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Incidence Rates of Psoriasis in Children With Inflammatory Bowel Disease and Juvenile Arthritis Treated With Tumor Necrosis Factor Inhibitors and Disease-Modifying Antirheumatic Drugs

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ABSTRACT. ***Objective.*** To estimate the differential effect of tumor necrosis factor inhibitor (TNFi) therapies and presence or absence of conventional synthetic disease-modifying antirheumatic drugs (DMARDs) on the incidence of psoriasis (PsO) in children with inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and chronic nonbacterial osteomyelitis (CNO).

Methods. This was a retrospective cohort study from 2008 to 2020. TNFi and DMARD exposures were dichotomized as ever/never. The primary outcome was incident PsO. Incidence rates (IRs) of PsO were stratified by underlying diagnosis, TNFi agent, and DMARD use. Poisson regression was used to assess the IR ratios (IRRs) between exposure groups.

Results. There were 5088 children who met the inclusion criteria: 3794 (75%) had IBD, 1189 (23%) had JIA, and 105 (2%) had CNO. Of the 2023 children with TNFi exposure, 613 (30%) and 1410 (70%) were with or without a DMARD, respectively. When controlling for DMARD, sex, and family history of PsO, the IRR of developing PsO in patients exposed to adalimumab (ADA) was 2.70 times higher (95% CI 1.53-4.75; $P < 0.001$) than those who did not receive any TNFi treatment. IRR was lower, but not significantly different, for patients exposed to infliximab (IFX; IRR 2.34, 95% CI 1.56-3.51; $P < 0.001$) and etanercept (ETN; IRR 2.21; 95% CI 1.17-4.21; $P = 0.006$) compared to TNFi-unexposed patients. IRR of TNFi exposure was lower by 0.25 ($P < 0.001$) in DMARD-exposed patients compared to non–DMARD-exposed patients.

Conclusion. IRR of TNFi-induced PsO was not significantly different among ADA, IFX, and ETN. However, for patients with exposure to any of the TNFi evaluated, the IRR was significantly lower in those also exposed to a DMARD.

Key Indexing Terms: disease-modifying antirheumatic agents, juvenile idiopathic arthritis, psoriasis, tumor necrosis factor inhibitors

Tumor necrosis factor inhibitors (TNFi) are a cornerstone in the treatment of several inflammatory conditions including psoriasis (PsO), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and chronic noninfectious osteomyelitis (CNO).[1-5] PsO, or a family history of PsO, is commonly seen in children with concomitant diagnosis of IBD, JIA, or CNO.[6,7,8] TNFi are also used to treat recalcitrant PsO.[9] Paradoxically, TNFi may trigger new-onset PsO or worsen preexisting PsO in some instances.[10-15]

Children with IBD, JIA, and CNO have an increased rate of PsO as compared to the general pediatric population.[16] Notably, the incidence of PsO in these conditions is higher if children are also exposed to TNFi.[16] Although TNFi are commonly used to treat recalcitrant PsO, several reports indicate an increased incidence of TNFi-induced PsO in adult and pediatric patients with IBD, JIA, and CNO without a prior history of PsO.[17,18] A family history of PsO is also significantly associated with increased hazard of PsO in children being treated with TNFi.[16] Increasing

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reports of cutaneous adverse reactions while on TNFi therapy raises several concerns, given the quality of life implications for children experiencing this adverse event.[19-21] PsO associated with TNFi use often involves the scalp and can be recalcitrant to topical therapies.[17] Given the relative paucity of data, further information is critically needed to assess the association of TNFi exposure and new-onset PsO in order to inform the management and treatment of this comorbidity.

Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), leflunomide (LEF), or sulfasalazine (SSZ), are commonly coadministered with TNFi agents to improve outcomes and drug persistence.[22] The primary aim of this study was to compare the differential effect of the 3 most commonly prescribed TNFi therapies and to examine whether the addition of a DMARD affects the incidence of new-onset PsO in children with IBD, JIA, or CNO.

METHODS

Data source. The Children's Hospital of Philadelphia (CHOP) electronic health record data warehouse served as the study's primary data source. This database included patient-level demographics, visit-level medical data, prescription drug data, and visit-level billing data in the form of International Classification of Diseases (ICD), 9th revision (ICD-9) and 10th revision (ICD-10) diagnosis codes. The research protocol was reviewed by the CHOP Institutional Review Board (IRB 18-015342) and it was determined that the study meets the exemption criteria per 45 CFR 46.104(d) 4(iii).

Subjects. The study population included children with IBD, JIA, or CNO who were evaluated at CHOP between January 2008 and June 2020. The following inclusion criteria were used: (1) the first diagnosis code for IBD, JIA, or CNO occurred prior to age 19 years; (2) the patient was assigned at least 2 diagnosis codes for IBD (555.xx, 556.xx, 558.9, K50.xx, K51.xx, K52.3, K52.89, K52.9), JIA (713.1, 714.xx, 721.9, M08.xx, M45.x, L40.5), or CNO (730.1x, M86.3x); and (3) the subject had at least 2 visits with a study center gastroenterologist or rheumatologist. The study population was restricted to children with a diagnosis at age ≤ 18 years to produce a cohort representative of patients typically treated by pediatric gastroenterologists, rheumatologists, and dermatologists. Subjects with a medical history or diagnosis code for PsO prior to IBD, JIA, or CNO diagnosis were excluded. This algorithm to identify subjects was previously reported.[16] Portions of this population have been reported previously; the 83 cases of PsO reported in Buckley et al[16] and the 6 cases of PsO reported by Groth et al[17] are included in this study. Subjects were analyzed according to the initial diagnosis in cases where > 1 eligible diagnostic code applied.

Outcome. The primary outcome was incident PsO defined as the first ICD-9 (696.1) or ICD-10 code (L40.0–40.4, L40.8, L40.9) during an outpatient visit with a rheumatologist, gastroenterologist, or dermatologist.

Medication exposure and other covariates. TNFi exposure was defined as at least 1 prescription for infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab pegol (CZP), or golimumab (GOL; ever/never). DMARD exposure was dichotomized as ever/never and included MTX (oral or subcutaneous), LEF, or SSZ. TNFi and DMARD exposures for our study population were defined as prescriptions occurring prior to the first visit with a PsO ICD code for patients with a PsO diagnosis, or end of follow-up for patients who did not develop PsO during the study period. If patients were exposed to > 1 TNFi therapy during follow-up, only the first therapy was used to define that exposure. Age- and sex-adjusted BMI (calculated as weight in kilograms divided by height in meters squared) z score[23] and family history of PsO were abstracted at the time of study entry. If BMI was missing at that visit, BMI from the closest visit was used. BMI z score was dichotomized as < 2 (nonobese) and ≥ 2 (obese).

Study follow-up. Study entry was the date at which the first diagnosis code occurred for IBD, JIA, or CNO in children without TNFi exposure. For children with TNFi exposure, study entry occurred at the date of their first TNFi prescription. Follow-up for all subjects continued until either (1) the first diagnosis code for PsO or (2) the last visit during the study period.

Analysis. Demographic information and baseline characteristics were summarized by frequencies and percentages for categorical variables (eg, sex, race) and by mean (SD) and median (IQR) for continuous or count variables. All TNFi were analyzed collectively as a single exposure group and also stratified by TNFi therapy, with and without the addition of a DMARD and according to underlying diagnosis of IBD, JIA, or CNO. Incidence rates (IRs) were calculated as the number of PsO cases per 1000 person-years (PY) of follow-up. IRs for CNO were not calculated due to small sample size. Standardized incidence ratios (SIRs) were calculated as the ratio of observed TNFi-induced PsO cases to expected number of PsO cases in the general pediatric population. The IR of PsO in the general pediatric population was estimated from a previously reported incidence of 0.41 cases per 1000 children per year.[24] Poisson regression was implemented with PY as offset to estimate the IR ratio (IRR) with 95% CI between exposure groups, adjusted for covariates of interest. Because children aged < 19 years were included in the cohort, a sensitivity analysis of the Poisson regression was performed excluding patients with a diagnosis of JIA at age ≥ 16 years in accordance with International League of Associations for Rheumatology diagnostic criteria.[25] Since a subset of patients was exposed to > 1 TNFi during the study period, we performed a sensitivity analysis of the Poisson regression to analyze patients using the TNFi prescribed at the time of PsO development as the exposure (instead of the first TNFi).

RESULTS

Subjects. Over the 10-year study period, a total of 5088 patients met the inclusion criteria (Figure 1). Patient characteristics are summarized in Table 1, of which age, sex, race, obesity, family history of PsO, and underlying diagnosis were similar between TNFi-exposed and TNFi-unexposed groups. DMARD use was higher in the TNFi-exposed vs -unexposed group (30% vs 12%). There were 3794 (75%) patients with IBD, 1189 (23%) patients with JIA, and 105 (2%) patients with CNO. Median disease duration at the last follow-up visit in this study was 952 days (IQR 388-1834) for patients with IBD, 950 days (IQR 364-1773) for patients with JIA, and 814 days (IQR 381-1477) for patients with CNO. Median time from disease diagnosis to first TNFi dose was 97 days (IQR 10-573) for patients with IBD, 84 days (IQR 0-340) for patients with JIA, and 105 days (IQR 0-707) for patients with CNO.

Three thousand sixty-five patients were TNFi-unexposed (60%) and 2023 patients were TNFi-exposed (40%). Of the TNFi-exposed patients, 1334 (66%), 304 (15%), and 383 (19%) were prescribed IFX, ETN, or ADA, respectively. Only 2 patients met the study exposure definition for GOL (1 patient) or CZP (1 patient). The most commonly prescribed TNFi varied by the underlying condition: ETN for JIA and IFX for IBD. ETN was not prescribed for any subjects with IBD. A subset of TNFi-exposed subjects was also prescribed a DMARD, most commonly MTX (98%). Of the TNFi-exposed patients, 45%, 14%, and 41% started DMARDs before, at the same time, or after TNFi therapy, respectively. Median gap to next medication was less than a year: 322 days to TNFi start when DMARD exposure was first, and 340 days to DMARD start when TNFi exposure was first. DMARD exposure with a TNFi was higher in the JIA

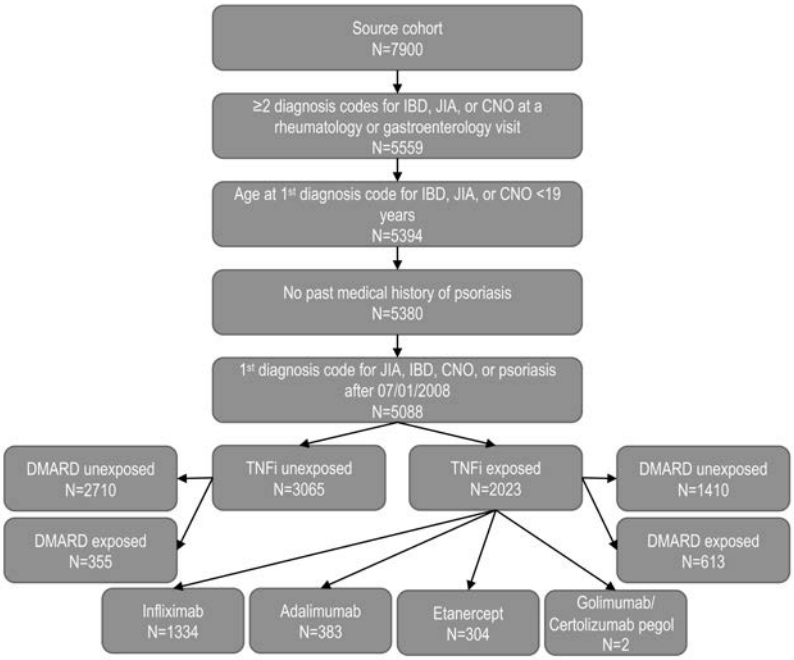

Figure 1. Participant flow diagram. CNO: chronic nonbacterial osteomyelitis; DMARD: disease-modifying antirheumatic drug; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; TNFi: tumor necrosis factor inhibitor.

Table 1. Patient characteristics by TNFi exposure.

	All, n	TNFi-unexposed, n (%)	TNFi-exposed, n (%)	Infliximab, n (%)	Etanercept, n (%)	Adalimumab, n (%)
Subjects	5088	3065	2023	1334	304	383
IBD[a]	3794	2250 (73.4)	1544 (76.3)	1301 (84.3)	0 (0.0)	241 (15.7)
JIA[a]	1189	733 (23.9)	456 (22.6)	23 (5.0)	300 (65.8)	133 (29.2)
CNO[a]	105	82 (2.7)	23 (1.1)	10 (43.5)	4 (17.4)	9 (39.1)
Age, yrs, mean (SD)	11.3 (4.7)	11.0 (5.1)	11.8 (4.1)	12.3 (3.5)	9.6 (5.0)	11.8 (4.5)
Female	2537	1561 (50.9)	976 (48.2)	581 (43.5)	207 (68.1)	188 (49.1)
Race						
White	3925	2379 (77.6)	1546 (76.4)	1010 (75.7)	238 (78.2)	296 (77.2)
Black	469	245 (8.0)	224 (11.1)	161 (12.1)	27 (8.9)	36 (9.4)
Other/unknown	693	440 (18.5)	253 (12.5)	163 (12.2)	39 (12.8)	51 (13.3)
Obesity	141	102 (3.3)	39 (1.9)	21 (1.6)	12 (3.9)	6 (1.6)
Family history of psoriasis[b]	161	85 (2.8)	76 (3.8)	26 (2.0)	29 (9.5)	21 (5.5)
DMARD	968	355 (11.6)	613 (30.3)	280 (21.0)	213 (70.0)	119 (31.1)

Certolizumab pegol and golimumab counts reflected in the TNFi-exposed column but not shown as separate TNFI columns due to small sample size. [a] For specific TNFi therapy columns, n (%) refers to that of the underlying condition (row). [b] First-degree relative. CNO: chronic noninfectious osteomyelitis; IBD: inflammatory bowel disease; DMARD: disease-modifying antirheumatic drug (including methotrexate, leflunomide, and sulfasalazine); JIA: juvenile idiopathic arthritis; TNFi: tumor necrosis factor inhibitor.

population (59%) compared to the IBD population (22%). Two hundred fifty (12%) TNFi-exposed patients received > 1 TNFi during the study period, of whom 16 (6%) developed PsO. The most frequent switch was from IFX to ADA (54%), followed by ETN to ADA (32%), and then ADA to IFX (11%).

Median time to development of PsO from IBD/JIA/CNO diagnosis was 728 days (IQR 255-1576) for the TNFi-unexposed patients and 1029 days (IQR 521-1945) for TNFi-exposed patients. In TNFi-exposed patients, the median (IQR) time to development of PsO from first TNFi dose was 674 days (336-1308): 522 days (276-1311) for ADA, 550 days (324-999) for IFX, and 1216 days (766-1841) for ETN.

TNFi exposure and incident PsO. The number of follow-up years, cases, and IRs for the entire cohort and for each diagnosis according to TNFi therapy and presence or absence of concomitant DMARD therapy is shown in Table 2. TNFi-unexposed patients had 8462 PY of follow-up. Of the children exposed to TNFi therapy, the IR of PsO in children with IBD, JIA, or CNO

Table 2. Follow-up duration, psoriasis cases, and unadjusted incidence rates per 1000 PY for entire cohort and for each underlying disease according to TNFi type and presence of a DMARD.

	Any TNFi Group			TNFi Only			TNFi + DMARD		
	All*	IBD	JIA	All*	IBD	JIA	All*	IBD	JIA
				Follow-up, yrs					
TNFi	6504	4909	1548	3906	3441	434	2598	1468	1114
IFX	4276	4162	93	3029	2981	42	1246	1181	51
ETN	1220	0	1214	296	0	293	924	0	930
ADA	1003	742	240	578	458	99	425	284	171
				Psoriasis cases					
TNFi	91	64	25	58	49	9	33	15	16
IFX	53	51	5	40	40	0	13	11	0
ETN	21	0	21	7	0	7	14	0	17
ADA	17	13	4	11	9	2	6	4	5
				Incidence rate per 1000 PY					
TNFi	14.0	13.0	16.1	14.8	14.2	20.7	12.7	10.2	14.4
IFX	12.4	12.3	0	13.2	13.4	0	10.4	9.3	0
ETN	17.2	–	17.3	23.6	–	23.9	15.2	–	18.3
ADA	16.9	17.5	16.6	19	19.6	20.2	14.1	14.1	29.3

* "All" patients includes those diagnosed with IBD, JIA, or CNO.. ADA: adalimumab; DMARD: disease-modifying antirheumatic drug (including methotrexate, leflunomide, and sulfasalazine); ETN: etanercept; IBD: inflammatory bowel disease; IFX: infliximab; JIA: juvenile idiopathic arthritis; PY: person-year; TNFi: tumor necrosis factor inhibitor.

was 14.0 per 1000 PY. Among all patients exposed to TNFi, the IR for PsO was lowest for IFX (12.4) and similar in ETN (17.2) and ADA (16.9). The IR for IFX remained lower than the other TNFi types when stratified by underlying diagnosis. IRs for the other TNFi types followed the same pattern during stratification: higher IRs in JIA vs IBD. There were no patients with IBD treated with ETN and, of the limited number of patients with JIA treated with IFX (n = 93), none developed PsO. The IRs of PsO in children with CNO were not calculated due to a small sample size.

The IRRs of IFX, ETN, and ADA exposure were compared to those with no TNFi exposure and are shown in Figure 2. Using Poisson regression that controlled for DMARD exposure, sex, and family history of PsO, the IRR of developing PsO in patients exposed to IFX was 2.34 times higher (95% CI 1.56-3.51; $P < 0.001$) than those who did not receive any TNFi treatment. The IRR was slightly higher for patients exposed to ADA (IRR 2.70, 95% CI 1.53-4.75; $P < 0.001$) and lowest for patients exposed to ETN (IRR 2.21, 95% CI 1.17-4.21; $P = 0.006$) compared to non–TNFi-exposed patients.

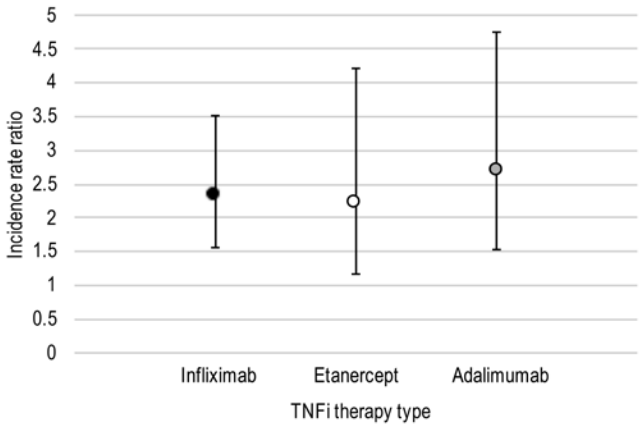

Figure 2. Incidence rate ratio of new-onset PsO for each TNFi adjusted for covariates using Poisson regression. Covariates included sex, family history of PsO, and exposure to disease-modifying antirheumatic drugs. PsO: psoriasis; TNFi: tumor necrosis factor inhibitor.

The results were similar in the sensitivity analysis restricting the patient population to only those diagnosed with JIA before age 16 years for IFX (IRR 2.39, 95% CI 1.57-3.66; $P < 0.001$), ADA (IRR 2.63, 95% CI 1.44-4.80; $P = 0.001$), and ETN (IRR 2.24, 95% CI 1.14-4.40; $P = 0.007$; data not shown). In a second sensitivity analysis, we analyzed patients with > 1 TNFi exposure using the TNFi prescribed at the time of PsO development and the IRRs were similar (IFX vs TNFi-unexposed: 2.60; ADA vs unexposed: 1.64; ETN vs unexposed: 2.91; data not shown).

DMARD exposure and incident PsO. A total of 139 cases of PsO were identified. Of these, 91 cases followed exposure to a TNFi: 58 in the TNFi only group and 33 in the TNFi plus DMARD group. For TNFi-exposed subjects, the IR of PsO was lower in children who were also DMARD-exposed (12.7 per 1000 PY), as compared to those without DMARD exposure (14.8 per 1000 PY). Results were similar when stratified by underlying condition. The IR for PsO was higher in patients with JIA than IBD in both the TNFi alone (20.7 vs 14.2) and TNFi plus DMARD (14.4 vs 10.2) groups with a risk difference of 6.5 and 4.2, respectively. Lower IRs were observed with the other TNFi agents when patients were also treated with a DMARD, except in ADA where a higher IR was seen in children with JIA receiving ADA plus a DMARD compared to those treated with ADA alone.

Using Poisson regression that adjusted for sex, DMARD use, family history of PsO, and an interaction between DMARD

and TNFi use, the difference in IRR of TNFi exposure between DMARD-exposed and -unexposed groups was by 0.25 ($P < 0.001$). Restricting the cohort to only patients with JIA diagnosed before age 16 years yielded a nearly identical difference in IRR (0.24, $P < 0.001$; data not shown).

SIRs. SIRs for the cohort and for each condition and TNFi agent with or without a DMARD are presented in Table 3. The SIR for children with IBD, JIA, or CNO was 34.3 (95% CI 27.9-42.1); for children with exposure to TNFi only, the SIR was 36.4 (95% CI 28.1-47.1) compared to 31.1 (95% CI 22.1–43.8) in children with TNFi plus DMARD exposure. For children with IBD, the SIR associated with TNFi exposure was 34.9 (95% CI 26.4-46.2) and 25.0 (95% CI 15.1-41.5) in children without and with DMARD exposure, respectively. For children with JIA exposed to TNFi therapy, the SIR was 50.8 (95% CI 26.4-97.6) for those without concomitant DMARD therapy and 35.2 (95% CI 21.6-57.5) for those comedicated with a DMARD.

DISCUSSION

Among children with IBD, JIA, and CNO, we found that in Poisson regression models that accounted for age, sex, family history of PsO and DMARD exposure, the IRR of PsO was higher for ADA than IFX or ETN, but the CIs for all 3 were overlapping, making these differences nonsignificant. For patients with exposure to any TNFi therapy, there was a significantly lower IRR of incident PsO in DMARD-exposed vs -unexposed patients by 0.25 in the adjusted models.

Several findings from our study warrant further discussion. Before controlling for other characteristics in our cohort, the risk of new-onset PsO after exposure to a TNFi was lowest for children and adolescents exposed to IFX. Once we accounted for potential confounders including age, sex, family history of PsO in a first-degree relative, and DMARD exposure, the IRRs for new-onset PsO had overlapping CIs; the estimate was second highest for IFX-exposed patients. Prior publications report IFX as being the most frequently implicated TNFi-induced PsO in adults.[14,26-27] These publications are mostly descriptive case reports/series in adults with IBD and do not include adjusted analyses or IRs.[14,26-27] One study in adults with IBD found no statistically significant difference between the IR of PsO with IFX vs ADA exposure[28] and another study reported ADA as an independent risk factor.[29] In children with JIA, IBD, and CNO, the IR of incident PsO for all 3 TNFi therapies was higher than the IR of incident PsO in children who were TNFi-unexposed (3.8 per 1000 PY).[16]

Second, we saw a significant association of DMARD use with TNFi and lower risk of new-onset PsO. While the cause of TNFi-induced PsO remains uncertain, we hypothesize several factors may contribute to the lower observed IR of PsO in children also exposed to a DMARD. In clinical practice, TNFi therapy is often prescribed with a DMARD to augment efficacy and to improve sustained remission by preventing the development of TNFi antibodies.[30] As the production of TNFi antibodies and TNFi-induced PsO are both thought to be immune-mediated reactions, DMARDs may protect against TNFi-induced PsO through a similar mechanism, but this needs further study. Previous studies suggest that adding MTX to IFX or ADA regimens correlate to a 50% increase in the probability of disease remission, whereas comedication with a DMARD provided little benefit to ETN therapy.[30] It is possible that some instances of PsO that develop after TNFi initiation are simply underlying disease manifestations that are appearing for the first time; combination therapy of a DMARD and TNFi may be more effective at suppressing this disease comorbidity. The DMARD dose typically used in clinical care for IBD, JIA,

Table 3. Standardized incidence ratios (SIRs) in entire cohort and by disease.

	All	IBD	JIA
Any TNFi group		SIR (95% CI)	
All	34.3 (27.9-42.1)	32.0 (25.0-40.8)	39.6 (26.8-58.6)
IFX	30.4 (23.2-39.8)	30.0 (22.8-39.5)	0
ETN	42.2 (27.5-64.7)	–	42.4 (27.6-65.0)
ADA	41.5 (25.8-66.8)	42.9 (24.9-73.9)	40.8 (15.3-108.6)
TNFi only			
All	36.4 (28.1-47.1)	34.9 (26.4-46.2)	50.8 (26.4-97.6)
IFX	32.4 (23.7-44.1)	32.9 (24.1-44.8)	0
ETN	58.0 (27.6-121.6)	–	58.6 (27.9-122.8)
ADA	46.6 (25.8-84.2)	48.1 (25.0-92.5)	49.4 (12.4-197.7)
TNFi + DMARD			
All	31.1 (22.1-43.8)	25.0 (15.1-41.5)	35.2 (21.6-57.5)
IFX	25.6 (14.8-44.0)	22.8 (12.6-41.2)	0
ETN	37.1 (22.0-62.67)	–	37.3 (22.1-62.9)
ADA	34.6 (15.5-77.0)	34.6 (13.0-92.1)	34.7 (8.7-138.7)

SIRs were calculated as the ratio of observed to expected number of psoriasis cases as estimated by the incidence in the general pediatrics population (40.8 per 100,000).[24] SIR > 1 indicates that more cases were observed than expected. ADA: adalimumab; DMARD: disease-modifying antirheumatic drug (including methotrexate, leflunomide, and sulfasalazine); ETN: etanercept; IBD: inflammatory bowel disease; IFX: infliximab; JIA: juvenile idiopathic arthritis; TNFi: tumor necrosis factor inhibitor.

and CNO can vary widely from 5 mg or 7.5 mg weekly to help prevent anti-TNFi antibody formation to 1 mg/kg (max 25 mg) for maximum clinical benefit. The role of DMARD dose on diminishing the risk of incident PsO needs further exploration.

This study has several limitations that should be acknowledged. Due to the retrospective design of the study, misclassification of PsO and selection bias are possible. Some patients may have been diagnosed with PsO by dermatologists outside the database, resulting in misclassification if those diagnosed elsewhere did not have the ICD-9/10 code for PsO added to their medical record. We anticipate the misclassification of PsO was nondifferential among the TNFi tested and also between the groups exposed and unexposed to DMARD. There is also no way to separate the risk of PsO as a result of TNFi treatment from the underlying diagnosis in this retrospective study design. Last, a subset of children was exposed to > 1 TNFi, but our primary analysis estimated risk based on first exposure, emulating an intention-to-treat analysis and not as-treated analysis. In a sensitivity analysis, the IRRs were similar when accounting for the exposure to the second TNFi. Importantly, the sensitivity analysis demonstrated that the main conclusions of the study were robust. Despite these limitations, this is the first study, to our knowledge, to evaluate the differential risk of the 3 most commonly used TNFi agents and the effect of DMARD use.

In conclusion, this study demonstrates that in children with JIA and IBD, the risk of TNFi-induced PsO was similarly high in children exposed to ADA, IFX, and ETN. The incidence of TNFi-induced PsO was significantly lower in children also exposed to a DMARD, even after adjusting for important covariates. These findings highlight the need to better understand the immunologic effects of TNFi in this population, including the development of paradoxical PsO. Importantly, the differential effect of TNFi and concomitant DMARDs on new-onset PsO and, ultimately, the effect on clinical practice and outcomes should be further investigated.

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