Prevalence of Paradoxical Psoriasis after Exposure to Tumor Necrosis Factor Inhibitors (TNFi) in Children - Results from A Single Tertiary Center

Sarah Kodama
  School of Medicine, Virginia Commonwealth University

Deepti Gupta
  Seattle Children's Hospital

Erin Sullivan
  Seattle Children's Hospital

Natalie Rosenwasser
  Seattle Children's Hospital

Yongdong Zhao (✉ ydzhao@uw.edu)
  Seattle Children's Hospital   https://orcid.org/0000-0003-3618-1379

Research article

Abstract

Objective: Paradoxical psoriasis has been increasingly reported in adults after exposure to tumor necrosis factor inhibitors (TNFi). Systematic studies in pediatric population are lacking. We aimed to investigate the relationship between TNFi therapy and the onset of new psoriasis in children.

Methods: Patients with diagnosis of chronic nonbacterial osteomyelitis (CNO), juvenile idiopathic arthritis (JIA), or inflammatory bowel disease (IBD) treated with TNFi between 2005 and 2015 were identified. Baseline characteristics were compared among those developing psoriasis versus those who did not using t-tests or Wilcoxon Rank Sum tests.

Results: A total of 1,092 patients were included with a median follow up of 21-36 months for CNO, JIA and IBD after the initiation of first TNFi. Psoriasis developed after exposure to TNFi in 4 of 28 CNO patients (14%), 3 of 620 JIA patients (0.5%) and 25 of 450 IBD patients (5.6%). There was no significant difference in distribution of age, gender, family history of psoriasis or concomitant medications between psoriasis subset and non-psoriasis subset. Among those who developed psoriasis, 38% had partial and 47% had complete responses to topical therapies or phototherapy. Eleven patients (35%) discontinued, none (0%) switched and twenty (65%) continued TNFi therapies.

Conclusion: Cumulative incidence rates of TNFi-associated psoriasis varied in three underlying diseases. Increasing awareness of this unwanted side effect in pediatric community is important to ensure timely diagnosis and treatment. Fortunately , the majority of children affected had a favorable outcome.

Introduction

Tumor necrosis factor inhibitors (TNFi) have demonstrated robust efficacy in the management of numerous inflammatory conditions including chronic nonbacterial osteomyelitis (CNO), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD) and psoriasis. Exposure to TNFi has been associated with the development of psoriasiform eruptions [1–10]. This paradoxical psoriasis after exposure to TNFi has been increasingly reported in the adult population, however systematic studies in pediatric population are lacking. Recently a single center followed the systematic development of paradoxical psoriasis in pediatric patients taking TNFi [2], however most case series available solely describe the courses of disease. The various risk factors, possible preventative measures, demographic trends, pathogenesis, clinical predictive risk information, and optimal treatment plans are still not well characterized or understood. The underlying disease for which TNFi is prescribed, may pose various degrees of risks of paradoxical psoriasis. The prevalence of TNFi-induced psoriasis among three major pediatric populations with JIA, IBD and CNO remains unknown. We aimed to investigate the relationship between TNFi therapy and the onset of new psoriasis in children with CNO, JIA, or IBD in a single tertiary center.

Patients And Methods

Inclusion and exclusion criteria

Institutional review board approval (#15732) was obtained from the authors' tertiary, multidisciplinary pediatric hospital prior to the study. Consent was waived due to its retrospective nature. Three groups of children, including children with CNO, children with JIA, and children with IBD were identified by evaluating the electronic medical database using standard ICD-9 codes (730.1 or 730.2 for chronic and unspecified osteomyelitis, 555.0, 555.1, 555.2, 555.9, 556.0, 556.1, 556.2, 556.3, 556.5, 556.6 for Crohn's disease or ulcerative colitis, 714.30, 714.31, 714.32, 714.33, for juvenile idiopathic arthritis). ICD 10 codes were implemented after the study ending date so they were not used. Inclusion criteria were: (a) younger than 18 years old at the diagnosis of CNO, JIA, or IBD; (b) treated with TNFi between January 1st, 2005 and July 31st, 2015; and (c) seen at least twice by prescribing specialist. Exclusion criteria included (a) incorrect diagnosis after chart review of clinical notes from gastroenterologist, dermatologist and rheumatologist; (b) patients who never started TNFi; (c) patients without follow-up visit(s) after initial TNFi was prescribed.

Case confirmation and chart extraction

A second clinical query was performed to combine the ICD-9 code of psoriasis (696.1, 696.2) with each of the other three conditions to identify patients with a diagnosis of psoriasis. Clinical and demographic characteristics were summarized descriptively by disease type (CNO, JIA, IBD) as well as psoriasis status. A board-certified pediatric dermatologist (DG) reviewed the diagnoses of psoriasis using clinical, photographic (if available), and pathological data. A diagnosis of psoriasis made by dermatologist, or gastroenterologist, or rheumatologist with supporting description of skin findings during physical exam was used to confirm the case. Characteristics including severity, associated symptoms, location, and percentage of body surface area were recorded for each patient population. Patients who had incorrect diagnosis, or insufficient clinical documentation for a TNFi-associated psoriasis were also excluded after the clinical notes were thoroughly reviewed. The research team then performed a chart review on all identified patients to extract detailed clinical data, which was then recorded in REDCap [11]. TNFi treatment was summarized by specific TNFi prescribed. The total duration of exposure represents the duration of exposure summed across all courses of the drug during observed follow-up; time to psoriasis from initiation of drug represents the time from initiation of the course of drug during which psoriasis developed to the onset of psoriasis symptoms. Clinical characteristics of patients developing psoriasis (including % body surface area (BSA), illness severity, and response to topical treatment) were recorded. Subsequent management including switch to another TNFi or discontinuation of TNFi were reported.

Statistics

Baseline characteristics were compared among those developing psoriasis versus those who did not using t-tests or Wilcoxon Rank sum tests. Clinical and demographic characteristics are summarized descriptively by disease type (CNO, JIA, IBD) as well as psoriasis status (developed during follow-up versus never developed during follow-up) using means and standard deviations or medians and

interquartile ranges for continuous variables and counts and proportions for categorical variables. An alpha of 0.05 was used for significancetesting.

Results

Patient inclusion

There were 1,783 patients with JIA, 1,424 patients with IBD, 178 patients with CNO identified by initial ICD code search at Seattle Children's Hospital between January 1, 2005 and July 31, 2015. Among these patients, a total of 1,092 patients met the inclusion criteria as shown in Fig. 1. There were 28 CNO patients, 620 JIA patients, and 450 IBD patients who were treated with TNFi for their primary disease and had at least 1 follow-up visit after initiation of TNFi by the study end date. For patients with both IBD and JIA diagnoses, we excluded patients with prior IBD diagnosis from the JIA cohort. Two patients had both CNO and JIA diagnoses, and four with both CNO and IBD. Family history data was excluded from IBD patients as < 14% had available data.

Prevalence Rate Of Paradoxical Psoriasis And Risk Factors

Psoriasis developed or worsened after exposure to TNFi in 4 out of 28 CNO patients (14%, 95% CI: 2.2–25.8%), 3 out of 620 JIA patients (0.5%, 95% CI: 0.1–1.0%), and 25 out of 450 IBD patients (5.6%, 95% CI: 3.8–7.4%). There was no significant difference in distribution of age, gender, race, family history of psoriasis, or concomitant medications between psoriasis and non-psoriasis subsets within each underlying disease as shown in Table 1. The majority of patients were white, non-Hispanic. The age of the diagnosis of primary disease was younger in children with JIA than those with IBD and CNO. However, the age at which the first TNFi was received was similar among all three populations. Family history of psoriasis was not present in the psoriasis subgroups within JIA and CNO and data were not available within IBD. Given the limited number of patients with CNO and JIA who developed psoriasis, data on antinuclear antibody (ANA) and human leukocyte antigen (HLA)-B27 positivity were descriptive. Lab findings for ANA and HLA-B27 were unavailable within the IBD subgroup. Across all three disease populations, disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, leflunomide, cyclosporine and prednisone were only used in a portion of patients at the time of initiation of first TNFi. Concurrent use of methotrexate was reported less frequently among IBD patients (34% vs. >70% in the other two disease populations). Within the IBD group, there was no difference in concurrent medication use among those who developed psoriasis versus those who did not.

Table 1. Demographic and Clinical Characteristics

	CNO			JIA			IBD			
	Total N=28	Psoriasis* N=4	No Psoriasis N=24	Total N=620	Psoriasis* N=3	No Psoriasis N=617	Total N=450	Psoriasis* N=25	No Psoriasis N=425	p-value
Gender (% Male)	16 (57.1%)	1 (25.0%)	15 (62.5%)	174 (28.0%)	0 (0.0%)	174 (28.2%)	269 (59.8%)	12 (48.0%)	257 (60.5%)	0.22
Race (% White)	25 (89.3%)	4 (1.00%)	21 (87.5%)	436 (70.3%)	3 (100.0%)	433 (70.2%)	349 (77.6%)	17 (68.0%)	332 (78.1%)	0.24
Age at Diagnosis**	11.0 (3.4)	8.9 (3.4)	11.4 (3.3)	8.7 (5.2)	8.4 (5.6)	8.7 (5.2)	12.3 (3.5)	11.6 (3.1)	12.3 (3.5)	0.32
Age at Initiation of 1st TNFi**	12.1 (3.7)	9.6 (3.1)	12.5 (3.7)	11.2 (4.7)	11.6 (0.6)	11.2 (4.7)	13.9 (3.2)	12.6 (3.1)	14.0 (3.1)	0.052
Family History of psoriasis	4 (14.3%)	0 (0.0%)	4 (16.7%)	52 (8.4%)	0 (0.0%)	52 (8.4%)	-	-	-	-
ANA										
Positive	2 (7.1%)	0 (0.0%)	2 (8.3%)	316 (51.0%)	2 (66.7%)	314 (50.9%)	-	-	-	-
Negative	12 (42.9%)	2 (50.0%)	10 (41.7%)	241 (38.9%)	0 (0.0%)	241 (39.1%)	-	-	-	-
Not done	14 (50.0%)	2 (50.0%)	12 (50.0%)	63 (10.2%)	1 (33.3%)	62 (10.1%)	-	-	-	-
HLA-B27										
Positive	7 (25.0%)	1 (25.0%)	6 (25.0%)	75 (12.1%)	1 (33.3%)	74 (12.0%)	-	-	-	-
Negative	15 (53.6%)	3 (75.0%)	12 (50.0%)	271 (43.7%)	1 (33.3%)	270 (43.8%)	-	-	-	-
Not done	6 (21.4%)	0 (0.0%)	6 (25.0%)	274 (44.2%)	1 (33.3%)	273 (44.2%)	-	-	-	-
Concurrent Med at Initiation of 1st TNFi										
NSAID	23 (82.1%)	4 (100.0%)	19 (79.2%)	430 (69.4%)	2 (66.7%)	428 (69.4%)				
Methotrexate	21 (75.0%)	2 (50.0%)	19 (79.2%)	493 (79.5%)	2 (66.7%)	491 (79.6%)	154 (34.2%)	10 (40.0%)	144 (33.9%)	0.53
Cyclosporine	3 (10.7%)	1 (25.0%)	2 (8.3%)	6 (1.0%)	0 (0.0%)	6 (1.0%)				
Prednisolone/Prednisone	10 (35.7%)	2 (50.0%)	8 (33.3%)	206 (33.2%)	2 (66.7%)	204 (33.1%)	130 (28.9%)	8 (32.0%)	122 (28.7%)	0.72
Azathioprine	1 (3.6%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	61 (13.6%)	2 (8.0%)	59 (13.9%)	0.4
Leflunomide	1 (3.6%)	1 (25.0%)	0 (0.0%)	5 (0.8%)	0 (0.0%)	5 (0.8%)	-	-	-	-
Sulfasalazine	1 (3.6%)	0 (0.0%)	1 (4.2%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	-	-	-	-

*Patient Developed Psoriasis at Any Point During Follow-up After initiation of TNFi

**Mean (Std. Dev)

Median follow-up time from initiation of first TNFi was 20 months for CNO patients, 35 months for JIA patients, and 36 months for IBD patients (Table 2). Exposure of >1 TNFi at the time of psoriasis development was recorded among 11/25 IBD, 2/3 JIA, and 2/4 CNO patients. Psoriasis developed during active administration of a TNFi for 23/25 IBD, 3/3 JIA, and 4/4 CNO patients. Two patients with IBD developed psoriasis while not actively on a TNFi, but after completing a course of infliximab; one developed psoriasis 50 days after a 16-month course of TNFi use, and another developed psoriasis 54 days after a 15-month course of TNFi use.

Table 2. Summary of TNFi Treatment in patient Population

	CNO			JIA			IBD***		
	Total N=28	Psoriasis* N=4	No Psoriasis N=24	Total N=620	Psoriasis* N=3	No Psoriasis N=617	Total N=450	Psoriasis* N=25	No Psoriasis N=425
Total Length of Follow-up After Initiation of First TNFi (Months)	20.0 (10.1 - 38.5)	15.5 (9.1 - 36.2)	20.4 (10.8 - 38.5)	34.5 (16.8 - 63.8)	47.6 (30.2 - 85.4)	34.5 (16.8 - 63.8)	35.9 (16.8 - 61.3)	38.8 (29.5 - 70.3)	35.4 (16.2 - 60.9)
Number of TNFis Used									
1	16 (57.1%)	2 (50.0%)	14 (58.3%)	402 (64.8%)	1 (33.3%)	402 (65.0%)	304 (67.6%)	9 (36.0%)	295 (69.4%)
2	11 (39.3%)	1 (25.0%)	10 (41.7%)	169 (27.3%)	2 (66.7%)	167 (27.1%)	133 (29.6%)	16 (64.0%)	117 (27.5%)
3	1 (3.6%)	1 (25.0%)	0 (0.0%)	49 (7.9%)	0 (0.0%)	49 (7.9%)	13 (2.9%)	0 (0.0%)	13 (3.1%)
Etanercept									
Ever Used	12 (42.9%)	0 (0.0%)	12 (50.0%)	477 (76.9%)	1 (33.3%)	476 (77.2%)	2 (0.4%)	-	2 (0.5%)
1st Therapy	13 (46.4%)	1 (25.0%)	12 (50.0%)	501 (80.8%)	1 (33.3%)	500 (81.0%)	2 (0.4%)	0 (0.0%)	2 (0.5%)
Total Duration of Exposure (Months)**	3 (23.1%)	0 (0.0%)	3 (25.0%)	236 (47.1%)	0 (0.0%)	236 (47.2%)	0 (0.0%)	-	0 (0.0%)
Ongoing at Last follow-up?	19.4 (9.0 - 26.2)	2.6	19.6 (13.0 - 28.2)	17.8 (6.5 - 34.7)	99.1	17.8 (6.4 - 34.9)	10.5 - 36.6	-	10.5 - 36.6
Developed Psoriasis During Exposure	0 (0.0)	0 (0.0)	-	1 (0.2%)	1 (100.0%)	-	0 (0.0%)	-	-
Time to Psoriasis from Initiation of Etanercept (Months)**	-	-	-	22.4	22.4	-	-	-	-
Adalimumab									
Ever Used	9 (32.1%)	1 (25.0%)	8 (33.3%)	84 (13.6%)	1 (33.3%)	83 (13.5%)	69 (15.3%)	7 (28.0%)	62 (14.6%)
1st Therapy	15 (53.6%)	3 (75.0%)	12 (50.0%)	221 (35.7%)	2 (66.7%)	219 (35.5%)	189 (42.0%)	20 (80.0%)	169 (39.8%)
Total Duration of Exposure (Months)**	10 (66.7%)	1 (33.3%)	9 (75.0%)	99 (44.8%)	0 (0.0%)	99 (45.2%)	128 (67.7%)	11 (55.0%)	117 (60.2%)
Ongoing at Last follow-up?	9.5 (6.8 - 16.7)	8.6 (1.4 - 24.0)	10.8 (6.9 - 16.4)	9.9 (3.5 - 23.2)	4.0 - 35.6	9.9 (3.5 - 23.0)	16.1 (6.1 - 27.3)	24.4 (16.7 - 48.8)	12.7 (5.6 - 26.7)
Developed Psoriasis During Exposure	1 (6.7%)	1 (33.3%)	-	1 (0.5%)	1 (50.0%)	-	14 (7.4%)	14 (70.0%)	-
Time to Psoriasis from Initiation of Adalimumab (Months)*	-	3.7	-	9.9	9.9	-	14.0 (10.6 - 18.2)	14.0 (10.6 - 18.2)	-
Infliximab									
Ever Used	7 (25.0%)	3 (75.0%)	4 (16.7%)	59 (9.5%)	1 (33.3%)	58 (9.4%)	366 (81.3%)	18 (72.0%)	348 (81.9%)
1st Therapy	13 (46.4%)	3 (75.0%)	10 (41.7%)	165 (26.6%)	2 (66.7%)	163 (26.4%)	395 (87.8%)	20 (80.0%)	375 (88.2%)
Total Duration of Exposure (Months)**	8 (61.5%)	0 (0.0%)	8 (80.0%)	92 (55.4%)	2 (100.0%)	90 (54.9%)	217 (54.9%)	6 (30.0%)	211 (56.3%)
Ongoing at Last follow-up?	7.7 (7.1 - 24.5)	7.1 (5.1 - 7.4)	20.2 (7.7 - 26.4)	21.2 (9.0 - 41.8)	12.0 - 30.2	21.2 (8.4 - 42.6)	23.7 (8.5 - 45.9)	12.2 (4.3 - 24.3)	24.3 (8.7 - 46.6)
Developed Psoriasis During Exposure	3 (23.1%)	3 (100.0%)	-	1 (0.6%)	1 (50.0%)	-	9 (2.3%)	9 (45.0%)	-
Time to Psoriasis from Initiation of Infliximab (Months)**	-	3.7 (1.5 - 3.7)	-	20.2	20.2	-	9.9 (4.0 - 12.4)	9.9 (4.0 - 12.4)	-

*Patient Developed Psoriasis at Any Point During Follow-up After initiation of TNFi

**Median (IQR) or Range/Value for N<3

***Not included: Certolizumab (N=22) and Golimumab (N=1) use, no patients developed psoriasis during the use of these drugs

Relationship Of Psoriasis With Specific Tnfi Administered

Among all three primary disease groups, only one patient (JIA) developed psoriasis while taking etanercept. In contrast, 16 patients (1 from CNO, 1 from JIA, and 14 from IBD) and 13 patients (3 from CNO, 1 from JIA, and 9 from IBD) developed psoriasis during exposure to adalimumab or infliximab respectively. No patients developed psoriasis while on certolizumab pegol (n = 22, median of 6.5 [2.6–11.5] months) or golimumab (n = 1, 5.5 months).

Characteristics Of Paradoxical Psoriasis And Outcome

Clinical presentation of psoriasis and treatment of these patients were summarized in Table 3. Among those who developed psoriasis, 88% had plaque psoriasis, 25% had alopecia, and 84% had scalp psoriasis.

Table 3
Clinical Presentation and Treatment of Patients Who Developed Psoriasis

	CNO* N = 4	JIA N = 3	IBD* N = 25
Morphology			
Plaque	4 (100.0%)	2 (66.7%)	23 (92.0%)
Guttate	1 (25.0%)	0 (0.0%)	3 (12.0%)
Pustular	0 (0.0%)	1 (33.3%)	1 (4.0%)
Erythrodermic	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palmoplantar	2 (50.0%)	0 (0.0%)	0 (0.0%)
Other	1 (25.0%)	0 (0.0%)	3 (12.0%)
Alopecia	3 (75.0%)	0 (0.0%	6 (24.0%)
Areas Affected			
Scalp	4 (100.0%)	2 (66.7%)	22 (88.0%)
Face	0 (0.0%)	3 (33.3%)	3 (12.0%)
Trunk	3 (75.0%)	0 (0.0%)	17 (68.0%)
Extremities	3 (75.0%)	1 (33.3%)	18 (72.0%)
Intertriginous locations	2 (50.0%)	0 (0.0%)	7 (28.0%)
Nails	1 (25.0%)	0 (0.0%)	4 (16.0%)
Palms	3 (75.0%)	1 (33.3%)	3 (12.0%)
Soles	2 (50.0%)	1 (33.3%)	4 (16.0%)
%BSA	10 (5.0−30.0)	5.0 (1.0−10.0)	12.5 (5.8−40.0)
Symptoms			
Pain	1 (25.0%)	0 (0.0%)	2 (8.0%)
Pruritis	4 (100.0%)	2 (66.7%)	13 (52.0%)
Bleeding	0 (0.0%)	0 (0.0%)	1 (4.0%)
Severity			
Mild	2 (50.0%)	3 (100.0%)	13 (52.0%)
Moderate	2 (50.0%)	0 (0.0%)	11 (44.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)

	CNO* N = 4	JIA N = 3	IBD* N = 25
Unknown	0 (0.0%)	0 (0.0%)	1 (4.0%)
Topical treatment/Phototherapy			
Topical Steroids	4 (100.0%)	3 (100.0%)	24 (96.0%)
Topical Retinoid	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vitamin D Analogue	1 (25.0%)	2 (66.7%)	12 (48.0%)
Coal Tar	3 (75.0%)	0 (0.0%)	10 (40.0%)
Phototherapy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Systemic Medications			
Cyclosporine	0 (0.0%)	0 (0.0%)	0 (0.0%)
Methotrexate	0 (0.0%)	3 (100.0%)	2 (8.0%)
Isotretinoin	0 (0.0%)	0 (0.0%)	0 (0.0%)
Azathioprine	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prednisone/Prednisolone	0 (0.0%)	0 (0.0%)	1 (4.0%)
Ustekinumab	0 (0.0%)	0 (0.0%)	1 (4.0%)
Other	0 (0.0%)	0 (0.0%)	1 (4.0%
Response to Topical/Phototherapy			
Worsened or Unchanged	0 (0.0%)	0 (0.0%)	2 (8.0%)
Partial Response	3 (75.0%)	1 (33.3%)	9 (36.0%)
Complete Response	1 (25.0%)	2 (66.7%)	12 (48.0%)
Unknown	0 (0.0%)	0 (0.0%)	2 (8.0%)

*1 patient is included in both groups

Within the CNO group, 4 out of the 4 patients developed psoriasis while on TNFi treatment characterized by plaque, guttate, palmoplantar, and pustular presentation. Areas affected included the scalp, trunk, extremities, intertriginous locations, nails, palms, and soles. The reported psoriatic lesions were rated from mild to moderate severity with associated pain and pruritis.

Within the JIA group (n = 3), psoriasis presented as pruritic plaques on scalp, face, palms and soles covering approximately 5% body surface area (BSA). These patients were documented to have mild presentations of psoriasis.

Within the IBD group (n = 25), psoriasis was described as pruritic, and/or painful. They presented as plaques, guttate lesions, pustules that affected the scalp, face, trunk, extremities, intertriginous locations, nails, palms, and soles. The lesions on average covered approximately 12.5% BSA. Out of the 25 IBD patients, 6 developed alopecia ranging from mild to moderate in severity.

Treatment And Outcomes

Treatments included topical glucocorticoids, topical retinoids, vitamin D analogues, coal tar, phototherapy, methotrexate, systemic glucocorticoids, ustekinumab, discontinuing the inciting TNFi or switching to another TNFi. Eleven patients (35%) discontinued, none (0%) switched and twenty (65%) continued TNFi therapies. Of all patients who developed psoriasis after exposure to TNFi, 38% had partial and 47% had complete responses to comprehensive management.

Discussion

The cumulative incidence rate of paradoxical psoriasis in the pediatric population is reported from a large pediatric tertiary center. TNFi-associated psoriasis is more common in patient populations with IBD and CNO compared to patient populations with JIA. The cumulative incidence rates of paradoxical psoriasis in IBD, CNO, and JIA from this cohort (5.6%, 14.0%, 0.5%) were not directly comparable to the report from Buckley *et al* [2]. The incidence rate of TNFi-associated psoriasis within children with IBD was 10.9 per 1,000 patient years, 33.5 per 1,000 patient years within children with CNO and 14.7 per 1,000 patient years within children with JIA. These differences may be due to variation of patient population, prescribing pattern of TNFi, and concomitant medications. Higher rates of psoriasis after TNFi exposure within the CNO cohort were consistent between two studies. The lower rate of paradoxical psoriasis within JIA in our cohort was unexpected. This finding might be related to the lower usage rate of monoclonal TNFi (adalimumab and infliximab) within JIA and underreporting of psoriasis by diagnostic codes or rheumatologists. A prospective study with intention to collect specific data surrounding initiation of TNFi and longitudinal monitoring for paradoxical psoriasis within these populations needs to be further investigated. Particular attention to specific TNFi (including dosage), and concomitant medications would provide additional information that may influence long-term treatment plan. In a study by Tollefson *et al.*, incidence rates of pediatric psoriasis were calculated (age and sex adjusted to 2000 American Caucasian population) with an overall age- and sex-adjusted annual incidence was 40.8 per 100,000 (95% CI: 36.6−45.1) and was 33.2 per 100,000 (95% CI: 29.3−37.0) when diagnosed by a dermatologist [12]. The standardized incidence ratio for all 3 primary diseases combined was 9.3 without exposure and 30 with exposure to TNFi compared to the general pediatric population [2].

The timing of the onset of paradoxical psoriasis varies among underlying diseases and individual TNFi. A recent study at the Cleveland Clinic demonstrated a median latency period of approximately 11 months [4]. In a case series of children with CNO (n = 5), the onset of paradoxical psoriasis occurred between 3 and 5 months after the initiation of adalimumab or infliximab [9]. Another case series (n = 5) revealed a

median of 7 (2–26) months between the onset of psoriasis and starting adalimumab or infliximab in children with IBD or JIA [8]. In our study, patients developed adalimumab-associated and infliximab-associated psoriasis between 2–18 monthsafter initiation.

TNFi-associated psoriasis is usually treated with topical medications. However, in severe cases, discontinuation or switching to another TNFi is necessary [4]. In our cohort, 35% patients discontinued, and 65% continued the same TNFi therapies. Most of the patients in all three populations had good responses to these therapies. Among all, 38% patients had partial response and 47% had complete response to topical medications and/or phototherapy. Other successful approaches included combining another biologic such as ustekinumab or reducing dose/frequency of the offending TNFi [9, 10]. Cyclosporine has also been shown to improve paradoxical psoriasis in 5 of 5 patients from an adult cohort [4].

Despite having a large patient population, the number of cases identified with TNFi-associated psoriasis was small, which did not allow for a risk model to be developed. Within our patient population, we focused on the IBD group. There was no significant difference or distribution in patient age, gender, race, family history, or concomitant medications between patients who developed psoriasis and those who did not. Genetic polymorphism of interleukin 23 receptor has been reported to be associated with paradoxical psoriasis in children with Crohn's disease after treatment of infliximab[5]. Further studies are needed to determine the risk or prognostic factors prior to the initiation of TNFi. Education for physicians and families is also important in order to identify this side effect earlier and manage this condition appropriately.

This study has several limitations. Firstly, this was a retrospective single-center study with incomplete data including family history and disease specific lab results. Secondly, the cutaneous lesions patients present with may be inaccurately diagnosed as psoriasis making the use of diagnostic codes inaccurate. Given the large patient population, this was the only feasible approach for this retrospective study. To minimize this inaccuracy, the diagnosis of psoriasis was confirmed by a pediatric dermatologist through detailed chart review. Thirdly, the relative risk of paradoxical psoriasis after exposure of TNFi cannot be estimated because the patient population who did not receive TNFi were not included. Nevertheless, our study showed more prevalent TNFi-associated psoriasis within children with IBD and CNO than those with JIA.

Conclusion

Cumulative incidence rates of TNFi-associated psoriasis varied in 3 underlying diseases. Education of this side effect and careful clinical monitoring are important at initiation and continuation of TNFi. Majority of affected children had a favorable outcome and were able to continue on TNFi treatment for their primary disease.

Declarations

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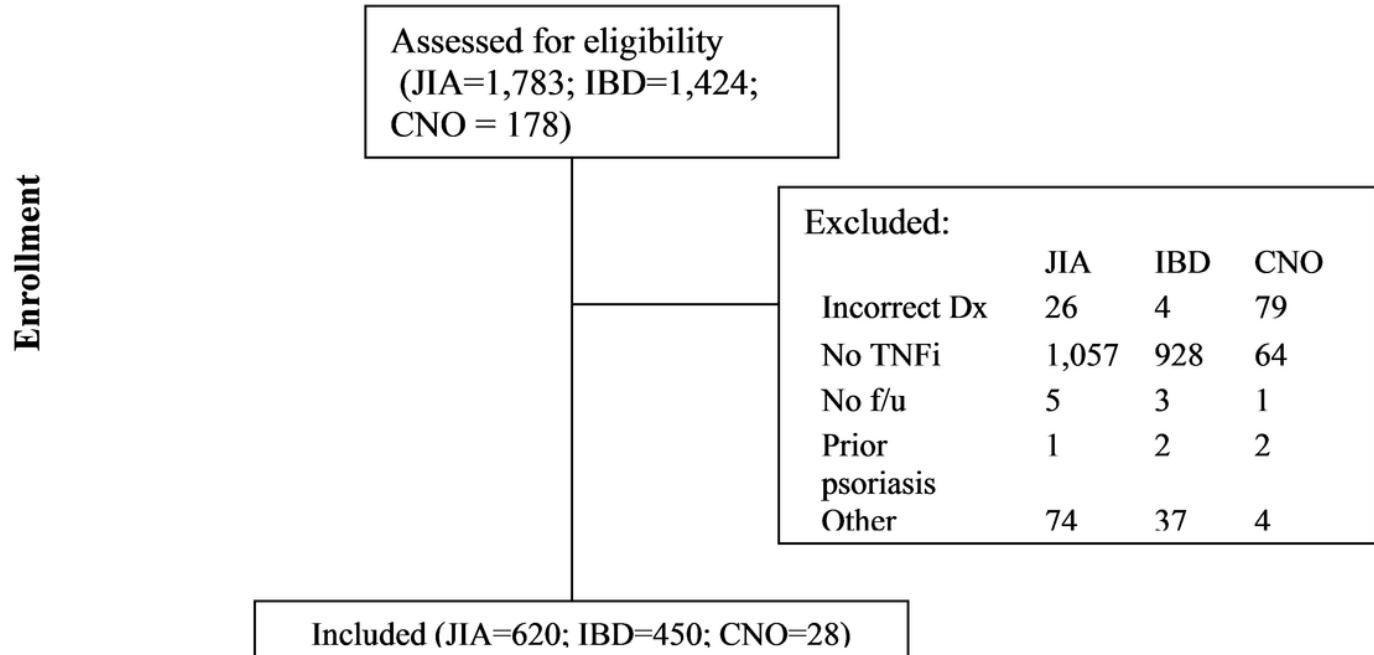
Figures

Figure 1

Patient Selection