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ORIGINAL ARTICLE

Impact of cardiovascular risk factors on the achievement of therapeutic goals in psoriatic arthritis: is there any association?

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Abstract

Cardiovascular risk factors (CVRFs) have been related to poorer responses to systemic therapy in psoriatic arthritis (PsA). We aimed to evaluate the potential association between CVRFs and the achievement of therapeutic goals in PsA patients receiving systemic therapy. A cross-sectional study was carried out at 25 rheumatology outpatient clinics in Spain. PsA patients with established disease who were treated with conventional and biologic systemic therapies were included. The treatment goals measured were minimal disease activity (MDA) and very low disease activity (VLDA) responses. The relationship between MDA/VLDA and CVRFs was evaluated by uni- and multivariate models. Of a total of 227 patients, 133 (58.6%) and 26 (11.5%) patients were in MDA and VLDA, respectively. Tobacco use (crude OR 0.54), sedentary lifestyle (crude OR 1.95), hyperuricemia (crude OR 2.01) and obesity (crude OR 1.54) were related to the likelihood of MDA in the univariate model ($p < 0.25$), while in multivariate analysis, a sedentary lifestyle (OR 3.13, 95%CI 1.50–6.53; $p = 0.002$) increased the odds of having reached MDA. Obesity (crude OR 2.2) and dyslipidaemia (crude OR 1.80) were associated with VLDA in univariate analysis, whereas dyslipidaemia (OR 5.3, 95%CI 1.7–16.6; $p = 0.004$) increased the odds of VLDA in the multivariate model. We found no association between the number of CVRFs and the MDA/VLDA responses. In this cross-sectional, multicentre study, we could not find any relationship between CVRFs and lower odds of achieving stringent therapeutic goals in PsA. In any case, patients with psoriatic disease should be encouraged to maintain healthy lifestyle habits.

Keywords Cardiovascular risk factors · Psoriasis · Psoriatic arthritis (PsA)

Introduction

Psoriasis and psoriatic arthritis (PsA) are immune-mediated diseases that affect a substantial proportion of the general population. Psoriasis affects 1–3% of the general population. One third of psoriasis patients develop PsA. In addition, both entities produce an important physical and psychological dysfunction, deteriorating the quality of life of those who suffer from them [1, 2]. In recent years, psoriatic disease has gained increasing recognition as an entity that extends beyond the skin and joints, encompassing other aspects such as osteoporosis, ocular inflammation, intestinal inflammation, liver disease and, above all, cardiovascular (CV) comorbidity [3].

In terms of CV comorbidity, it is known that patients with psoriasis and PsA have a higher prevalence of traditional CV risk factors (CVRFs) than the general population, and a higher prevalence of adverse CV events, exceeding that which could be explained by the presence of classical CVRFs [4–6]. It has been speculated that these patients also have subclinical atherosclerosis, which contributes to the overall increased risk of CV events [7, 8]. A relevant aspect of pharmacological therapy with traditional and biologic disease-modifying anti-rheumatic drugs (DMARDs) is that the anti-inflammatory action of these therapies may partially reverse CV comorbidity in this population and may even reduce the mortality rate of CV origin [9]. In the last decade, several studies have related the presence of CVRFs (e.g. obesity) and metabolic syndrome with lower retention and response rates to biological therapy in these patients [10–13]. Moreover, some experiences have shown that weight reduction in PsA patients is associated with

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an increased likelihood of minimal disease activity (MDA) in patients treated with anti-TNF-α therapy [14].

Treatment to target (T2T) by measuring disease activity, and adjusting therapy accordingly, improves outcomes in rheumatic diseases [15]. The target of treatment in PsA should be remission or inactive disease. Minimal disease activity is the only target evaluated in a T2T study to date [16, 17]. A potential definition that would fit with the T2T recommendations would be MDA meeting all seven criteria, proposed as a definition of very low disease activity (VLDA) in PsA [15, 18]. Therefore, MDA has become one of the main therapeutic targets of traditional and/or biological DMARDs, as patients in this state develop less structural damage, and the disease has a lower impact on their lives [17, 19].

Despite the above-mentioned evidence, the relationship between CV comorbidity and the therapeutic response is not completely defined. We aimed to evaluate the potential link between therapeutic targets and the presence of CVRFs in patients treated with traditional and/or biological DMARDs.

Patients and methods

This is a post hoc analysis of the MAAPs study, an observational, cross-sectional, multicentre study carried out at 25 rheumatology outpatient clinics in Spain. This study evaluated the prevalence of MDA and its associated factors in patients with PsA who were receiving routine clinical care [20]. MAAPs included outpatients of both genders, over 18 years of age, with PsA according to the ClASssification for Psoriatic ARthritis (CASPAR) criteria [21], with at least 1 year of disease duration, in whom hand and foot radiological tests had been carried out during the 6 months prior to the study visit and who were on treatment with biological and/or conventional synthetic (cs) DMARDs.

All patients provided written informed consent. In accordance with the Spanish recommendations, the study was approved by the Clinical Research Ethics Committee of La Fe Hospital [(ref number: FPNT-07-14-EO (C)] and was conducted in accordance with the principles contained in the Declaration of Helsinki for studies in humans. Data were collected between May 2014 and February 2015 at a single study visit. Patient data collection included demographic and clinical characteristics (age, sex, body mass index, educational level, employment status, toxic habits and comorbidities), detailed PsA clinical history [evolution time of PsA, time from onset of skin and articular symptoms, pattern of PsA at onset (peripheral, axial, mixed), enthesitis, dactylitis, involvement of distal interphalangeal joints, familial history (psoriasis, PsA, ankylosing spondylitis, others), C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), human leukocyte antigen-B27 (HLA-B27) positivity] and record of current use of medications (NSAIDs, local injection of corticosteroids, biological and csDMARDs, corticosteroids). Radiological findings (erosions in hands and feet, joint space narrowing in hands or feet, sacroiliitis, syndesmophytes) from radiological tests carried out during the 6 months prior to the study visit were also recorded. The Psoriasis Area Severity Index (PASI) was assessed. In addition, patients completed self-report questionnaires including the Health Assessment Questionnaire (HAQ), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) if necessary and the Psoriatic Arthritis Impact of Disease (PsAID).

Patients were considered to have MDA when they met ≥ 5 of the following criteria: tender joint count ≤ 1, swollen joint count ≤ 1, PASI score ≤ 1 or body surface area ≤ 3%, patient pain visual analogue scale (VAS) score ≤ 15, patient global disease activity VAS score ≤ 20, HAQ score ≤ 0.5 and tender entheseal points ≤ 1 [16]. Patients who meet all seven MDA criteria are now considered in very low disease activity (VLDA), a clinical situation regarded by some authorities as disease remission [18]. We also collected information of those patients in VLDA.

The impact of disease was evaluated by the PsAID, a questionnaire recently developed by the EULAR that reflects the impact of PsA from the patient's perspective [22]. It is comprised of 12 physical and psychological domains. Each domain is rated from 0 to 10 with a different weighting. The total score is divided by 20. The final score has a range from 0 (best status) to 10 (worst status) with a cut-off of 4.

Statistical methodology

A descriptive statistical analysis of all variables was performed, including measures of central tendency and dispersion for continuous variables and absolute and relative frequencies for categorical variables. Patients were analysed and distributed into two groups according to MDA and VLDA status. A Student's *t* test, Mann-Whitney *U* test or Kruskal Wallis *H* test was used to compare quantitative variables, and Pearson's chi-square or Fisher's exact tests were used for qualitative variables. Univariate and multivariate models were carried out to identify factors independently associated with MDA and VLDA. Tests were two-tailed with a significance level of 5%. Data were analysed using SPSS V19.0 statistical software.

Results

Of the 227 patients included, 133 (58.6%) had MDA at the study visit. Demographic and clinical characteristics of the study population with respect to the presence of MDA are shown in Table 1. MDA was achieved by 62.7% of the patients who received anti-TNF-α alone, by 52.5% on anti-TNF

Table 1 Demographic and clinical characteristics of the study population

	Total *N* 227	MDA *N* 133	No MDA *N* 94	*p*
Male, *n* (%)	123 (54.2)	82 (61.7)	41 (43.6)	< 0.05
Age, mean (SD) (years)	53.2 (12.4)	53.5 (13.3)	52.8 (10.9)	NS
PsA characteristics				
PsA clinical pattern, *n* (%)				NS
Axial	8 (3.5)	3 (2.3)	5 (5.3)	
Peripheral	189 (83.3)	113 (85.0)	76 (80.9)	
Mixed	30 (13.2)	17 (12.8)	13 (13.8)	
Dactylitis	112 (49.3)	67 (50.4)	45 (47.9)	
Enthesitis	81 (35.7)	46 (34.6)	35 (37.2)	
DIP disease	93 (41)	50 (37.6)	43 (45.7)	
Familial history, *n* (%)				
Psoriasis	112 (49.3)	64 (48.1)	48 (51.1)	NS
PsA	28 (12.3)	10 (7.5)	18 (19.1)	< 0.05
PsA duration, mean (SD), (years)	9.6 (7.7)	9.80 (8.1)	9.38 (7.3)	NS
Psoriasis duration, mean (SD), (years)	22.1 (14.7)	20.6 (14.3)	24.2 (15.1)	NS
PsA status at study visit				
Radiologic findings				
Erosions in hands, *n* (%)	83 (36.6)	41 (30.8)	42 (44.7)	< 0.05
Joint in hands with erosion, mean (SD)	4.3 (4.2)	4.9 (4.5)	3.7 (3.9)	NS
Erosions in feet, *n* (%)	67 (29.5)	38 (28.6)	29 (30.9)	NS
Joint in feet with erosion, mean (SD)	3.7 (3.4)	3.9 (3.3)	3.5 (3.7)	NS
PsAID, mean (SD)	4.9 (4.5)	3.3 (3.1)	7.1 (5.2)	< 0.001
PASI, mean (SD)	1.6 (3.8)	0.9 (1.6)	2.8 (5.7)	< 0.05
BASDAI[a], mean (SD)	2.8 (2.4)	2.0 (1.8)	3.6 (2.5)	< 0.001
HAQ, mean (SD)	0.8 (0.6)	0.3 (0.5)	0.5 (0.6)	< 0.001

MDA minimal disease activity, *SD* standard deviation, *DIP* distal interphalangeal joint, *PASI* Psoriasis Area and Severity Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *HAQ* Health Assessment Questionnaire, *PsAID* Psoriatic Arthritis Impact of Disease

[a] Only axial disease

plus csDMARDs treatment and by 62.7% on monotherapy with csDMARDs. Overall, the most frequent anti-TNFs used were etanercept (37.5%) and adalimumab (31.3%), and among the csDMARDs, the most common was methotrexate (76.0%). The mean exposure time to biologics and csDMARDs was not different between the two groups. Statistically significant differences were not observed between non-MDA and MDA patients regarding the use of any kind of treatment except for corticoids. The proportion of patients who received corticoids was significantly higher among non-MDA than that among MDA patients (59% non-MDA vs. 41% MDA; $p < 0.05$).

Cardio-metabolic RF were distributed as follows: hypertension 27.3%, DM 10.1%, dyslipidaemia 30.4%, obesity 21.1%, tobacco 27.3%, habitual alcohol intake 9.7%, sedentary lifestyle 29.1% and hyperuricemia 12.8%. The prevalence of CV events was as follows: 4.0% ischemic heart disease, 1.8% stroke and 2.6% peripheral ischemic arterial disease. Table 2 represents the comparison between MDA and non-MDA patients as a function of the CVRF profile. There were no differences between MDA and non-MDA patients with respect to the number of CVRFs.

Twenty-six of the 227 patients met seven of the seven MDA criteria (11.5%). When this small group was compared with the rest of the patients, the prevalence of overweight (60 vs. 41.5%) and obesity (28% vs 17%) was significantly higher among these VLDA responders ($p < 0.05$). We also found a higher frequency of coronary events among patients who met seven of the seven criteria (11.5 vs. 3%, $p < 0.05$).

Tobacco (crude OR 0.54), sedentary lifestyle (crude OR 1.95), hyperuricaemia (crude OR 2.01) and obesity (crude OR 1.54) were associated with MDA in the univariate model ($p < 0.25$). Multivariate analysis showed that male gender increased the odds of having achieved MDA (OR (95%CI 2.75 (1.47–5.12); $p = 0.001$) as well as living a sedentary lifestyle (3.13 (1.50–6.53); $p = 0.002$). Having a familial history of PsA (0.39 (0.16–0.94); $p = 0.038$), current elevated CRP level (0.92 (0.86–0.98); $p = 0.010$) or use of corticosteroids (0.33 (0.15–0.74); $p = 0.007$) decreased the odds of having achieved MDA. Dyslipidaemia (5.33 (1.71–16.61); $p = 0.004$)

Table 2 Distribution of cardiovascular risk factors among MDA and non-MDA responders

Variable	MDA (*n* 133)	No MDA (*n* 94)	*P* values
BMI (mean ± SD)	26.9 ± 4.2	26.8 ± 4.5	NS
Smokers	22.5%	34.04%	NS
Habitual alcohol intake	6.8%	14.3%	NS
Sedentary lifestyle	34.6%	21.3%	< 0.05
HT	26.3%	28.7%	NS
DM2	11.3%	8.5%	NS
Dyslipidaemia	33%	26.6%	NS
Hyperuricemia	15.8%	8.5%	NS
Obesity	24.1%	17%	NS
Coronary heart disease	5.3%	2.1%	NS
Stroke	2.3%	1.1%	NS
Peripheral arteriopathy	1.5%	4.3%	NS

BMI body mass index, *HT* hypertension, *DM2* diabetes mellitus 2

increased the odds of having achieved VLDA whereas csDMARDs use decreased this odds (0.24 (0.074–0.780); $p = 0.018$).

Discussion

In this multicentre, cross-sectional study, we were unable to demonstrate a relationship between CV comorbidity and a lower response rate to systemic therapies. We also did not observe an association between the number of CVRFs and MDA or VLDA. Even in VLDA responders, higher percentages of overweight and obesity, as well as coronary events, were found. Therefore, our data do not corroborate the aforementioned association between CVRFs and worse responses to systemic treatments [10–13]. Although in the univariate analysis some factors such as smoking were associated with a lower probability of achieving MDA, other factors had a positive relationship (hyperuricaemia and obesity) with this response. When the multivariate analysis model was applied, only a sedentary lifestyle was associated with the MDA response, whereas dyslipidaemia increased the odds of having achieved VLDA.

Earlier studies associated lower response rates to biological therapies with the presence of metabolic syndrome and obesity [10–13]. There are several reasons as to why obesity may lead to a proinflammatory state, lowering the odds of achieving good therapeutic results. Obesity increases the synthesis and release of adipokines, which in turn may decrease the effectiveness of systemic treatments used for psoriatic disease or, in addition, increase the global inflammatory burden of the disease [23, 24]. Metabolic abnormalities (including those of the metabolic syndrome) are linked to the extent of psoriatic disease-related inflammation [23, 24]. The severity of psoriasis and PsA is associated with abnormal levels of serum biomarkers that reflect metabolic abnormalities and predict future CV morbidity [23, 24]. Moreover, there is a positive relationship between obesity and the risk of psoriasis or PsA, and this relationship is dose-dependent (the greater the weight and the longer the time a patient has been obese, the greater the risk of disease) [25]. Despite this, our data do not support these results.

Recent studies have suggested that metabolic comorbidities affect disease activity and medication effectiveness. In that sense, di Minno and colleagues performed a randomised study in which patients beginning therapy with TNF-α inhibitors were assigned to either a 'hypocaloric diet' (< 1500 kcal/day) or a 'self-managed diet'. Regardless of the assigned diet, the likelihood of achieving sustained MDA was closely linked to weight loss in a dose-dependent manner [14]. Reinforcing that vision, Eder et al. have also demonstrated a dose-response association between obesity and achieving sustained MDA [12].

We found sedentary lifestyle to be a factor positively associated with MDA, which could be again in contradiction with previous studies where obesity and metabolic syndrome (factors related to sedentary lifestyle) have been associated with a lower probability of achieving MDA. Indeed, the benefit of programs that encourage physical activity has been reported recently [26]. Although unexpected and controversial, according to the hypothesis that mechanical stress is associated with musculoskeletal inflammation, a sedentary lifestyle in PsA could theoretically reduce clinical complications associated with strenuous physical activity over joints and entheses [27].

Some limitations derived from the cross-sectional nature of this study should be borne in mind. PsA is known to be a heterogeneous disorder with a highly variable progression. The data presented here are a snapshot of a specific moment of the state of illness of patients with a long disease evolution. We cannot be sure what proportion of patients achieved the MDA or VLDA state due to the natural history of the disease and what effect treatment success had on outcome. For the same reason, a precise interpretation of the potential role of cardio-metabolic factors in the achievement (or not) of the

MDA/VLDA response is not possible. Thus, it is difficult to know whether the management of these patients was appropriate. Furthermore, we do not know the proportion of patients who reached sustained MDA or how long they remained in this state. Moreover, given the small percentage of patients in the VLDA situation, it is difficult to obtain solid association data. A better way to answer the question posed in this study would have been through a prospective study. Although some prospective studies link obesity with poorer therapeutic results, it is necessary to go deeper into this issue with more studies in this regard.

Despite the limitations of this study, a remarkable fact of this study is that the majority of patients were patients with long-standing disease with prolonged use of systemic drugs, therefore representative of a standard population of patients with moderate-severe PsA treated under routine clinical conditions. It is possible to speculate that the cultural and gastronomic conditions of each country may have influences on PsA activity outcomes. In fact, the mean weight of our patients (MDA 76 ± 14.7 kg and non-MDA 74 ± 15.3 kg) was lower than that reported in the aforementioned Di Minno and Eder studies [12, 14]. Therefore, it would be interesting to study the MDA response (or other outcomes) in different geographic regions in order to reach clear conclusions about the effect of cardio-metabolic factors on the probability of reaching good therapeutic results.

In summary, in this study, we could not find any association between traditional CVRFs and lower odds of an MDA/VLDA response. Despite this, patients with psoriatic disease should be encouraged to maintain healthy lifestyle habits.

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Compliance with ethical standards

All patients provided written informed consent. In accordance with the Spanish recommendations, the study was approved by the Clinical Research Ethics Committee of La Fe Hospital [(ref number FPNT-07-14-EO (C)] and was conducted in accordance with the principles contained in the Declaration of Helsinki for studies in humans.

Disclosures None.

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