Evidence that systemic therapies for psoriasis may reduce psoriatic arthritis occurrence

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Abstract

Objective

Contemporary biologic therapies for psoriasis are independently licensed for psoriatic arthritis (PsA). Since skin disease generally predates PsA and PsA has a subclinical phase, we investigated the pattern of PsA evolution in psoriasis treated with biologic agents compared to other medications including oral therapy, topical agents or no treatments.

Methods

A retrospective chart review was performed in psoriasis patients with musculoskeletal symptoms referred for rheumatological assessment. Patients who had a final diagnosis of PsA were identified. The frequency and clinical features of PsA were compared for biologics versus the other strategies.

Results

Between 2015 and 2018, 203 psoriasis patients were referred for musculoskeletal symptoms with 25 on biologics, 31 on non-biologic systemic therapies and 147 on topical/no therapies. A final diagnosis of PsA was similar in all groups (biologics: 36%; non-biologic systemic treatments: 35.4%; none/local treatments: 37.4%). Most patients had musculoskeletal symptoms before systemic therapy initiation but new onset PsA was evident in 12% (3/25) biologics treated patients, 9.6% (3/31) in non-biologic systemic therapy patients and was significantly higher in patients on topical/no therapy (55/147; 37.4%, p<0.001). Among patients with PsA, none of the patients on biologics exhibited dactylitis compared to 28.6% of other systemic treatments and 48.6% of none/local treatments (p=0.046).

Conclusion

New symptoms and signs leading to PsA diagnosis appear to decrease with systemic treatments. The characteristic PsA dactylitis lesion was not evident in the biologic therapy group.

Key words

psoriatic arthritis, psoriasis, biologic therapy, systemic treatment, musculoskeletal symptoms

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Introduction

Psoriasis is a chronic inflammatory skin disease, associated with psoriatic arthritis (PsA) in 7–48% of cases 1. Most of the studies the epidemiology studies on the frequency of PsA were done when the biologics were less commonly used or prior. Currently around 20% of patients affected by psoriasis are treated with biological drugs (2-4), virtually all of which show efficacy in separate trials in PsA (5-7). As the majority of patients with PsA have skin manifestations first, the biological therapy for psoriasis may alter the presentation of PsA.

There is very limited data on the link between biological therapies for psoriasis and subsequent arthritis development. Case series of psoriasis patients treated with ustekinumab reported subsequent PsA development, especially in subjects with high body mass index (BMI), long standing psoriasis and prior tumor necrosis factor inhibitor (TNFi) exposure (8-10). In another study, 22/327 patients with plaque psoriasis, treated with TNFis or Ustekinumab reported to develop PsA (11).

To the best of our knowledge no studies have looked at whether biologic therapies change disease manifestations of PsA in subjects developing arthritis whilst under biologic therapy. In this study, we explored the frequency and disease characteristics of patients diagnosed with PsA whilst being treated with systemic therapies for psoriasis in comparison to patients on other treatments.

Methods

Patient selection

This study was a retrospective chart review. Ethics approval was obtained from Ottawa Health Science Network Research Ethics Board, Ottawa (20180200-01H). All patients referred to two rheumatologists (JK and SZA) between Jan 2015 and Jan 2018 were screened to identify patients who had psoriasis and were referred to rheumatology for musculoskeletal (MSK) symptoms, either from dermatology or family medicine. The screening was made through the referral letters and/or the initial consult notes. If patients had psoriasis and MSK symptoms, their charts were retracted for further data collection. All psoriasis treatments (local therapies, DMARDs and biologics) and duration of utilisation were noted. The final diagnoses were categorised as 1) PsA, 2) not PsA or 3) "non-specific arthralgia, still under follow-up".

Statistical analysis

Descriptive analyses were performed using mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Chi-square test, Fisher exact test, Kruskall-Wallis test or Mann-Whitney U-test were applied, as appropriate. Bonferroni correction was made when multiple groups were compared. Statistical Package for Social Sciences software (SPSS v. 22.0, IBM® corp., Armonk, NY, USA) was used for analyses.

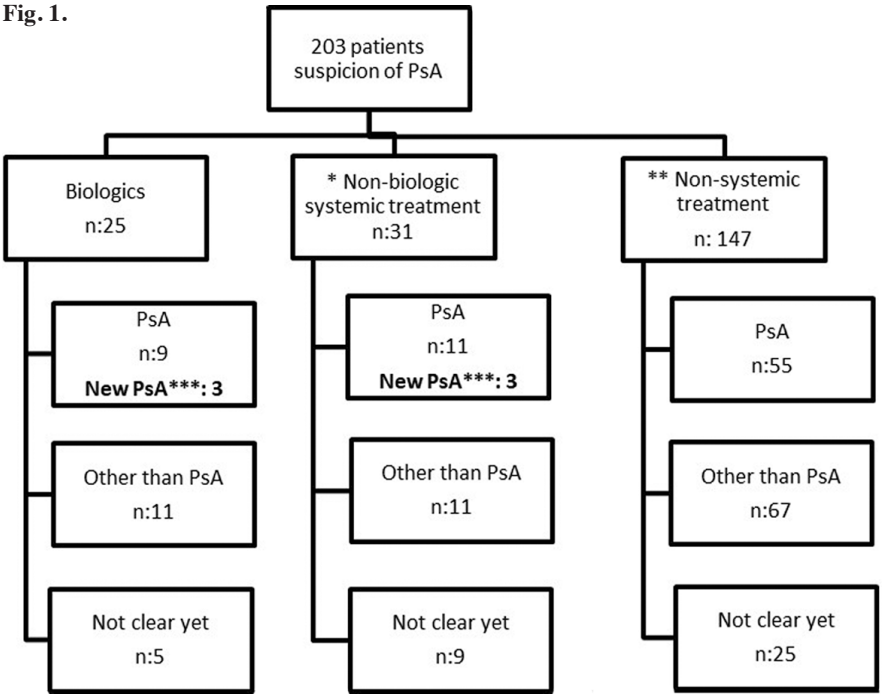
Results

Demographics and clinical features at baseline

In total, 203 psoriasis patients with MSK symptoms were referred during the defined time period (Fig. 1). The mean age at first rheumatology visit was 50.4±13.9 years and 90 (44%) of these patients were men. The most frequent initial MSK symptom was isolated peripheral joint pain (64.2%) followed by a combination of spinal and peripheral joint symptoms (24.4%). The mean symptom duration was 6.5±7.8 years. In the majority of patients, MSK symptoms had started after the skin manifestations (79.9%). Seventy percent of the patients were not on any systemic therapies at the time of referral. Other demographic and clinical features are summarised in the online Supplementary file, Suppl. Table S1.

Within patients referred to rheumatology, 25 patients were under biologic therapies for psoriasis (8 TNFis, 8 Secukinumab and 9 Ustekinumab). Patients treated with biologics had higher BMI than patients on non-biologic systemic treatments and patients not on systemic treatments (37.4±7.4 *vs.* 31.8 ±5.5, 30.0±6.3, respectively; p=0.001). There were no differences for the other characteristics (Suppl. Table S2).

Fig. 1.



Patient characteristics depending on the diagnosis of PsA

Seventy-five patients (36.9%) were diagnosed with PsA. Eighty-nine patients were diagnosed with alternate rheumatological diagnoses, most frequently osteoarthritis (53%) and fibromyalgia (16%). Thirty-nine patients (19.2%) with arthralgia without a clearly defined diagnosis are still under follow-up.

Patients diagnosed with PsA were more frequently males (57.3% *vs*. 31.5% p=0.001) and were younger at the first rheumatology visit (46.6±14.1 *vs*. 53.9±14.0; p=0.001). This group also had a shorter duration of psoriasis (13.4±12.2 *vs*. 19.1±14.2; p=0.021). The mean tender (6.4 ±9.6 *vs*. 3.2±4.9; p=0.003) and swollen (2.3±2.9 *vs*. 0.4±1.5; p<0.001) joint counts at the first visit were higher in the PsA group with more frequent nail disease (67.5% *vs*. 45.0%; p=0.037), dactylitis (38.7% *vs*. 7.2%; p<0.001) and uveitis (20.4% *vs*. 4.4%; p=0.027) (Suppl. Table S1). The final diagnosis of PsA (including the onset of symptoms before or after systemic therapies) was similar in patients treated with biologics, non-biologic systemic treatments and no systemic treatments [9/25 (36%) *vs*. 11/31 (35.4%) *vs*. 55/147 (37.4%), respectively] (Fig. 1). Half of the patients (5/9) with PsA on biologic therapy group had treatment modifications by the rheumatologist due to uncontrolled disease activity (Table I).

New onset of symptoms after the systemic treatments

We evaluated whether musculoskeletal symptoms predated therapy commencement or developed following therapy. The frequency of new onset of PsA after systemic therapies was 3/25 (12%) with biologic therapies (all 3 with Secukinumab, 2 of which were on other biologics prior including TNFis and Ustekinumab) and 3/31 (9.6%) [two on Apremilast and one on Methotrexate (MTX)] in non-biologic systemic therapies (Table I). The frequency of new onset PsA was significantly lower in the systemic treatment groups (either biologics or non-biologic therapies) compared to the group with no systemic therapies [biologics 3/25 (12%), non-biologic systemic therapies 3/31 (9.6%), no systemic therapies 55/147 (37.4%)] (biologics *vs*. none p=0.013; non-biologic therapies *vs*. none p=0.003).

Dactylitis assessment on different therapies

Within patients that were diagnosed with PsA, patients on biologics never had any dactylitis *versus* 19/42 (45.2%) of patients that are treated with other therapies had dactylitis (Suppl. Table S3).

Discussion

In this study, 36% of psoriasis patients referred for MSK symptoms were diagnosed with PsA, consistent with previous studies (1, 2, 12). However, our study showed that new onset PsA was much less common following systemic therapies, either biologics or non-biological systemic therapies, compared to topicals or non-treated cases suggesting a decreased risk of "de novo PsA" in patients treated with systemic therapies. There was no difference for de novo PsA with biologics vs non-biologic systemic therapies which supports the concept that prevention of PsA can be achieved regardless of the pathway used to reduce inflammation.

Although the risk of "de novo PsA" was decreased with systemic therapies, the frequency of all-time symptoms leading to PsA diagnosis was similar in patients with or without systemic therapies, when excluding the timing of the symptoms onset. In the present study, for biologic therapies, around 68% of patients who were recently diagnosed with PsA had prior symptoms and continued to have symptoms following treatment. This may be due to primary or secondary non-responders or partial responders to biologics or certain disease manifestations of PsA not responding to biologics given for their psoriasis (such as Ustekinumab given for their psoriasis, persistent axial symptoms leading to the diagnosis of PsA). Despite the decreased frequency of new onset PsA, it is likely that rheumatologists will still keep on seeing similar number of PsA cases in practice, the majority having persistent symptoms while being on systemic therapies.

Among patients treated with biologics, there were minor differences between groups such as numerically more patients on Secukinumab with joint symptoms after the onset of the biologics and more frequently diagnosed with PsA, although the numbers were low and most of them had previously failed other biologics so it is not possible to make a firm conclusion or a statistical comparison. In terms of the

Table I. Demographics and clinical features of patients.

Variables	All study population n=203	PsA# n=75	non-PsA n=89	*p*-value*
Age at first rheumatology visit (years), mean ± SD	50.4 ±13.9	46.6 ±14.1	53.9 ±14.0	**0.001**
Age at diagnosis of psoriasis (years), mean ± SD	33.3 ±17.2	31.3 ±17.6	32.7 ±17.7	0.642
Men	90, 44.3	43, 57.3	28, 31.5	**0.001**
Smoking (ever)	81/168, 48.2	30/62, 48.3	36/69, 52.1	0.665
BMI, mean ± SD	31.0 ± 6.6	30.9 ± 6.6	30.9 ± 7.3	0.695
Psoriasis duration (years), mean ± SD	15.4 ± 13.1	13.4 ± 12.2	19.1 ±14.2	**0.021**
Type of psoriasis				
Plaque	126/140, 90.0	46/53, 86.7	53/60, 88.3	0.058
Pustular	10/140, 7.1	7/53, 13.2	3/60, 5.0	
Others	4/140, 2.9	0	4/60, 6.7	
Duration of MSK symptoms (years), mean ± SD	6.5 ± 7.8	6.4 ± 9.6	7.0 ±6.4	0.084
Initial symptom type				
Peripheral joint	129/201, 64.2	45/75, 60.0	63/88, 71.6	0.603
Spine	18/201, 8.9	6/75, 8.0	6/88, 6.8	
Peripheral joint + Spine	49/201, 24.4	21/75, 28.0	17/88, 19.3	
Peripheral joint + Enthesis	3/201, 1.5	2/75, 2.7	1/88, 1.1	
Peripheral joint + Spine + Enthesis	2/201, 1.0	1/75, 1.3	1/88, 1.1	
The onset of MSK symptoms				
Before the skin manifestations	32/189, 16.9	16/74, 21.6	9/80, 11.3	0.061
At the same time with the skin	6/189, 3.2	4/74, 5.4	1/80, 1.3	
After the skin manifestations	151/189, 79.9	54/74, 73.0	70/80, 87.5	
TJC at first visit, mean ± SD	4.8 ±7.7	6.4 ±9.6	3.2 ±4.9	**0.003**
Type of arthritis				
Monoarthritis	10/78, 12.8	5/57, 8.8	5/17, 29.4	0.079
Oligoarthritis	17/78, 21.8	13/57, 17.3	4/17, 23.5	
Polyarthritis	51/78, 65.4	39/57, 68.4	8/17, 47.1	
SJC at first visit, mean ± SD	1.2 ±2.3	2.3 ±2.9	0.4 ±1.5	**<0.001**
Enthesitis (ever)	35/128, 27.3	17/48, 35.4	12/54, 22.2	0.187
Dactylitis (ever)	25/131, 19.0	19/49, 38.7	4/55, 7.2	**<0.001**
Uveitis (ever)	13/116, 11.2	9/44, 20.4	2/45, 4.4	**0.027**
Nail involvement (ever)	55/111, 49.5	27/40, 67.5	23/51, 45.0	**0.037**
ESR at first visit, mean ± SD	11.4 ± 11.5	10.7 ±11.4	12.6 ±12.5	0.207
CRP at first visit, mean ± SD	5.9 ± 7.3	7.0 ±8.3	4.9 ±6.1	0.236
RF positivity n,%	9/107, 8.4	1/41, 2.4	7/43, 16.2	0.058
Anti-CCP positivity n,%	10/79, 12.6	2/33, 6.0	7/34, 20.5	0.150
HLA B27 positivity n,%	18/69, 26.0	11/39, 28.2	2/19, 10.5	0.473

BMI: Body Mass index; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HLA: human leukocyte antigen; MSK: musculoskeletal; RF: rheumatoid factor; PsA: psoriatic arthritis; SJC: swollen joint count; SD: standard deviation; TJC: tender joint count.

PsA group defines the patient population who was given the diagnosis of PsA by the rheumatologist at follow up. The group whose diagnose was still not clear at follow-up (PsA or non-PsA) and PsA could not be ruled out were not included in this table. Numbers are given as n/known cases (%), unless stated otherwise.

*p-value was between PsA and non-PsA groups.

clinical manifestations, dactylitis had never occurred in patients treated with biologics despite being seen in 44% of the other groups, suggesting an impact of the biologics given for psoriasis on the characteristic PsA manifestations (13). There is currently a paucity of data on the mechanisms of how biological therapies and oral disease-modifying agents may reduce the incidence of PsA. Imaging studies suggest that biological therapies may lead to regression of subclinical enthesopathy in psoriasis subjects which may be relevant (14).

This study has some limitations. The retrospective nature of the study may result with a non-standardised data collection. In the absence of information on how often the biologics are used by the dermatologists in the population not referred to rheumatology, further analysis cannot be made to understand the frequency of PsA with different biologics.

Our findings also support the concept that therapy for psoriasis might also impact on other SpA associated features including uveitis and Inflammatory bowel disease evolution (15). How such therapy might impact of disease co-morbidities including ischaemic heart disease and metabolic syndrome also warrant further studies (16).

In summary, this study points toward an effect of systemic therapy in modifying PsA and also provides evidence that all systemic therapies currently available may reduce the prevalence of de novo PsA in treated psoriasis subjects. Even though the biologics are effective treatment options for both psoriasis and joint manifestations, PsA is still diag-

Table II. Case summary of psoriatic arthritis diagnosis after systemic treatments for psoriasis with the timing of onset of symptoms.

Case	Age	Sex	Psoriasis duration (years)	Current systemic treatment	MSK symptom timing	Duration of the current treatment	Previous biologics	Treatment change
1	72	F	4	ETN	Before biologic	3 years	None	ADA
2	71	M	33	ADA	Before biologic	1 year	None	No change
3	42	F	15	ADA	Before biologic	1 year	None	No change
4	42	M	5	SEC	After biologic	8 months	ETN/UST	No change
5	52	F	15	SEC	After biologic	1 year	INF/ETN/ADA	Added MTX
6	68	F	17	SEC	After biologic	9 months	None	Added Leflunomide
7	38	M	20	SEC	Before biologic	3 months	UST	No change
8	57	M	25	SEC	Before biologic	6 months	UST	Change to ADA
9	45	M	1	UST	Before biologic	3 months	None	Added MTX
10	28	M	18	Apremilast	After non-biologic therapy	2 years	N/A	Change to SEC
11	37	M	20	Apremilast	After non-biologic therapy	3 months	N/A	Added NSAID
12	47	F	2	Apremilast	Before non-biologic therapy	1 year	N/A	Added MTX
13	50	M	9	MTX	Before non-biologic therapy	4 months	N/A	Increased dosage
14	64	M	3	MTX	Before non-biologic therapy	1 year	N/A	Change to SEC
15	66	F	16	MTX	Before non-biologic therapy	3 years	N/A	Added NSAID
16	24	M	3	MTX	Before non-biologic therapy	6 months	N/A	Increased dosage
17	33	M	17	MTX	Before non-biologic therapy	3 months	N/A	Change to ADA
18	18	M	19	MTX	After non-biologic therapy	4 years	N/A	Increased dosage
19	67	F	1	Vitamin A analog	Before non-biologic therapy	3 months	N/A	Added NSAID
20	50	M	17	Vitamin A analog	Before non-biologic therapy	6 months	N/A	Added NSAID

ADA: adalimumab; BMI: Body Mass index; ETN: etanercept; INF: infliximab; F: female; M: male; MSK: musculoskeletal; MTX: methotrexate; N/A: not applicable; NSAID: non-steroidal anti-inflammatory drug; SEC: secukinumab; PsA: psoriatic arthritis; UST: ustekinumab.

nosed for patients being treated with biologics for psoriasis, in a similar rate with patients that are on other therapies. New onset of PsA may be decreasing with systemic treatments and biologics cause a change in disease pattern with a reduction in dactylitis. Further studies are needed, especially in the era of more potent skin therapies and in an era of biologic switching.

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