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ORIGINAL RESEARCH

From Psoriasis to Psoriatic Arthritis: Decoding the Impact of Treatment Modalities on the Prevention of Psoriatic Arthritis

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ABSTRACT

***Introduction*:** Biologic therapies are licensed for both psoriasis (PsO) and psoriatic arthritis (PsA) with some electronic medical record data suggest that IL (Interleukin)-23 blockers might be more protective in PsA prevention than TNF blockers; however, the findings have been inconsistent. Higher Psoriasis Area and Severity Index (PASI) scores have also been linked to an increased PsA risk. To clarify these unresolved issues we investigated biologic agents, methotrexate, phototherapy, and topical therapy for PsA prevention in patients with psoriasis.

***Methods*:** This retrospective cohort study analyzed data from 58,671 patients with psoriasis from the Israeli Meuhedet Health Services Organization database was evaluated for incident PsA. Patients were categorized on the basis of treatment: group 1, topical therapy; group 2, phototherapy; group 3, conventional disease-modifying antirheumatic drugs (cDMARDs; methotrexate); group 4, biologic DMARDs which was also stratified according to biologic class.

***Results*:** The PsA incidence rate was lower in the biologic agents' group versus the methotrexate group (HR 0.46 [95% CI 0.35–0.62]). The incidence rates per 100 person-years varied across biologic treatment groups, with the anti-IL-12/23 or anti-IL-23p19 group at 4.57, the anti-IL-17 group at 4.35, and the TNF inhibitor group at 2.55. No differences were found between various biological agents in terms of preventing PsA. The phototherapy group exhibited a higher PsA development rate than the topical therapy group (HR 1.85 [95% CI 1.65–2.07]).

***Conclusion*:** Biological agents are more effective than methotrexate in reducing incident PsA in patients with psoriasis. This lower rate of PsA on topical therapy compared to phototherapy supports the importance of psoriasis severity as a risk factor.

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Key Summary Points

Psoriasis (PsO) and psoriatic arthritis (PsA) are chronic diseases with a significant impact on patients' quality of life, highlighting the need for effective preventative strategies. With conflicting evidence on the impact of biologic therapies and other treatments on the risk of developing PsA in patients with psoriasis, this study aims to clarify the role of different treatment modalities.

The study investigated the effectiveness of biologic agents, methotrexate, phototherapy, and topical therapy in preventing the onset of PsA in patients with psoriasis.

Biological agents significantly reduce the risk of developing PsA in patients with psoriasis compared to methotrexate, with no significant difference observed between different biologics.

Topical therapy linked to lower PsA development than phototherapy, highlighting role of psoriasis severity.

INTRODUCTION

Psoriatic arthritis (PsA) represents a chronic immune-mediated disorder with the potential for substantial debilitation and a profound impact on the quality of life for those affected. Its clinical spectrum varies considerably, encompassing mild, intermittent joint symptoms in some individuals while inflicting severe and progressive joint damage leading to disabling consequences in others [1]. The precise immunopathogenic mechanisms governing PsA remain elusive but are believed to result from a multifaceted interplay of genetic predisposition, environmental influences, and immune system dysregulation [2]. Noteworthy risk factors include a familial history of psoriasis or PsA, nail involvement, obesity, and severe skin involvement [3, 4]. Environmental triggers, such as infections or traumatic injuries, may catalyze the development of PsA in genetically predisposed individuals [5].

Beneath the surface, a shared immunopathogenic underpinning unites psoriasis and PsA, mediated through common immunogenetic elements, inflammatory cellular processes, and cytokine cascades, contributing to the confluence of cutaneous and articular pathology [6]. While the presence of shared immunopathogenic factors between psoriasis and clinical PsA is well established, the precise mechanistic details remain an enigma [7, 8].

The intriguing proposition that treating psoriasis may forestall the onset of PsA has garnered attention but is clouded by contradictory evidence. Notably, data from electronic healthcare databases have raised concerns about a potential association between the use of TNF inhibitors (TNFi) in psoriasis management and an increased risk of PsA development [9]. Furthermore, hypotheses have emerged suggesting that blockade of the interleukin (IL)-23 pathway may offer superior efficacy compared to TNFi for PsA prevention [10].

Systematic literature reviews have also suggested a positive correlation between higher Psoriasis Area and Severity Index (PASI) scores and a heightened risk of PsA, potentially implying a lower PsA risk for individuals with milder psoriasis not requiring biologics [11]. Given that mild psoriasis is treated with topical agents and more severe psoriasis is treated with phototherapy, then an opportunity exists to look at the potential role of both of these non-systemic therapies in relationship to PsA development to further explore the issue of skin severity and PsA.

Preventative strategies for PsA encompass a spectrum, ranging from lifestyle modifications, including weight management, to pharmacological interventions aimed at psoriasis control and inflammation suppression. Within this armamentarium, biologic medications, including TNFi, anti-IL-12/23 or anti-IL-23p19 subunit agents, and anti-IL-17 agents, have exhibited efficacy in managing both psoriasis and PsA [12, 13]. Nevertheless, the conflicting evidence

regarding the role of biologics in PsA prevention within the psoriasis population persists.

In light of these considerations, we investigated the impact of biologic medications, spanning TNFi, anti-IL-12/23 or anti-IL-23p19 subunit agents, and anti-IL-17 agents, juxtaposed against conventional disease-modifying antirheumatic drugs (DMARDs) or topical therapy, in PsA prevention in patients with psoriasis. A distinctive facet of our inquiry lies in its discerning assessment of two non-systemic strategies: topical therapy for individuals with lower PASI scores and phototherapy for those with elevated PASI scores. Our findings hold the potential to reshape the paradigms governing the management of psoriasis and PsA, potentially paving the way for innovative therapeutic approaches.

METHODS

Ethics

The study was approved by the Ethical Committee of Meuhedet Health Maintenance Organization (MHMO). The study was exempt from obtaining informed consent.

Study Design

The study was approved by the institutional review board of the Meuhedet Health Services Organization. This was a retrospective cohort study that utilized the Meuhedet MHMO electronic database to evaluate the incidence of PsA in patients with psoriasis treated with different regimens. The study included all patients with psoriasis first diagnosed between January 1, 2000 and December 31, 2020, and compared the incidence of PsA between different treatment groups.

The MHMO provides healthcare coverage to 1.2 million patients across Israel and operates under the Israeli National Health Insurance Act, which ensures universal healthcare coverage. MHMO's comprehensive database compiles patient medical records from various healthcare providers, including diagnostic visits, pharmacological interventions, in-office procedures, laboratory test results, imaging studies, and summaries of hospital encounters such as outpatient clinic visits, emergency department visits, and in-patient discharge records. MHMO's database integrity is a reliable source for research purposes, and it has contributed to several studies published in reputable peer-reviewed journals [14–16].

The study was exempt from obtaining informed consent because of its retrospective design.

Population and Measures

Psoriasis diagnosis was defined on the basis of at least one recorded diagnosis of this condition (ICD-9 codes 696, 696.0, 696.1) between January 1, 2000 and December 31, 2020. For each patient with psoriasis all drug dispenses of TNFi, anti-IL-17, anti-IL-12/23 or anti-IL-23p19 subunit, MTX, and phototherapy/topical were collected. Patients were grouped on the basis of treatment regimen into biologics (based on the first biologic agent administered before outcome regardless of whether treated with MTX or phototherapy) and MTX only (if treated with MTX and no biologic agent prior to outcome). Another group was designated for those who underwent only phototherapy. Lastly, a separate group was formed for patients who received topical treatments. A particular focus of our study was on patients with psoriasis that only required topical therapy as such a group may have milder psoriasis which has previously been linked to a lower risk of PsA evolution. It is important to note that prior to enrollment in the study, patients in both the phototherapy and topical therapy groups had not received any systemic treatments.

The outcome was defined as a recorded diagnosis of PsA (ICD-9 codes 696.0, 713.3, 720.x, 713.1, 718.5) after the diagnosis of psoriasis. For the biologic group, follow-up began at the date of first administration of the first-line agent and continued until PsA diagnosis, switching to a different biologic agent, death, or the end of study follow-up on February 10, 2022. For the MTX group follow-up began at the first administration of MTX and

continued until PsA diagnosis, death, or the end of study follow-up. Patients with a diagnosis of PsA prior to psoriasis, with administration of a biologic agent or MTX prior to the diagnosis of psoriasis, or patients with first administration of a biologic agent after the diagnosis of IBD were excluded.

Other Variables

Demographic variables included age, gender, ethnicity (classified as Arab or Jewish), and body mass index (BMI), which was calculated on the basis of recorded height and weight measurements nearest to the date of psoriasis diagnosis and was divided into ≥ 30 (obese) and < 30 kg/m^2. SpA-related comorbidities including uveitis (ICD-9 codes 363.x, 364.x), Crohn's disease (ICD-9 codes 555.x), and ulcerative colitis (ICD-9 codes 556.x) were defined on the basis of the date of first recorded diagnosis of these conditions. The presence of chronic comorbidities such as diabetes, ischemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and cancer were obtained from the MHMO and national chronic diseases registry, which has been demonstrated to have high validity in prior studies.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation and were compared using Student's *t* test. Categorical variables were reported as percentages and were compared using Pearson's chi-square test. The incidence of PsA was compared between different treatment groups using Cox proportional hazard regression using both univariate and multivariate models and expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Predictors of PsA within the patients with psoriasis treated with biologic agents were evaluated using a multivariate logistic regression model which was conducted using the "Enter" method and included only variables found significant in the univariate model. All *P* values were two tailed, and the null hypothesis was considered true if $P \geq 0.05$. All statistical analysis was done using SPSS software, version 26 (SPSS, Armonk, NY: IBM Corp).

RESULTS

Study Population

The study cohort consisted of 58,671 patients, of which 360 were treated with TNFi, 186 with anti-IL-12/23 (IL-12/23 or anti-IL-23p19), only 71 with anti-IL-17, 969 with methotrexate, 4357 with phototherapy, and 53,917 with topical therapy. The baseline characteristics of the study population are presented in Table 1. The mean age at psoriasis diagnosis ranged from 32.2 (± 15) years in the anti-IL-12/23 or anti-IL-23p19 group to 43.3 (± 17) years in the methotrexate group. The median duration of psoriasis prior to the initiation of therapy was longest in the anti-IL-12/23 or anti-IL-23p19 group (9.5 years [4.2–16.1]) and shortest in the methotrexate group (2.2 years [0.9–8.3]). Before the initiation of biologic treatment, the majority of patients in the anti-IL-17 and anti-IL-23 (anti-IL-12/23 or anti-IL-23p19) groups had received phototherapy (63.4% and 70.4%, respectively), while in the TNFi group, most of the patients were treated with MTX (49.2%). The prevalence of comorbidities varied across the treatment groups, with the highest prevalence of diabetes, COPD, obesity, and hypertension observed in all groups. For more information, see Table 1.

Risk of PsA in Patients with Psoriasis with Different Therapies

The median follow-up time varied across the treatment groups, with the longest observed in the topical therapy and phototherapy groups (9.6 years [4.8–15.4] and 4.5 years [1.9–8.1], respectively), followed by the methotrexate group (3.3 years [1.2–6.2]). In the biologic treatment groups, the median follow-up time ranged from 1.4 (0.7–2.6) years in the anti-IL-12/23 or

Table 1 Baseline characteristics of the study population of patients with psoriasis

Characteristics	TNFi ($n = 360$)	Anti-IL-17 ($n = 71$)	Anti-IL-12/23 or anti-IL-23p19 ($n = 186$)	Methotrexate ($n = 969$)	Phototherapy ($n = 4357$)	Topical ($n = 53,917$)
Demographics						
Age at PsO diagnosis, mean ± SD	37.5 ± 16	35.9 ± 15	32.2 ± 15	43.3 ± 17	35.8 ± 19	35.7 ± 18
Age at initiation of therapy, mean ± SD	43.5 ± 16	44.1 ± 15	42.4 ± 15	47.9 ± 17	46.9 ± 15	35.7 ± 18
PsO duration in years, median (IQR)	4.8 (1.5–9.9)	8.0 (2.2–11.9)	9.5 (4.2–16.1)	2.2 (0.9–8.3)	3.3 (0.3–9.5)	–
Male gender, *n* (%)	185 (51.4)	47 (66.2)	122 (65.6)	477 (49.2)	2143 (49.2)	26,562 (49.3)
Arab ethnicity, *n* (%)	54 (15.0)	16 (22.5)	16 (8.6)	156 (16.1)	318 (7.3)	6324 (11.7)
Prior treatment						
Phototherapy, *n* (%)	124 (34.4)	45 (63.4)	131 (70.4)	281 (29.0)	281 (29.0)	4357 (7.5)
Methotrexate, *n* (%)	177 (49.2)	26 (36.6)	72 (38.7)	–	–	–
Baseline comorbidities						
Obesity [†], *n* (%)	109 (30.3)	25 (35.2)	47 (25.3)	321 (33.1)	1077 (24.7)	12,596 (23.4)
Diabetes, *n* (%)	57 (15.8)	8 (11.3)	24 (12.9)	164 (16.9)	265 (6.1)	4073 (7.6)
Hypertension, *n* (%)	103 (28.6)	21 (29.6)	36 (19.4)	322 (33.2)	629 (14.4)	8728 (16.2)
COPD, *n* (%)	29 (8.1)	5 (7.0)	13 (7.0)	127 (13.1)	188 (4.3)	2377 (4.4)
CHF, *n* (%)	3 (0.8)	1 (1.4)	3 (1.6)	18 (1.9)	24 (0.6)	425 (0.8)
Uveitis, *n* (%)	7 (1.9)	0	3 (1.6)	19 (2.0)	21 (0.5)	256 (0.5)
Cancer, *n* (%)	18 (5.0)	5 (7.0)	8 (4.3)	90 (9.3)	148 (3.4)	2368 (4.4)

CHF congestive heart failure, *COPD* chronic obstructive pulmonary disease, *IBD* inflammatory bowel disease, *IL* interleukin, *TNFi* tumor necrosis factor inhibitors, *PsO* psoriasis

[†]Defined as body mass index higher than 29.9 kg/m^2 at the measurement closest to psoriasis diagnosis

Table 2 Incidence of PsA during the study period across the different therapeutic agents groups

	TNFi (*n* = 360)	Anti-IL-17 (*n* = 71)	Anti-IL-12/23 or anti-IL-23p19 (*n* = 186)	Methotrexate (*n* = 969)	Phototherapy (*n* = 4357)	Topical (*n* = 53,917)
PsA events, *n* (%)	42 (11.7)	6 (8.5)	17 (9.1)	199 (20.5)	788 (18.1)	4273 (7.9)
Peripheral	41 (11.4)	6 (8.5)	16 (8.6)	189 (19.5)	733 (16.8)	3510 (6.5)
Axial	4 (1.1)	0	2 (1.1)	17 (1.8)	122 (2.8)	1030 (1.9)
Age at PsA, mean ± SD	45.8 ± 11	38.2 ± 14	46.7 ± 16	49.5 ± 15	46.9 ± 15	51.3 ± 16
Follow-up time (years)						
Median (IQR)	3.7 (1.5–7.4)	1.6 (0.7–2.9)	1.4 (0.7–2.6)	3.3 (1.2–6.2)	4.5 (1.9–8.1)	9.6 (4.8–15.4)
Mean ± SD	4.6 ± 3	1.9 ± 1	2.0 ± 2	3.8 ± 3	4.4 ± 5	10.2 ± 6
Cumulative person-years	1650	138	372	3727	19,181	554,880
PsA incidence per 100 person-years (95% CI)	2.55 (1.8–3.4)	4.35 (1.6–9.5)	4.57 (2.7–7.3)	5.34 (4.6–6.1)	4.11 (3.8–4.4)	0.77 (0.75–0.79)

COPD chronic obstructive pulmonary disease, *IBD* inflammatory bowel disease, *IL* interleukin, *TNFi* tumor necrosis factor inhibitors, *PsA* psoriatic arthritis, *PsO* psoriasis

anti-IL-23p19 group to 3.7 (1.5–7.4) years in the TNFi group (Table 2).

The incidence rate of PsA per 100 person-years varied across treatment groups. The methotrexate group exhibited the highest incidence rate at 5.34 (95% CI 4.6–6.1) per 100 person-years. This was followed by the anti-IL-12/23 or anti-IL-23p19 group with an incidence rate of 4.57 (95% CI 2.7–7.3) per 100 person-years and the anti-IL-17 group with an incidence rate of 4.35 (95% CI 1.6–9.5) per 100 person-years. The phototherapy group had an incidence rate of 4.11 (95% CI 3.8–4.4) per 100 person-years. The TNFi group reported an incidence rate of 2.55 (95% CI 1.8–3.4) per 100 person-years. Lastly, the topical therapy group had the lowest incidence rate of 0.77 (95% CI 0.75–0.79) per 100 person-years.

In the comprehensive analysis using the Cox proportional hazards model (as summarized in Table 3), the risk of developing PsA exhibited distinct patterns when associated with various treatment modalities. First and foremost, when compared to the methotrexate treatment group, all biologic treatment groups collectively demonstrated a reduction in the risk of developing PsA. This significant difference was underscored by an adjusted HR of 0.46 (95% CI 0.35–0.62). When the individual biologic agents were scrutinized, their respective associations with reduced PsA risk also attained statistical significance when contrasted with methotrexate treatment. Conversely, when the biologic treatment as a whole was compared to the topical treatment group, the risk of developing PsA was notably higher for individuals treated with biologics, with an adjusted HR of 2.16 (95% CI 1.44–3.24).

Table 3 Cox proportional hazards model of time to onset of psoriatic arthritis in patients with skin psoriasis with different therapies

Comparison groups	Crude HR (95% CI)	Adjusted† HR (95% CI)
Anti-IL-12/23 or anti-IL-23p19 vs. TNFi	1.43 (0.80–2.55)	1.20 (0.64–2.22)
Anti-IL-12/23 or anti-IL-23p19 vs. anti-IL-17	1.07 (0.42–2.74)	1.31 (0.49–3.52)
Anti-IL-12/23 or anti-IL-23p19 vs. MTX	0.55 (0.34–0.91)*	0.45 (0.27–0.75)**
Anti-IL-12/23 or anti-IL-23p19 vs. topical therapy	4.12 (2.55–6.64)***	6.54 (2.94–14.53)***
Anti-IL-12/23 or anti-IL-23p19 vs. phototherapy	2.62 (1.60–4.29)***	4.03 (1.76–9.23)***
Anti-IL-17 vs. TNFi	1.23 (0.51–2.92)	1.11 (0.46–2.69)
Anti-IL-17 vs. MTX	0.49 (0.22–1.11)	0.44 (0.19–0.99)*
Anti-IL-17 vs. topical therapy	3.82 (1.71–8.51)***	6.70 (2.03–22.05)**
Anti-IL-17 vs. phototherapy	2.41 (1.07–5.43)*	4.47 (1.34–14.96)*
TNFi vs. MTX	0.52 (0.37–0.73)***	0.47 (0.34–0.67)***
TNFi vs. topical therapy	2.92 (2.15–3.96)***	1.36 (0.79–2.33)
TNFi vs. phototherapy	1.64 (1.19–2.27)**	0.86 (0.49–1.49)
Biologics§ vs. MTX	0.53 (0.40–0.70)***	0.46 (0.35–0.62)***
Biologics§ vs. topical therapy	3.22 (2.51–4.11)***	2.16 (1.44–3.24)***
Biologics§ vs. phototherapy	1.86 (1.42–2.43)***	1.36 (0.88–2.08)
MTX vs. topical therapy	5.79 (5.01–6.69)***	3.26 (2.68–3.96)***
MTX vs. phototherapy	3.20 (2.68–3.83)***	2.19 (1.74–2.77)***
Phototherapy vs. topical therapy	1.79 (1.60–2.01)***	1.85 (1.65–2.07)***

IL interleukin, *TNFi* tumor necrosis factor inhibitors, *MTX* methotrexate, *HR* hazard ratio, *CI* confidence interval

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

†Adjusted for age, gender, ethnicity, psoriasis duration, and body mass index

§Include TNFi, anti-IL-17, anti-IL-12/23 or anti-IL-23p19, and JAKi

This increased risk was further emphasized when examining the anti-IL-17 and anti-IL-12/23 or anti-IL-23p19 groups individually, which displayed adjusted HRs of 6.70 (95% CI 2.03–22.05) and 6.54 (95% CI 2.94–14.53), respectively. However, the TNFi group did not exhibit a statistically significant difference in PsA risk when compared to the topical therapy group, with an adjusted HR of 1.36 (95% CI 0.79–2.33). Furthermore, when juxtaposed against the phototherapy treatment group, the biologic treatment collectively did not display a statistically significant difference in PsA risk, yielding an adjusted HR of 1.36 (95% CI 0.88–2.08). However, a nuanced distinction emerged when examining the anti-IL-17 and anti-IL-12/23 or anti-IL-23p19 groups independently. Both exhibited a notably elevated risk of developing PsA when compared to the phototherapy group, with adjusted HRs of 4.47 (95% CI 1.34–14.96) and 4.03 (95% CI 1.76–9.23), respectively. In contrast, the TNFi group, in comparison to the phototherapy cohort, did not reveal a statistically significant difference in PsA risk, as reflected by an adjusted HR of 0.86 (95% CI 0.49–1.49).

In the comparative analysis among different biological treatments, our study did not reveal statistically significant differences in

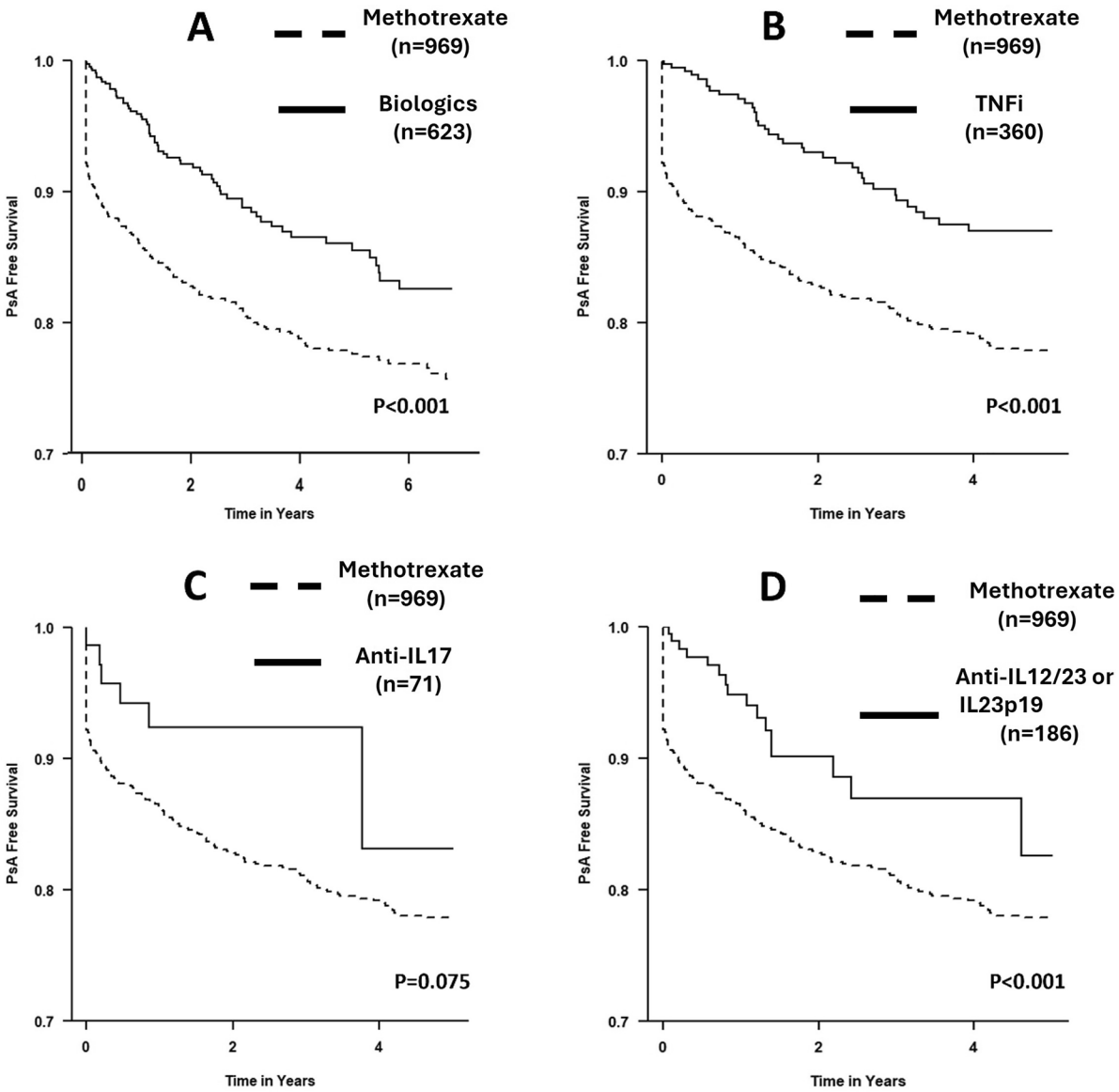

Fig. 1 Kaplan–Meyer PsA free survival times for the MTX vs. biologics (**a**) or TNFi (**b**), or anti-IL-17 (**c**), or anti-IL-12/23 or anti-IL-23p19 (**d**)

PsA risk between the TNFi, anti-IL-12/23 or anti-IL-23p19, and anti-IL-17 treatment groups. Patients within the MTX group exhibited a significantly higher risk of developing PsA when compared to both the topical or phototherapy groups, as reflected by an adjusted HR of 3.26 (95% CI 2.68–3.96) and HR of 2.19 (95% CI 1.74–2.77), respectively. Lastly, it is worth noting that patients subjected to phototherapy demonstrated a higher PsA risk compared to those receiving topical treatments with an adjusted HR of 1.85 (95% CI 1.65–2.07). For a visual representation of these findings, Kaplan–Meier survival curves illustrating the cumulative PsA-free survival time, both in the context of MTX versus other treatments and biologics versus other treatments, are presented in Figs. 1 and 2, respectively.

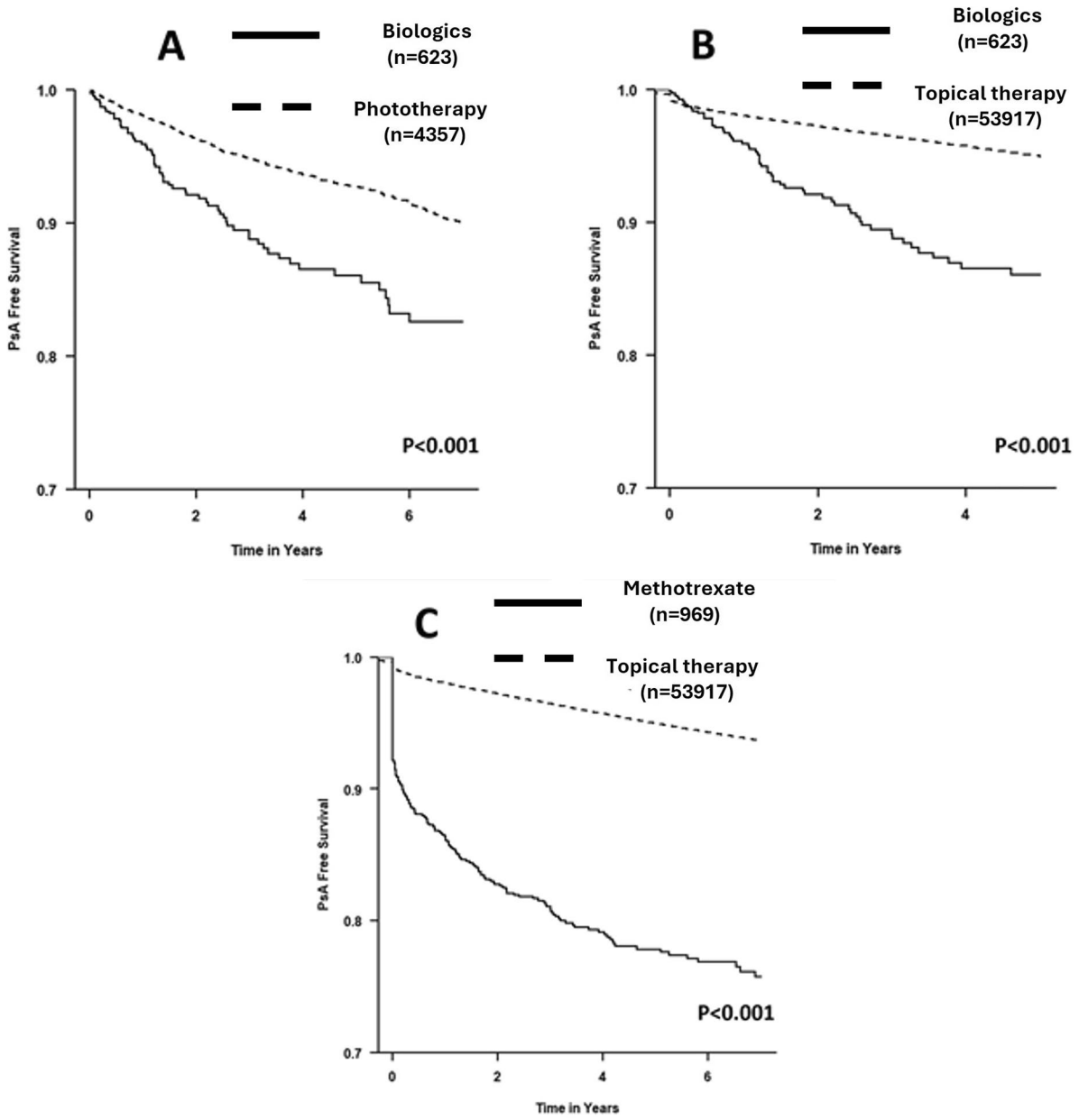

Fig. 2 Kaplan–Meyer PsA free survival times for biologics vs. phototherapy (**a**) or topical therapy (**b**) and MTX vs. topical therapy (**c**)

Predictors of PsA Within Patients with Psoriasis Treated with Biologic Agents

The results of the multivariate logistic regression analysis of predictors for the incidence of PsA in patients with psoriasis treated with biologic agents are presented in Table 4. Being exposed to at least two biological agents was associated with a significantly higher risk of PsA (OR 6.09, 95% CI 3.49–10.64, $p<0.001$), as was prior methotrexate therapy (OR 1.88, 95% CI 1.07–3.27, $p=0.026$).

Table 4 Predictors for the incidence of psoriatic arthritis in patients with psoriasis treated with biologic agents

Variables	SE	Wald	OR	95% CI	*p* value
Age, 1 year increment	.009	.704	.992	0.97–1.01	0.401
Psoriasis duration, 1 year increment	.026	.111	1.009	0.96–1.06	0.739
Body mass index, 1 kg/m^2 increment	.000	.012	1.000	1.0–1.0	0.913
Male gender vs. female	.294	2.031	1.520	0.85–2.70	0.154
Arab ethnicity	.457	2.590	.479	0.19–1.17	0.108
Prior methotrexate therapy	.284	4.929	1.877	1.07–3.27	0.026
Prior phototherapy	.291	.586	1.250	0.71–2.21	0.444
Exposure ≥ 2 biological agents	.284	40.386	6.093	3.49–10.64	< 0.001

All information is presented in Tables 1, 2, 3, and 4.

DISCUSSION

In this study, we found that biological agents demonstrated a significantly higher potential in preventing the onset of PsA in patients with psoriasis, compared to methotrexate. However, when we compared the outcomes of topical and biological therapies, patients receiving topical therapy exhibited a lower risk of developing PsA. In the assessment of biologic treatments versus phototherapy, biologics as a whole did not demonstrate a significantly higher risk of developing PsA. However, exceptions were noted with specific biologics such as anti-IL-17 and anti-IL-12/23 or anti-IL-23p19, which did show an increased risk. Furthermore, when phototherapy was compared with topical therapy, our findings indicated an increased PsA risk in the phototherapy group.

Consistent with our findings, similar results using another Israeli electronic medical record database were recently reported [17]. That study analyzed data from 13,261 individuals and revealed a statistically significant increased risk of PsA in the control group compared to the biologic treatment group, with an adjusted HR of 1.39 (95% CI 1.03–1.87) over a 10-year follow-up period. However, unlike our study, that study did not differentiate between the various biological and non-biological treatments, precluding analysis of the effects of specific treatments.

It is essential to note the results of other studies that do not align with ours. Gisondi et al. [18], in their retrospective Italian-based cohort, compared the incidence of PsA in patients with psoriasis treated with bDMARDs versus phototherapy. Among the 464 patients followed between 2012 and 2020, the annual incidence rate of PsA was 1.20 per 100 patients/year in the bDMARDs group and 2.17 cases per 100 patients/year in the phototherapy group. The results indicated a lower risk of PsA in the bDMARDs group compared to the phototherapy group (HR 0.29, 95% CI 0.12–0.70, $p = 0.006$). The authors confined their analysis solely to patients with moderate to severe psoriasis. In contrast, in our analysis, a comparison of biologics with phototherapy suggested that some of these comparatively increased the PsA risk. Either phototherapy has well-recognized immunomodulatory effects or maybe the PASI was much higher in the biological group—something that we could not evaluate [19].

A retrospective cohort study by Meer et al. [9], which examined patients initiating therapy for psoriasis (oral, biologic, or phototherapy), aimed to calculate the incidence of PsA within each therapy group. The incidence per 1000 person-years of PsA among biologic users was 77.26, while it was 61.99 among oral therapy users, 26.11 among phototherapy users, and 5.85 among those without any treatment that

yielded an adjusted HR for biologics of 4.48 (4.23–4.75) compared to oral or phototherapy users. Nevertheless, even the authors admit that confounding factors and bias may influence this negative association.

Prior work suggested that there was a differential impact of biological therapy on PsA prevention. In our cohort, we found no statistically significant difference when comparing anti-IL-12/23 or anti-IL-23p19, IL-17, and TNF inhibitors which contradicts the findings of Singla et al. [10] utilizing a USA-based electronic health records database that suggested that IL-12/23 and IL-23 inhibitors were associated with a lower risk of inflammatory arthritis compared to TNF inhibitors (adjusted HR 0.58, 95% CI 0.43–0.76) or IL-23 inhibitors (0.41, 0.17–0.95). This discrepancy between the studies may be partly explained by the smaller number of patients in our study treated with different biological medications, which could have made it challenging to find any statistically significant differences between the groups especially in our study where numbers on IL-17 inhibition were very small.

Our investigation also brought to light an intriguing observation: when juxtaposed with the topical therapy group, the biologics group displayed a significantly higher risk of developing PsA, especially when more than one biologic was used, which might indicate more severe disease. This discovery invites further consideration and aligns well with the prevailing notion that PsA risk is intricately tied to high PASI scores. It is plausible that individuals relying solely on topical therapy may have presented with lower PASI scores, thus contributing to the reduced risk of PsA. Indeed, patients undergoing topical therapy demonstrate a remarkably low incidence of arthritis development compared to other treatment groups. In this context, the use of biological treatment could be seen not as a cause but rather as a marker for more severe disease characteristics, which inherently carry a higher risk for the development of PsA [4].

Indeed, the phototherapy group, typically characterized by higher PASI scores, did not present a lower risk for developing PsA when compared to biologics as a whole, unlike the topical therapy group. Intriguingly, this trend diverges when considering specific biologic treatments including anti-IL-17 and anti-IL-12/23 or anti-IL-23p19. Additionally, when comparing the topical group that equates with mild disease, although we were unable to formally measure this, and the phototherapy group, the latter, with its higher PASI scores, exhibited a pronounced risk of PsA. This further emphasizes the role of disease severity, as indicated by PASI scores, in the progression to PsA. It is plausible that the group receiving just topical therapy had milder and less inflammatory disease with lower PASI, and therefore these patients had a lower inherent PsA.

These findings collectively support the notion that severe psoriasis is a significant risk factor for PsA. Merola et al. [20] were the first to hypothesize that the incidence and prevalence of PsA among patients with psoriasis could be dependent on the severity of psoriasis, stratified by specific treatment modalities. By categorizing psoriasis severity on the basis of the treatments received—nonsystemic, nonbiological systemic therapy, and biologics—they demonstrated that the incidence rate per 100 person-years escalated with increasing disease severity. This suggests that the treatment regimen can shed light on the severity of the dermatological condition and the PASI. Despite this, and even considering the potential for higher PASI scores and increased disease severity in the biologics group, our study demonstrated a reduced risk of developing PsA compared to the MTX group, suggesting that biologics may exert a protective effect.

The protective effect of biological agents in preventing PsA can be attributed to the increasingly recognized shared immune-pathological mechanisms between the skin and the enthesis. The skin and enthesis exhibit microanatomical similarities, including avascular zones such as the epidermis and fibrocartilage zone. The immune homeostasis mechanisms converging at both sites involve resident myeloid cells capable of IL-23 production highlighting the pivotal role of the IL-23/IL-17 axis in the pathogenesis of both PsA and psoriasis [21].

Several limitations of our study need to be considered. First, the study was retrospective and observational in nature, and there may be

confounding factors that were not accounted for in our analysis. Second, we only examined the incidence of PsA and did not consider other outcomes such as joint damage, functional impairment, and quality of life. Future studies should consider these outcomes to provide a more comprehensive evaluation of the effectiveness of different treatment strategies for preventing PsA in patients with psoriasis. Another significant limitation of our study is the minority of patients on systemic therapy compared to those on non-systemic therapy. This imbalance potentially decreases the statistical power needed to conclusively determine the impact of these biological treatments on PsA development. Regarding the low rate of axial involvement in these patients who developed PsA, due to the retrospective design of this study and the reliance on administrative data without access to detailed imaging, there is a potential underestimation of the rate of axial involvement, which could affect the comprehensiveness of our findings in representing the full spectrum of the disease.

Lastly, it is crucial to note that dermatologists frequently use systemic treatments, including biologics, to manage PsA or its symptoms. Frequently, patients with psoriasis undergoing systemic therapy might exhibit signs of subclinical psoriatic arthritis, which are not captured by the administrative nature of our study. Several studies have highlighted a preclinical phase in patients with PsA, characterized by nonspecific musculoskeletal symptoms such as joint pain, fatigue, and stiffness. Moreover, musculoskeletal ultrasound has been shown to detect subclinical inflammation in patients with psoriasis, which can predict progression to PsA [22–24]. This could introduce a bias, as patients with psoriasis showing early signs of PsA or at higher risk of developing it are more likely to receive biologics.

CONCLUSIONS

Our study provides evidence that biological agents are more effective in preventing PsA in patients with psoriasis than methotrexate. Further research is needed to confirm these findings and to identify the most effective and cost-effective strategies for preventing PsA in patients with psoriasis. The optimal management strategy for preventing PsA in patients with psoriasis should be based on a personalized approach that takes into account the patient's individual characteristics, preferences, and underlying pathogenesis of the disease.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy of MHMO.

Declarations

Conflict of Interest. Abdulla Watad, Yonatan Shneor Patt, Omer Gendelman, Arad Dotan, Niv Ben-Shabat, Lior Fisher, Dennis McGonagle, Howard Amital – have nothing to disclose. Alen Zabotti—is an editorial board member of *Rheumatology and Therapy*. Alen Zabotti was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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