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Psoriatic arthropathy in patients with previous neoplasia: a case series of four patients treated with secukinumab and literature review

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Abstract. – OBJECTIVE: Psoriasis and psoriatic arthritis (PsA) are closely linked to cancer, as supported by the literature. Systemic treatments for psoriasis and PsA, namely non-biological disease-modifying anti-rheumatic drugs (DMARDs), have been associated with increased cancer risk in both conditions. New, more effective biological DMARDs (bDMARDs) do not seem to be associated with higher overall cancer risk compared to those not receiving bDMARDs, opening up possibilities for treating patients with previous or ongoing oncological disease alongside psoriasis and PsA. However, limited literature exists on treating PsA patients with cancer with bDMARDs.

This study aims to assess the safety of secukinumab, a bDMARD, in patients with PsA and concurrent cancer. Here, we describe a case series of four patients with PsA treated with bDMARD secukinumab and review the literature on the subject.

CASE SERIES: We assessed the laboratory parameters and clinical characteristics of 4 patients with PsA treated with the bDMARD secukinumab and followed up until 30 months. Three patients had oncological disease in remission, while one had active neoplasia.

No cancer progression was observed during the treatment of these patients with secukinumab.

CONCLUSIONS: In conclusion, our case series, consisting of four PsA patients with concurrent neoplasia treated with secukinumab, showed no evidence of cancer progression and represents the first case of PsA described in the literature treated during active oncological disease, lending support to the safety of secukinumab for the treatment of patients with PsA and concomitant neoplasia.

Key Words:
Psoriasis, Psoriatic arthritis, bDMARDs, Secukinumab, Neoplasia, Malignancy.

Abbreviations

PsA, psoriatis arthritis; TNF-α, tumor necrosis factor-α; IL, interleukin-23; IL-17, interleukin-17; NMSC, non-melanoma skin cancer; bDMARDs, biological disease-modifying anti-rheumatic drugs; JAK-STAT, janus kinase/signal transducer and activator of transcription; IL-12, interleukin-12; SCC, squamous cell cancer; BCC, basal cell carcinoma; PUVA: psoralen and long-wave ultraviolet radiation (UV-A); aHR, adjusted hazard rate; OR: odds ratio; CI, confidence interval, PSOLAR, psoriasis longitudinal assessment and registry; AS, ankylosing spondylitis; SIR, standardized incidence rates; SSZ, sulfasalazine, MTX, methotrexate; cyclosporine A, CsA; EAIR: exposure-adjusted incidence rate; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; HR, hazard risk; NSAIDs: non steroidal anti-inflammatory drugs; PGA, physician global assessment; PtGA, patient's global assessment, VAS, visual analogue scale; PsARC, psoriatic arthritis response criteria, DAPSA, disease activity in psoriatic arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PASI, psoriasis area severity index; COX-2, cyclooxygenase-2; PET, positron emission tomography; PCR, polymerase chain reaction; qRT-PCR: quantitative Real Time PCR.

Introduction

Cutaneous psoriasis is a common chronic inflammatory skin disease with a worldwide estimated prevalence of 2-3%[1]. Approximately 20-30% of the population affected by psoriasis is estimated to develop psoriatic arthritis (PsA)[2-4], a chronic inflammatory arthropathy associated with psoriasis. PsA can affect the spine, the peripheral joints, and entheses. PsA and psoriasis can be considered unique immune-mediated diseases, and multiple pro-inflammatory cytokines are involved in their pathogenesis, including tumor necrosis factor-α (TNF-α), interleukin-23 (IL-23) and IL-17[5].

Numerous systematic reviews and meta-analyses[6-9] reported an increased cancer risk in patients with psoriasis. The increased inflammatory burden associated with the disease[10] is probably an important contributing factor. Different studies

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in the literature, including patients with psoriasis, observed an increased incidence of cancer overall[6,7,11-13] and site-specific cancers, such as non-melanoma skin cancer (NMSC)[6-8,14], lymphoma[6,14,15] and neoplastic diseases, affecting various body districts, including esophagus[9], upper aerodigestive tract[7,9], liver[7], pancreas[7,9], colon[9], kidney[9], bladder[6], urinary tract[7] and lung[6,7].

The systematic review and meta-analysis published by Vaengebjerg et al[6] also investigated the risk of cancer-related PsA. Even if only six studies were included, the authors did not observe an increased incidence of overall cancer compared to the general population, but the lack of significant association may be due to the limited number of studies available. Nonetheless, the study identified a significant association between PsA and increased risk of breast cancer, based on three studies[6]. Accordingly, Hagberg et al[16] and Rohekar et al[17] also did not observe an increased incidence of overall cancer in cohorts of patients with PsA compared to the general population, but the study of Hagberg et al[16] evidenced a slightly increased incidence of hematologic cancer[16]. Hellgren et al[18] did not identify an increased incidence of lymphoma in a cohort of patients affected by PsA, while, in contrast with this study and with those mentioned before, a nationwide cohort study by Eun et al[19] carried out in Korean patients with PsA found an increased risk of overall cancer and lymphoma, but also NMSC and thyroid cancer, compared to the general population. In partial agreement, another cohort-based study[20] reported an increased incidence of overall malignancy, excluding data on NMSC and breast cancer in the PsA cohort compared to the non-PsA cohort. Subsequently, they examined the incidence of NMSC alone and found no increase in the incidence of overall malignancy[20].

Concerns regarding the association of systemic treatments for psoriasis and the risk of cancer have been identified in multiple studies[21,22]: the advent of new biologic therapies for patients with psoriasis and PsA, such as TNF-α inhibitors and other biological disease-modifying anti-rheumatic drugs (bDMARDs), in particular, anti-IL-17A, secukinumab, and ixekizumab, prompted the need to understand whether the use of such therapies in the population affected by psoriasis and PsA would lead to an increase in the risk of cancer, since a protective role of these cytokines against tumor progression is known[21,22]. In particular, janus kinase/signal transduction and activator of transcription (JAK-STAT), IL-12, IL-23, and IL-17 pathways are involved in the pathogenesis of psoriasis and PsA[23-25], and inhibiting these pathways is a therapeutic option. However, the dysregulation of the JAK-STAT pathway is linked to the development of hematological cancers[26]. *In vitro* and animal studies[27-31] have suggested that IL-12 and IL-23 may contribute to protective immune responses to tumors, and IL-17 has antitumor effects in immunocompetent mice[32,33] and pro-tumor effects in immunodeficient mice[34-36]. In theory, therapies targeted to these pathways carry a theoretical risk of decreased tumor surveillance.

Some reports[37-45] are available on the safety of biological agents for treating patients with psoriasis and previous oncological disease: the results obtained so far are encouraging since optimal control of psoriasis is achieved in most cases with no progression of oncological disease. With regard to the safety of treatment of patients with PsA and concomitant neoplasia with biological agents, only a few cases have been reported in the literature[46-49]. Furthermore, bDMARDs that target cytokines apart from TNF-α have limited literature on their use in patients with recent tumor resolution or ongoing cancer.

In this case series, we report four cases of patients affected by PsA with a previous diagnosis of neoplasia, one of which is currently active ocular melanoma. The patients were all treated with secukinumab, a human monoclonal anti-IL-17 antibody licensed for the treatment of psoriasis and PsA[50-52]. None of them reported a worsening of the oncological disease: three cases have a follow-up period ranging from 12 to 30 months, while one patient changed the referral center and was hence monitored only for 12 months.

Case Presentation

Four patients with a history of neoplasia and PsA who failed to achieve remission with non-biologic drugs [i.e., sulfasalazine (SSZ), methotrexate (MTX), cyclosporine A (CsA), hydroxychloroquine sulfate and corticosteroids] and subsequently treated with subcutaneous (s.c.) secukinumab were retrospectively identified and included in the case series. Secukinumab was administered per the dosing regimen for PsA (300 mg weekly on weeks 0, 1, 2, 3, and 4 and 300 mg every 4 weeks thereafter), except for one patient (case 4) who followed the protocol of treatment for ankylosing spondylitis (AS) and was started on secukinumab 150 mg and then shifted to 300 mg after 4 months. One patient (Case 2)

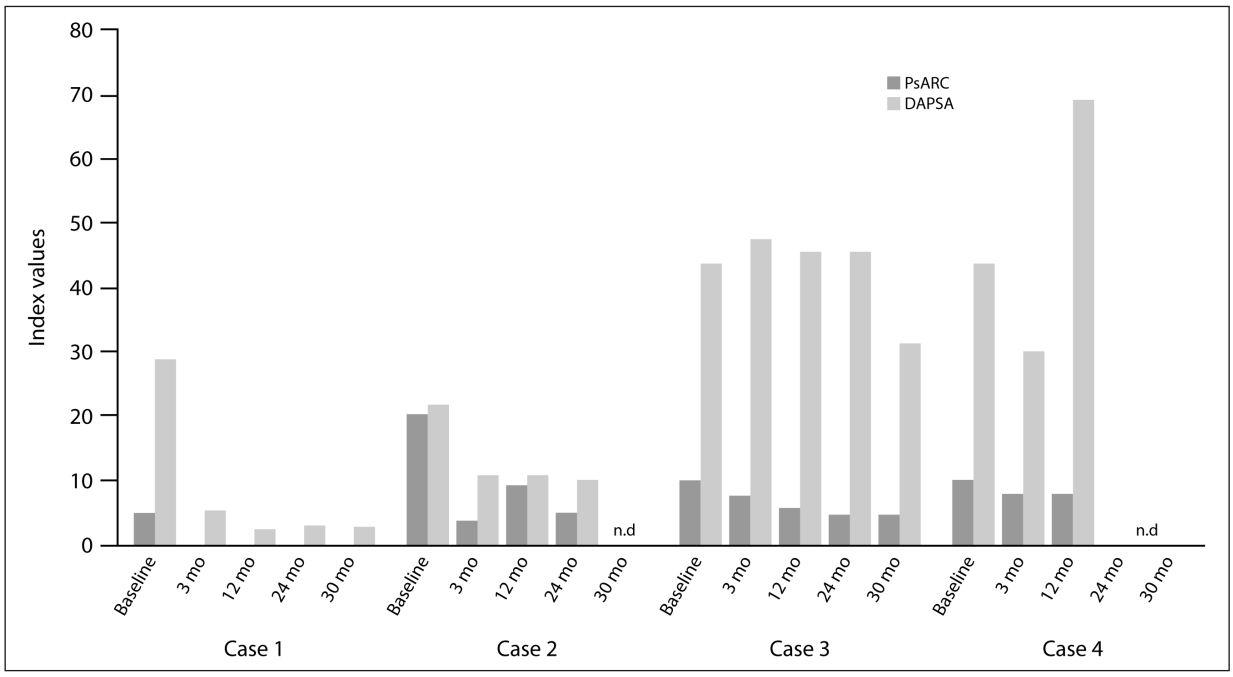

Figure 1. PsARC and DAPSA scores at the baseline and at 3, 12, 24, and 30 months of follow-up. n.d.: not detected.

received secukinumab, prednisone and SSZ for the first three months, then SSZ was withdrawn due to leucopenia, while another patient (Case 3) was treated with combined secukinumab, MTX and methylprednisolone.

All patients underwent bi-monthly blood tests, including hemochrome, hepatic, and renal function analysis, as well as urinalysis, which yielded normal results.

The review of patient data did not require ethical approval in accordance with local/national guidelines. All subjects provided informed written consent for data publication. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

Case 1

A 35-year-old man was first diagnosed with non-Hodgkin lymphoma in 2009 at 18 years and recovered after chemotherapy. The patient developed PsA with polyarticular and enthesopathy involvement at the age of 27 years and was unresponsive to a 4-year-long therapy with MTX, CsA, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids (Table I); the patient also suffered from arterial hypertension and obstructive sleep apnea syndrome, on therapy with angiotensin-converting enzyme inhibitors and nocturnal continuous positive airway pressure; in consideration of the persistently high disease activity, of the need to work (he works as a baker) and of family needs (he is father of two children), the patient agreed to undertake therapy with secukinumab 300 mg, after carrying out the screening tests [i.e., chest X-ray, Quantiferon-TB Gold (QFT) assay and serological markers of hepatitis B and hepatitis C infection] with normal results.

When started on therapy, the patient had 12 painful joints, four swollen joints, a Physician Global Assessment (PGA) of 5 and a Patient's Global Assessment (PtGA) of 5.5, a pain Visual Analogue Scale (VAS) of 6/10 (Table II), a Psoriatic Arthritis Response Criteria (PsARC) index of 4, a Disease Activity in Psoriatic Arthritis (DAPSA) score of 28.5 (Figure 1) with a plasmatic content of C-reactive protein (CRP) of 0.6 mg/L and an erythrocyte sedimentation rate (ESR) of 5 mm/hr (Table II). Skin involvement was very modest at baseline, with a Psoriasis Area Severity Index (PASI) of 1.4.

The patient immediately responded excellently to the treatment: the DAPSA value was drastically reduced at 12 months to 1 (indicative of remission), and the PsARC index was 0 within 12 months (Figure 1). The excellent clinical response was maintained and consolidated at 24 and 30 months of follow-up, with a DAPSA of 2 and PsARC index of 0 at both time points (Figure 1). Dermatitis

Table I. Patient's demographic and characteristics.

Case	Gender	Age (years)	Type of PsA (duration of disease)	Type of cancer (diagnosis)	Prior therapies	Initiation of secukinumab treatment	Tumor recurrence during secukinumab treatment
1	Male	35	Oligoarticular with enthesopathy (8 years)	NHL (2009) in remission	MTX, CsA, NSAIDs, steroids	February 2020	No
2	Female	42	Oligoarticular with enthesopathy (4 years)	Cutaneous melanoma (2014) in remission	MTX, SSZ, NSAIDs, steroids	November 2019 (combination therapy with SSZ till January 2020)	No
3	Female	58	Rheumatoid arthritis-like (20 years)	Ocular melanoma (2006), recurred in 2016 and is still active	NSAIDs steroids, opioids, hydroxychloroquine sulfate, SSZ, MTX, denosumab	August 2021 (combination therapy with metilprednisolone 16 mg/day) and MTX (15 mg/week)	No
4	Female	48	Oligoarticular with enthesopathy (3 years)	Cutaneous melanoma (2019) in remission	MTX, SSZ, leflunomide	July 2021	No

NHL: non-Hodgkin lymphoma; MTX: methotrexate; SSZ: sulfasalazine; CsA: cyclosporine A, NSAIDs: non-steroidal anti-inflammatory drugs.

disappeared at 12 months with no flare-up at 24 and 30 months (PASI 0).

The patient showed no sign of non-Hodgkin lymphoma recurrence in the 30-month follow-up period and is still under treatment. He undergoes hematological checks every 3 months: protidogram, β2-microglobulin, and other markers indicate that his bone marrow is totally quiescent.

Case 2

A 42-year-old woman was first diagnosed with a cutaneous melanoma in 2014 that was surgically excised and did not recur. The patient, who is not affected by any comorbidity, developed enthesopathy and oligoarticular PsA at the age of 38 years (Table I): she was intolerant to MTX therapy and unresponsive to SSZ therapy at a dosage of 2 g/day combined with selective Cyclooxygenase-2 (COX-2) inhibitors and steroids.

After performing screening tests, the patient was started on biological agents with secukinumab 300 mg s.c. At the time of treatment initiation, the patient presented with polyarthritis and enthesitis: in particular, she presented with six painful joints, four swollen joints, a pain VAS of 7, a PtGA of 7, a PGA of 5.5 (Table II), a PsARC index of 12, a DAPSA score of 21 (Figure 1); the CRP plasmatic level was 1 mg/L, and the ESR was 17 mm/h (Table II). Dermatitis involvement was modest, with a PASI score of 1.4.

After treatment initiation, the patient developed an excellent clinical response to the joints and the enthesis (Table II). The 12-month DAPSA index dropped to 10, the PsARC index to 8 (Figure 1) and the PASI to 0.7.

The satisfactory clinical results obtained at 12 months were maintained at the 24-month follow-up, where a DAPSA of 10, a PsARC of 4 (Figure 1) and a PASI of 1.1 were recorded.

During the 24-month follow-up, dermatological checks did not show any recurrence of the previous melanoma nor the development of new skin tumor localizations.

The patient is still under treatment. She is monitored and gets her moles evaluated every 6 months by a dermatologist. No recurrence of melanoma has been observed.

Case 3

A 58-year-old woman with inoperable ocular melanoma was diagnosed with rheumatoid-like PsA at the age of 38 years. She had a recurrence of ocular melanoma after 10 years, 5 years before starting secukinumab therapy. The patient's comorbidities include hypertension, dyslipidemia, and osteoporosis due to chronic use of glucocor-

ticoids. Therapeutic interventions have been limited to NSAIDs, steroids, and opioids for over 10 years due to the concern to induce tumor progression with immunosuppressive therapies (Table I). The worsening of the clinical symptoms led to the introduction of hydroxychloroquine sulfate, SSZ, and MTX at a dosage of 20 mg/week as well as denosumab 60 mg 1 vial every 6 months (Table I), without producing significant benefits on the patient's clinical status. After the screening tests and the collection of the informed consent signed by the patient, therapy with secukinumab 300 mg was started.

The disease activity of the patient, who has a polyarticular rheumatoid-like but also enthesopathic form, was extremely high at baseline; the patient had 26 tender joints, 19 swollen joints, a pain VAS of 9 and a PGA and PtGA of 9 (Table II); DAPSA was 44, the PsARC index was equal to 8 and the baseline PASI of 2.1 (Figure 1) while CRP plasmatic content was 1.9 g/L and ESR 18 mm/h (Table II).

The patient did not respond positively in terms of disease activity: DAPSA index at 12 months and 24 months were 46 and 46, respectively (Figure 1); the PsARC index instead improved at 12 months (4) and 24 months (3) (Figure 1); PASI decreased to 0.7 at 12 months and increased to 1.1 at 24 months. At the 30-month follow-up, however, a partial clinical response was found with a significant drop in DAPSA to 31 and PsARC still at 3 (Figure 1) with PASI 1.1. During the 30-month follow-up, the ocular melanoma remained unchanged in size; PET control showed no development of metastases. She undergoes computed tomography with contrast every 6 months, which has shown no progression of melanoma. The patient is still under treatment.

Case 4

A 48-year-old woman had a cutaneous melanoma removed from her right leg at 44 years. At 45 years old, she was diagnosed with the oligoarticular enthesopathic variant of PsA. The patient also suffers from fibromyalgia. She did not tolerate MTX and did not respond to therapy with 2 g SSZ per day and 20 mg leflunomide per day (Table I). The patient refused therapies for fibromyalgia, except for ineffective nutritional supplements. After performing the screening tests, the patient started therapy with secukinumab 300 mg s.c.

At baseline, the patient presented 18 painful joints, eight swollen joints, pain VAS of 8, a PGA of 6, a PtGA of 8 with a CRP dosage of 1 mg/L and ESR 5 mm/h (Table II); the baseline DAPSA score was 44, and the PsARC index was 8 (Figure 1). The patient had no active dermatitis involvement at the start of therapy (PASI 0). At the 12-month follow-up, the patient presented a reduction of DAPSA to 30 while the PsARC index was 7 (Figure 1). No skin involvement had occurred. She was monitored by a dermatologist and underwent mole checks every 6 months. No recurrence of the previous melanoma was found in the dermatological follow-ups. The patient, not deeming the clinical response satisfactory, changed the referral center of care and voluntarily interrupted the biological pharmacological treatment with secukinumab after 14 months of therapy.

Table II. Comparison of the number of painful joints and swollen joints, CRP and ESR values, and VAS and PGA scores of patients before being started on secukinumab therapy (0 months) through up to 30 months of follow-up.

	Case 1					Case 2					Case 3					Case 4				
Months	**0**	**3**	**12**	**24**	**30**	**0**	**3**	**12**	**24**	**30**	**0**	**3**	**12**	**24**	**30**	**0**	**3**	**12**	**24**	**30**
Painful joints (n)	12	2	0	0	0	6	4	8	3	n.d.	26	20	21	21	14	18	15	15	n.d.	n.d.
Swollen joints (n)	4	0	0	0	0	4	0	2	1	n.d.	19	14	12	12	4	8	7	7	n.d.	n.d.
CRP (mg/L)	0.6	0.2	0.2	0.2	0.2	1	1	1	1	n.d.	1.9	0.5	0.4	1	1	1	1	1	n.d.	n.d.
ESR (mm/h)	5	12	5	13	12	17	16	3	3	n.d.	18	12	5	14	32	5	14	14	n.d.	n.d.
VAS	6	20	1	1	1	7	2	7	3	n.d.	9	8	8	8	6	8	8	8	n.d.	n.d.
PtGA	5.5	1.5	1	1.5	1	7	3.5	5.5	2	n.d.	9	8	7	7	6	8	8	8	n.d.	n.d.
PGA	5	1.5	5	1	1	5.5	2.5	5.5	1	n.d.	9	7.5	6	**6.5**	**6**	6	7	3	n.d.	n.d.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: Visual Analogue Scale; PtGA: Patient Global Assessment; PGA: Physician Global Assessment; n.d.: not detected.

Review of Literature

Risk of Cancer Associated with the Treatment of Psoriasis

Non-biological agents

A review of the literature[53] published in 2018 reported an association between MTX and CsA therapies and an increased risk of cancer, particularly squamous cell cancer (SCC), in patients with psoriasis, especially when in combination with PUVA therapy, long-term studies[54-56] have confirmed that exposure to high-dosage PUVA treatments for skin disorders greatly increases the risk of NMSC. No overall increased risk for malignancy was reported in the analysis of the Psoriasis Longitudinal Assessment Registry data[57] in the subgroup of patients treated with MTX up to more than 12 months relative to no MTX treatment. A recent nationwide case-control study[58] verified the association between cases of SCC, basal cell carcinoma (BCC), and cutaneous melanoma and therapy with MTX, while in the entire population, the risk of BCC and SCC was dose-dependent when they restricted the analysis to the subgroup of patients affected by psoriasis the association was not consistent, suggesting the presence of a surveillance bias. Hong et al[59] reported an increased risk for malignancy excluding NMSC in patients with psoriasis treated with CsA [adjusted hazard rate (aHR), 1.20; 95% CI, 1.04-1.39] including hematologic (aHR, 3.46; 95% CI, 1.90-6.30) and pancreatic (aHR, 1.97; 95% CI, 1.25-3.10) cancers.

Biologic Agents

TNF-α inhibitors

Concern for an increased risk of malignancy has been raised with TNF-α inhibitors, owing to the role of TNF-α in tumor growth inhibition[21].

In a 3-year meta-analysis[12] of overall malignancy incidence, including general population, psoriasis patients, and subgroups on non-biologic or biologic therapies, malignancy rates excluding NMSC were 0.92 per 100 person-years for etanercept and 0.84 per 100 person-years for other anti-TNF-α drugs.

This incidence was lower than or comparable to the incidence in the psoriatic population (1.14 per 100 person-years) and the general one (0.95 per 100 person-years)[12]. Accordingly, a nationwide Korean cohort study[59] with a mean follow-up time of 6.6 years did not find an increased risk of malignancies other than NMSC in the subgroup of patients with psoriasis treated with anti-TNF-α agents compared to the non-psoriasis population (aHR, 1.19; 95% CI, 0.66-2.16). Conversely, a nested case-control analysis[57] of first-time malignancies excluding NMSC in patients from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study observed a significantly increased malignancy risk in patients treated with TNF-α inhibitors *vs.* no TNF-α inhibitor treatment with long-term [≥12 months; odds ratio (OR), 1.54; 95% CI, 1.10-2.15], but not short-term treatment.

In a comprehensive safety analysis of data[60] from clinical trials covering rheumatoid arthritis, juvenile idiopathic arthritis, AS, PsA, psoriasis, and Crohn's disease, a cohort of patients with psoriasis treated with adalimumab reported a modest but significantly increased risk for NMSC (standardized incidence rates, SIR 1.76; 95% CI, 1.26-2.39). However, no increased risk was observed for all malignancies, excluding NMSC and lymphomas[60]. The median duration of treatment was 0.7 years, with 40.8% of patients treated for at least two years[60]. Accordingly, another safety analysis[61] of adalimumab exposure in clinical trials with a duration of up to 60 weeks reported an increased risk of NMSC in patients with psoriasis treated with adalimumab with SIR values of 1.15 (95% CI, 1.04-2.11). In particular, the study identified an increased risk of SCC, an NMSC subtype, with a SIR of 3.84 (95% CI, 1.54-7.92)[61], which is in agreement with the increased risk for SCC found in etanercept-treated psoriasis patients (SIR, 1.78; 95% CI, 1.11-2.69) reported in the integrated safety analysis of short-term placebo-controlled clinical trials (up to 12 weeks) and long-term uncontrolled open-label clinical trials (up to 144 weeks) of etanercept published by Pariser et al[62]. A post-hoc analysis of four clinical trials of etanercept with a follow-up of 4 years performed by Papp et al[63] reported a lower increase in SCC risk (SIR, 1.08; 95% CI, 0.29-2.76) compared to the previously mentioned studies[61,62]. In a cohort study[64] with an average follow-up of 5.48 patient-years, including a subgroup of patients with psoriasis treated with biologics, mostly TNF-α inhibitors (97%), an aHR of 1.81 (95% CI, 1.23-2.67), for SCC was found. The post-hoc analysis performed by Papp et al[63] failed to identify an increased risk of BCC, an NMSC subtype, in patients with psoriasis treated with etanercept, with a SIR of

0.55 (95% CI, 0.37-0.80), which is in agreement with the SIR of 0.52 (95% CI, 0.23-1.03) for BCC reported in the safety analysis published by Pariser et al[62].

Despite the lack of a clear relationship between anti-TNF-α agents and cancer, international guidelines[65] suggest waiting 5 years after the resolution of a tumor before starting therapy with anti-TNF-α biologics.

IL-12/23 inhibitors

The evidence available on the risk for malignancy occurrence in patients with psoriasis treated with anti-IL-12/23 is contrasting. The safety analysis of phase II and III clinical trials[66] of ustekinumab, an IL-12/23 inhibitor, in patients with psoriasis did not identify higher rates of malignancy. Accordingly, a 5-year-long safety study[67] of ustekinumab in 3,117 patients with psoriasis reported rates of NMSC and other tumors comparable to those of the general population. This aligns with the findings of nested case-control analyses conducted by Fiorentino et al[57] on first-time malignancies, excluding NMSC, in patients from the PSOLAR study. The analyses did not identify an increased risk of malignancy in patients with psoriasis treated with ustekinumab with a follow-up of more than 12 months[57]. In agreement with these studies, the nationwide Korean cohort[59] study published by Hong et al in 2022 did not find an increased risk of malignancies excluding NMSC in patients with psoriasis treated with IL-12/23 inhibitors compared to those without psoriasis.

Conversely, a safety analysis[68] including 2,520 patients from five randomized, controlled clinical trials and an open-label extension study in patients with psoriasis treated with briakinumab, an anti-IL-12/23 agent, reported that 2.6% of patients had an incident tumor [exposure-adjusted incidence rate (EAIR), 1.7 per 100 patient-years], the vast majority being NMSC (EAIR, 1.2 per 100 patient-years).

A study[69] published in 2018 reviewed the literature on the risk of malignancy in patients with psoriasis treated with IL-12/23 inhibitors and found contrasting evidence with trials and post-marketing safety data reporting an increased risk of NMSC in patients with psoriasis treated with ustekinumab and other studies finding rates of malignancy comparable to the general population, suggesting the need for monitoring the risk of cancer in patients with psoriasis treated with anti-IL-12/23 agents.

JAK inhibitors

There is scant information on the risk of malignancy related to the inhibition of the JAK pathway in patients with psoriasis. Two identical phase III clinical trials[70] of tofacitinib treatment in patients with psoriasis, PIVOTAL 1 and PIVOTAL 2, including approximately 900 patients per study, identified four cases of malignancy excluding NMSC in PIVOTAL 1 and one case of SCC and one case of BCC in PIVOTAL 2. Further studies on the risk of malignancy related to the inhibition of the JAK pathway in patients with psoriasis are advocated since JAK inhibitors hold promise for efficacy and safety, have a low incidence of side effects, and are orally taken.

IL-17 inhibitors

Two meta-analyses[71,72], including data from 21 and 49 clinical trials each on the safety of secukinumab in patients affected by psoriasis, PsA, and AS, were published in 2019 and 2021, respectively.

The pool of patients with psoriasis in the first study by Deodhar et al[71] included 5,181 patients. The EAIR for malignant or unspecified tumors was 0.8 per 100 patient-years, and most were non-hematological malignant tumors[71]. The pool of patients with psoriasis in the second study by Lebwohl et al[72] included 10,685 patients. The EAIR for malignancy was 0.83 per 100 patient-years[72].

A study[73] comparing the efficacy and safety of secukinumab and ustekinumab in patients with psoriasis over 52 weeks confirmed the superior efficacy of secukinumab over ustekinumab in clearing psoriatic lesions and found an incidence of malignant or unspecified tumors of 0.9% for secukinumab-treated patients and of 1.3% for ustekinumab-treated patients.

A long-term efficacy and safety study[74] analyzed the incidence of malignancies over 5 years of treatment with ixekizumab in patients with psoriasis and found an incidence rate of 0.6. Accordingly, a phase III trial[75] of ixekizumab in patients with psoriasis did not observe increased incidence rates of NMSC and malignancies, excluding NMSC.

A phase III placebo-controlled trial[76] of bimekizumab, a monoclonal IgG1 antibody that selectively inhibits IL-17F and IL-17A, in patients with psoriasis reported one case of malignancy out of 349 patients treated with bimekizumab for 16 weeks and 0 cases in the subsequent follow-up period till week 56.

A recent study[77] evaluated the efficacy and safety of switching the treatment of patients affected by psoriasis previously treated with adalimumab, ustekinumab, and secukinumab to bimekizumab. The EAIRs of malignancies were low during the treatment with all the bDMARDs and remained low after switching to bimekizumab[77].

A comparison of the guidelines for the use of anti-IL-17 agents in psoriasis patients in the USA[78], UK, and Europe reveals that European guidelines mention the presence of oncological disease as a relative contraindication to the use of secukinumab. Long-term studies based on real-world evidence are needed to support the encouraging safety signals regarding malignancy occurrence obtained in clinical trials.

Risk of Cancer Associated with the Treatment of PsA

Non-biolologic agents

MTX and SSZ have been associated with increased lymphoma risk in a cohort of patients with PsA compared with PsA patients treated with oral glucocorticoids alone[18]. Accordingly, a systematic review and meta-analysis[79] showed that PsA patients treated with conventional synthetic DMARDs (csDMARDs) exhibit an increased cancer risk compared to the general population.

Biologic Agents

TNF-α inhibitors

A comparative safety analysis of TNF-α inhibitors in patients affected by multiple immune-mediated diseases demonstrated that the incidence of solid cancers was not elevated in the PsA subgroup (HR, 0.74; 95% CI, 0.20-2.76) during anti-TNF-α therapy compared to disease-specific alternative treatment strategies[80]. Accordingly, a study on a Nordic cohort of patients with PsA treated with anti-TNF-α agents[81] found no increased significant risk for solid tumors (SIR, 1.0; 95% CI, 0.9-1.1) with respect to biologics naïve patients and another cohort study[82] did not observe an increased risk of malignancy occurrence in patients with PsA treated with anti-TNF-α agents compared to patients receiving csDMARDs. In agreement with these findings, a systematic review and meta-analysis[83] did not find any association between treatment with anti-TNF agents and cancer in patients with PsA [fixed-effects odds ratio (OR), 1.57; 95% CI, 0.29-8.49 and random-effects OR, 1.34; 95% CI, 0.17-10.5]. Another meta-analysis[84] indirectly compared the efficacy and safety of several biologics approved for treating PsA. The analysis revealed that the rates of malignancy in patients with PsA ranged from 1% to 5.7% for etanercept, 0.16 to 5.1% for infliximab, and 0.1 to 1.1% for adalimumab[84]. The safety analysis of data from clinical trials of adalimumab conducted by Burmester et al [60] found an increased incidence of lymphomas (SIR, 5.88; 95% CI, 0.66-21.2) and of NMSC (SIR, 1.25; 95% CI, 0.46-2.72) in the cohort of patients with PsA, while the risk for all malignancies, excluding NMSC, was not increased (SIR, 0.68; 95% CI, 0.22-1.59) in agreement with the previously cited studies[80-84]. A significantly increased risk of NMSC (SIR 2.12; 95% CI, 1.19-3.50) with no increased risk of malignancy overall compared to the general population (SIR, 0.94; 95% CI, 0.65-1.34) was also reported in a cohort study[85] including patients with PsA treated with anti-TNF-α inhibitors. No increased incidence of lymphoma was observed in a subgroup of patients with PsA treated with anti-TNF-α compared to the untreated counterpart in a nationwide cohort study[18]. No increased incidence of hematologic malignancies was found in patients with PsA treated with anti-TNF-α agents compared to the general population in the cohort study performed by Cordtz et al[86].

IL-12/23 inhibitors

The incidence of malignancies in clinical trials[87-89] of ustekinumab in patients with PsA has been remarkably low. To our knowledge, no other relevant data on the incidence of malignancies in patients with PsA treated with IL-12/23 inhibitors is available.

JAK inhibitors

A short follow-up study of patients with rheumatoid arthritis or PsA demonstrated that the risk for cancer other than NMSC associated with JAK inhibitors was comparable to that of anti-TNF-α agents in the cohort of patients with PsA, while the risk for NMSC was increased[90]. The EQUATOR study did not report malignancy occurrence in 65 patients with PsA treated with filgotinib, a JAK inhibitor[91]. We were not able to find other relevant data on this topic.

IL-17 inhibitors

The data available so far on the safety of secukinumab for the treatment of patients with PsA, from the perspective of the incidence of oncological diseases, are encouraging, even if the number

of patients analyzed is limited. The meta-analysis on the safety of secukinumab in patients affected by psoriasis, PsA and AS performed by Deodhar et al[71] cited above, included 1,380 patients with PsA. The EAIR for malignant or unspecified tumors was 1.1 per 100 patient-years; also, in this case, the majority of the oncological diseases reported were represented by non-hematologic malignant cancers[71]. The pool of patients with PsA included in the safety meta-analysis of secukinumab performed by Lebwohl et al[72] included 2,523 patients. The EAIR for malignancy was 1.04 per 100 patient-years[72]. A phase III placebo-controlled study[92] investigating synovitis response in 83 patients with PsA treated with secukinumab found no malignancy occurrence over 12 weeks of treatment.

A phase III placebo-controlled trial[93] on patients, including 431 patients with PsA naïve to bDMARDs treated with bimekizumab, reported one BCC occurrence in the bimekizumab group in the first 16 weeks of treatment and one case of NMSC in the following eight weeks of treatment with an incidence of less than 1%, comparable to that of the placebo group. The same authors also performed a phase III placebo-controlled trial[94] including 267 patients with PsA refractory or intolerant to anti-TNF-α agents and treated with bimekizumab. They did not observe cases of the oncological disease in the group of patients treated with bimekizumab, while one case of BCC was reported in the placebo group[94].

Safety of Biologicals For Patients With Psoriasis and Concominant Neoplasias

Data from the literature on the association between bDMARDs for treating psoriasis and cancer recurrence are scarce since the presence of a previously diagnosed oncological disease usually represents an exclusion criterion in clinical trial protocols. Furthermore, dermatologists have many concerns before initiating therapy with bMARDS in patients with previous or ongoing neoplasia due to the immunosuppressive effect of these drugs. However, most of the cases reported in the literature about patients with psoriasis and oncological disease treated with secukinumab do not identify any association between bDMARDs and the risk of progression or recurrence of cancer.

A case report study[38] of 14 patients with a history of previous cancer (melanoma, n=2; non-cutaneous solid tumors: n=12;) treated with biological agents (infliximab, etanercept, adalimumab, secukinumab, ixekizumab) for psoriasis for a minimum of 6 and a maximum of 180 months reported no recurrence of neoplastic disease. Valenti et al[39] analyzed 16 patients with a diagnosis of malignant cancer in the previous 10 years treated with biologic agents (ixekizumab, secukinumab, ustekinumab, etanercept, risankizumab, guselkumab) for up to at least 96 weeks. The dermatological response was excellent; no cancer progression, recurrence, or new malignancy onset occurred during the observation period[39]. Mastorino et al[40] published a case series of 37 patients with psoriasis who had a previous diagnosis of neoplasia. The majority were treated with secukinumab (n=21) and the remaining with other biologics against TNF-α, IL-17, IL-23 and IL-12[40]. Also, in this case, no tumor recurrence was observed[40].

A case report[95] on a patient with psoriasis treated with etanercept reported a melanoma recurrence 4 weeks after starting the treatment with the TNF-α inhibitor.

A psoriasis patient with a history of melanoma was switched from etanercept to ustekinumab with excellent dermatological response and no melanoma relapse after 7 consecutive years of treatment[41]. A patient with HIV-associated psoriasis and Kaposi's sarcoma was treated with ustekinumab for 15 months with excellent dermatologic response and stability of cancer[42].

Bellinato et al[37] performed a systematic review of the literature and retrospective cohort analysis of patients with previous malignancy and psoriasis treated with anti-IL-17 biologics (secukinumab and ixekizumab) and reported excellent dermatological response with no tumor recurrence except for tumor progression reported in two of three patients with advanced/metastatic disease. A case report[43] about a patient with psoriasis and laryngeal squamous cell carcinoma treated with ixekizumab reported resolution of psoriasis symptoms and no recurrence of cancer.

A patient suffering from psoriasis with concomitant bladder cancer, treated with secukinumab, for a 24-week follow-up achieved a good dermatological response without oncological worsening[44]. Pellegrini et al[45] published a retrospective observational study including 42 patients with psoriasis treated with secukinumab for at least 24 weeks and a previous diagnosis of cancer. No tumor recurrence nor progression was observed, three patients developed a new malignancy unrelated to previous cancer, and the dermatological response was optimal[45].

Safety of Biologicals For Patients with PsA and Concomitant Neoplasias

Literature on the safety of the treatment with biologicals of patients affected by PsA and previous neoplasia is even more scarce, but also, in this case, no apparent relationship between bDMARDs and cancer is observed. Pai et al[46] reported the case of a 46-year-old man with recurrent non-Hodgkin lymphoma and refractory PsA treated for 5.5 years with the TNF-α inhibitor etanercept, without recurrence of lymphoproliferative disease, even if he died 6.5 years later due to pancreatic adenocarcinoma. Another case report[47] described a patient with PsA and prostate cancer, treated with adalimumab for 2 years, then with ustekinumab for 6 months and finally with secukinumab for 1 year, without tumor worsening and with partial clinical response. A patient with psoriasis, PsA and melanoma treated with secukinumab had an excellent response with no signs of melanoma recurrence after 26 months[48]. Ghazanfar et al[49] reported a case of a 53-year-old woman with both psoriasis and PsA and a recent history of cerebral malignant melanoma metastasis who has been treated with sequential secukinumab and ustekinumab for almost 2 years with no relapse of cancer.

Discussion

The well-demonstrated correlation between psoriasis and PsA and the increased risk of tumors, especially keratinocyte cancer, lung and bladder cancers, and non-Hodgkin and Hodgkin lymphomas[6,7,12,14,15,96] means that dermatologists and rheumatologists may therefore face the challenge of managing patients with previous diagnosed, or ongoing neoplasms, concomitantly affected by psoriasis or PsA, resistant to non-biologic DMARDs.

International guidelines[65] advise against using anti-TNF-α biologics within 5 years of the resolution of previous neoplasia, further limiting the therapeutic options. Literature data on the safety of non-anti-TNF-α biologics in the management of patients with previous or ongoing cancer affected by psoriasis or PsA are still limited and inconclusive; however, the mechanism of action of IL-17, which showed a tumor-promoting effect in immunodeficient animal models[34-36], provides a rationale for the use of IL-17 inhibitor drugs in immunocompromised subjects.

The case studies[37-45] published regarding patients affected by psoriasis, with previous or ongoing neoplasia, mainly managed with secukinumab, but also, in smaller numbers, with ixekizumab, ustekinumab and guselkumab, seem to confirm the safety of these therapies also in subjects suffering from psoriasis with previous malignancies, while progression was found in patients with advanced or metastatic disease[37].

Also, the few cases in the literature[46-49] of patients affected by PsA and concomitant cancer treated with bDMARDs seem to support the data obtained in patients affected by psoriasis with a lack of association between the treatment and progression of oncological disease. Interestingly, a beneficial effect of secukinumab, prescribed for the treatment of a patient affected by PsA in a case of giant cell tumor of bone, has also been described[97]. Treatment with anti-IL-17 antibodies is associated with the development of reparative intralesional calcifications of giant cell tumor of bone, like what has been seen with denosumab therapy[97]. Histological examination showed ossification, new bone formation, and remodeling with depletion of giant cell-type osteoclasts, with decreased osteoclastic activity highlighted by real-time quantitative PCR (qRT-PCR) analysis[97].

However, most of the safety data available on the incidence of new malignancies during therapy in patients with psoriasis or PsA come from clinical trials, and the number of patients included is limited, especially regarding patients affected by PsA. This prevents drawing any firm conclusion on the risk of malignancy recurrence or progression during secukinumab treatment in patients with PsA, despite the reassuring data from studies[71,72] on post-marketing safety surveillance results of secukinumab across different indications (psoriasis, PsA and AS); however, it is important to note that these results have not been separated by pathology.

Despite the small number, the present series of four patients represents the largest published on the use of biologic therapies in patients with PsA and previous neoplasia. To our knowledge, among the cases described in the present study, case 3 is the first patient treated with biologic therapy during active neoplasia (ocular melanoma) present in the literature regarding PsA.

The most relevant clinical data emerging from the present study is that three patients at the 24-month follow-up and two at the 30-month follow-up did not show any progression of their oncological disease, lending some support to the safety of long-term treatment with secukinumab

in patients with PsA and previously diagnosed neoplasia. Particularly significant is that the patient with active ocular melanoma had no disease progression in the 30 months of follow-up during treatment with secukinumab and MTX.

Regarding the effectiveness of secukinumab for treating PsA in these subjects, the joint clinical response and the improvement of the enthesitic damage were optimal in two out of four cases at the 24-month follow-up. In contrast, a slow and partial response was recorded on the joint damage, but with a significant improvement of the enthesitic damage in the patient affected by inoperable ocular melanoma. Case 4, who showed an encouraging trend of joint response, suspended on her initiative the treatment with secukinumab; it should be considered that the concomitant fibromyalgia played a very significant role in the reported pain symptoms. Our results align with a recent meta-analysis[98] that demonstrated that IL-17 inhibitors were effective in improving joint disease compared to a placebo in PsA patients.

All our patients had minimal skin involvement but showed a dermatological improvement, in line with the cases reported in the literature[37,39,44] regarding treating patients with psoriasis and previous neoplasia.

Conclusions

Managing patients with a prior diagnosis of neoplasia or ongoing neoplasia concurrently with psoriasis or PsA and resistance to non-biologic DMARDs is an exceptionally challenging task. The present case series lends support to the safety of secukinumab in three patients with previous neoplasia and one patient with active melanoma. These findings suggest the need for future studies aimed at confirming the safety profile of non-anti-TNF-α biologics, specifically of secukinumab, in the treatment of patients with PsA who have a history of or current neoplasia.

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Authors' Contributions
Dr. Umberto Massafra conceived and designed the study; Dr. Umberto Massafra and Dr. Francesca Giovannangeli collected, analyzed and interpreted the data; Dr. Umberto Massafra drafted the article. Dr. Alberto Migliore participated to the discussion of data. All the authors critically revised and approved the final version of the manuscript before submission.

Conflict of Interest
UGM received a fee for editorial activities from Novartis Farma and fees for teaching and editorial activities from Janssen, Abbvie, Galapagos, Lilly, and Chiesi Farmaceutici. The other authors have no conflict of interest to declare.

Data Availability
All data generated or analyzed during this study are included in this published article.

Ethics Approval
The review of patient data did not require ethical approval in accordance with local/national guidelines. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent
All subjects provided informed written consent for data publication.

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