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Tumor necrosis factor inhibitor-related autoimmune disorders in pediatric rheumatology practice: a multicenter nationwide study

Deniz Gezgin Yıldırım[1*], Batuhan Küçükali[1], Nergis Akay[2], Sultan Nilay Yoğun[3], Eray Tunce[4], Hüseyin Taştanoğlu[5], Ayşenur Doğru[6], Yunus Emre Bayrak[7], Seher Şener[8], Mehmet Orhan Erkan[9], Rüya Torun[10], Semra Ayduran[11], Nesibe Gökçe Kocamaz[12], Elif Küçük[13], Ozan Anıl Akın[14], Çisem Yıldız[1], Ece Aslan[2], Fatma Gül Demirkan[15], Belde Kasap Demir[16], Rabia Miray Kışla Ekinci[17], Selçuk Yüksel[18], Serkan Türkuçar[11], Erdal Sağ[9], Nihal Şahin[7], Elif Çelikel[3], Kübra Öztürk[13], Semanur Ozdel[12], Ayşenur Paç Kısaarslan[5], Nuray Aktay Ayaz[6], Betül Sözeri[4], Erbil Ünsal[10], Özgür Kasapçopur[2] and Sevcan A. Bakkaloğlu[1]

Abstract

Background The purpose of the study is to evaluate the demographic characteristics, clinical features, and management strategies of TNF inhibitor-related autoimmune disorders (TIRAIDs) in pediatric rheumatology practice.

Methods The medical records of 71 pediatric patients treated with a TNF inhibitor for a rheumatologic disease and who exhibited any TIRAIDs during a 10-year period were retrospectively evaluated.

Results The prevalence of TIRAIDs was 2.8% among 2450 pediatric patients who needed to use any TNF inhibitor drugs due to a rheumatologic disease. There was a female predominance ($n=40$, 56%). TIRAIDs were observed in 49 patients (69%) receiving etanercept, 16 patients (23%) receiving adalimumab, and 6 patients (8%) receiving infliximab. The median time to TIRAIDs was 21.6 months. Non-infectious uveitis (38%) was the most common TIRAID, followed by paradoxical psoriasis (PP) (25%), lupus-like disease (8%), multiple sclerosis (7%), episcleritis (7%), and hidradenitis suppurativa (1%). In 58% of patients, treatment was switched to another TNF inhibitor, while in 42%, it was switched to a non–TNF biological therapy and/or cDMARDs. Complete resolution of TIRAIDs was observed in 63% of the patients. C-reactive protein levels and Juvenile Arthritis Disease Activity Score-27 were significantly higher during the development of TIRAIDs in patients with juvenile idiopathic arthritis compared to the remission period ($p<0.001$ and $p=0.041$, respectively).

*Correspondence:
Deniz Gezgin Yıldırım
gezgindeniz@gmail.com

Full list of author information is available at the end of the article

Conclusions Among TIRAIDs, non-infectious uveitis and PP were the most frequently observed manifestations, predominantly occurring during etanercept treatment. Disease activity tended to increase during the onset of TIRAIDs. Discontinuation of TNF inhibitor therapy and switching to another biological treatment may be effective in achieving clinical remission.

What is known

• TNF inhibitor-related autoimmune disorders (TIRAIDs) may develop after the prescription of TNF inhibitors.

What is knew

• TIRAIDs most frequently develop during etanercept treatment, followed by adalimumab and infliximab.
• Management of TIRAIDs involves discontinuation of TNF inhibitor therapy and switching to another biological treatment to help achieve remission.
• Raising awareness about the risk of TIRAIDs during TNF inhibitor treatments and routinely monitoring patients is essential for early detection and effective treatment of TIRAIDs.

Keywords Paradoxical reactions, Paradoxical psoriasis, TNF inhibitor-related autoimmune disorders, Treatment outcome

Introduction

Monoclonal antibodies and receptor antagonists targeting tumor necrosis factor (TNF) have been used successfully as an alternative to conventional immunosuppressive therapies over the last 25 years in many chronic inflammatory disorders, such as juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), non-infectious uveitis, psoriasis, inflammatory bowel disease (IBD), and various vasculitides [1–6]. In Türkiye, etanercept (ETC), a soluble TNF receptor fusion protein, and the monoclonal antibodies adalimumab (ADA) and infliximab (INF) are approved TNF inhibitors for the treatment of pediatric rheumatic diseases [7].

Biological agents are high-molecular-weight proteins typically administered by parenteral or subcutaneous routes. They are not metabolized like other small chemical compounds but are digested and processed, which may enhance their inherent immunologic activity [8]. Although TNF inhibitor treatments are generally well tolerated and considered safe, side effects may occur during treatment, including infections and immune-mediated adverse effects [8, 9]. Furthermore, TNF inhibitors may induce intrinsic compensatory adaptations in the innate immune system, potentially leading to either asymptomatic or symptomatic TNF inhibitor-related autoimmune disorders (TIRAIDs) [10, 11]. The pathogenesis of TIRAIDs could be summarized as: (a) disruption of cytokine balance [12, 13], (b) impaired apoptotic clearance [14, 15], (c) autoimmunity triggered by emerging infections [16], and (d) worsening demyelinating disease with several hypothesis, (i) as TNF inhibitors cannot cross the blood-brain barrier but can increase the number of autoreactive peripheral T cells that can penetrate the central nervous system leading to increased disease activity, (ii) a decrease in the expression of TNFR2, which is essential for oligodendrocyte proliferation and tissue repair, (iii) a reduction in the production of cytokines and an increase in the production of IL-12 and IFN-γ associated with the demyelinating disease, and (iiii) a latent infection due to TNF antagonists leads to a role in triggering the autoimmune demyelinating process [11, 17].

TIRAIDs can be categorized into three subgroups: (i) subclinical serologic autoimmunity without clinical manifestations, (ii) autoimmune diseases for which TNF inhibitors are not indicated, such as lupus-like disease induced by TNF inhibitors, and non-infectious neurologic inflammatory events induced by TNF inhibitors, (iii) paradoxical reactions (PRs) which involve the emergence or exacerbation of diseases similar to those treated with TNF inhibitor drugs, such as paradoxical psoriasis (PP), IBD, sarcoidosis, inflammatory myopathies and non-infectious uveitis [11] (Fig. 1). Subclinical serologic autoimmunity is defined as the development of autoantibodies in patients who were previously negative for autoantibodies, such as anti-nuclear antibody (ANA), anti-dsDNA, and/or antiphospholipid antibodies, after exposure to TNF inhibitor therapies, especially INF [18–21]. Also, some patients treated with TNF inhibitors may develop a lupus-like syndrome and/or inflammatory myopathies [10, 22–24]. Although PP is the most commonly reported paradoxical reaction during TNF inhibitor treatment, other PRs include neutrophilic dermatosis, hidradenitis suppurativa, IBD, sarcoidosis, episcleritis, and non-infectious uveitis [11, 25].

There are limited case reports and/or case series in the current literature describing autoimmune disorders induced by TNF inhibitors in childhood rheumatic diseases [26–29]. Furthermore, the prevalence of TIRAIDs in children remains unknown. Therefore, this study aims to evaluate the demographic characteristics, clinical features, and general management approaches for TIRAIDs in a large cohort of pediatric patients with any rheumatologic disease treated with TNF inhibitors in Türkiye.

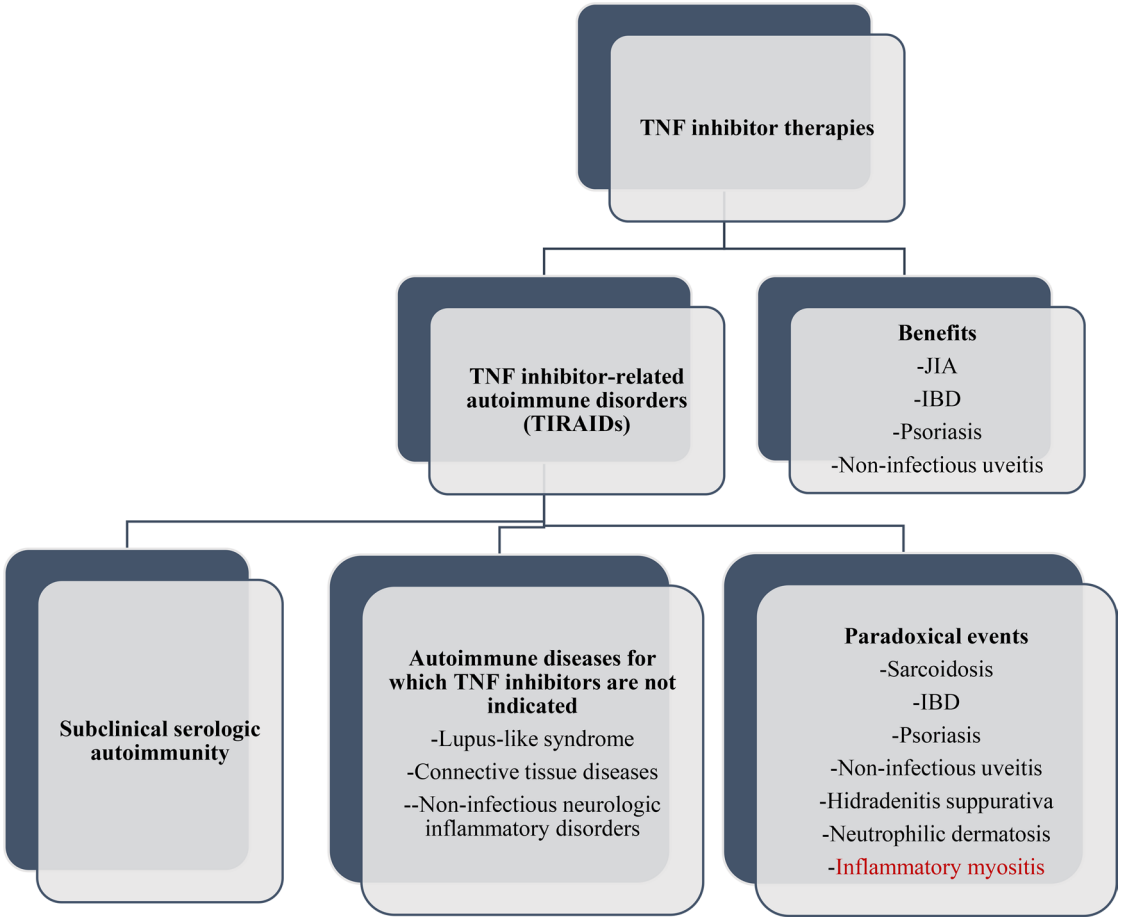

Fig. 1 The diseases that are treated and benefit from TNF inhibitor therapies, and the paradoxical pathologies that have emerged in response to TNF inhibitor therapies

Methods

This is a retrospective, multicenter study.

Study population

The medical records of pediatric patients under 18 years old who were treated with a TNF inhibitor for a rheumatologic disease and exhibited any TIRAIDs between January 2015 and January 2025 were retrospectively reviewed from 18 pediatric rheumatology centers in Türkiye. TIRAIDs due to ETC, ADA, and/or INF were assessed, as these agents are available in our country.

Patient recruitment

The inclusion criteria of the patients were being ≤18 years old, diagnosed with any rheumatologic disease, experiencing at least one of the TIRAIDs, and having at least 6 months of follow-up after the emergence of TIRAIDs. The exclusion criteria for patients were being ≥19 years and having less than 6 months of follow-up time after the emergence of TIRAIDs. Among TIRAIDs, patients with clinical autoimmune diseases and/or PRs induced by TNF inhibitors were included, whereas those with subclinical serologic autoimmunity induced by TNF inhibitors were excluded.

Medical records

Age at study entry, at diagnosis, and at emergence of TIRAIDs, gender, diagnosis, follow-up time, ANA, anti-citrullinated protein antibody (ACPA), rheumatoid factor (RF), and HLA-B27 positivity, Mediterranean fever (MEFV) gene mutation, hemoglobin (Hb) level, white blood cell (WBC), and platelet (PLT) counts, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels, time of onset of TIRAIDs after the rheumatologic disease diagnosis, management of TIRAIDs, time to resolution of TIRAIDs, and type of PP were noted.

The indications for TNF inhibitor therapy were JIA, JDM, non-infectious uveitis, Behçet's disease (BD), familial Mediterranean fever (FMF)-related arthritis, chronic non-bacterial osteitis (CNO), and/or Adenosine deaminase 2 (ADA2) deficiency. The diagnosis of JIA was made based on the criteria of the International League of Associations for Rheumatology (ILAR) [31], the Bohan and Peter criteria for JDM [32], the BD PEDBD criteria [33],

and the Yalçınkaya criteria for FMF [34]. The diagnosis of non-infectious uveitis and CNO was based on the exclusion of all infectious etiologies. The diagnosis of ADA2 deficiency was established by the presence of a homozygous or compound heterozygous mutation in the ADA2 gene in patients with polyarteritis nodosa-like vasculitis. The diagnosis of lupus-like disease was accepted based on fulfillment of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria under anti-TNF treatment [35].

Table 1 The demographics of the patients who experienced any TIRAIDs

Variable	*n* (%)	mean (SD) / median (min-max)
Total	71 (100)	
Male	31 (44)	
Female	40 (56)	
Age, years		15 (4–23)
Age at diagnosis of rheumatologic disease, years		7.9 (4.5)
Time of follow-up, months		82.5 (49.6)
Presence of a family history of rheumatic disease	12 (17)	
Diagnosis		
JIA	55 (77)	
JIA + FMF	8 (11)	
JIA+Behçet's disease	1 (1)	
Non-infectious uveitis	3 (4)	
JDM	2 (3)	
CNO	1 (1)	
ADA2 deficiency	1 (1)	
JIA subtype	64 (100)	
Oligoarticular	31 (48)	
ERA	17 (27)	
RF negative poliarticular	14 (22)	
RF positive poliarticular	1 (2)	
Undifferentiated JIA	1 (2)	
JADAS27 at the diagnosis of patients with JIA		6.5 (8.1)
JADAS27 at starting anti-TNF agent		5.5 (7.2)
Laboratory features of patients with JIA		
ANA positivity	34 (53)	
RF positivity	1 (1.5)	
HLAB27 positivity	14 (22)	
ACPA positivity	2 (3)	
Laboratory features of patients with JDM		
ANA positivity	1 (50)	
MEFV gene analysis of FMF patients	8 (100)	
M694V homozygous	2 (25)	
M694V/M680I	4 (50)	
M694V heterozygous	2 (25)	

TIRAIDs; TNF inhibitor-related autoimmune disorders, JIA; juvenile idiopathic arthritis, FMF; familial Mediterranean fever, BD; Behçet's disease, JDM; juvenile dermatomyositis, CNO; chronic nonbacterial osteitis, ADA2; Adenosine deaminase 2, ERA; enthesitis-related arthritis, ANA; anti-nuclear antibody, RF; rheumatoid factor, ACPA; anti-citrullinated protein antibody, MEFV; Mediterranean fever

If the patient was diagnosed with JIA, Juvenile Arthritis Disease Activity Score 27 (JADAS27) was recorded during both the development and the resolution of the TIARIDs. The JADAS27 is an assessment scale ranging from 0 to 57 for evaluating disease severity in patients with JIA, including physician global assessment, parent/patient global assessment, active joint count of 27 joints, and range of acute-phase reactants. It evaluates the following joints: hips, knees, ankles, cervical spine, elbows, wrists, the first to third metacarpophalangeal joints, and the proximal interphalangeal joints [30].

Among TIRAIDs, lupus-like syndrome, sarcoidosis, and inflammatory myopathy were diagnosed by a pediatric rheumatologist; non-infectious neurologic inflammatory events by a pediatric neurologist; non-infectious uveitis and episcleritis by an ophthalmologist; psoriasis, neutrophilic dermatosis, and hidradenitis suppurativa by a dermatologist; and IBD by a pediatric gastroenterologist.

The treatment strategies and, where applicable, the resolution time of TIRAIDs were noted.

Statistical analysis

The data were analyzed using SPSS version 23.0 software program (Chicago, IL, USA). Numbers and percentages were given for the continuous variables. The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Variables were given as mean ± standard deviation or median (interquartile range) according to the distribution of the data. The differences between the two independent groups were compared using an independent-samples t-test for normally distributed variables and a Mann–Whitney U test for non-normally distributed variables. The Pearson chi-square test and Fisher's exact test were applied to compare categorical variables. The time to development and resolution of TIRAIDs was evaluated using Kaplan-Meier analyses. A p-value of <0.05 was considered statistically significant.

Ethics

The present study was approved by the ethics committee of Gazi University (2025, approval number: 806) in accordance with the Declaration of Helsinki.

Results

Demographic data of patients with TIRAIDs

Among 2450 pediatric patients who needed to use any TNF inhibitor drugs due to a rheumatologic disease, 71 (2.8%) exhibited TIRAIDs during 10 years of follow-up. The demographics of the patients who experienced any TIRAIDs were presented in Table 1. 40 (56%) patients were female. The mean age at diagnosis of rheumatologic disease was 7.9 (4.5) years, while the mean age at

diagnosis of TIRAIDs was 9 (5) years. JIA was the most common diagnosis (90%). The most common subtypes of patients with JIA were oligoarticular (48%), enthesitis-related arthritis (ERA) (27%), and RF-negative polyarticular (22%), respectively. Among JIA patients, half of the patients were ANA-positive, 1 in 5 were HLA-B27-positive, and 2 (3%) were ACPA-positive. The mean JADAS27 at the diagnosis of JIA was 6.5 (8.1), while the mean JADAS27 at starting anti-TNF agent was 5.5 (7.2). Among FMF patients, 2 (25%) had the M694V homozygous mutation, 4 (50%) had the M694V/M680I compound heterozygous mutation, and 2 (25%) had the M694V heterozygous mutation.

The features of TIRAIDs

The features of TIRAIDs are shown in Table 2. 49 (69%) of the patients had experienced a TIRAID during ETC treatment, 16 (23%) ADA, and 6 (8%) INF. The mean time of onset of TIRAIDs after the diagnosis of rheumatic disease was 49.7 (42.2) months, while after TNF inhibitor therapy, it was 21.6 (23.7) months. There is no significant difference in TIRAID development time after rheumatic disease diagnosis or after starting anti-TNF therapy, by anti-TNF therapy type ($p = 0.340$ and $p = 0.603$, respectively). At the time of TIRAID development, in addition to anti-TNF therapy, 30 of these patients were taking MTX as a conventional disease-modified anti-rheumatic drug (cDMARD), and three were taking SSZ.

Table 2 Features of TIRAIDs

Variable	Total, *n* = 71 (%)	TIRAIDs under Etanercept, *n* = 49 (%)	TIRAIDs under Adalimumab, *n* = 16 (%)	TIRAIDs under Infliximab, *n* = 6 (%)	*p* value
Anti-TNF agent caused the development of TIRAIDs	71 (100)	49 (69)	16 (23)	6 (8)	
Development time of TIRAIDs after the diagnosis of rheumatic disease, months, mean (SD)	49.7 (42.2)	47 (43.1)	53.6 (41.2)	66 (42.6)	0.340
Development time of TIRAIDs after anti-TNF starting, months, mean (SD)	21.6 (23.7)	22.6 (27)	16.6 (10.8)	26.8 (20.8)	0.603
Concomitantly used other treatments with anti-TNF agents when TIRAIDs develop					
NSAIDs	8 (11)	8 (16)	-	-	
Systemic corticosteroid	7 (10)	3 (6)	4 (25)	-	
Methotrexate	30 (42)	19 (39)	9 (56)	2 (33)	
Sulfasalazin	3 (4)	2 (4)	-	1 (17)	
Leflunomide	5 (7)	5 (10)	-	-	
MMF	3 (4)	-	1 (6)	2 (33)	
Colchicine	9 (13)	6 (12)	2 (12.5)	1 (17)	
Under which anti-TNF treatment did TIRAIDs develop?					
Non-infectious uveitis	27 (100)	27 (100)	-		
Psoriasis	18 (100)	8 (44)	7 (39)	3 (17)	
IBD	9 (100)	8 (89)	1 (11)	-	
Lupus-like disease	6 (100)	1 (17)	2 (33)	3 (50)	
MS	5 (100)	2 (40)	3 (60)	-	
Episcleritis	5 (100)	3 (60)	2 (40)	-	
Hidradenitis suppurativa	1 (100)	-	1 (100)	-	
Family history of psoriasis	-	-	-	-	
Type of psoriasis as TIRAIDs	18 (100)				
Plaque psoriasis	9 (50)	2 (11)	5 (28)	2 (11)	
Pustular psoriasis	7 (40)	5 (28)	1 (5.5)	1 (5.5)	
Guttate psoriasis	1 (5)	-	1 (5.5)	-	
Diffuse psoriasis	1 (5)	1 (5.5)	-	-	
Localisation of psoriasis	18 (100)				
Knee and/or elbow extensor surfaces	9 (50)	3 (17)	4 (22)	2 (11)	
Palm /Sole	7 (40)	5 (28)	1 (5.5)	1 (5.5)	
Trunk	4 (22)	3 (17)	1 (5.5)	-	
Face	4 (22)	2 (11)	2 (11)	-	
Scalp	2 (11)	1 (5.5)	1 (5.5)	-	
Diffuse	1 (5)	-	1 (5.5)	-	

TIRAIDs; TNF inhibitor-related autoimmune disorders, PP; paradoxical psoriasis, IBD; inflammatory bowel disease, MS; multiple sclerosis

Non-infectious uveitis (38%) was the most common TIRAID, followed by PP (25%), lupus-like disease (8%), multiple sclerosis (MS) (7%), episcleritis (7%), and hidradenitis suppurativa (1%). In all patients with non-infectious uveitis, a paradoxical reaction occurred under ETC treatment. Of the five patients who developed episcleritis, three were receiving ETC, and two were receiving ADA. PP occurred in 8 patients under ETC, 7 under ADA, and 3 under INF. None of these patients had a family history related to psoriasis. At the time of TIRAID development, in addition to anti-TNF therapy, five of these patients were taking MTX as a cDMARD, and one was taking SSZ. The most common subtypes of psoriasis were plaque psoriasis (9 patients) and pustular psoriasis (7 patients). Psoriasis localization was on the extensor surfaces of the joints in 9 patients and on the palms and soles in 7 patients.

Treatment approaches for TIRAIDs

Treatment strategies for TIRAIDs are given in Table 3. Accused respective TNF inhibitor treatments had been discontinued and had not been restarted. The 58% of patients switched to another TNF inhibitor, while 42% switched to biological treatments other than TNF inhibitors and/or cDMARDs. The 63% of patients achieved complete resolution of TIRAIDs, with a mean resolution time of 6.3 (5.5) months. Among anti-TNF treatments, patients with TIRAIDs due to INF therapy had the longest resolution time compared to others ($p = 0.034$).

6 patients developed lupus-like disease during TNF inhibitor treatment. These patients had ANA and anti-dsDNA positivity, with clinical findings consistent with SLE, especially arthritis and cutaneous involvement. All patients were treated with systemic corticosteroids; only one patient received additional MTX and RTX.

Table 3 Treatment features of TIRAIDs

Variable	Total, $n = 71$ (%)	TIRAIDs under Etanercept, $n = 49$ (%)	TIRAIDs under Adalimumab, $n = 16$ (%)	TIRAIDs under Infliximab, $n = 6$ (%)	p value
Have TIRAIDs declined?					
Complete resolution	45 (63)	31 (63)	10 (62)	4 (67)	
TIRAIDs resolution time, months, mean (SD)	6.3 (5.5)	5.7 (4.9)	4.3 (3.4)	12.6 (7.4)	0.034
Incomplete resolution	9 (13)	4 (8)	3 (19)	2 (33)	
Progression	7 (10)	7 (14)	-	-	
Unknown	10 (14)	7 (14)	3 (19)	-	
Management of TIRAIDs					
Biologic agent stopped	71 (100)	49 (100)	16 (100)	6 (100)	
Same biologic agent continued	-	-	-	-	
Switched to another anti-TNF	41 (58)	38 (78)	-	3 (50)	
Switched to a biologic treatment other than anti-TNF	13 (18)	3 (6)	7 (44)	3 (50)	
Treatments used for TIRAIDs					
Topical corticosteroid	29 (41)	23 (47)	5 (31)	1 (17)	
Systemic corticosteroid	26 (37)	15 (31)	7 (44)	4 (67)	
Mesalazine	9 (13)	8 (16)	1 (6)	-	
Methotrexate	16 (23)	14 (29)	1 (6)	1 (17)	
Sulfasalazin	7 (10)	6 (12)	-	1 (17)	
Leflunomide	3 (4)	3 (6)	-	-	
Another biologic therapy for the treatment of TIRAIDs	54 (76)				
Adalimumab	40 (56)	37 (75)	-	3 (50)	
Secukinumab	2 (3)	-	1 (6)	1 (17)	
Tofacitinib	2 (3)	1 (2)	1 (6)	-	
IFN beta	2 (3)	-	2 (12)	-	
Natalisumab	2 (3)	-	2 (12)	-	
Tocilisumab	2 (3)	1 (2)	1 (6)	-	
Infliximab	1 (1)	1 (2)	-	-	
Abatacept	1 (1)	1 (2)	-	-	
Rituximab	1 (1)	-	-	1 (17)	
Upadacitinib	1 (1)	-	-	1 (17)	

TIRAIDs; TNF inhibitor-related autoimmune disorders, IFN; interferon

Table 4 Comparison of laboratory and JADAS27 between development and resolution time of TIRAIDs

Variable	Emergence phase of TIRAIDs	Resolution phase of TIRAIDs	
	mean (SD)	mean (SD)	*p* value
Laboratory findings			
WBC/Ul	8712 (2877)	7814 (3221)	0.929
Hb g/dL	13.6 (10)	14.8 (12)	0.425
Plt/uL	339,000 (251000)	326,000 (305000)	0.224
ESR mm/h	18 (14)	16 (14)	0.164
CRP mg/dL	15.4 (32.9)	2.8 (3.3)	< **0.001**
Disease activity			
JADAS27	4.5 (6.8)	2.1 (2.6)	**0.041**

TIRAIDs; TNF inhibitor-related autoimmune disorders, WBC; white blood cell, Hb; hemoglobin, Plt; platelet, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, JADAS27; Juvenile Arthritis Disease Activity Score 27

Laboratory findings and disease activity of patients with TIRAIDs during the emergence and remission phases

The comparison of laboratory tests at the onset and during remission of TIRAIDs is exhibited in Table 4. Only the CRP level was significantly higher during TIRAID development than during remission ($p < 0.001$). JADAS27 of patients with JIA, which consisted of 90% of our cohort, was also higher during the development of TIRAIDs compared to the remission period ($p = 0.041$). Kaplan Meier analyses of the development and remission time of TIRAIDs were presented in Fig. 2.

Discussion

In this study, we present the first evaluation of TNF inhibitor-related autoimmune disorders, excluding subclinical autoimmune seropositivity, in a large cohort of pediatric patients who were treated with TNF inhibitor drugs due to various rheumatologic diseases over a ten-year period. We have shown that TIRAIDs emerged more commonly during ETC treatment, followed by ADA and INF. Non-infectious uveitis and PP were the most common events among TIRAIDs. Higher CRP value and severe disease activity were observed during the emergence of TIRAIDs compared to the remission phase. Discontinuing the TNF inhibitor and switching to another biological treatment, especially ADA, led to remission in most patients.

In previous studies focusing on adult rheumatoid arthritis patients, the prevalence of paradoxical reactions associated with TNF inhibitor treatments has been reported as 1.6% and 3.2% [35, 36]. In our study, the prevalence of TIRAIDs was found as 2.8%, and the vast majority was seen in JIA patients. TIRAIDs were more commonly seen in females (56%), compatible with the literature [36–38]. Oligoarticular and polyarticular JIA, which account for the majority of our JIA patients and are more common in girls [39], may explain why anti-TNF-associated autoimmune reactions were observed more frequently in women in our cohort. Yagiz et al. reported a mean time to onset of PRs after exposure to biologic agents of 21 months [36]. In line with this, it was 21.6 months in our study.

There is inconsistent data regarding which TNF inhibitor therapy is more likely to trigger PRs after exposure, both in children and adults. Generally, IBD, non-infectious uveitis, sarcoidosis, and MS develop more frequently after ETC, while lupus-like disease develops more frequently after INF [40]. In our pediatric cohort, TIRAIDs were most commonly seen during ETC (69%) treatment, followed by ADA (23%) and INF (8%). All patients with non-infectious uveitis emerged with ETC; PP, IBD, MS, and episcleritis were again with ETC; MS with ADA; and lupus-like disease with INF. In the adult series, PP was the most common event among PRs, possibly due to its cutaneous, easily identifiable localization [36, 37]. Pontikaki et al. reported 4 JIA patients complicated with skin manifestations induced by TNF inhibitor therapies, and 2 of them had experienced palmoplantar pustulosis under ETC and ADA [26]. In our study, PP was the second most common PR after non-infectious uveitis, and 90% of our cohort had JIA. Patients with JIA complicated by non-infectious uveitis while treated with ETC, and it is difficult to determine whether this condition developed secondarily to ETC treatment as a TIRAIDs or whether it emerged due to the inadequacy of ETC treatment. In line with this, we believe that ADA treatment, not ETC, should be the first choice for preventing the development of uveitis in patients with oligoarticular JIA who are at high risk of chronic anterior uveitis, characterized by unresponsiveness to non-steroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modified anti-rheumatic drugs (DMARDs), ANA positivity, and young age. Pustular psoriasis of the palms and soles was the most common type of PP in adult patients [36], whereas plaque psoriasis was the second most common PP type in our cohort. None of the patients who developed PP met the ILAR criteria for juvenile psoriatic arthritis at the time of their initial JIA diagnosis [31], and none had a family history of psoriasis; typical psoriatic skin lesions emerged after initiation of TNF inhibitor therapy. Among anti-TNF therapies, ETC treatment is ineffective in the treatment of IBD, and sometimes IBD may occur during ETC therapy [37]. In our study, there were eight patients who experienced IBD as a PR related to ETC, and one had IBD during ADA treatment.

Bataille et al. reported an increased risk for PRs in adult patients with IBD, together with at least two additional inflammatory diseases, and a reduction of PRs with the conventional DMARDs and systemic corticosteroids [38]. Faivre et al. described hidradenitis suppurativa as a PR to TNF inhibitor therapy in a large cohort of adult patients with inflammatory diseases, with complete remission

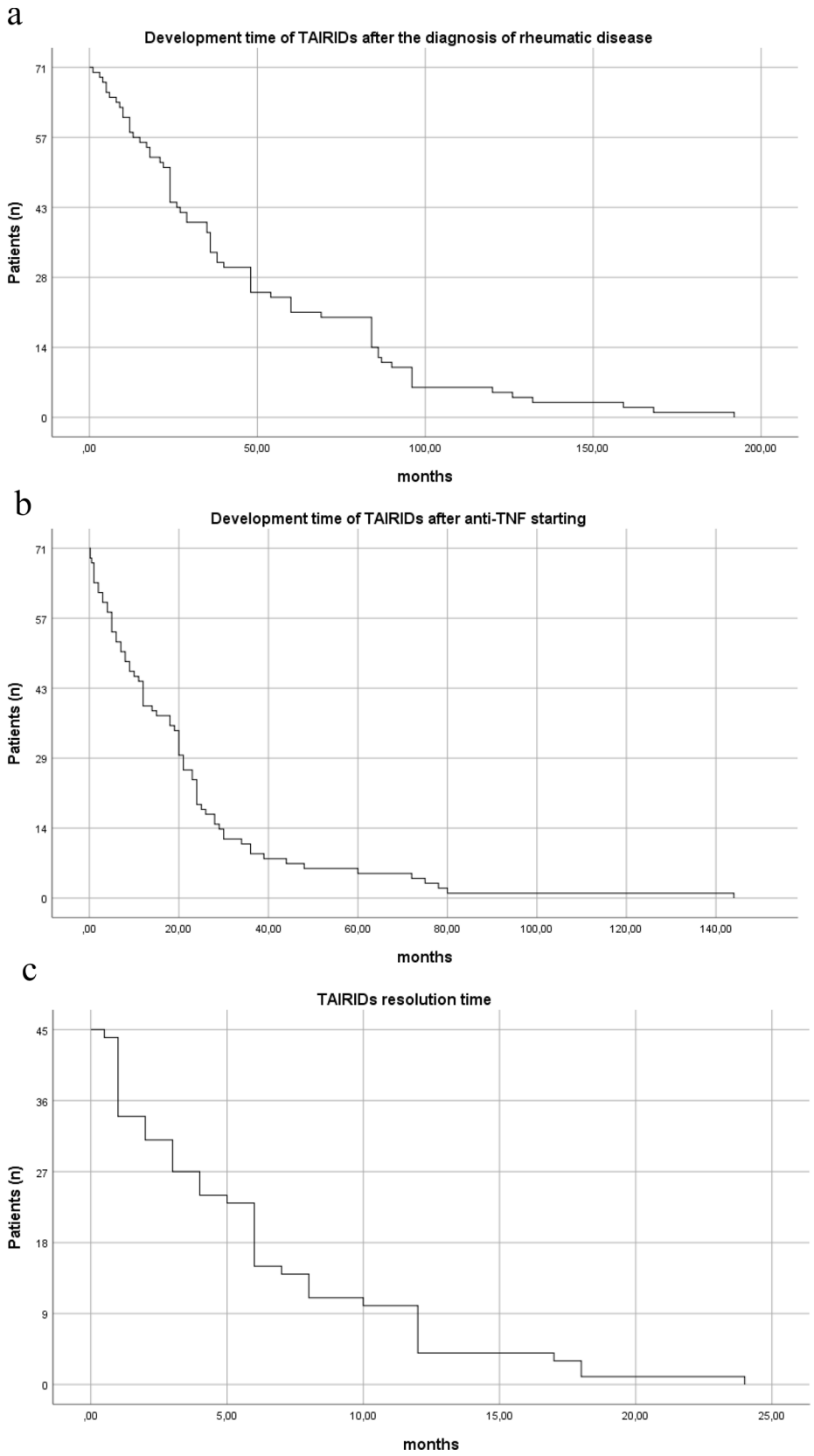

Fig. 2 **a**. Kaplan Meier analyses for the development time of TIRAIDs after the diagnosis of rheumatic diseases, **b**. Development time of TIRAIDs after a TNF therapy starting, **c**. complete resolution of the TIRAIDs resolution time

upon discontinuation of the TNF inhibitor and/or switching to another biologic therapy. They also stated that hidradenitis suppurativa recurred when restarting the first TNF inhibitor therapy [41]. In our study, only 1 pediatric patient experienced hidradenitis suppurativa as a TIRAID under ADA treatment. In another study evaluating the emergence of paradoxical psoriasis as a TIRAID after exposure to TNF inhibitor therapy in adult patients with rheumatoid arthritis or spondyloarthropathy, switching to another TNF inhibitor in 46% of patients and to other therapies in 27% showed a significant benefit in approximately half of patients [36]. One-third of our patients with PP were taking cDMARDs, such as MTX or SSZ, when the emergence of PP occurred. We discontinued TNF inhibitor treatment in all patients who experienced TIRAID. The 58% of patients switched to another TNF inhibitor, while the remaining patients were switched to a non-TNF inhibitor biological treatment. The 63% of the patients in our cohort achieved complete remission. TIRAIDs may improve very quickly with a change in the disease treatment, or improvement may take months (Fig. 2c). In our study, the slowest recovery was observed in patients who developed TIRAID following treatment with INF. Additionally, our paradoxical reaction progression rate when switching from one TNF inhibitor to another biologic was similar reported in the literature [36].

When we compared laboratory findings and JADAS27 scores at onset and resolution of TIRAIDs, patients showed higher CRP levels and JADAS27 scores during the emergence phase. Based on that, we think our JIA patients were in the higher disease activity phase during the development of TIRAIDs. After switching to another biologic treatment, the disease activity also decreased in parallel with the TIRAIDs remission period. In line with this, we speculate that the rapid recognition of TIRAIDs and prompt treatment changes are essential for the successful management of rheumatologic diseases. Therefore, raising awareness among clinicians about TIRAIDs is of importance.

The main limitation of the study is its retrospective design. Another important limitation is that data on ADA and INF antibody levels were not given because these tests could not be performed in all centers' laboratories. However, the main strengths of our study include the first report of pediatric TIRAIDs in the literature based on country-wide data, a large sample size, and a ten-year follow-up period.

In conclusion, this is the first study to evaluate TIRAIDs in a pediatric rheumatology practice over a 10-year period. TIRAIDs were most frequently developed secondary to ETC, followed by ADA and INF. Along with this, non-infectious uveitis and PP were the most frequent TIRAIDs. The inflammatory disease may be active, and the CRP may be high during the phase of TIRAIDs emergence. In the management of TIRAIDs, discontinuation of TNF inhibitor therapy and switching to another biological treatment may provide a benefit to achieve remission. Increasing awareness of the likelihood of TIRAIDs and close monitoring of patients treated with TNF inhibitors are essential for the rapid detection and treatment of TIRAIDs.

Abbreviations

ACPA	Anti-citrullinated protein antibody
ADA	Adalimumab
ADA2	Adenosine deaminase 2
ANA	Anti-nuclear antibody
BD	Behçet's disease
CNO	Chronic non-bacterial osteitis
CRP	C-reactive protein
DMARDs	Disease-modified anti-rheumatic drugs
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
ETC	Etanercept
FMF	Familial Mediterranean fever
Hb	Hemoglobin
IBD	Inflammatory bowel disease
INF	Infliximab
NSAIDs	Non-steroidal anti-inflammatory drugs
JADAS27	Juvenile Arthritis Disease Activity Score 27
JDM	Juvenile dermatomyositis
JIA	Juvenile idiopathic arthritis
MEFV	Mediterranean fever
Plt	Platelet
PRs	Paradoxical reactions
PP	Paradoxical psoriasis
RF	Rheumatoid factor
TIRAIDs	TNF inhibitor-related autoimmune disorders
TNF	Tumor necrosis factor

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Author contributions
DGY and SAB conceptualized and designed the study, conducted the data analyses, drafted the initial manuscript, and had full access to all data. BK, NA, SNY, ET, HT, AD, YEB, SŞ, MOE, RT, SA, NGK, EK, OAA, ÇY, EA, FD, BKD, RMKE, SY, ST, ES, NŞ, EÇ, KÖ, SO, APK, NAA, BS, EÜ, and ÖK were responsible for data collection. DGY and SAB drafted the initial manuscript. All authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability
All data from the study are available from the corresponding author.

Declarations

Ethical approval
This study was performed in line with the principles of the Declaration of Helsinki. The present study was approved by the Ethics Committee of Gazi University (2025, approval number: 806).

Consent to participate
Consent was obtained from the patients' legal guardians.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pediatric Rheumatology, Gazi University Faculty of Medicine, Ankara 21000, Türkiye
[2]Department of Pediatric Rheumatology, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[3]Department of Pediatric Rheumatology, Ankara Bilkent City Hospital, University of Health Sciences, Ankara, Türkiye
[4]Department of Pediatric Rheumatology, Ümraniye Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye
[5]Department of Pediatric Rheumatology, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[6]Department of Pediatric Rheumatology, İstanbul University Faculty of Medicine, İstanbul, Türkiye
[7]Department of Pediatric Rheumatology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye
[8]Department of Pediatric Rheumatology, Adana City Hospital, Adana, Türkiye
[9]Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[10]Department of Pediatric Rheumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[11]Department of Pediatric Rheumatology, Pamukkale University Faculty of Medicine, Denizli, Türkiye
[12]Department of Pediatric Rheumatology, Ankara Etlik City Hospital, University of Health Sciences, Ankara, Türkiye
[13]Department of Pediatric Rheumatology, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye
[14]Department of Pediatric Rheumatology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[15]Department of Pediatric Rheumatology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
[16]Department of Pediatric Rheumatology, İzmir City Hospital, İzmir, Türkiye
[17]Department of Pediatric Rheumatology, Çukurova University Faculty of Medicine, Adana, Türkiye
[18]Department of Pediatric Rheumatology, Onsekiz Mart University Faculty of Medicine, Çanakkale, Türkiye

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