Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

The Skin May Clear But the Arthritis Won't Disappear: Focusing on Concomitant and New-Onset Psoriatic Arthritis in a Daily Practice Cohort of Psoriasis Patients on Biologic Therapy

This article was published in the following Dove Press journal:
Psoriasis: Targets and Therapy

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Background: Previously identified risk factors for psoriatic arthritis (PsA); nail dystrophy and scalp lesions are highly prevalent in patients with moderate-to-severe psoriasis. Therefore, these variables may not be useful as predictors for PsA in this population.

Objective: We assessed the predictive value of demographic and clinical characteristics for development of PsA in a cohort of patients with moderate-to-severe psoriasis, currently treated with biologics. Furthermore, we reported the incidence of new-onset PsA in this population and described the characteristics of patients that developed PsA during biologic treatment.

Methods: Demographics and treatment characteristics of psoriasis patients currently using biologic therapy were extracted from the BioCAPTURE database (n=427). Poisson regression was used to calculate incidence rates. Multivariable logistic regression was performed to identify factors independently associated with PsA onset. Patient and treatment characteristics of patients that developed PsA during biologic treatment were described.

Results: The incidence of PsA was 1.0 (95% CI 0.8–1.2) per 100 psoriasis-years. Except for a lower risk for PsA in male gender (OR 0.58, 95% CI 0.34–0.98, p-value 0.04), no clinical factors were significantly associated with an altered risk of developing PsA. During biologic therapy, 32 patients (9.4%) newly developed PsA. In this group, 53.8% had PASI<5 at PsA diagnosis. The incidence rate of PsA was 1.6 (95% CI 1.1–2.2) per 100 years on biologic therapy.

Conclusion: Clinical risk factors might be inaccurate to predict PsA onset in patients with moderate-to-severe psoriasis on biologics. Even with low disease activity, psoriasis patients on biologics are still prone to develop PsA.

Keywords: psoriasis, psoriatic arthritis, risk factors, biologic therapy, phenotype, localization

Introduction

Psoriatic arthritis (PsA) is strongly associated with cutaneous psoriasis; about 25% of the patients with moderate-to-severe psoriasis will eventually develop PsA compared to 16% of the patients with mild disease.[1] It is of clinical importance to diagnose PsA as early as possible, to prevent irreversible damage of the joints and loss of function.[2] Dermatologists play a key role in the detection of joint involvement, and in order to facilitate the screening for PsA, various studies have identified clinical factors such as nail dystrophy and scalp lesions to be associated

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http://doi.org/10.2147/PTT.S270619

with PsA onset.[3] However, since nail psoriasis is also associated with higher psoriasis disease severity,[4] nail psoriasis may not be suitable as a predictor for PsA in a population of patients with severe psoriasis.

Systemic therapies may reduce the occurrence of PsA in psoriasis patients.[5] Especially biologic therapies could theoretically mask or delay PsA onset. However, despite receiving biologic therapy, psoriasis patients are still prone to develop PsA.[6–8] Currently, there is a lack of data regarding the demographics and treatment characteristics of patients that develop PsA while receiving biologic therapy in the treatment of psoriasis. Knowledge of these factors might prove useful in future research in this specific population.

In this study, we assessed the predictive value of demographic and clinical factors for the onset of PsA in a daily practice cohort of patients with moderate-to-severe psoriasis, currently receiving biologic therapy. Furthermore, we tried to provide insight in the characteristics of psoriasis patients that developed PsA during biologic treatment as well as report the incidence rate of new-onset PsA in our cohort of psoriasis patients on biologic therapy.

Methods

The BioCAPTURE Registry

In this prospective cohort study, all adult patients with a history of plaque psoriasis that were enrolled in the prospective BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics) registry-[9,10] and had been treated with biologic therapy at the Radboud university medical center (Radboudumc) before May 1, 2018 were included. All patients had one or more treatment episodes with TNF-α inhibitors (adalimumab, etanercept, infliximab), an IL-12/IL-23 inhibitor (ustekinumab), IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) or an IL-23 inhibitor (guselkumab). Some patients underwent treatment with the currently withdrawn drugs alefacept (T-cell CD2 receptor blocker) or efalizumab (monoclonal IgG1antibody against CD11a) in their medical history. A total of 427 patients were included.

Data Collection

Data were collected from the BioCAPTURE database from May 1, 2005 until May 1, 2018. Baseline characteristics extracted from the registry were sex, age, dates of psoriasis onset and start of biologic therapy, PsA diagnosis (as confirmed by a rheumatologist), family history of psoriasis (both first and second degree), first PASI (Psoriasis Area and Severity Index) score that was measured in the Radboudumc, Body Mass Index (BMI), and historic psoriasis phenotypes and localizations. For all patients, data on psoriasis phenotypes and localizations were collected until either data lock or loss to follow up occurred. Psoriasis phenotypes were subdivided in plaque, guttate, pustular and erythrodermic psoriasis. The presence of these phenotypes was noted if they appeared at some point during follow-up, not exclusively presenting as the main phenotype. Specific psoriasis localizations and types were recorded: scalp lesions, nail psoriasis, inverse psoriasis (including intergluteal and perianal lesions, and lesions in the axilla, groin and inframammary folds), and palmoplantar psoriasis.

In patients with a rheumatologist-confirmed diagnosis of PsA, the following additional data were collected: date of PsA diagnosis, type of articular involvement at diagnosis (first presentation), PASI score at PsA diagnosis (allowing a timeframe of 3 months prior to 6 weeks after PsA diagnosis), and prior and current use of biologics. Additionally, a distinction was made between psoriasis phenotypes and localizations that presented either prior, or subsequent to PsA onset. Types of articular involvement at PsA diagnosis were classified by a resident rheumatologist using the classification by Moll and Wright, into the following subgroups: distal interphalangeal (DIP) arthritis, arthritis mutilans, polyarthritis, asymmetrical oligoarthritis and spondylitis.[11] In patients with a history of biologic therapy prior to PsA onset, the exact number of patient-years "on drug" was calculated, accepting a treatment interruption with a maximum of 90 days.

Statistical Analysis

Descriptive statistics using standard parameters were used to display patient and treatment characteristics. The incidence rate of PsA expressed as new cases per 100 psoriasis-years was calculated using Poisson regression. Since the onset of cutaneous and musculoskeletal symptoms could be overlapping in patients that were diagnosed with psoriasis and PsA within the same year, the determination of the chronological course of events would most likely be arbitrary. Therefore, this group was excluded in calculating percentages/incidence rates of new-onset PsA in psoriasis patients at risk.

Part 1: Assessing the Predictive Value of Psoriasis Phenotype and Localizations For PsA in Patients with Moderate-To-Severe Psoriasis from the BioCAPTURE Cohort

Based on the absence or presence of PsA, patients were divided into two groups: patients with cutaneous psoriasis only (PsO-group) or with concomitant PsA (PsoPsA-group). In the PsoPsA-group in our primary analysis, only the patients with data available on psoriasis phenotype and localization that presented prior to PsA onset were included. For comparisons, Pearson X2 tests or Fisher's exact tests were performed for categorical variables. Continuous variables were first checked for normality, after which independent sample t-tests were performed for parametric, and Mann–Whitney *U*-tests for nonparametric data, respectively. Only the variables of interest with a p-value <0.20 were selected to be incorporated in a logistic regression analysis using the enter method, in order to identify factors associated with PsA onset.

In order to detect possible bias due to missing values or selection, two sensitivity analyses were performed by repeating the abovementioned procedures. For the first sensitivity analysis, all patients with PsA, even if psoriasis phenotypes or localizations presenting prior to PsA diagnosis were unknown, were included in the PsoPsA-group. Furthermore, all psoriasis phenotypes and localizations that had ever presented prior to data lock were included, instead of only including the characteristics that manifested prior to PsA onset only. For the second sensitivity analysis, also patients with musculoskeletal complaints suspected for PsA were included in the PsoPsA-group, as well as all psoriasis phenotypes and localizations that had ever presented prior to data lock.

Part 2: Focusing on the Patients with PsA Onset During Biologic Therapy

The incidence rate of PsA expressed as new cases per 100 patient-years on biologic therapy was calculated using in Poisson regression, in which the time on biologic therapy was calculated from the administration of the first biologic until data lock or end of follow-up (not corrected for temporary interruptions of biologic therapies).

The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS (Version 25.0, Armonk, NY: IBM Corp).

Results

In our daily practice cohort of psoriasis patients on biologic therapy, 117 patients (27.4%) had rheumatologist-confirmed PsA. In this group, 4 (3.4%) patients had developed PsA prior to the onset of cutaneous symptoms, and 13 (11.1%) patients were diagnosed with both disease entities within the same year. For the entire cohort, the incidence of PsA was 1.0 case (95% CI 0.8–1.2) per 100 psoriasis-years.

Part 1: Association between Psoriasis Phenotype and Localization and PsA in Patients with Moderate-to-Severe Psoriasis

Figure 1 depicts the inclusion and exclusion of patients with psoriasis and, if applicable, PsA. Out of all 427 psoriasis patients that were treated at the Radboudumc and included in BioCAPTURE, 70 patients with PsA (PsoPsA-group A) and 288 patients with cutaneous psoriasis only (PsO-group) were included in our primary analysis. Baseline patient characteristics are presented in Table 1. Of the 69 patients that were initially excluded, 47 patients had PsA, but data on psoriasis phenotype or localization prior to PsA onset were not available, or PsA developed prior to or simultaneously with psoriasis. (PsoPsA-group B). Twenty-two patients were excluded due to a clinically suspected yet not rheumatologist-confirmed diagnosis of PsA (PsoPsA-group C). PsoPsA-group B and C were excluded from the primary analysis, but included in the sensitivity analyses.

Male gender was more prevalent in the PsO group (63.9%), compared to PsoPsA-group A (51.4%) with a nearly statistically significant difference (p=0.06). Mean age at psoriasis onset and age at the initiation of biologic therapy were comparable. The distribution of phenotypes and psoriasis localizations was similar in both groups, with only inverse psoriasis showing a trend towards an inversed relationship with the onset of PsA (p=0.06). Scalp and nail psoriasis had a high prevalence in both PsO (97.2% and 81.9%, respectively) and PsA groups (95.7% and 78.6%, respectively). The prevalence of scalp and nail psoriasis was not significantly different between both groups.

Gender and inverse psoriasis were incorporated in a multivariable logistic regression model. Male gender was the only factor that showed a significant, *negative* association with the onset of PsA (Odds ratio (OR) 0.58, 95% CI 0.34–0.98, p-value 0.04). Inverse psoriasis (OR 0.61, 95% CI 0.36–1.05, p-value 0.07) proved nearly significant.

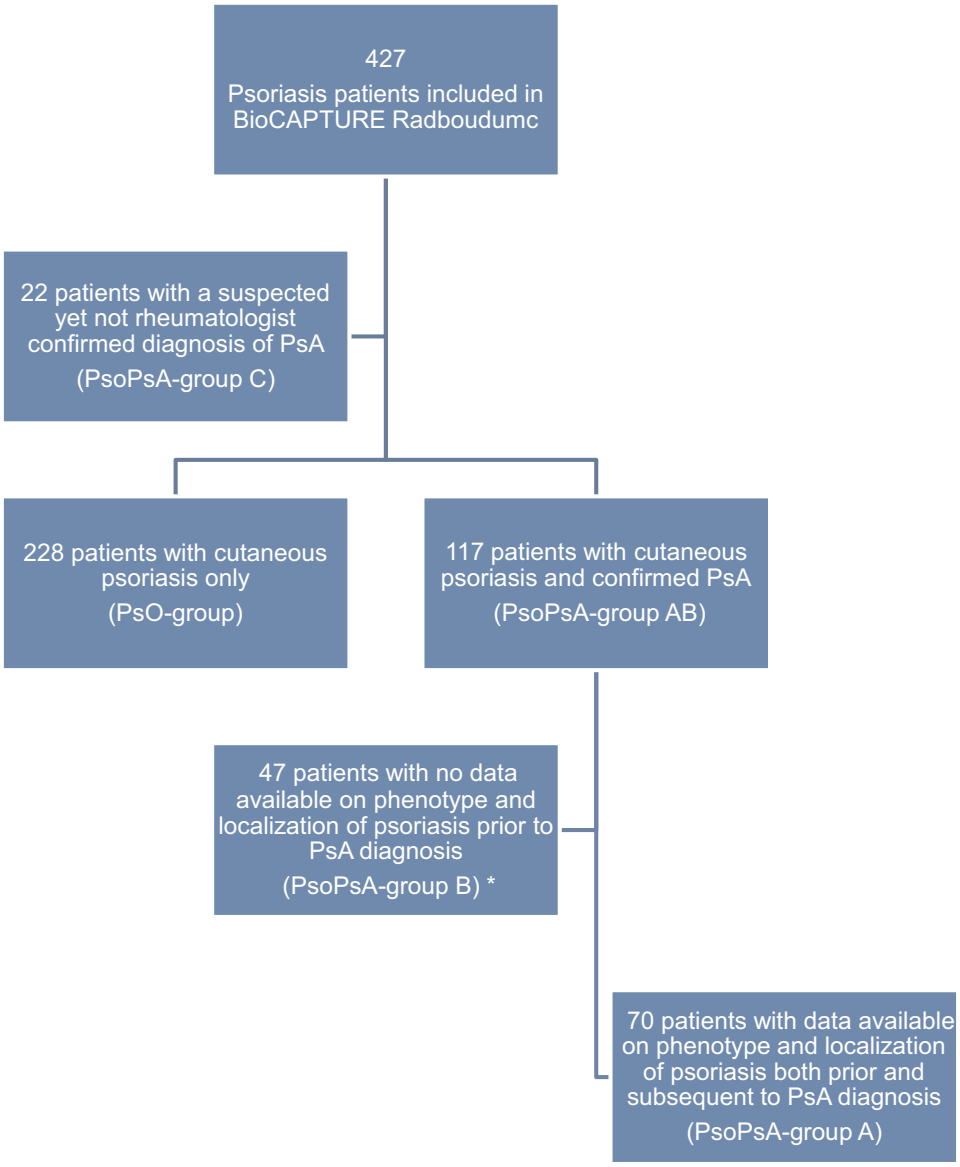

Figure 1 Flow chart of the inclusion and exclusion for primary and sub-analysis in part 1 of the study, of patients with psoriasis and, if applicable, PsA. * PsOPsA-group B also includes patients who developed PsA prior to or simultaneously with psoriasis.

In sensitivity analyses, all phenotypes and localizations of psoriasis that had ever presented prior to data lock or end of follow up were included. In the first sensitivity analysis, all 117 patients with PsA were included (PsoPsA-group AB, Figure 1). Univariable and multivariable analyses for the PsO-group vs PsoPsA-group AB were repeated. Gender, BMI and inverse psoriasis were included in the multivariable model. Male gender (OR 0.65, 95% CI 0.41–1.01, p-value 0.06) and inverse psoriasis (OR 0.67 95% CI 0.43–1.06, p-value 0.09) proved nearly significant in logistic regression. In the second sensitivity analysis, the 22 patients with an unknown PsA status were also included in the PsA group (N= 139, PsoPsA-group AB + PsoPsA-group C). Gender, age at psoriasis diagnosis, BMI and inverse psoriasis were included in the multivariable model. Male gender (OR 0.64, 95% CI 0.42–0.97, p-value 0.04) and inverse psoriasis (OR 0.64, 95% CI 0.42-0.98, p-value 0.04) proved a significant, *negative* association with having a diagnosis of PsA.

Part 2: Development of New-Onset PsA During Biologic Therapy

Thirty-two patients (27.4%) developed PsA during biologic therapy. Patient and treatment characteristics of this group are

Table 1 Socio-Demographic and Clinical Characteristics in Patients with Only Psoriasis (PsO-Group) and Psoriasis with Confirmed Psoriatic Arthritis (PsoPsA Group A)

	PsO-Group (n=288)	PsoPsA-Group A (n=70)	*P*-value
Gender (male)	184 (63.9%)	36 (51.4%)	0.06[a]
Age (years)	53.1 ± 13.8	56.5 ± 14.0	0.06[b]
Average duration of psoriasis (years)	28.6 ± 13.3	31.3 12.0	0.05[c]
Mean age at psoriasis diagnosis (years)	24.5 ± 13.0	25.2 ± 14.5	0.95[c]
Mean age at PsA diagnosis (years)	n/a	45.9 ± 13.7	n/a
Mean age at start biologic therapy (years)	45.1 ± 13.0	47.0 ± 12.9	0.27[b]
Mean psoriasis duration at start biologic therapy (years)	20.6 ± 12.5	21.9 ± 10.7	0.21[c]
Family history of psoriasis (yes)	145 (50.3%)	39 (55.7%)	0.42[a]
First PASI score in Radboudumc	12.8 ± 7.1	14.2 ± 8.3	0.19[c]
BMI (kg/m^2)	28.4 ± 6.2[d]	28.6 (4.7)[e]	0.33[c]
Psoriasis phenotypes (multiple options)			
Plaque	288 (100%)	70 (100%)	
Guttate	136 (47.2%)	29 (41.4%)	0.38[a]
Pustular	19 (6.6%)	4 (5.7%)	> 0.99[a]
Erythrodermic	14 (4.9%)	6 (8.6%)	0.25[a]
Topographic psoriasis localizations (multiple options)			
Scalp lesions	280 (97.2%)	67 (95.7%)	0.51[a]
Inverse	191 (66.3%)	39 (55.7%)	0.10[a]
Palmoplantar	54 (18.8%)	11 (15.7%)	0.56[a]
Psoriatic nail changes	236 (81.9%)	55 (78.6%)	0.52[a]

Notes: Data are in N (%) or Mean ± SD. [a]Pearson Chi-square test/Fisher's exact test; [b]Independent sample *T*-Test; [c]Mann–Whitney *U*-test; [d]2 missing values; [e]1 missing value.

Abbreviation: PASI, Psoriasis Area and Severity Index; BMI, body mass index.

depicted in Table 2. Of all psoriasis patients without PsA when starting biologics, 9.4% developed PsA during biologic therapy. We found an incidence rate of 1.6 new cases of PsA (95% CI 1.1–2.2) per 100 years on biologic therapy.

In patients that developed PsA despite biologic therapy, the mean PASI score around the time of PsA diagnosis was 6.6 ± 6.6. Fourteen patients (53.8%) had a PASI score <5 around PsA diagnosis, and 8 patients (30.8%) had a PASI score <3. Most patients (67.9%) presented with asymmetrical oligoarthritis at the time of diagnosis, and had one or more treatment episodes with adalimumab or etanercept prior to diagnosis. Fourteen patients (44%) were on adalimumab therapy when PsA was diagnosed, which is in line with the proportion of patients that had been treated with adalimumab (59%). The total number of patient-years "on drug" per patient ranged from 0.21 to 9.74 years, with a median of 2.64 years. Year of PsA diagnosis ranged from 2004 to 2018.

Discussion

In this observational study on a daily practice cohort of patients with moderate-to-severe psoriasis treated with biologic therapy, the incidence rate of PsA was 1.0 (95% CI 0.8–1.2) per 100 psoriasis-years. Male gender was associated with a lower risk of developing PsA when compared to female gender. Inverse psoriasis showed a trend towards significance for a lower risk of PsA onset, and was significantly associated with a lower risk of having PsA in one sensitivity analysis. None of the other psoriasis phenotypes and localizations, regardless whether they presented prior to PsA onset or not, were significantly associated with an altered risk of PsA in the multivariable analyses. Furthermore, in our cohort of psoriasis patients on biologic therapy, 9.4% of the patients at risk (without a prior history of PsA) developed PsA during biologic treatment. The incidence rate of PsA was 1.6 (95% CI 1.1–2.2) per 100 years on biologic therapy. In this group, PsA even developed in psoriasis patients with low psoriasis activity on biologic therapy; 53.8% had a PASI < 5 around the time of PsA diagnosis.

In our study population, due to the high prevalence of psoriatic nail changes and scalp lesions in both patient groups with and without PsA, these factors could not

Table 2 Patient and Treatment Characteristics of Psoriasis Patients from the Radboudumc BioCAPTURE Cohort That Developed PsA During Biologic Therapy (n=32)

Gender (male)	15 (46.9%)
Age (years)	57.2 ± 14.1
Average duration of psoriasis (years)	29.6 ± 12.1
Mean age at psoriasis diagnosis (years)	27.6 ± 14.6
Mean age at start biologic therapy (years)	47.3 ± 12.4
Mean age at PsA diagnosis (years)	50.6 ± 13.0
Mean psoriasis duration at start biologic therapy (years)	19.7 ± 10.5
Mean psoriasis duration at PsA onset (years)	23.0 ± 11.1
Mean time between first biologic use and PsA onset (years)	3.3 ± 2.2
Mean PASI score at PsA diagnosis	6.6 ± 6.6; range 0–31.6[a]
Type of articular involvement at PsA diagnosis[b]	
DIP arthritis	0 (0%)
Arthritis mutilans	0 (0%)
Polyarthritis	9 (32.1%)
Asymmetrical oligoarthritis	19 (67.9%)
Spondylitis	0 (0%)
PsA diagnosed after/during first biologic	16 (50.0%)
PsA diagnosed after/during second biologic	10 (31.3%)
PsA diagnosed after/during third biologic	5 (15.6%)
PsA diagnosed after/during fourth biologic	1 (3.1%)
Number of patients on biologic treatment at time of PsA diagnosis	
Adalimumab	14 (43.8%)
Etanercept	6 (18.8%)
Infliximab	3 (9.3%)
Ustekinumab	2 (6.3%)
Secukinumab	1 (3.1%)
Alefacept	1 (3.1%)
Efalizumab	1 (3.1%)
Biologic treatment temporarily interrupted (>90 days)	4 (12.5%)
Total number of years on biologics prior to PsA diagnosis (sum)	89.75
Mean number of years on biologics prior to PsA diagnosis	2.80 ± 2.01
Median number of years on biologics prior to PsA diagnosis	2.64 [2.99]
Minimum number of years on biologics prior to PsA diagnosis	0.21
Maximum number of years on biologics prior to PsA diagnosis	9.74
Mean number of years on biologic prior to PsA diagnosis	
Adalimumab (n=19)	1.26 ± 1.10
Etanercept (n=16)	2.02 ± 1.49
Infliximab (n=5)	1.66 ± 0.62
Ustekinumab (n=6)	2.98 ± 2.53
Secukinumab (n=1)	0.33
Alefacept (n=3)	0.28 ± 0.12
Efalizumab (n=5)	1.21 ± 1.29

Notes: Data are in N (%), Mean ± SD, or Median [IQR] unless indicated otherwise; [a]6 missing values; [b]4 missing values.

discriminate between patients at risk. It must be noted that these results are only generalizable in cohorts of patients with moderate-to-severe psoriasis that are treated with biological therapy. This is probably the reason why in contrast to our results, in a population-based prospective study by Wilson et al, scalp lesions (HR 3.89; 95% CI 2.18–6.94), nail dystrophy (HR 2.93; 95% CI 1.68–5.12) and intergluteal/perianal lesions (HR 2.35; 95% CI 1.32–4.19) were significantly associated with an increased risk of developing PsA.[3] In looking for associations rather than predictors for PsA, several other studies performed in populations of psoriasis patients with a mean BSA>10% or PASI>10 also found a positive association or a higher prevalence of nail involvement in concomitant PsA.[12–17] These findings are supported by the growing evidence for an anatomical correlation between nail psoriasis and enthesitis of the DIP joints, as a manifestation of PsA.[18,19] Besides a higher psoriasis severity,[4] a longer duration of psoriatic skin lesions is also associated with a higher frequency in nail changes.[20] The relatively long duration of disease could partly account for the high prevalence of nail changes in our population.[20] Likewise, this could also be the reason for the high prevalence of scalp lesions. Although scalp lesions are sometimes reported as more prevalent in patients with PsA,[14,21] there is no consensus regarding the association between scalp lesions and PsA in literature, since both positive,[3] negative[17] and no associations[13,22] have been reported.

In our study, inverse psoriasis was significantly associated with a lower risk of PsA when patients with a "suspected yet not rheumatologist-confirmed" diagnosis of PsA were included. However, only a trend towards significance was shown in our primary analysis. Since we used the umbrella term 'inverse psoriasis' instead of one of its subsets, we could not directly compare our results to others who reported on the relationship between subgroups of inverse psoriasis and PsA.[14,17,23] No other psoriasis phenotypes were associated with PsA onset, which is in line with previous studies.[24] In our present

study, male gender was the only variable that was associated with a lower risk of PsA in patients treated with biologics. Literature states that in the general population, the gender distribution in both psoriasis and psoriatic arthritis is balanced.[25,26] It could be possible that gender would have some association in other cohorts of psoriasis patients on biologic therapy, as it has been suggested that due to a higher psoriatic disease severity amongst males, the use of biologics is higher in men.[27,28]

In this cohort of psoriasis patients on biologic therapy, 9.4% of the patients at risk developed PsA despite using biologic therapy. Similar results were reported by Napolitano et al, who reported that 22 out of 327 (6.7%) patients with plaque psoriasis developed PsA while on biologic therapy.[6] In the patients in our study that developed PsA despite being on biologic therapy, the mean duration of psoriasis prior to PsA onset was 23 years. This was relatively long, since most psoriasis patients that develop PsA do so within 10 years following their psoriasis diagnosis.[29] Oligoarthritis was the most common manifestation pattern of PsA at diagnosis (67.9%), followed by polyarthritis (32.1%). In psoriasis patients not exclusively on biologic therapy, Eder et al reported similar results in a prospective cohort study in which they annually assessed symptoms of PsA (76.2% oligoarthritis vs 23.8% polyarthritis at PsA diagnosis [N=51]). In this study, patients were mainly recruited from phototherapy centers and through local advertisement. They reported an annual incidence rate of PsA of 2.7 per 100 psoriasis patients, which is relatively high compared to our findings in a hospital-based population.[30] In a cross-sectional study by Haroon et al, 29 psoriasis patients were newly diagnosed with PsA. Eleven of them (38%) were treated with biologic therapy at the moment of diagnosis. The percentage of patients with oligoarthritis and polyarthritis were both 31% at initial presentation. Contrary to our findings, seven patients (24%) had inflammatory axial disease.[8] The imbalance of PsA manifestation pattern between different cohorts may be a result of differences regarding systemic agents used to treat psoriasis, or various screening methods for PsA (either repetitive or cross-sectional). Adequate psoriasis control does not guarantee adequate control of joint inflammation, as 53.8% of the patients in our study had a PASI <5, and 30.8% had a PASI <3 at the time of PsA diagnosis.

One of the main limitations of this study is the possible underestimation of the presence of psoriasis localization or phenotype. As data on phenotypes and psoriasis localization were derived from medical files, data could be lacking or not be detailed enough to subtract localizations. Despite thorough screening procedures, some patients with early symptoms of PsA might have been left unnoticed.

Our study points out that the potential of a clinical predictor for the onset of PsA greatly depends on the population that is observed. Clinicians should keep this in mind when referral to a rheumatologist is considered, given the risk of both under- and overdiagnosis, and the subsequent additional burden on the feasibility and costs of healthcare. On the other hand, we showed that patient characteristics in psoriasis patients that clinicians might associate with a lower risk of PsA, such as a relatively long disease duration, low disease activity, and even treatment with biologic therapy, are not in fact that reassuring after all. Although self-administered screening tools for PsA seem to have moderate accuracy,[31] implementation of questionnaire-based screening tools could increase the detection rate, and improve the recognition of PsA in dermatology clinics.

In conclusion, in this prospective cohort study on patients with moderate-to-severe psoriasis on biologic therapy, psoriasis phenotypes and localizations were not clearly associated with the onset of PsA, in contrast to studies on less-selected psoriasis patients. Male gender was associated with a lower risk of developing PsA. In this group of patients with moderate-to-severe psoriasis, other biomarkers are therefore needed for PsA prediction. In our cohort of psoriasis patients at risk, 9.4% developed PsA during biologic treatment. Even though biologic therapy can potentially mask or delay the onset of PsA, psoriasis patients on biologic therapy are still at risk, and should be carefully screened for signs and symptoms of musculoskeletal involvement.

Ethics Approval and Informed Consent

Data were extracted from the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE). The registry was approved by our regional medical ethics committee (CMO regio Arnhem-Nijmegen). Every patient provided written informed consent to be included in the BioCAPTURE registry. Data from the BioCAPTURE are not freely available.

Disclosure

Marloes E van Muijen carries out clinical trials for Abbvie, Celgene, Janssen and Novartis, and has received a speaking fee from Janssen. All funding is not personal but goes to the

independent Research Fund of the Department of Dermatology of the Radboud university medical center Nijmegen (Radboudumc), The Netherlands. Tamara W van Hal has acted as a paid speaker for Lily Eli and has received reimbursement for attending a symposium from UCB. Juul M P A van den Reek carries out clinical trials for AbbVie, Celgene and Janssen; has received speaking fees/attended advisory boards from AbbVie, BMS and Janssen and has received reimbursement for attending a symposium from Celgene and AbbVie. All funding is not personal but goes to the independent research fund of the department of dermatology of Radboud university medical center Nijmegen (Radboudumc), the Netherlands. Elke M G J de Jong has received research grants for the independent research fund of the department of dermatology of the Radboud university medical center Nijmegen, the Netherlands from AbbVie, Pfizer, Novartis, Janssen Pharmaceuticals and Leo Pharma and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Janssen, Novartis, Lily, Celgene, Leo Pharma, UCB and Almirall. All funding is not personal but goes to the independent research fund of the department of dermatology of Radboud university medical center Nijmegen (Radboudumc), the Netherlands. The authors report no other conflicts of interest in this work.

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