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Treatment Patterns, Survival and Long-Term Effectiveness of Biological Agents in Psoriatic Arthritis Patients

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ABSTRACT

Aim: To evaluate treatment patterns, cumulative survival and long-term effectiveness of biologic disease-modifying anti-rheumatic drugs (bDMARD) in patients with Psoriatic Arthritis (PsA).

Materials and methods: Observational retrospective multicentre study. Patients diagnosed with PsA treated with bDMARDs were included. Socio-demographic and clinical data was collected. We gathered information on bDMARD start date, concomitant treatment, suspension or change in treatment, and reasons for discontinuation. Therapeutic response was defined according to MDA (Minimal Disease Activity) at 6 and 12 months and then annually since the beginning of bDMARD treatment.

Statistical analysis: Student and Chi-square Test; Kaplan Meier and Log Rank curves; Cox regression analysis.

Results: 72 PsA patients were included, 39 (54.2%) were male. Median age was 54.5 years (IQR 45-61) and median disease duration was 11 years (IQR 6-15). 71.2% of patients presented comorbidities. bDMARs used in decreasing order of frequency were Adalimumab (45.83%), Etanercept (36.1%), Certolizumab (5.6%), Infliximab (4.2%), Ustekinumab (4.2%), Abatacept (2.7%) and Golimumab (1.4%). 15 patients (25.4%) received bDMARD as monotherapy. Mean bDMARD survival was 82 months (SD ± 7.4), without significant differences between the different agents. Older patients had a shorter drug survival (≥ 55 years: $\bar{X}$59.8 (SD ± 10.5) vs. <55 years: $\bar{X}$101.2 (SD ± 9.7), p=0.006), which remained significant after adjusting for different confounders in the Cox regression analysis [(HR=1.064 (IC=1.01-1.11) p=0.005)]. The LUNDEX of the first biologic agent was 24.7% at 6 months and 44.3% at 12 months. LUNDEX was lower in obese patients (16% vs. 66% at 1 year, p=0.89; 10.5 vs. 74.9% at 2 years, p=0.011 and 5.9 vs. 81.8% at 3 years, p=0.005).

Conclusion: The average survival of the first bDMARD was 6.8 years. Older age was the only variable associated to shorter survival.

Keywords: Psoriatic arthritis, Treatment patterns, Cumulative survival, Anti-rheumatic drugs

INTRODUCTION

Psoriatic Arthritis (PsA) is a chronic inflammatory and multifaceted disease which can be expressed clinically with arthritis, enthesitis, dactylitis and is generally associated to psoriasis [1,2]. This disease causes significant deterioration of quality of life, mainly due to its effects on physical function, with reduced work productivity [3]. The introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs) has substantially improved the disease's prognosis. Numerous controlled randomized clinical trials

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have proved their efficacy; however they have some external validation limitations, such as strict inclusion criteria, relatively short follow-up periods with no data regarding drug survival or treatment adherence in real-life patients [4]. Various countries have developed registers of patients receiving bDMARDs, many of which analyzed long-term survival [5-13]. DANBIO, the Danish register, has not shown differences in drug survival between Etanercept, Adalimumab and Infliximab after an 8 year follow-up period; further morefurthermore, male sex, concomitant treatment with methotrexate, and high CRP levels were associated to a higher drug survival raterate [5]. The SSATG register (Southern Sweden Arthritis Treatment Group) showed no significant differences amongst various TNFi (Tumor Necrosis Factor inhibitors) either, although Etanercept presented 50% less possibility of treatment discontinuation vs. Infliximab and no differences were found compared to Adalimumab [6]. An observational study carried out by Saougou et al. [14], reported similar efficacy between TNFi with a higher persistence rate for Etanercept. Favalli et al. [15] observed that the rate of persistence of Etanercept was higher in comparison to Adalimumab and Infliximab, maintaining this trend after 3, 5 and 8 years of treatment. The Finn register, ROB-FIN (National Register for Biologic Treatment in Finland) observed higher survival for Adalimumab compared to Infliximab, while there were no differences between Etanercept and Golimumab, and these were not affected by concomitant treatment with conventional synthetic (cs) DMARDs [9,16].

To the best of our knowledge there are no studies in our country estimating biologic survival rates in patients with PsA and studies of this type in Latin America are very scarce. Therefore, the aim of this study was to evaluate bDMARD treatment patterns in PsA patients, as well as to determine the survival rate of the first bDMARD, causes for discontinuation and the variables associated with their survival.

MATERIALS AND METHODS

A retrospective multicentre study was carried out (PATTERNS-PsA study). Patients ≥ 18 years old, diagnosed with PsA according to CASPAR criteria [17], who received treatment with bDMARDs during the course of their disease were included. Socio-demographic data (age, sex, marital status, education, occupation, health coverage), disease duration, clinical PsA type (olygoarticular, polyarticular or mixed) and associated comorbidities were recorded. Data regarding previous treatments causes for discontinuation and concomitant treatments with bDMARD were also documented. Additionally, baseline data was collected at the moment prior to the start of the first bDMARD treatment, at 6 months and then annually. Height (cm) and weight (kg) were recorded and Body Mass Index (BMI) was calculated. Disease activity was measured by 66/68 swollen and painful joints [18], physician and patient assessments of pain and disease activity by means of a Visual Numeric Scale (VNS) [19]. Acute phase reactants were registered (ESR -mm/h- and CRP -mg/dl-). Minimal Disease Activity (MDA) [20] was considered as a criteriaas a criterion of treatment response. The LUNDEX index was used in order to evaluate drug survival and effectiveness simultaneously [21]. This index results from the product of the proportion of patients which continued a given bDMARD and the proportion of patients fulfilling MDA criteria at the same time.

STATISTICAL ANALYSIS

Categorical variables were expressed as frequencies and percentages, while continuous variables as mean and median with their corresponding standard deviation (SD) or interquartile range (IQR). Categorical variables were compared using the Chi Square test and continuous variables by Student T test or Mann Whitney test according to their distribution. Cumulative drug survival was analyzed using Kaplan Meier curves and comparisons using Log Rank test. Variables associated to bDMARD survival were analyzed using Cox regression analysis using survival as a time variable, drug permanence as a dependent variable and various demographic, clinical and therapeutic factors as independent variables. Up to 15% of missing data was solved through data imputation by means of linear interpolation. A p value <0.05 was considered significant.

RESULTS

Seventy two patients with PsA were included, 39 (54.2%) were male with a median age of 54.5 years (IQR 45-61) and a median disease duration of 11 years (IQR 6-15). 51 (71.2%) patients presented comorbidities and 29 (40.3%) patients had a BMI ≥ 30. Other socio-demographic and clinical characteristics are described in **Table 1**. 33 patients received Adalimumab (45.83%), 26 patients Etanercept (36.1%), 4 Certolizumab (5.6%), 3 Infliximab (4.2%), 3 Ustekinumab (4.2%), 2 Abatacept (2.7%) and 1 Golimumab (1.4%). 15 patients (25.4%) received bDMARD in monotherapy. For the rest of the patients, the concomitant treatments with csDMARD were: 36 (61%) Methotrexate, 7 (11.9%) Leflunomide and 1 (1.7%) Sulfasalazine. Only 1 patient received combined treatment with Methotrexate and Leflunomide. Additional treatments included 47 (79.7%) patients received NSAIDs (Non-steroid anti-inflammatory drugs) and 15 (25.4%) prednisone in doses ≤ 10 mg/day.

Table 1. Socio-demographic and clinical characteristics in PsA patients.

Variables	n=72
Males n (%)	39 (54.2)
Age (years) *m* (IQR)	54.5 (45-61)
PsA disease duration (years) *m* (IQR)	11 (6-15)
Comorbidities n (%)	51 (71.2)
Smoking n (%)	22 (30.6)
Unemployed n (%)	21 (29.5)
BMI ≥ 30 n (%)	29 (40.3)
Previous treatments	
NSAIDs n (%)	66 (91.5)
Methotrexate n (%)	67 (93.2)
Leflunomide n (%)	19 (27.1)
Sulfasalazine n (%)	11 (15.3)
Prednisone<10 mg/day n (%)	34 (47.5)
Prednisone ≥ 10 mg/day n (%)	13 (18.6)
Combined treatment n (%)	14 (20.3)

PsA: Psoriatic Arthritis; BMI: Body Mass Index; NSAIDs: Non-Steroid Anti-Inflammatory Drugs

The average survival rate of the first bDMARD was 82 months (SD ± 7.4) **(Figure 1)** and the survival rates of the two most frequently used biologic agents were: a mean of 90 months for Adalimumab (SD ± 10.5) and 79 months for Etanercept (SD ± 11.9) **(Figure 2)**. Twenty-six (36.1%) patients discontinued the first bDMARD. Causes for discontinuation in decreasing order of frequency were: inefficacy (38.4%), lack of supply (23%), adverse events (23%) and patient's decision (15.3%). Amongst adverse events: 50% of patients presented infections, 33.3% allergic reactions and 16.6% injection site reactions. As regards treatment response, 26.6% (17/64 patients) of patients reached MDA at 6 months, 54.2% (26/48 patients) at 12 months and 54.8% (17/31 patients) after 2 years. Due to the fact that most frequently used bDMARDs were Adalimumab and Etanercept, only variables associated to the discontinuation of these two agents were analyzed. We observed that patients ≥ 55 years old, presented significantly less survival rates of the first bDMARD in comparison to younger patients ($\bar{X}$ 59.8 (SD ± 10.5) versus 101.2 (SD ± 9.7), p=0.006) **(Table 2 and Figure 3)**. The LUNDEX for the first bDMARD was 24.7% at 6 months and 44.3% at 12 months. When analyzing survival of the first bDMARD according to BMI, we observed that obese patients (BMI ≥ 30) tended to have a shorter survival in comparison to non-obese patients ($\bar{X}$ 59.8 (SD ± 8.8) versus $\bar{X}$ 90.9 (SD ± 9.08), p=0.2). The LUNDEX was lower in obese patients in comparison to non-obese patients: 16% vs. 66% the first year (p=0.89), 10.5% vs. 74.9% at 2 years (p=0.011) and 5.9% vs. 81.8% at 3 years (p=0.005). After adjusting for confounding variables, patient age ≥ 55 remained significantly associated with a lower survival of the first bDMARD (HR=1.064 (CI95%=1.01-1.11), p=0.005).

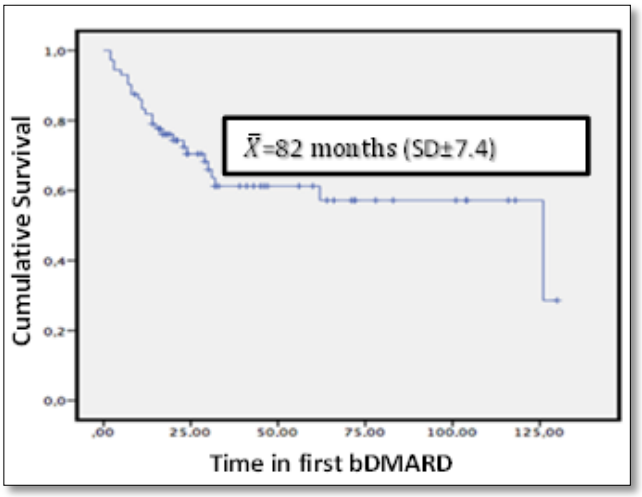

Figure 1. Survival of the first bDMARD in PsA patients.
PsA: Psoriatic Arthritis; bDMARD: Biologic Disease-Modifying Anti-Rheumatic Drug; $\bar{X}$: Mean; SD: Standard Deviation

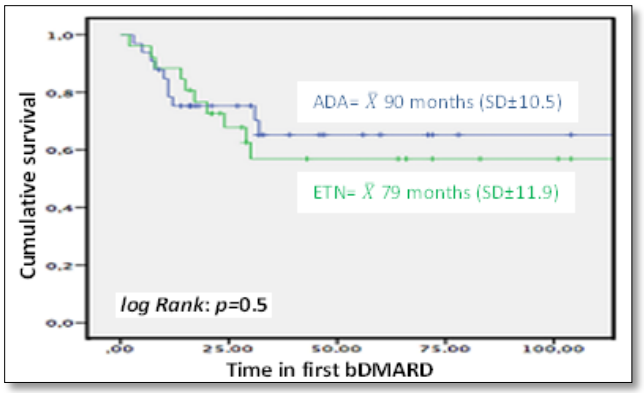

Figure 2. Survival of Adalimumab and Etanercept in PsA patients.
ADA: Adalimumab; ETN: Etanercept; X̄: Mean; SD: Standard Deviation; bDMARD: Biologic Disease-Modifying Anti-Rheumatic Drug

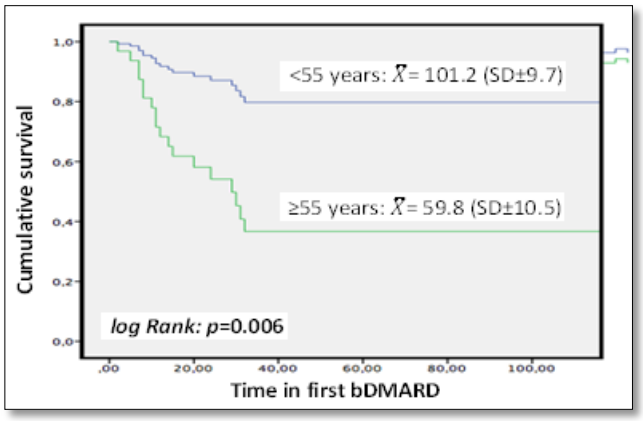

Figure 3. Survival of bDMARD in comparision to younger patients.
bDMARD: Biologic Disease-Modifying Anti-Rheumatic Drug; X̄: Mean; SD: Standard Deviation

Table 2. Comparison of socio-demographic, clinical and therapeutic variables amongst patients which continued and discontinued first bDMARD.

Variables	Discontinuation of first bDMARD		p
	YES n (%)	NO n (%)	
Male	14 (42.4)	19 (57.6)	NS
Age <55 years	7 (21.9)	25 (78.1)	0.017
PsA disease duration	21 (35.5)	38 (64.4)	NS
Smoking	13 (68.4)	25 (62.5)	NS
Education ≥ 8 years	20 (35)	37 (64.9)	NS
Comorbidities	16 (38.1)	26 (61.9)	NS
bDMARD monotherapy	4 (26.7)	11 (73.3)	NS
Concomitant Methotrexate	13 (36.1)	23 (63.9)	NS

bDMARD: Biologic Disease-Modifying Anti-Rheumatic Drug

DISCUSSION

Our results show an average survival of biologic therapy of approximately 7 years in patients with PsA, with greater survival for Adalimumab, but without significant differences. The only variable associated to less survival was patient age ≥ 55. There was a trend to lower survival in obese patients; nevertheless the LUNDEX was significantly lower in those patients. In our study, Adalimumab was the first bDMARD most frequently used, data which coincides with the DANBIO and ROB-FIN registers [5,9]. According to our results, Adalimumab presented a longer survival in comparison to Etanercept, which differs from other studies that have shown that Etanercept was the TNFi agent with the highest survival rate [14-16]. In the Finnish register, Adalimumab survival was only superior to Infliximab, while it did not differ to the survival of Etanercept or Golimumab [9]. Similar to the DANBIO register, in our study the main cause for drug discontinuation was lack of efficacy [5]. The second most frequent cause of discontinuation in our study was the lack of provision, which is usually the result of irregularities by the supplying institution of the medication, causing the stoppage of the treatment beyond the patients' will. A non-frequent variable in studies conducted in developed countries.

Some studies have observed that concomitant csDMARD use in patients treated with TNFi agents favored survival. The Danish register proved that the lack of concomitant Methotrexate in patients treated with bDMARD was

associated to less drug survival [5]. Likewise, in the Swedish register the same results were found, determining that concomitant use of csDMARD paradoxically decreased the frequency of adverse events [6]. An Italian study evaluating 8 year-long treatment with TNFi found that concomitant use of Methotrexate was associated to a lower risk of bDMARD discontinuation [15]. In our study, the use of csDMARD showed no influence on biologic survival. In contrast to other studies, we found that patient's ≥ 55 years old presented a significantly lower survival to TNF inhibitors. In the DANBIO register, young patients presented a better response to treatment, but not a greater survival [5].[5] According to the BIOBADASER register, which evaluated patients with Spondyloarthritis including 570 patients with PsA, patients >60 years old (HR=1.21), females, and those treated with Infliximab had a higher risk of discontinuing bDMARD treatment [12]. Though the design of our study does not allow us to know the causes leading to lower survival in these patients, one could hypothesize that longer disease duration, higher number of comorbidities, concomitant drugs, risks of infections and functional impairment or disability may have some impact on drug survival.

Despite obese patients (BMI ≥ 30) had a tendency towards lower bDMARD survival in univariate analysis, the LUNDEX was significantly lower for obese patients after the second year of treatment. These results are similar to those observed in CORRONA register, in which a high BMI was found to be a significant predictor of a lower drug survival [22].

Our study has some limitations. First, the number of patients included is relatively small, secondly, some biological agents were administered to a low percentage of patients impeding their separate analysis, and lastly, some data may be biased given that it is a retrospective cohort.

MDA was used to estimate treatment response; this differs to most studies which consider ACR response criteria. We decided to use this outcome measure as it is a simple and accessible tool that takes into consideration not only articular but extra-articular manifestations of this disease.

One of the strengths of our study is that, to the best of our knowledge, it is the first in our country to provide information regarding biologic treatment survival in patients with PsA. Another advantage is that it reflects a wide socioeconomic spectrum given that the data corresponds to patients from diverse health centers, both public and private. An additional advantage was the use of LUNDEX index to evaluate simultaneously evaluates drug survival and effectiveness.

CONCLUSION

In conclusion, the average survival of the first bDMARD was 6.8 years. Older patients with PsA had a significantly lower biologic survival rate.

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