entheses.” It can also involve other locations such as the skin, intestines and eyes [1]. The European Spondyloarthropathy Study Group (ESSG) has identified five primary subtypes of SpA based on their proposed classification criteria. It includes ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), arthritis linked to inflammatory bowel disease (SpA-IBD), and undifferentiated spondyloarthritis (uSpA) [2].

Spondyloarthritis encompasses a spectrum of diseases with diverse clinical presentations. A hallmark feature is the presence of inflammatory back pain, characterized by prolonged lumbar or buttock/hip discomfort lasting over three months, demonstrating improvement with physical activity, exacerbation during periods of rest, responsiveness to nonsteroidal anti-inflammatory drugs (NSAIDs), and the presence of morning stiffness persisting for more than 30 minutes. This condition predominantly affects young individuals, often engaged in sports and athletic activities [3]. Additionally, there is a familial predisposition, and a notable association with specific human leukocyte antigen (HLA) genes, particularly HLA-B27, within the major histocompatibility complex (MHC) [4]. The precise cause and development of spondyloarthritis remain elusive, however, the genetic component appears to be primarily associated with the pathogenesis of spondyloarthritis. Numerous studies have shown the involvement of

microorganisms in initiating the disease. From a genetic perspective, SpA exhibits a strong association with the major histocompatibility complex (MHC) class I antigen, specifically HLA-B27 [2]. Spondyloarthritis can manifest in various forms, including spinal damage, peripheral arthritis (which means the swelling and inflammation of one or more joints), enthesopathy (which mean a disorder involving the attachment of a tendon or ligament to a bone), and extra-articular damage [5]. The pathophysiologyof spondyloarthritis involves a pivotal role played by the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα). Targeted therapies directed against TNFα, such as antibodies and soluble receptors, have been identified to significantly impact disease control by mitigating symptoms associated with inflammation [6]. The treatment landscape for spondyloarthritis has witnessed substantial advancements with the advent of biological therapies. Despite the widespread utilization of these treatments, predicting patient response before initiation remains a challenge. TNF alpha inhibitors, comprising infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP), are commonly considered as the first-line biologic disease- modifying antirheumatic drug (bDMARD) therapy for spondyloarthritis [7]. They are characterized by multiple advantages like efficacy in reducing inflammation, improving symptoms, and slowing disease progression. Other biologic treatments include interleukin-17 (IL-17) inhibitors, such as secukinumab and ixekizumab, which target a different inflammatory pathway have shown promising results in some AS patients. The effectiveness of biologic treatments varies from individual to individual, and considerations such as tolerability, safety, and individual response must be taken into account when selecting a specific therapy. While these treatments have revolutionized the approach to inflammatory rheumatic diseases, a considerable number of patients experience challenges associated with the failure of their initial biologic therapy. This phenomenon necessitates a comprehensive understanding of the factors influencing treatment outcomes and prompts the exploration of alternative therapeutic strategies. Identifying predictors of biologic treatment failure, optimizing patient selection, and choosing treatment regimens based on individual profiles are imperative to take on the challenges associated with the initial biologic therapeutic failures in spondylarthritis.Failure of the first biological treatment can be divided into two groups: primary failure (no response within 6 months after treatment initiation, or lack of efficacy) and secondary failure (initial response within 6 months but subsequent loss, or loss of efficacy over time). Failure of biologic treatment can be detected by objective and subjective parameters such as significant biological inflammatory syndrome, joint manifestations, active synovitis on ultrasound...and concluding that treatment has failed requires correct adherence from patients [8]. The objective of this study was to estimate the prevalence of failure of the first biological treatment during spondyloarthritis and the factors associated with this failure to take them into consideration when caring for patients.

Materials and Methods:-

Study design:

This was a cross-sectional multicenter, analytical study using the RBSMR registry database, and included 194 patients who fulfilled the ASAS criteria for axial SpA or peripheral SpA.

The RBSMR (Register of Biotherapies of the Moroccan Society of Rheumatology) is a registry of biological therapies in rheumatic diseases established by the Moroccan Society of Rheumatology. It is a historical, prospective, and multicenter registry, which includes departments of rheumatology from 10 different university medical centers. The criteria for inclusion involved patients aged 18 and above, diagnosed with spondyloarthritis (SpA), and treated with biologic therapy (either initiating or continuing) in different university medical centers in Morocco [9]. These patients had provided their written informed consent to participate in the registry. The inclusion period was from May 2017 to January 2019, and the follow-up was three years. The primary goal of the RBSMR registry was to evaluate the tolerability of patients with SpA to treatment by biotherapy in rheumatology. The secondary objectives were to identify the prevalent side effects of this biologic therapy and to evaluate its effectiveness in rheumatology, and also to assess the impact of biotherapies on the patients' quality of life. The details of the data collected have been published previously. The protocol for the original RBSMR study was reviewed and approved by local institutional review boards and the national ethics committee, namely, the Ethics Committee for Biomedical Research Mohammed V University - Rabat, Faculty of Medicine and Pharmacy of Rabat. The committee's reference number: 117/17.

Study Aims:

The objective of this study was to estimate the prevalence of failure of the first biological treatment during spondyloarthritis and the factors associated with this failure to take them into consideration when caring for patients. Failure of first biological treatment was the main outcome measure in our study, defined as the discontinuation of

the treatment for ineffectiveness between two visits. We determined the first biological treatment for each patient and we looked for failure at each medical visit. The following information was collected:

Age,sex, duration of evolution, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), presence or absence of HLA B27 (human leucocyte antigen B27), the various axial and/or peripheral damage, different extra articular manifestations, the different treatment used (corticosteroids, csDMARDs (conventional synthetic disease-modifying antirheumatic drugs) and bDMARDs (biological disease-modifying anti- rheumatic drugs).

Disease activity was assessed using various measures, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP), Bath Ankylosing Spondylitis Functional Index (BASFI).

Furthermore, the study evaluated comorbidities like diabetes, high blood pressure, heart disease, tuberculosis..., as well as extra-articular involvement like uveitis, psoriasis, and inflammatory bowel disease (IBD).

The statistical analysis:
A general description has been made, quantitative variables were presented as means and standard deviations (SD), while qualitative variables were presented as percentages.

The statistical analysis was performed Using an SPSS (Statistical Package for the Social Sciences) software version 26.0. A bivariate analysis was performed to determine factors associated with failure of first biological treatment using test of khi 2 to compares the percentages and test of student to compares the averages and p values less than 0.05 were considered statistically significant.

Results:-

A total of 194 patients were included in our study with a predominance of male patients, the sex ratio was 1,73 M/F. The average age of all patients was 40,23 years +/- 13,68, the average duration of evolution was 11,81 years +/- 6,69 and the average BASDAI was 4,87.The HLA B27 antigen tested positivein 66% of patients. Peripheral involvement was found in 70% of patients, axial involvement in 96.4% of patients and enthesis involvement in 61.5% of patients. Radiographic sacroiliitis was present in 87.6% of patients, radiographic coxitis in 40.7% and sonographic coxitis in 19.8%. Family involvement was present in 14.5% of the patients. A biological inflammatory syndrome tested positive in 41.1% for ESR (erythrocyte sedimentation rate) and 34.2% for CRP (C-reactive protein). Regarding extra-articular manifestations, 14.5% of patients had anterior uveitis, 6.9% had cutaneous psoriasis, and 10.7% had associated chronic inflammatory bowel disease. The ASDAS CRP was in high activity in 50.9% of the patients and the BASDAI (spondyloarthritis activity index) more than four in 79.2% of the patients. At the first visit, 22.5% of patients were taking corticosteroid therapy and 53.8% were taking csDMARDs. Only 5,7% of patients had a high blood pressure (11 patients), 5,2 % were diabetic (10 patients), 10,8 % were smokers (21 patients) and two patients had heart disease (1%). Treatments inhibiting TNFα (anti-TNFα) have certainly revolutionized the management of chronic inflammatory rheumatism and intestinal diseases, but at the cost of a major risk of opportunistic infections, in particular tuberculosis (TB), 6,9 % of our patients had tuberculosis (13 patients), 12% had a history of notion of positive IDR for tuberculin (19 patients) and 20,6% had a positive quantiferon test. (Table 1)

Table 1:- Characteristics of included patients (baseline data).

	N=194
Sex ratio (M/F)	1,73 M/F
Average age (years)	40,73 +/- 13,68
Average duration of evolution (years)	11,81 +/- 6,69
Average BASDAI	4,87
HLA B27 (%)	66%
Radiographic sacroiliitis (%)	87,6%
Radiographic coxitis (%)	40,7%
Sonographic coxitis (%)	19,8%
Treatment	
Corticosteroid therapy (%)	22,5%
Analgesic (%)	52,4%

Dmards (%)	56,3%
Comorbidity	
High blood pressure (%)	5,76%
Smoking (%)	10,6%
Diabetes (%)	5,2%
Heart disease (%)	1 %
Tuberculosis (%)	6,9%
Extra-articular manifestations	
Uveitis (%)	14,5%
Psoriasis (%)	6,9%
IBD (%)	10,7%

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

Dmards: Disease-Modifying Antirheumatic Drugs. IBD: Inflammatory Bowel Diseas

Five types of biological treatments were used: etanercept 50mg/week subcutaneously, golimumab 50mg/month subcutaneously, adalimumab 40mg/15 days subcutaneously, infliximab 5mg/kg/month infused at weeks zero, two, and six, then every eight weeks thereafter and secukinumab 150mg at weeks zero, one, two, three and four, then every four weeks. The most widely used biological was etanercept with a percentage of 33% followed by adalimumab (30,4%) then infliximab (26,3%) then golimumab (9,8%) and finally secukinumab (1,5%). Over a follow-up period of three years, five primary failures were objectified and 17 secondary failures to the first biological treatment (eight failures at the 12th month, six failures at the 18th month and three failures at the 24th month), the prevalence of failure of the first biological was 11,85% and Infliximab was the biological agent most responsible for first-line failure with a percentage of 36 %. The majority of patients experiencing failure with their initial biologic treatment were women, constituting 63.6% of the cases. Their mean age was 40.82 ± 15.67, and the average disease duration was 585.94 ± 337.07 weeks. All these patients exhibited axial involvement, while peripheral involvement was observed in only 77.3%, and enthesitis was present in 63.3%. Family history of rheumatoid conditions was noted in 27.3%, radiographic sacroiliitis in 86.4% of patients, and coxitis in 36.4%. Those who experienced failure with their first biologic treatment predominantly exhibited high disease activity, with 63.6% having an Ankylosing Spondylitis Disease Activity Score (ASDAS) CRP >3.5 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4. A biological inflammatory syndrome, indicated by elevated CRP, was present in 55% of patients, while an increased erythrocyte sedimentation rate (ESR) was observed in 40.9%. It is noteworthy that patients who did not respond to the initial biologic treatment did not show any associated comorbidities (Table 2). The mean CRP (C-reactive protein) level was higher in patients who experienced failure with the initial biologic treatment, and all these patients did not exhibit any associated infectious episodes that could explain the elevation in CRP. Additionally, there were no occurrences of neoplasia or extra-articular manifestations in this patient subset. A limited number of patients demonstrated extra-articular manifestations: one had uveitis, two had cutaneous psoriasis, and two others had associated inflammatory bowel disease.

Table 2:- Characteristics of patients who have failed biological treatment.

	N=23
Sex ratio (M/F)	0,57 M/F
Average age (years)	40,82+/-15,67
Average duration of evolution (years)	585,94 +/- 337,07
Average BASDAI	4,86+/-1,41
Axial involvement (%)	100%
Peripheral involvement (%)	77,3%
Enthesis damage (%)	63,6%
Uveitis (%)	4,5%
Psoriasis (%)	9,1%
Inflammatory bowel disease (%)	9,1%
Family history of rheumatoid conditions (%)	27,3%
Radiographic sacroiliitis (%)	86,4%
Coxitis (%)	36,4%
High disease activity (%)	63,6%

High CRP (%)	55%
High ESR (%)	40,9%

BASDAI: Bath ankylosing spondylitis Disease Activity Index CRP: C-reactive protein ESR: Erythrocyte Sedimentation Rate

The evolution over time doesn't influence failure of first biological, this is shown in the following table where the failure of the first biological treatment was lower at the sixth month then increased at the 12th month then experienced a progressive decline over time. In bivariate analysis, no statistically significant factors were observed associated with the failure of the first biological during the visit of the 6th month, the 12th month or that of the 24th month. At the visit of the 18th month, the average BASDAI as well as that of the C reactive protein (CRP) was statistically higher in patients who failed the first biological. (Table 3)

Table 3:- Biological character and evaluation of patients in each visit and factors associated with failure of first biological treatment.

	Patients with failure of biological treatment	Patients without failure of biological treatment	P value
6th month visit	(N=5)	(N=189)	
BASDAI	3,14	2,78	P=0,679
BASFI	3,56	3,27	P=0,780
CRP (mg/l)	21,8	12,9	P= 0,315
ESR (mm/h)	35,33	24,21	P=0,392
ASDAS CRP	2,3	2,1	P=0,685
12th month visit	(N=8)	(N=181)	
BASDAI	3	2,42	P=0,379
BASFI	3,45	2,88	P=0,560
CRP (mg/l)	18,7	14,7	P=0,70
ESR (mm/h)	19,1	25,4	P=0,466
ASDAS CRP	2,03	1,86	P=0,695
18th month visit	(N=6)	(N=175)	
BASDAI	4,7	2,4	P=0,04
BASFI	4,27	2,03	P=0,152
CRP (mg/l)	40,67	9,87	P=0,002
ESR (mm/h)	70	77	P=0,062
ASDAS CRP	2,4	1,87	P=0,349
24th month visit	(N=3)	(N=172)	
BASFI	3,93	2,49	P=0,155
CRP (mg/l)	6,99	5,33	P=0,646
ESR (mm/h)	31,5	17,68	P= 0,292
ASDAS CRP	3,35	1,82	P=0,103

BASDAI: Bath ankylosing spondylitis Disease Activity Index BASFI: Bath ankylosing spondylitis functional index. CRP: C-reactive protein ESR: Erythrocyte Sedimentation Rate ASDAS CRP: Ankylosing Spondylitis Disease Activity Score

Discussion:-

Several studies have focused on the failure of biological treatments; in our study, the failure of the initial biologic was infrequent, and only two identified parameters could influence this failure, namely the CRP (C- reactive protein) levels and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), which were statistically significant at the 18-month follow-up visit indicating their association with secondary failure. Indeed, patients who experienced failure with the initial biologic treatment exhibited a higher average CRP (C-reactive protein) level, which is not explained by an apparent cause, particularly the absence of infections or extra-articular manifestations.

PraveenaChiowchanwisawakit, MD and al. had carried out a study of 138 patients (97 SpA et 41 psoriatic arthritis), the prevalence of first biologic treatment failure was 12,8%, also in our study we had a decreased prevalence of first biologic treatment failure. They have found that in multivariate analysis, a basic PGA (physicist global assessment)

< 3/10 and a high BASDAI value initially were significantly associated with the discontinuation of biological treatment (anti TNF alpha) with HR (95% IC) of 20.9 (3.3 to 131.5) and 1.8 (1.1 to 2.9) respectively, which was close to our study concerning BASDAIwhose average was significantly high in patients who failed the first biological treatment. In this thai study, we found that the median duration of the first TNFi use was 19 (22.9) months for ankylosing spondylitis (AS) and 15 (21.3) months for psoriatic arthritis PsA [10].

Bárbara P. Fafá and al had carried out a study using data from the Brazilian Registry of Biological Therapies in Rheumatic Diseases (BIOBADABRASIL) between 2008 and 2012 including 1303 patients (372 had ankylosing spondylitis (AS) and 931 had rheumatoid arthritis (RA), the aim of this study was to assess and compare drug survival rates and reasons for discontinuation of anti-tumoral necrosis factor (anti-TNF) therapy between ankylosing spondylitis (AS) and rheumatoid arthritis (RA) , they have found that the drug survival is significantly higher in AS and it could be explained by having younger male patients , they also discovered that female patients using corticosteroids, without being of advanced age, exhibited lower survival rates for both diseases (log-rank, $p \leq 0.001$) [11]. In contrastto our study, there was no influence of age and gender, nor of treatments, on the failure of the first biological treatment.

Randomized controlled trials (RCTs) have shown that raised inflammatory markers, lower Bath Ankylosing Spondylitis Functional Index (BASFI), and younger age at baseline were associated with clinical response to treatment [12-13]. This is partially consistent with our study, especially regarding the biological inflammatory syndrome, primarily a high CRP levels (C-reactive protein), which was associated with the failure of the first biological treatment. This link could be explained by the severity of rheumatism with a high biological inflammatory syndrome.

Suzanne Arends and al conducted a study aimed at identifying baseline predictors for the response and discontinuation of TNF-α blocking therapy in patients with ankylosing spondylitis (AS) in routine clinical practice. Their findings, as revealed through univariate Cox regression analysis, highlighted that female gender (HR: 0.503) and the absence of peripheral arthritis (HR: 0.382) were significantly associated with treatment discontinuation [14]. In the multivariate Cox regression analysis, independent baseline predictors for anti-TNF-α treatment discontinuation were identified, including female gender (HR: 0.406), absence of peripheral arthritis (HR: 0.320), higher BASDAI score (HR: 1.225), and lower ESR level (HR: 0.983) or, alternatively, lower CRP level (HR: 0.984) [14]. Unlike our study where the average C reactive protein (CRP) was statistically higher in patients who failed the first biological and at the same time consistent for the increased BASDAI value.

In a study conducted by Carolina Barata and al involving 515 patients from the Portuguese register of rheumatic diseases, insights were gained into factors influencing the failure and drug survival of biological treatments for spondyloarthritis. The results of Cox regression analysis revealed several notable findings. Factors indicative of a favorable prognosis for biologic drug survival included being male, starting biologic therapy at an older age, having a larger time interval between disease onset and the initiation of the first biologic therapy, and being HLA-B27 positive. On the contrary, a disease onset or initiation of biologic therapy in more recent years, a higher number of years of education, and elevated baseline values of C-reactive protein (CRP) or Bath Ankylosing Spondylitis Functional Index (BASFI) were identified as predictors associated with a greater risk of failure of the initial biologic therapy [15].

Indeed, the initiation year of the first biologic therapy, years of education, baseline CRP levels, and initial BASFI scores emerge as statistically significant predictors of the first biologic therapy's failure [15]. However, in our study, there was no association between the initiation date of biologic therapy and the failure of biologic treatments.

In the study by Ulf Lindström and al ., it was discovered that half of bio -naïve patients with ankylosing spondylitis (AS) who initiate their first TNFi discontinue the treatment within the next 5 years. The reasons for discontinuation were categorized as follows: adverse effects (27%), primary ineffectiveness (20%), secondary ineffectiveness (19%), "other" (26%), and missing data (1%). Furthermore, the study revealed that approximately half of the patients who discontinue their first TNFi proceed directly to a second TNFi. Additionally, the 5-year drug retention rate is higher for the first TNFi when compared to the second and third TNFi [16]. And finaly K Pavelka and al have found that among the factors significantly associated with stopping biological treatment were female gender (RR 2.22, p=0.001) and CRP (RR 1.33, p=0.025) [17].

The value of CRP appears to be significant in almost all the studies including our own underscoring the importance of considering this parameter when selecting biological treatments.

Conclusion:-

The failure of the first biologic treatment is a rather rare situation in our study. Certain factors were significantly associated with this failure and must be taken into account when managing patients, namely high values of BASDAI and CRP. These factors were also found in the literature to be associated with the failure of first biological treatment and also others factors. According to our recommendations, the failure of a first biological treatment implies the switch to another biological treatment and therefore this situation of failure doesn't constitute an obstacle to biological therapies which constitute a miraculous alternative for chronic inflammatory rheumatism.

In conclusion, our study revealed that the occurrence of initial biologic treatment failure in spondyloarthritis was relatively uncommon. Notably, the factors influencing this outcome were narrowed down to two significant parameters: CRP (C-reactive protein) levels and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). The identification of these specific markers as predictors of failure provides valuable insights for clinicians in assessing and managing patients undergoing biologic therapies. Further research and a nuanced understanding of these contributing factors will contribute to refining treatment strategies and enhancing overall outcomes for individuals with spondyloarthritis.

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