Effectiveness of early adalimumab therapy in psoriatic arthritis patients from Reuma.pt – EARLY PsA

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ABSTRACT

Objective: To compare outcomes in psoriatic arthritis (PsA) patients initiating adalimumab (ADA), with short- and long-term disease duration and to evaluate the potential effect of concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARD) or glucocorticoids.

Methods: Analyses included adult PsA patients registered in the Rheumatic Diseases Portuguese Register (Reuma.pt) between June 2008–June 2016 who received ADA for ≥3 months. Psoriatic Arthritis Response Criteria (PsARC) response, tender and swollen joint count, inflammatory parameters, patient (PtGA) and physician global assessment (PhGA), Disease Activity Score-28 joints (DAS28), and Health Assessment Questionnaire Disability Index (HAQ-DI) were compared between patients with <5 years of disease (early PsA) and those with ≥5 years of disease duration (late PsA). Time to achieving PsARC response was estimated using the Kaplan-Meier method.

Results: Of 135 PsA patients treated with ADA, 126 had information on disease duration (earlyPsA, n=41). PsARC response was achieved by 72.9% of the patients (88.0% early PsA vs 62.2% late PsA; P=0.022) after 3 months and by 85.4% after 24 months (100% early PsA vs 75.9% late PsA; P=0.044). Early PsA patients achieved significantly less painful joints (2.7 vs 6.7, p=0.006), lower mean C-reactive protein (0.5 mg/dL vs 1.3 mg/dL; P=0.011), and PhGA (18.3 vs 28.1; P=0.020) at 3 months. In the long term, early PsA patients also had fewer swollen joints (0.3 vs 1.7; P=0.030) and lower PhGA (6.3 vs 21.9; P<0.001), C-reactive protein (0.4 mg/dL vs 1.0 mg/dL; P=0.026), and DAS28 (2.2 vs 3.2; P=0.030). HAQ-DI decreased in both groups reaching a mean value at 24 months of 0.4 and 0.8 (P=ns) in early and late PsA, respectively. Early PsA patients obtained PsARC response more rapidly than late PsA (3.8 and 7.4 months, respectively; P=0.008). Concomitant csDMARDs showed clinical benefit (2-year PsARC response, 88.3% vs 60.0%; P=0.044). Concomitant glucocorticoids had no effect on PsARC response over 2 years of follow-up. Persistence on ADA was similar in both groups.

Conclusion: Early PsA patients had a greater chance of improvement after ADA therapy and better functional outcome, and achieved PsARC response more rapidly than late PsA. In this cohort, comedication with csDMARDs was beneficial over 2 years.

Keywords: Reuma.pt; Psoriatic arthritis; Adalimumab; Early therapy; Treatment effectiveness

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INTRODUCTION

Patients with psoriatic arthritis (PsA) present with chronic inflammation, with joint and skin manifestations that adversely impact function and quality of life (QoL)[1]. PsA is a remarkably heterogeneous disease in the extent and type of tissue involvement, which may include peripheral and axial joint inflammation, dactylitis, enthesitis, and skin and nail psoriasis. Heterogeneity is observed not only in clinical manifestations, but also in the severity and the course of the disease[2-7].

The prevalence of PsA has been estimated to range from 0.3% to 1% of the global population, and psoriasis usually precedes the development of arthritis by several years[3,8,9]. The disease burden can be significant; as many as 20% of patients with PsA will have a progressive and disabling form of arthritis[3,4]. Due to the physical and functional limitations imposed by PsA, indirect costs, due to disability and lost productivity, are a substantial portion of the total costs of care[10]. Thus, PsA represents an economic and QoL burden to patients and society. Available data are sometimes conflicting; however, cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, Crohn's disease, ocular disease, depression, and anxiety are common comorbidities associated with PsA[11].

Treatment patterns generally mirror those of rheumatoid arthritis[12]. Methotrexate is the most commonly used disease-modifying antirheumatic drug (DMARD), either prescribed as monotherapy (39% of patients with PsA) or in combination with other conventional synthetic DMARDs (csDMARDs) or biologic DMARDs (bDMARDs)[13]. However, based on pathologic and clinical features that are distinct, it does not necessarily follow that treatment results will be the same[14]. A treat-to-target strategy, with the aim of remission or low disease activity and an early diagnosis, are vital to minimize joint damage. Early detection of PsA signs and symptoms with an early therapeutic intervention may reduce the risk of clinical progression[15]. Nevertheless, there is a need for evidence that early versus delayed treatment with csDMARDs is beneficial in the long term[16]. Furthermore, the role of bDMARDs in patients with early PsA is still unclear[17].

Thus, our aim was to evaluate the effect of adalimumab, a TNF inhibitor bDMARD indicated for the treatment of patients with PsA[12], in patients treated earlier in the disease course (<5 years symptom duration) and to determine the potential effect of concomitant csDMARDs and glucocorticoids on clinical and functional outcomes.

METHODS

STUDY DESIGN AND DATA SOURCE

This study was a multicenter, non-interventional, open cohort study using data from the Rheumatic Diseases Portuguese Register (Reuma.pt). Adult patients with PsA with peripheral arthritis, diagnosed according to the Classification Criteria for Psoriatic Arthritis,18 who were registered in the Reuma.pt database between June 2008 and June 2016, and received adalimumab therapy for ≥3 months, were included. Patients with a previous diagnosis of rheumatoid arthritis or other inflammatory arthropathies were excluded.

The baseline study visit corresponded to the start of adalimumab therapy (as a first-, second-, or third-line biologic). Patients were reassessed every 3 to 4 months; clinical data were recorded for each patient by the treating rheumatologist. For the current study, researchers from each participating center were assigned to review the local medical records and to complete missing data, whenever possible. This data quality assessment strategy has been proved to decrease the risk of information bias[19].

The study was conducted in accordance with the Declaration of Helsinki. Use of the Reuma.pt database was approved by the Portuguese Data Protection Authority and the study protocol was approved by the ethics committee of the Instituto Português de Reumatologia.

CLINICAL EVALUATIONS

For each patient, demographic data (age, sex, race, ethnicity, height, weight, body mass index [BMI]), age at diagnosis, disease type, comorbidities (hyperuricemia, hypertension, diabetes mellitus, and dyslipidemia), and information on concomitant therapy (csDMARDs and oral glucocorticoids) were collected. At each visit, patient-reported outcomes (PROs), including the Patient Global Assessment (PtGA) and HAQ-DI, were collected. In addition, the Physician Global Assessment (PhGA), tender joint count (68 joints) and swollen joint count (66 joints), enthesitis and dactylitis count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and extra-articular manifestations related to PsA (psoriasis area and severity index [PASI], uveitis, inflammatory bowel disease) were recorded. Recorded data on work status were analyzed whenever available.

STUDY ENDPOINTS

The primary endpoint was the proportion of patients that achieved a short-term (3 months) and a long-term (24 months) PsARC response; secondary endpoints included time to PsARC response; reduction in swollen and tender joint count, PhGA, PtGA, ESR, CRP level, DAS28 (ESR) score, and HAQ-DI score; PsARC response in patients with and without concomitant therapy with csDMARDs and with and without concomitant

glucocorticoids; and the treatment persistence on therapy with adalimumab and the reasons for discontinuation.

STATISTICAL ANALYSIS

The statistical analyses were conducted using Stata IC version 12 (StataCorp LLC, College Station, TX, USA). Collected data were summarized by descriptive statistics. Continuous variables were reported as mean (standard deviation) and nominal variables were reported as proportions.

We compared patients with <5 years of disease duration (early PsA) with patients with ≥5 years of disease duration (late PsA). This arbitrary cut-off was established to assure enough patients on biologics in both groups. To compare baseline characteristics, PsARC response, joint counts, PhGA, PtGA, ESR, CRP, and HAQ at 3 and 24 months between patients with early and late PsA, we used an independent t test for equal and unequal variances, proportion test, and Fisher exact test, as appropriate. Logistic regression and linear regression analyses were used to adjust for baseline characteristics (age at the beginning of treatment with biologic agents, sex, smoking habits, and BMI). Time to PsARC response was analyzed using the Kaplan-Meier method and was adjusted using a Cox regression analysis, with the Efron method for ties with robust estimates of variance for baseline characteristics (age at the beginning of treatment with biologic agents, sex, smoking habits, and BMI). Treatment persistence with adalimumab was analyzed using the Kaplan-Meier method. P<0.05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS

One hundred thirty-five patients with PsA who were treated with adalimumab (as a first-, second-, or third-line biologic treatment) for ≥3 months between June 2008 and June 2016 were included in the study. Data on disease duration from symptom onset were available for 126 patients; data from these patients were included in the subsequent analysis. Demographic characteristics of the studied cohort are reported in Table I. Patients with early PsA had an average disease duration of 2.6±1.3 years (mean±SD); patients with late PsA had an average disease duration of 13.4±8.1 years. As expected, patients with early PsA were significantly younger and began treatment with biologic agents at a younger age. There were also more male patients, current smokers, and patients with arterial hypertension in this group. No major differences were observed between the 2 groups regarding ethnicity, age at diagnosis, employment status, BMI, disease type, extra-articular manifestations, and concomitant glucocorticoid or csDMARD use. The median time from first use of csDMARDs to the initiation of treatment with adalimumab was 1.95 years in patients with early PsA and 5.08 years in patients with late PsA (P<0.001). There were no significant differences between patients with early and late PsA in disease activity and function at baseline (Table II).

EFFECTIVENESS ASSESSMENTS

A PsARC response was achieved by 72.9% patients (54/74 evaluable patients) at 3 months. Of the patients receiving adalimumab at month 24, 85.4% had a PsARC response (41/48 evaluable patients). More patients with early PsA achieved PsARC at 3 months (88.0% vs 62.2%; P=0.022) and 24 months (100% vs 75.8%; P=0.044). After adjustment for baseline characteristics (sex, age at starting ADA, smoking, and BMI), these differences remained significant at 3 months (P=0.043); however, this adjustment was not possible to perform in the long term due to the small number of patients (supplementary file; Table III). The group with early PsA achieved, on average, a PsARC response 3.8 months after treatment initiation with ADA; the mean time to PsARC response in patients with late PsA was 7.4 months (adjusted P=0.001; Figure 1).

Considering clinical assessments at 3 months, patients with early PsA had a greater reduction in disease activity that translated into less painful joints (2.7 vs 6.7, P=0.006), lower mean CRP levels (0.5 mg/dL vs 1.3 mg/dL; P=0.011), lower PhGA (18.3 vs 28.1; P=0.020), and a greater proportion of PsARC response (88.0% vs 62.2%; P=0.022; Figure 2). After adjustment for sex, age at the beginning of biologic, smoking, and BMI, only PhGA and PsARC response remained significantly different between patients with early and late PsA (P=0.043 for both; supplementary file; Table III). After 2 years of treatment with ADA, patients with early PsA showed consistently better outcomes, including fewer swollen joints (0.3 vs 1.7; P=0.030), lower PhGA score (6.3 vs 21.9; P<0.001), lower disease activity as evaluated by the DAS28 (2.2 vs 3.2; P=0.030), and more patients achieving PsARC response (100% vs 75.9%; P=0.044; Figure 2). No adjustments were made

TABLE I. BASELINE DEMOGRAPHIC CHARACTERISTICS BY PSA DISEASE DURATION

	PsA <5 years (n=41)	PsA ≥5 years (n=85)	P value
Age, years, mean (SD)	47.3 (11.5)	53.3 (10.9)	**0.005**
Male sex, n (%)	22 (53.7)	29 (34.1)	**0.036**
Ethnicity, Caucasian/European origin, n (%)	37 (100)	76 (93.4)	≈1
Age at diagnosis, years, mean (SD)	41.1 (11.6)	38.4 (11.6)	0.214
Age of beginning of treatment with biologic agents, years, mean (SD)	42.9 (11.3)	47.4 (11.3)	**0.039**
Disease duration until treatment with biologic agents, years, mean (SD)	2.6 (1.3)	13.4 (8.1)	<0.001
Employment status full-time, n (%)	33 (91.7)	68 (88.3)	≈1
Current smokers, n (%)	6 (16.2)	5 (6.6)	**0.044**
Disease Type			0.855
Symmetric polyarthritis	35 (87.5)	69 (81.1)	
Predominant arthritis of distal interphalangeal joints	1 (2.5)	3 (3.5)	
Asymmetric oligoarthritis	4 (10.0)	10 (11.8)	
Mutilating arthritis	0 (0)	3 (3.5)	
BMI, kg/m^2, mean (SD)	26.1 (4.1)	28.0 (5.1)	0.065
Iridicyclitis, n (%)	2 (?5.1)	8 (9.4)	0.416
Nail dystrophy, n (%)	8 (20.5)	11 (12.9)	0.277
Dactylitis, n (%)	11 (28.2)	13 (15.2)	0.091
Ulcerative colitis, n (%)	0 (0)	1 (1.2)	0.496
Comorbidities			
Hyperuricemia, n (%)	0 (0)	2 (2.82)	0.323
Arterial hypertension, n (%)	5 (14.7)	31 (41.3)	**0.006**
Diabetes mellitus, n (%)	0 (0)	6 (7.23)	0.08
Dyslipidemia, n (%)	5 (14.7)	13 (18.3)	0.646
Sequence of adalimumab, n (%)			
First-line biologic	27 (65.9)	50 (59.8)	
Second-line biologic	13 (31.7)	26 (30.6)	
Third-line biologic	1 (2.4)	9 (10.6)	
Concomitant csDMARD, n (%)	39 (95.1)	74 (87.0)	0.163
Oral steroids, n (%)	22 (53.7)	44 (51.8)	0.841

BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; PsA, psoriatic arthritis.
Sample size is not constant. PsA <5 years: BMI (n=34); form (n=40); ethnicity (n=37); employment status at baseline (n=36); iridocyclitis (n=39); nail dystrophy (n=39); dactylitis (n=39); ulcerative colitis (n=39); smoking habits (n=37). PsA >5 years: BMI (n=66); ethnicity (n=81); employment status at baseline (n=77); smoking habits (n=76).
P<0.05 presented in bold.
Differences were assessed by Independent sample t test for equal with equal and unequal variances, proportion test, Fisher exact test, as appropriate.

for other baseline characteristics due to the small number of patients.

Mean CRP concentrations, in univariate analysis, were consistently lower in the group with shorter disease duration throughout all time point evaluations after the beginning of adalimumab therapy (0.5 mg/dL vs 1.3 mg/dL, P=0.011 at 3 months; 0.4 vs 1.0, P=0.026 at 24 months). These results, at 3 months and 2 years, were similar when patients receiving adalimumab as a first-line biologic were analyzed separately.

Regarding functional outcomes, HAQ-DI improvement was numerically greater in early PsA in all time point evaluations, but without reaching statistically significant differences, as shown in Figure 2.

TABLE II. BASELINE DISEASE ACTIVITY AND FUNCTION BY PSA DISEASE DURATION

	PsA <5 years (n=34)	PsA ≥5 years (n=75)	P value
DAS28, mean (SD)	4.9 (1.4)	5.0 (1.4)	0.717
Painful joints, mean (SD)	10.2 (8.4)	11.3 (10.8)	0.554
Swollen joints, mean (SD)	6.1 (4.2)	5.8 (6.2)	0.756
PtGA, mean (SD)	60.2 (23.5)	60.3 (23.4)	0.978
PhGA, mean (SD)	50.7 (20.4)	48.3 (22.8)	0.633
HAQ, mean (SD)	1.0 (0.7)	1.1 (0.7)	0.554
CRP, mg/dL, mean (SD)	1.7 (2.1)	2.0 (1.9)	0.490
ESR, mean (SD)	31.8 (22.2)	36 (25.8)	0.438
PASI, mean (SD)	2.2 (3.4)	5.0 (9.9)	0.412

CRP, C-reactive protein; DAS28, disease activity score – 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; PASI, psoriasis area and severity index; PhGA, physician global assessment; PsA, psoriatic arthritis; PtGA, patient global assessment.

We evaluated the influence of csDMARDs therapy on response to adalimumab by comparing patients receiving csDMARDs with those who did not receive csDMARDs. The only difference between these 2 groups was observed after 2 years of therapy; more patients treated with csDMARDs achieved a PsARC response (88.3% for patients with csDMARDs vs 60.0% for patients without csDMARDs; P=0.044). Because of the small number of patients, no adjustment was possible for baseline characteristics, and results need to be interpreted cautiously (supplementary file; Tables IV and V). We also compared patients receiving glucocorticoid therapy with those who did not receive glucocorticoid therapy. At baseline, patients receiving glucocorticoid therapy had more painful joints (12.3% vs 8.6%; P=0.044). All efficacy assessments evaluated showed no difference (supplementary file; Tables VI and VII).

ADALIMUMAB DISCONTINUATION

During study follow-up, 51 patients (37.8%) discontinued treatment with adalimumab. The average duration of therapy until discontinuation was 25.7±21.2 months (14.7±16.5 months for early PsA and 29.9±22.6 months for late PsA; P=0.033) and the most common reason for discontinuation was lack of efficacy. The proportion of patients with early PsA (31.7%) and late PsA (40%) that discontinued adalimumab was similar. No difference in persistence on treatment with adalimumab was detected between the groups (P=0.632). In addition, concomitant csDMARD and concomitant glucocorticoid therapy did not influence the persistence of treatment with adalimumab in any of the groups.

DISCUSSION

The present study provides information on the impact of disease duration on response to adalimumab therapy, in a real-world setting. Patients with early PsA achieved better clinical and functional outcomes compared with patients with longer disease duration, and the clinical improvement was obtained more rapidly.

In the past, PsA was considered a mild disease; however, recent evidence attests to its severity[3,4]. Nevertheless, studies on the effect of disease duration on treatment response and long-term outcomes in patients with PsA are limited, and the role of biologics in the management of early PsA is still unclear. In our study cohort, patients with early PsA had a better response to adalimumab in the short term, as well as in the long term. The reduction of inflammatory parameters, joint counts, and PROs translated in lower mean DAS28 and more patients achieving a PsARC response. While there is some evidence that patients who present within 2 years of diagnosis and receive therapy earlier had lower damage progression than those with longstanding PsA20, data regarding specifically the benefit of early introduction of a bDMARD is still lacking. A sub-analysis of a randomized controlled trial assessing the efficacy of etanercept in patients with psoriasis and PsA, concluded that patients with a shorter duration of disease (≤ 2 years) achieved greater improvements in arthritis

TABLE III. DISEASE CHARACTERISTICS BY PSA DISEASE DURATION AND RESPONSE TO ADALIMUMAB

	Baseline			3 months				2 years			
	Disease duration			Disease duration				Disease duration			
	<5 years (n=34)	≥5 years (n=75)	P value	<5 years (n=30)	≥5 years (n=66)	P value	Adjusted P value	<5 years (n=19)	≥5 years (n=46)	P value	Adjusted P value
DAS28, mean (SD)	4.9 (1.4)	5.0 (1.4)	0.717	3.0 (1.4)	3.5 (1.6)	0.154	0.942	2.2 (1.0)	3.2 (1.6)	**0.030**	0.167
Painful joints, mean (SD)	10.2 (8.4)	11.3 (10.8)	0.554	2.7 (3.5)	6.7 (10.0)	**0.006**	0.976	0.4 (0.8)	2.7 (4.7)	0.150	0.249
Swollen joints, mean (SD)	6.1 (4.2)	5.8 (6.2)	0.756	1.4 (2.0)	1.9 (2.2)	0.271	0.725	0.3 (0.7)	1.7 (4.0)	**0.002**	0.555
PtGA, mean (SD)	60.2 (23.5)	60.3 (23.4)	0.978	30.4 (22.6)	40.4 (23.6)	0.066	0.230	23.7 (22.1)	34.5 (29)	0.192	0.957
PhGA, mean (SD)	50.7 (20.4)	48.3 (22.8)	0.633	18.3 (17.4)	28.1 (17.9)	**0.020**	**0.043**	6.3 (5.2)	21.9 (23.4)	**0.000**	0.212
HAQ, mean (SD)	1.0 (0.7)	1.1 (0.7)	0.554	0.6 (0.7)	0.8 (0.7)	0.212	0.599	0.4 (0.5)	0.8 (0.7)	0.119	0.753
CRP, mg/dL, mean (SD)	1.7 (2.1)	2.0 (1.9)	0.490	0.5 (0.8)	1.3 (2.1)	**0.011**	0.134	0.4 (0.4)	1.0 (1.6)	**0.026**	0.301
ESR, mean (SD)	31.8 (22.2)	36 (25.8)	0.438	16.4 (14.1)	22.9 (20.7)	0.13	0.512	17.7 (21.7)	27.6 (25.9)	0.179	0.263
PASI, mean (SD)	2.2 (3.4)	5.0 (9.9)	0.412	NA	NA		NA	NA	NA		NA
PsARC yes, n (%)			NA	22 (88.0)	28 (62.2)	**0.022**	**0.043**	14 (100)	22 (75.8)	**0.044**	NA

BMI, body mass index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not available; PASI, psoriasis area and severity index; PhGA, physician global assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PtGA, patient global assessment.

Sample size is not constant: PsA <5 years: baseline – DAS28 (n=28); swollen joints (n=31); painful joints (n=31); PtGA (n=30); PhGA (n=29); HAQ (n=20); CRP (n=31); ESR (n=31); PASI (n=9); 3 months – DAS28 (n=28); PtGA (n=28); PhGA (n=28); HAQ (n=21); CRP (n=29); ESR (n=29); PsARC (n=25); 2 years – DAS28 (n=13); swollen joints (n=17); painful joints (n=17); PtGA (n=15); PhGA (n=15); HAQ (n=13); CRP (n=16); ESR (n=16); PsARC (n=14). PsA >5 years: baseline – DAS28 (n=60); swollen joints (n=71); painful joints (n=72); PtGA (n=65); PhGA (n=63); HAQ (n=53); CRP (n=70); ESR (n=70); PASI (n=28); 3 Months - DAS28 (n=49); Swollen joints (n=60); painful joints (n=59); PtGA (n=56); PhGA (n=54); HAQ (n=39); CRP (n=57); ESR (n=62); PsARC (n=45); 2 years - DAS28 (n=38); swollen joints (n=45); painful joints (n=45); PtGA (n=43); PhGA (n=40); HAQ (n=32); CRP (n=43); ESR (n=43); PsARC (n=29).
P value adjusted for sex, age at beginning of biologic therapy, smoking, and BMI.

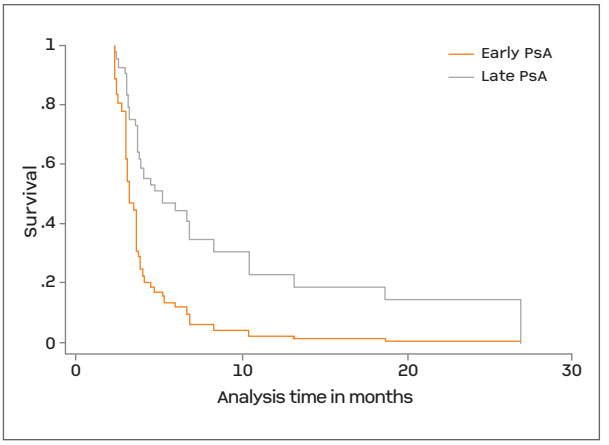

FIGURE 1. Time from the start of treatment with adalimumab to PsARC achievement, by years of disease duration until biologic treatment, adjusted for sex, age at the beginning of biologic therapy, smoking, and BMI. Units of time were measured in months.
BMI, body mass index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria.

scores and several PROs measures[21]. To our knowledge, the present study is the first one using real-world clinical data, prospectively collected in the Portuguese registry (Reuma.pt), that evaluates the influence of disease duration on the outcomes of treatment with a TNF inhibitor (adalimumab) in patients with PsA.

The benefit of concomitant csDMARDs with anti-TNF therapy in the treatment of patients with PsA is still a matter of debate. In the ADEPT trial, American College of Rheumatology (ACR)20, ACR50, and ACR70 response rates did not differ between patients receiving adalimumab in combination with MTX and patients receiving adalimumab monotherapy[22]. Combe *et al*. evaluated the impact of methotrexate in addition to treatment with etanercept in patients with PsA and concluded that in patients with both axial and peripheral involvement, comedication with methotrexate had no relevant impact on efficacy, safety, or treatment adherence[23]. In fact, a recent systematic review of the literature that included randomized controlled trials (RCTs) and observational studies comparing TNF inhibitor monotherapy vs combination therapy with MTX concluded that concomitant MTX adds little or no improvement in PsA patients, although MTX might prolong TNF inhibitor drug survival[24].

In our study, more patients receiving csDMARDs achieved a PsARC response at 2 years of follow-up; however, the numbers at this time point were small. Regarding all other parameters and time points, comedication with csDMARDs had no noticeable effect on the effectiveness of adalimumab. However, our study was not powered nor designed to definitely answer this question. In long-term drug persistence, csDMARDs were not considered to be useful. A recent study, from the Corrona registry, which included 519 patients with PsA, also found similar persistence in patients receiving TNF inhibitors monotherapy and in combination with other drugs[25]. Conversely, in a recent Italian study that retrospectively evaluated drug retention rates and treatment discontinuation in 268 patients who received a total of 353 anti-TNF treatment courses (97 adalimumab, 180 etanercept, 76 infliximab), combination therapy with csDMARDs was associated with better persistence rates[26].

The use of glucocorticoids in the treatment of patients with PsA is still controversial; according to the 2016 European League Against Rheumatism recommendations, long-term use of systemic glucocorticoids should be avoided[12]. However, in clinical practice, the use of steroids in the treatment of patients with PsA is common, and 53.3% of the patients in this study (n=72) received low-dose oral glucocorticoids. In our cohort, steroids neither influenced the effectiveness nor did they influence treatment persistence on adalimumab.

Among patients who discontinued adalimumab therapy, those with early disease discontinued therapy more rapidly than those with late disease. This may be related to more therapeutic options for PsA, in recent years, and to a new paradigm in the treatment of PsA, aiming to a specific target (treat-to-target approach).

This study had several limitations. The cut-off of 5 years to separate early from late PsA was arbitrarily established; one could argue that this cut-off does not really separate patients with early PsA (usually accepted as <2 years of disease duration) from those with more advanced disease. Nevertheless, the mean disease duration of the patients in the early PsA group was 2.6 years. As expected in this type of observational studies, we had several missing data. Incomplete data are a potential issue in registries, and in order to minimize this fact, physicians at all of the participating centers were asked to complete as much as possible in the central database by reviewing medical records. Even so, because of missing information, we were unable to include all patients receiving treatment with adalimumab at all time point evaluations. Additionally, the effect on skin involvement, dactylitis and enthesitis were not systematically recorded, which precluded the analysis of

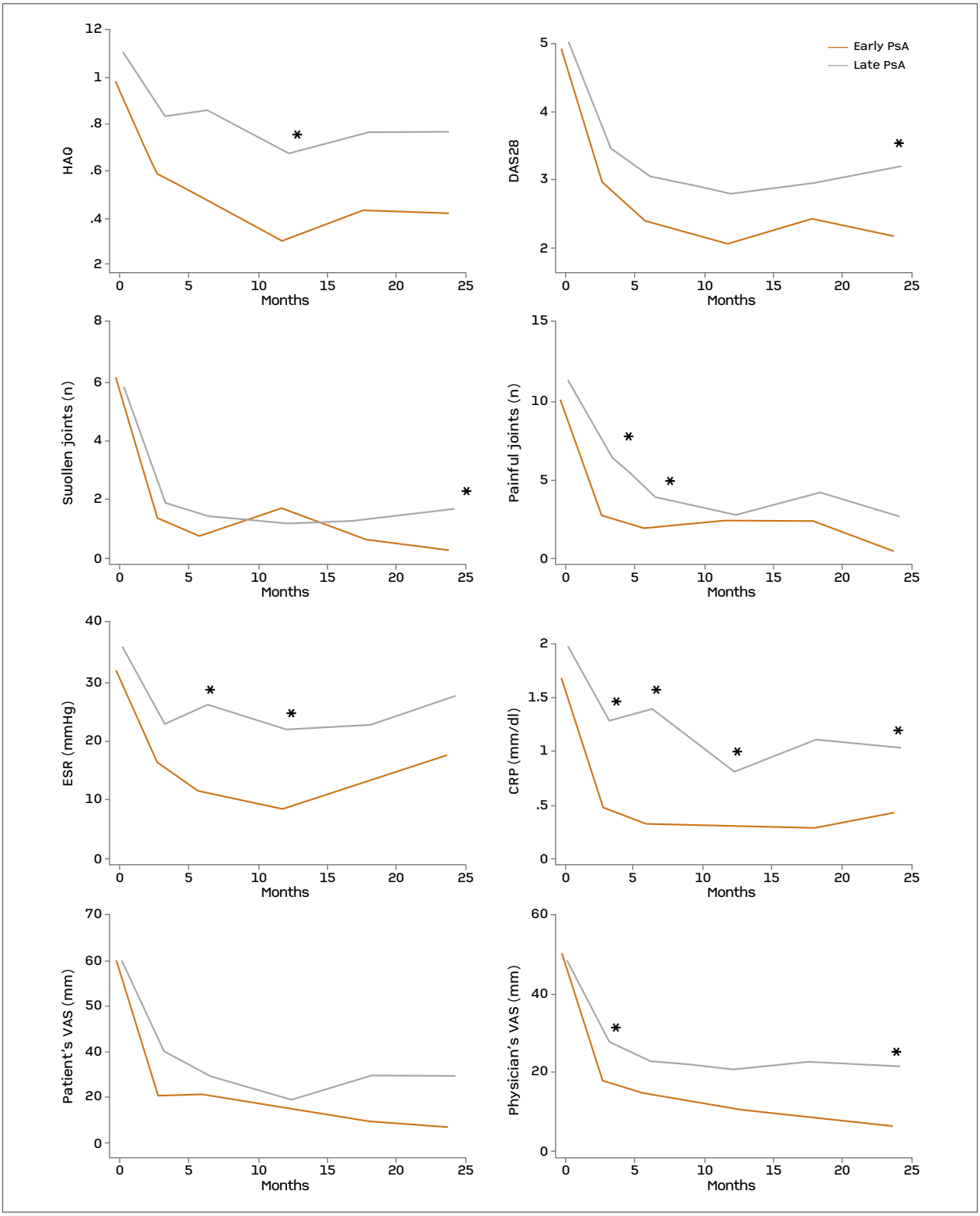

FIGURE 2. The effect of disease duration on clinical assessments (HAQ, DAS28, swollen joints, painful joints, ESR, CRP, PtGA, PhGA) over 24 months of treatment with adalimumab.
CRP, C-reactive protein; DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; PhGA, physician global assessment; PsA, psoriatic arthritis; PtGA, patient global assessment; VAS, visual analogue scale.
*P<0.05.

TABLE IV. DISEASE CHARACTERISTICS AND RESPONSE TO ADALIMUMAB, IN PATIENTS WITH AND WITHOUT CONCOMITANT THERAPY WITH csDMARDS

	Baseline			3 months				2 years			
	With csDMARDs (n=105)	Without csDMARDs (n=12)	P-value	With csDMARDs (n=88)	Without csDMARDs (n=13)	P value	Adjusted P value	With csDMARDs (n=65)	Without csDMARDs (n=7)	P value	Adjusted P value
DAS28, mean (SD)	5.0 (1.4)	5.0 (1.4)	0.930	3.2 (1.6)	3.2 (1.3)	0.991	0.476	2.8 (1.5)	3.0 (1.6)	0.74	0.084
Painful joints, mean (SD)	10.9 (10.0)	8.3 (9.8)	0.399	5.3 (8.6)	4.2 (7.1)	0.685	0.483	2.0 (4.0)	2.1 (4.1)	0.904	0.676
Swollen joints, mean (SD)	6.0 (5.7)	4.0 (3.1)	0.246	1.7 (2.1)	1.7 (2.2)	0.990	0.405	1.3 (3.4)	0.7 (1.1)	0.645	0.740
PtGA, mean (SD)	60.5 (23.2)	64.5 (20.1)	0.590	35.7 (23.6)	44.4 (24.1)	0.267	0.306	32.2 (26.4)	24.3 (31.8)	0.495	0.892
PhGA, mean (SD)	50.0 (22)	52.6 (24.5)	0.713	23.9 (18.1)	28.7 (18.7)	0.417	0.159	17.9 (20.9)	15 (23.5)	0.746	0.891
HAQ, mean (SD)	1.0 (0.7)	1.2 (0.8)	0.507	0.7 (0.7)	0.8 (0.4)	0.810	0.409	0.7 (0.7)	0.3 (0.5)	0.293	0.936
CRP, mg/dL, mean (SD)	2.0 (2.3)	1.7 (1.5)	0.670	1.0 (1.8)	0.9 (1.1)	0.833	0.775	0.8 (1.3)	1.3 (2.5)	0.453	0.520
ESR, mean (SD)	35.3 (25.7)	35.4 (28.5)	0.994	20.2 (19.4)	18.6 (16.0)	0.777	0.490	21.4 (21.4)	36.7 (42.3)	0.378	**0.001**
PASI, mean (SD)	3.1 (6.4)	11.2 (17.4)	0.359				NA				NA
PsARC yes, n (%)				48 (73.85)	6 (66.67)	0.649	0.181	38 (88.37)	3 (60.0)	**0.044**	NA

BMI, body mass index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not available; PASI, psoriasis area and severity index; PhGA, physician global assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PtGA, patient global assessment.

Sample size is not constant. Patients with csDMARDs: baseline – DAS28 (n=85); swollen joints (n=97); painful joints (n=98); PtGA (n=90); PhGA (n=87); HAQ (n=64); CRP (n=98); ESR (n=99); PASI (n=33); 3 months – DAS28 (n=72); swollen joints (n=83); painful joints (n=82); PtGA (n=77); PhGA (n=75); HAQ (n=55); CRP (n=80); ESR (n=83); PsARC (n=65); 2 years – DAS28 (n=51); swollen joints (n=62); painful joints (n=62); PtGA (n=58); PhGA (n=55); HAQ (n=45); CRP (n=60); ESR (n=59); PsARC (n=43). Patients without csDMARDs: Baseline – DAS28 (n=9); PtGA (n=11); PhGA (n=11); HAQ (n=11); CRP (n=11); ESR (n=10); PASI (n=5); 3 months – DAS28 (n=9); swollen joints (n=12); painful joints (n=12); PtGA (n=11); PhGA (n=11); HAQ (n=8); CRP (n=11); PsARC (n=9); 2 years – DAS28 (n=6); PtGA (n=6); PhGA (n=6); HAQ (n=5); CRP (n=6); PsARC (n=5).
P value adjusted for sex, age at beginning of biologic therapy, smoking, and BMI.

TABLE V. DISEASE CHARACTERISTICS AND RESPONSE TO ADALIMUMAB BY DISEASE DURATION IN PATIENTS WITH CONCOMITANT THERAPY WITH csDMARDS

	Baseline			3 months				2 years			
	Disease duration			Disease duration				Disease duration			
	<5 years (n=32)	≥5 years (n=66)	P value	<5 years (n=28)	≥5 years (n=56)	P value	Adjusted P value	<5 years (n=18)	≥5 years (n=41)	P value	Adjusted P value
DAS28, mean (SD)	4.9 (1.4)	5.1 (1.4)	0.536	2.9 (1.4)	3.5 (1.7)	0.100	0.940	2.3 (1.0)	3.2 (1.6)	0.069	0.278
Painful joints, mean (SD)	10.4 (8.5)	11.6 (10.9)	0.594	2.7 (3.5)	7.1 (10.3)	**0.008**	0.226	0.4 (0.8)	2.7 (4.7)	**0.005**	0.265
swollen joints, mean (SD)	6.1 (4.1)	6.2 (6.5)	0.934	1.3 (2.0)	1.9 (2.2)	0.199	0.714	0.3 (0.7)	1.8 (4.2)	0.158	0.503
PtGA, mean (SD)	69.4 (23.4)	59.9 (24.1)	0.915	29.1 (22.4)	39.8 (23.4)	0.062	0.317	25.4 (22.0)	35.2 (28.8)	0.252	0.994
PhGA, mean (SD)	50.1 (18.8)	47.8 (23.2)	0.656	17.7 (17.1)	27.8 (18.0)	**0.022**	0.095	6.8 (5.1)	22.4 (23.6)	**0.000**	0.174
HAQ, mean (SD)	1.0 (0.7)	1.1 (0.7)	0.506	0.6 (0.7)	0.8 (0.8)	0.215	0.557	0.5 (0.5)	0.8 (0.7)	0.133	0.742
CRP, mg/dL, mean (SD)	1.7 (2.2)	2.0 (2.0)	0.553	0.5 (0.8)	1.3 (2.2)	**0.017**	0.148	0.4 (0.4)	1.0 (1.4)	**0.038**	0.449
ESR, mean (SD)	31.0 (22.6)	36.4 (25.1)	0.322	15.9 (13.9)	23.6 (21.5)	0.096	0.553	18.5 (22.2)	25 (21.6)	0.334	0.424
PASI, mean (SD)	2.4 (3.6)	3.5 (7.2)	0.676				NA				NA
PsARC yes, n (%)				20 (86.96)	24 (63.1)	**0.044**	0.081	13 (100)	20 (80.0)	0.083	NA

BMI, body mass index; CRP, C-reactive protein;DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not available; PASI, psoriasis area and severity index; PhGA, physician global assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PtGA, patient global assessment.

Sample size is not constant. PsA <5 years: baseline – DAS28 (n=26); swollen joints (n=29); painful joints (n=29); PtGA (n=28); PhGA (n=27); HAQ (n=18); CRP (n=29); ESR (n=29); PASI (n=8);
3 months - DAS28 (n=26); PtGA (n=26); PhGA (n=26); HAQ (n=19); CRP (n=27); ESR (n=27); PsARC (n=23); 2 years – DAS28 (n=12); swollen joints (n=16); painful joints (n=16); PtGA (n=14); PhGA (n=14); HAQ (n=12); CRP (n=16); ESR (n=15); PsARC (n=13); PsA >5 years: baseline – DAS28 (n=53); swollen joints (n=62); painful joints (n=63); PtGA (n=56); PhGA (n=54); HAQ (n=44); CRP (n=62); ESR (n=63); PASI (n=24); 3 months – DAS28 (n=42); swollen joints (n=51); painful joints (n=50); PtGA (n=47); PhGA (n=45); HAQ (n=33); CRP (n=49); ESR (n=52); PsARC (n=38); 2 years – DAS28 (n=33); swollen joints (n=40); painful joints (n=40); PtGA (n=38); PhGA (n=35); HAQ (n=28); CRP (n=38); ESR (n=38); PsARC (n=25).
P value adjusted for sex, age at beginning of biologic, smoking, and BMI.

TABLE VI. DISEASE CHARACTERISTICS AND RESPONSE TO ADALIMUMAB IN PATIENTS WITH AND WITHOUT CONCOMITANT THERAPY WITH GLUCOCORTICOIDS

	Baseline			3 months				2 years			
	With glucocorticoids (n=65)	Without glucocorticoids (n=52)	P value	With glucocorticoids (n=55)	Without glucocorticoids (n=46)	P value	Adjusted P value	With glucocorticoids (n=37)	Without glucocorticoids (n=35)	P value	Adjusted P value
DAS28, mean (SD)	5.1 (1.4)	4.8 (1.3)	0.295	3.3 (1.5)	3.1 (1.6)	0.551	0.892	3.1 (1.6)	2.5 (1.3)	0.194	0.552
Painful joints, mean (SD)	12.3 (11.0)	8.6 (8.2)	**0.044**	5.4 (8.9)	4.9 (7.7)	0.749	0.728	4.6 (6.8)	1.0 (2.0)	**0.039**	0.422
Swollen joints, mean (SD)	6.1 (4.9)	5.2 (6.1)	0.395	1.9 (2.3)	1.4 (2.0)	0.354	0.277	1.6 (2.3)	0.6 (0.9)	0.097	0.415
Patient VAS, mean (SD)	60.3 (23.8)	61.7 (21.9)	0.766	34.4 (24.5)	40.0 (22.4)	0.269	0.135	31 (25.1)	27.6 (23.7)	0.290	0.895
Physician VAS, mean (SD)	50.5 (20.7)	50.0 (24.2)	0.906	25.7 (18.7)	23.0 (17.4)	0.494	0.477	20.8 (20.9)	13.2 (14.3)	0.113	0.187
HAQ, mean (SD)	1.1 (0.8)	1.1 (0.6)	0.865	0.8 (0.8)	0.7 (0.6)	0.848	0.211	0.7 (0.7)	0.5 (0.5)	0.252	0.920
CRP, mg/dL, mean (SD)	2.2 (2.6)	1.6 (1.5)	0.216	1.1 (2.0)	0.8 (1.4)	0.531	0.974	1.1 (2.4)	0.8 (1.4)	0.857	0.769
ESR, mean (SD)	33.9 (25.2)	37.1 (26.8)	0.514	20.4 (19.4)	19.5 (19.8)	0.812	0.370	18.4 (22.2)	23.2 (26.1)	0.960	0.067
PASI, mean (SD)	3.2 (6.7)	5.6 (11.0)	0.446				NA				NA
PsARC yes, n (%)				31 (72.09)	23 (74.19)	0.840	0.756	22 (88.00)	19 (82.61)	0.597	0.298

BMI, body mass index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not available; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; VAS, visual analogue scale.

Sample size is not constant. Patients with glucocorticoids: baseline – DAS28 (n=51); swollen joints (n=60); painful joints (n=61); PtGA (n=56); PhGA (n=56); HAQ (n=39); CRP (n=60); ESR (n=60); PASI (n=22); 3 months – DAS28 (n=47); swollen joints (n=54); painful joints (n=53); PtGA (n=51); PhGA (n=50); HAQ (n=36); CRP (n=52); ESR (n=54); PsARC (n=43); 2 years - DAS28 (n=32); PtGA (n=35); PhGA (n=33); HAQ (n=26); CRP (n=35); ESR (n=34); PsARC (n=25). Patients without glucocorticoids: baseline – DAS28 (n=43); swollen joints (n=49); painful joints (n=49); PtGA (n=45); PhGA (n=42); HAQ (n=36); CRP (n=49); ESR (n=49); PASI (n=16); 3 months – DAS28 (n=34); swollen joints (n=41); painful joints (n=41); PtGA (n=37); PhGA (n=36); HAQ (n=27); CRP (n=39); ESR (n=42); PsARC (n=31); 2 years – DAS28 (n=25); swollen joints (n=32); painful joints (n=32); PtGA (n=29); PhGA (n=28); HAQ (n=24); CRP (n=31); ESR (n=32); PsARC (n=23).
P value adjusted for sex, age at beginning of biologic treatment, smoking, and BMI.

TABLE VII. DISEASE CHARACTERISTICS AND RESPONSE TO ADALIMUMAB BY DISEASE DURATION IN PATIENTS WITH CONCOMITANT THERAPY WITH GLUCOCORTICOIDS

	Baseline			3 months				2 years			
	Disease duration			Disease duration				Disease duration			
	<5 years (n=20)	≥5 years (n=40)	P value	<5 years (n=18)	≥5 years (n=35)	P value	Adjusted P value	<5 years (n=9)	≥5 years (n=24)	P value	Adjusted P value
DAS28, mean (SD)	4.7 (1.5)	5.3 (1.3)	0.189	3.0 (1.4)	3.5 (1.6)	0.277	0.793	2.1 (0.7)	3.2 (1.6)	**0.003**	0.348
Painful joints, mean (SD)	11.2 (10.2)	13.7 (11.5)	0.431	2.7 (3.0)	7.1 (10.8)	**0.034**	0.217	0.3 (0.7)	2.7 (4.7)	**0.005**	0.365
Swollen joints, mean (SD)	5.9 (4.2)	6.6 (5.4)	0.639	1.6 (2.3)	2.0 (2.3)	0.590	0.851	0.0 (0.0)	1.8 (4.2)	**0.020**	0.507
PtGA, mean (SD)	53.9 (25.7)	63.0 (23.6)	0.205	29.8 (24.1)	37.7 (25.2)	0.287	0.240	12.5 (12.8)	35.2 (28.8)	**0.000**	0.270
PhGA, mean (SD)	46.2 (19.9)	50.3 (20.5)	0.498	20.8 (19.1)	28.8 (18.4)	0.157	**0.039**	5.5 (3.3)	22.4 (23.6)	**0.001**	0.284
HAQ, mean (SD)	1.0 (0.8)	1.1 (0.8)	0.601	0.6 (0.8)	0.9 (0.8)	0.418	0.148	0.2 (0.2)	0.8 (0.7)	**0.001**	0.854
CRP, mg/dL, mean (SD)	1.7 (2.5)	2.2 (2.2)	0.492	0.6 (0.9)	1.4 (2.4)	0.120	0.131	0.5 (0.5)	1.0 (1.4)	0.272	0.996
ESR, mean (SD)	30.0 (21.7)	34.4 (24.3)	0.512	19.1 (15.6)	21.8 (20.0)	0.619	0.932	21.1 (28.1)	25 (21.6)	0.589	0.778
PASI, mean (SD)	1.3 (2.1)	4.3 (8.1)	0.346				NA				NA
PSARC yes, n (%)				14 (82.3)	15 (62.5)	0.168	0.250	8 (100)	20 (80.0)	0.158	NA

bmi, body mass index; crp, c-reactive protein; das28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not available; PASI, psoriasis area and severity index; PhGA, physician global assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PtGA, patient global assessment.

Sample size is not constant. PsA <5 years: baseline – DAS28 (n=17); swollen joints (n=19); painful joints (n=19); PtGA (n=19); PhGA (n=18); HAQ (n=13); CRP (n=19); ESR (n=19); PASI (n=7);
3 months – HAQ (n=13); PsARC (n=17); 2 years – DAS28 (n=7); PtGA (n=8); PhGA (n=8); HAQ (n=6); ESR (n=8); PsARC (n=8). PsA >5 years: baseline – DAS28 (n=30); swollen joints (n=37); painful joints (n=38); PtGA (n=33); PhGA (n=34); HAQ (n=24); CRP (n=36); ESR (n=36); PASI (n=14); 3 months – DAS28 (n=27); swollen joints (n=34); painful joints (n=33); PtGA (n=31); PhGA (n=30); HAQ (n=21); CRP (n=32); ESR (n=34); PsARC (n=24); 2 years – DAS28 (n=21); PtGA (n=23); PhGA (n=21); HAQ (n=17); CRP (n=22); ESR (n=22).
P value adjusted for sex, age at beginning of biologic treatment, smoking, and BMI.

these components of the disease. Furthermore, radiographic progression was not evaluated. Though the small number of patients that fulfilled inclusion criteria might hamper some conclusions, one of the main strengths of this study is that it includes patients from all-over the country, followed in private practices as well as in public hospitals, and prospectively assessed in a standardized way.

CONCLUSIONS

In conclusion, in this real-life clinical setting, patients with PsA with a shorter disease duration achieved better results after treatment with adalimumab than those patients with a longer disease duration, adding further support to the notion that shorter symptom duration and earlier treatment with a bDMARD (adalimumab) predicts a more favorable outcome in patients with PsA. Further studies are needed to confirm these results.

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