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SHORT COMMUNICATION

Serious Adverse Events Associated with Anti-Tumor Necrosis Factor Alpha Agents in Pediatric-Onset Inflammatory Bowel Disease and Juvenile Idiopathic Arthritis in A Real-Life Setting

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Abstract

Objectives Anti-tumor necrosis factor alpha (anti-TNF-α) agents are generally well tolerated, yet they can be associated with serious adverse events (SAEs) in a minority of patients. We examined the incidence of SAEs in a pediatric referral center for chronic rheumatologic and gastroenterological inflammatory disorders.

Methods Retrospective analysis of SAEs occurring during treatment with anti-TNF-α agents in patients with juvenile idiopathic arthritis (JIA) ($n = 78$) or pediatric-onset inflammatory bowel disease (IBD) ($n = 105$) seen at the Institute for Maternal and Child Health IRCCS "Burlo Garofolo" in Trieste, Italy, between June 2001 and February 2016. Only SAEs grade 3–5 according to the Common Terminology Criteria for Adverse Events version 4.03 and/or requiring definitive therapy discontinuation were reported.

Results Total anti-TNF-α exposure was 390.5 patient-years (PYs). The overall incidence rate of SAEs for etanercept was 4.14/100 PYs. Four patients developed uveitis, two had anxiety disorders, one had a serious zoster infection, and one developed TNF-α antagonist–induced lupus-like syndrome (TAILS). The overall incidence rate of SAEs for infliximab was 22.49/100 PYs. The most common SAEs were anaphylactoid reactions ($n = 18$), followed by infectious events ($n = 9$) and TAILS ($n = 3$). The overall incidence rate of SAEs for adalimumab was 4.71/100 PYs (two infectious SAEs). No malignancies or deaths were observed. A greater incidence rate of infectious SAEs was observed in IBD patients receiving infliximab compared to JIA patients receiving etanercept (8.11 vs 0.52 per 100 PYs).

Conclusions Anti-TNF-α therapy was generally well tolerated. SAEs leading to anti-TNF-α discontinuation were rare and non-fatal. Infliximab was associated with the highest incidence of SAEs. Infectious SAEs were more frequently observed in IBD patients treated with infliximab than in JIA patients receiving etanercept.

Key Points

Serious adverse events (SAEs) associated with anti-tumor necrosis factor alpha (anti-TNF-α) therapy in children with chronic inflammatory disorders were rare and non-fatal; most SAEs regressed after drug withdrawal.

Infliximab was associated with the highest incidence of SAEs, mostly anaphylactoid reactions.

Infectious SAEs were more frequent in patients with inflammatory bowel disease treated with infliximab than in patients with juvenile idiopathic arthritis receiving etanercept.

1 Introduction

Juvenile idiopathic arthritis (JIA) and pediatric-onset inflammatory bowel disease (IBD) are chronic disorders that pose a significant toll in terms of morbidity and quality

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of life in affected children [1, 2]. While a definitive cure is not yet available, achieving disease remission can lead to normal quality of life and prevent complications [3, 4]. The advent of biologic anti-tumor necrosis factor alpha (anti-TNF-α) drugs in the late 90s has led to a revolution in the therapeutic approach to these conditions, especially in patients refractory to other medications. The most commonly used anti-TNF-α agents in pediatric patients are etanercept, a fusion protein combining TNF-α receptor with the constant end of an IgG1 antibody; infliximab, a chimeric monoclonal antibody; and adalimumab, a fully human monoclonal antibody. Etanercept is approved for JIA, but has no therapeutic indication for IBD; adalimumab is approved for both JIA and IBD; infliximab is approved for IBD, but has been used off-label in JIA patients before etanercept and adalimumab approval. In 2016, a new anti-TNF-α, golimumab, was approved for polyarticular JIA. While these drugs have been shown to be generally cost-effective, concerns still exist on their safety, since their use has been associated with serious infectious [5], neoplastic [6], and immunologic disorders [7]. We examined the incidence of serious adverse events (SAEs) in a single pediatric referral center for chronic rheumatologic and gastroenterological inflammatory disorders.

2 Methods

We retrospectively reviewed all patients with a diagnosis of JIA or IBD before 18 years of age seen at the Institute for Maternal and Child Health IRCCS "Burlo Garofolo" in Trieste, Italy, between June 2001 and February 2016. We included patients < 18 years of age, as well as young adults (age 18–30 years) with pediatric-onset diseases who were continuing to be treated at the center. Institutional review board approval is not required for retrospective studies at our institution. Only patients treated with anti-TNF-α agents (etanercept, infliximab, adalimumab) were selected. The following data were collected: gender, age at disease onset, age at anti-TNF-α start, concurrent medications (immunosuppressants and corticosteroids), number and type of SAEs, which were defined as adverse events requiring definitive therapy discontinuation and/or adverse events classified as severe, life threatening, or fatal (grade 3–5) according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [8]. All patients underwent infectious disease screening prior to starting anti-TNF-α therapy. 'Drug exposure' refers to time between the first drug administration and the moment of discontinuation or the last available follow-up visit. Continuous data are expressed as medians and interquartile ranges (IQR), and categorical data are expressed as absolute frequencies and percentages. Incidence rates are reported as events per 100 patient-years (PYs) and 95% confidence intervals (CIs). CIs are calculated with the mid-p exact test. Comparisons of incidence rates were performed by means of Fisher's exact test. The statistical test was two-sided, and a p value of less than 0.05 was considered as statistically significant. The Bonferroni correction was applied for multiple comparisons, multiplying the uncorrected p values by the number of comparisons made. Relative risk (RR) was calculated as the conditional maximum likelihood estimate of the rate ratio with the mid-p exact test.

3 Results

We identified 183 patients (78 with JIA and 105 with IBD) who were exposed to anti-TNF-α drugs; their characteristics and exposure to anti-TNF-α drugs are summarized in Table 1. Nine patients with JIA and 13 patients with pediatric-onset IBD were aged 18–30 at treatment start. During follow-up, 34 patients (18.6%) experienced at least one SAE. Numbers and incidence rates of SAEs are summarized in Table 2. No cases of tuberculosis, malignancies, or deaths were observed for any of the anti-TNF-α drugs.

3.1 Serious Adverse Events (SAEs) Related to Etanercept Therapy

Etanercept was used only in patients with JIA. A total of eight SAEs were recorded, for an overall incidence rate of 4.14/100 PYs (95% CI 1.97–7.85) (Table 2). Four patients developed uveitis; all of them were female, with early-onset (< 3 years of age), extended oligoarticular JIA with positive anti-nuclear antibody (ANA). Median treatment duration before uveitis onset was 14 months, with two patients experiencing uveitis in the first 3 months of treatment. Only one patient had a history of previous uveitis. Two patients continued to have relapsing uveitis after etanercept discontinuation. Two patients developed an anxiety disorder with panic attacks, after 8 and 12 months of drug exposure, respectively, which resolved after drug discontinuation. One patient had a serious herpes zoster infection. TNF-α antagonist–induced lupus-like syndrome (TAILS) developed in a 12-year-old boy with rheumatoid factor (RF)-negative polyarticular JIA, as reported elsewhere [9].

3.2 SAEs Related to Infliximab Therapy

Infliximab was used both in JIA and in IBD patients. A total of 30 SAEs were recorded in patients receiving infliximab, for an overall incidence rate of 22.49/100 PYs (Table 2). The most common SAEs were anaphylactoid

Table 1 Characteristics of the patients included in the study and exposure to anti-TNF-α drugs

	Total ($N = 183$)	JIA ($N = 78$)	IBD ($N = 105$)
Gender, *N* (%)			
Male	72 (39.3)	21 (26.9)	51 (48.6)
Female	111 (60.7)	57 (73.1)	54 (51.4)
Age (years) at disease onset, median (IQR)	9.90 (5.01–12.85)	5.11 (2.03–8.98)	11.18 (9.37–13.67)
Age (years) at first anti-TNF-α, median (IQR)	12.94 (9.58–15.91)	10.59 (5.68–14.56)	13.47 (11.47–16.53)
Disease duration before anti-TNF-α start (years), median (IQR)	1.84 (0.66–4.50)	3.09 (1.34–6.30)	1.17 (0.54–3.11)
Disease categories, *n* (%)			
Crohn's disease			71 (67.6)
Ulcerative colitis			34 (32.4)
Polyarticular JIA		34 (43.6)	
RF-positive		4 (5.1)	
RF-negative		30 (38.5)	
Oligoarticular JIA		35 (44.9)	
Persistent		22 (28.2)	
Extended		13 (16.7)	
Systemic JIA		8 (10.2)	
Psoriatic JIA		1 (1.3)	
ANA-positive		37 (47.4)	
ANA-negative		41 (52.6)	
Anti-TNF-α therapy, no. patients (%)			
Infliximab	121 (66.1)	18 (23.1)	103 (98.1)
Etanercept	64 (35)	64 (82.1)	–
Adalimumab	48 (26.2)	28 (35.9)	20 (19)
Drug exposure, PYs			
Infliximab	133.42	22.46	110.96
Etanercept	193.42	193.42	–
Adalimumab	63.67	45.75	17.92
Total	390.51	261.63	128.88
Anti-TNF-α drugs per patient, *n* (%)			
One anti-TNF-α	138 (75.4)	51 (65.4)	87 (82.9)
Two anti-TNF-α	40 (21.9)	22 (28.2)	18 (17.1)
Three anti-TNF-α	5 (2.7)	5 (6.4)	–

ANA anti-nuclear antibody, *IBD* inflammatory bowel disease, *IQR* interquartile range, *JIA* juvenile idiopathic arthritis, *PYs* patient-years, *RF* rheumatoid factor, *TNF* tumor necrosis factor

reactions to drug infusion. Median drug exposure before anaphylactoid reaction occurrence was 1.5 months (IQR 0.5–13), with eight reactions occurring at the second infliximab infusion. Nine infectious SAEs occurred in six IBD patients treated with infliximab (one complicated pneumonia, one scrotal abscess, one cytomegalovirus infection; three patients had infectious SAEs twice: two patients had two episodes of sepsis each; one patient had two episodes of peritonsillar abscesses). In six cases, patients were on concomitant therapy with another immunosuppressive drug. Median exposure to infliximab before infection occurrence was 3.5 months (IQR 1.5–5.5).

Three patients with ulcerative colitis developed TAILS after a median drug exposure of 7 months [10]. A boy developed cutaneous leukocytoclastic vasculitis, mild arthritis, microscopic hematuria, and proteinuria, with normal complement levels and negative autoantibodies. A girl developed malar rash with transient ANA positivity. The third patient was a girl who developed fever, diffuse pyoderma, malar rash, laryngitis and pulmonary infiltrates, with markedly increased inflammatory markers, normal complement levels and no evidence of autoantibodies. The first two patients did not require specific treatment beyond drug withdrawal, which led to resolution of all symptoms except for a persisting mild proteinuria in the first patient,

Table 2 Absolute number and specific incidence rates of SAEs

	Etanercept		Infliximab		Adalimumab	
	SAEs, *N*	SAEs/100 PYs (95% CI)	SAEs, *N*	SAEs/100 PYs (95% CI)	SAEs, *N*	SAEs/100 PYs (95% CI)
Type of SAE						
Uveitis						
JIA	4	2.07 (0.66–4.99)	0	0 (0–12.49)	0	0 (0–6.34)
IBD	–	–	0	0 (0–2.66)	0	0 (0–15.39)
JIA + IBD	–	–	0	0 (0–2.22)	0	0 (0–4.60)
Psychiatric disorders						
JIA	2	1.03 (0.17–3.42)	0	0 (0–12.49)	0	0 (0–6.34)
IBD	–	–	0	0 (0–2.66)	0	0 (0–15.39)
JIA + IBD	–	–	0	0 (0–2.22)	0	0 (0–4.60)
Infections						
JIA	1	0.52 (0.03–2.55)	0	0 (0–12.49)	1	2.19 (0.11–10.78)
IBD	–	–	9	8.11 (3.96–14.88)	1	5.58 (0.28–27.52)
JIA + IBD	–	–	9	6.75 (3.29–12.38)	2	3.14 (0.53–10.38)
Immunologic disorders						
JIA	1	0.52 (0.03–2.55)	0	0 (0–12.49)	0	0 (0–6.34)
IBD	–	–	3	2.70 (0.69–7.36)	0	0 (0–15.39)
JIA + IBD	–	–	3	2.25 (0.57–6.12)	0	0 (0–4.60)
Anaphylactoid reactions						
JIA	0	0 (0–1.54)	3	13.36 (3.40–36.35)	0	0 (0–6.34)
IBD	–	–	15	13.52 (7.85–21.80)	0	0 (0–15.39)
JIA + IBD	–	–	18	13.49 (8.25–20.91)	0	0 (0–4.60)
Gastrointestinal disorders						
JIA	0	0 (0–1.54)	0	0 (0–12.49)	1	2.19 (0.11–10.78)
IBD	–	–	0	0 (0–2.66)	0	0 (0–15.39)
JIA + IBD	–	–	0	0 (0–2.22)	1	1.57 (0.08–7.75)
Total						
JIA	8	4.14 (1.92–7.85)	3	13.36 (3.40–36.35)	2	4.37 (0.73–14.44)
IBD	–	–	27	24.33 (16.36–34.91)	1	5.58 (0.28–27.52)
JIA + IBD	–	–	30	22.49 (15.45–31.69)	3	4.71 (1.20–12.82)
Median drug exposure before SAEs (months), median (IQR)	19.5 (11–24)		8.5 (1.5–15.5)		12 (7.5–15)	
SAEs occurred with concomitant immunosuppressant therapy, *n* (%)	1 (12.5)		11 (36.7)		0 (0)	
SAEs occurred with concomitant steroid therapy, *n* (%)	0 (0)		1 (3.3)		0 (0)	

CI confidence interval, *IBD* inflammatory bowel disease, *IQR* interquartile range, *JIA* juvenile idiopathic arthritis, *PYs* patient-years, *SAE* serious adverse event

while the third patient required treatment with intravenous steroids and antibiotics.

3.3 SAEs Related to Adalimumab Therapy

A total of three SAEs were recorded in JIA and IBD patients receiving adalimumab, for an overall incidence rate of 4.71/100 PYs (Table 2). Two patients experienced recurrent herpetic infections. The third patient, a 14-year-old girl with polyarticular JIA, discontinued treatment because of fatigue, myalgia, nausea and epigastric pain after adalimumab injections.

3.4 Incidence Rates Comparisons

Patients treated with infliximab had a higher incidence of SAEs compared to patients treated with etanercept (RR 5.44, 95% CI 2.57–12–64, $p < 0.01$) and adalimumab (RR

Table 3 Studies on SAEs incidence in children treated with anti-TNF-α drugs

First author	Disease	Type of study	Patients (PYs)	Drug	Total SAEs/ 100 PYs	Infectious SAEs/100 PYs	Malignancies/ 100 PYs	Deaths/ 100 PYs
Horneff [11]	JIA	PRO	322 (592)	ETA	2.03	NA	NA	NA
Gerloni [12]	JIA	RETRO	68 (140)	INF	NA	0.7	0	0
			95 (258)	ETA	NA	0.7	0.4	0
Prince [13]	JIA	PRO	146 (312)	ETA	2.9	1.28	0	0
Schmeling [14]	JIA	PRO	289 (435.7)	ADA	2.5	0.2	0	0
Tarkiainen [15]	JIA	RETRO	213 (710)	ETA	11.4	4.2	0	0.2
			214 (591)	INF	11.8	3.4	0	0
			94 (188)	ADA	10.1	2.1	0	0
Windschall [16]	JIA	PRO	1678 (2805)	ETA	3.49	0.25	0.07	0
Klotsche [17]	JIA	PRO	1414 (4461)	ETA	4.46	0.92	0.09	0.05
			320 (493)	ADA	4.67	0.41	0.27	0
Verazza [18]	JIA	RETRO	1038 (NA)	ETA	NA	13[a]	2[a]	1[a]
Baldassano [19]	IBD	PRO	2503 (4347)	INF	NA	4.88	NA	NA
Colletti [20]	IBD	PRO	2503 (4347)	INF	NA	NA	0.09[b]	NA
Vahabnezhad [21]	IBD	RETRO	188 (NA)	INF	NA	1[a]	1[a]	0[a]
Cameron [22]	IBD	RETRO	127 (NA)	INF	NA	6[a]	0[a]	0[a]
			29 (NA)	ADA	NA	2[a]	0[a]	0[a]
Hyams [23]	IBD	PRO	5766 (24543)	INF	NA	NA	0.04	NA

ADA adalimumab, *ETA* etanercept, *IBD* inflammatory bowel disease, *INF* infliximab, *JIA* juvenile idiopathic arthritis, *NA* not available, *PRO* prospective, *PYs* patient-years, *RETRO* retrospective, *SAEs* serious adverse events, *TNF-α*, tumor necrosis factor alpha

[a]Data not available as SAEs/100 PYs. Data are reported as absolute number of SAEs

[b]Data only for lymphoma

4.77, 95% CI 1.62–19.70, $p = 0.01$); no differences were observed between etanercept and adalimumab (RR 0.88, 95% CI 0.24–4.09, $p =$ not significant). IBD patients treated with infliximab experienced more infectious SAEs than JIA patients treated with etanercept (RR 15.69, 95% CI 2.58–346.80, $p < 0.001$).

4 Discussion

There are several limitations to our study, including the relatively small size of our cohort and the retrospective design; in addition, follow-up was not equally long for every anti-TNF-α drug. Nevertheless, keeping in mind these limitations, our data confirm the long-term tolerability of anti-TNF-α therapy for pediatric-onset inflammatory disorders and the very low risk of persistent SAEs. These results are in line with previous studies on safety of anti-TNF-α drugs in children (Table 3) [11–23]. In our experience, etanercept was associated with a low incidence of SAEs, comparable to that of previous reports. Notably, most SAEs associated with etanercept in our cohort were immune-mediated (uveitis, TAILS), while infectious SAEs were uncommon. Data from published studies on uveitis occurrence in JIA patients receiving etanercept are contrasting. In fact, while uveitis is a known complication of JIA, etanercept has been postulated to be associated with increased risk of ocular inflammation [24]. However, other studies suggested a role for methotrexate discontinuation rather than a direct association of etanercept [17]. In our experience, uveitis occurred only in children with pre-existing risk factors for uveitis. Etanercept was the only drug associated with neuropsychiatric SAEs, which were the second most common reason for drug discontinuation. This association has been already described in previous studies [18], yet causality seems difficult to prove. Notably, in our patients, neuropsychiatric symptoms resolved after drug discontinuation.

Similarly to data from previous reports [12, 15], infliximab was associated with the highest incidence of SAEs in our cohort. Anaphylactoid reactions were equally present in JIA and IBD patients, most commonly at infliximab second infusion, while infections and autoimmune disorders occurred only in patients with IBD, possibly due to the small number of JIA patients exposed to infliximab. Notably, a greater incidence rate of infectious SAEs in IBD patients treated with infliximab was observed as compared to JIA patients treated with etanercept (8.11 vs 0.52 per 100 PYs). While a substantial heterogeneity exists among previous studies (Table 3), this trend seems in accordance

with results from comprehensive meta-analyses on anti-TNF-α safety in children. A recent meta-analysis on etanercept safety in JIA reported a low number of infectious SAEs (1.2 per 100 PYs) [25]. On the other hand, results from a meta-analysis on the risk of severe infections in children receiving anti-TNF-α for IBD identified an overall risk of 3.52 per 100 PYs [26]. Several explanations may exist for this difference, including the different pharmacodynamic properties of etanercept [27], intrinsic risk factors associated with the disease itself (e.g., loss of gut barrier in IBD patients), as well as the greater use of concomitant immunosuppressants in IBD patients in our cohort.

Three patients with IBD, all treated with infliximab, and one patient with JIA, treated with etanercept, developed TAILS. TAILS is a rare condition with an incidence of less than 1% [28, 29]; specific criteria for the diagnosis of TAILS have not been established yet. The most accepted diagnostic criteria include a temporal relationship between clinical manifestations and anti-TNF-α therapy, and at least one serologic and one non-serologic American College of Rheumatology criteria for systemic lupus erythematous [15]. Although two of our patients lacked the serologic criteria, the clinical manifestations and the temporal relationship with anti-TNF-α therapy clearly suggested a diagnosis of TAILS, which occurred, in our experience, more frequently than in other studies, especially in IBD patients treated with infliximab.

Most SAEs resolved with treatment discontinuation; only two uveitis cases, occurring with etanercept, and one case of TAILS, occurring with infliximab, persisted. No patients died during the follow-up period and we did not observe malignancies, yet the follow-up was too short to draw any conclusion. Nevertheless, data from larger studies do not seem to support an increased risk of malignancies in children receiving anti-TNF-α agents [17, 23, 26].

5 Conclusions

Despite the small number of patients in our cohort, our data confirm that treatment with anti-TNF-α agents in patients with JIA or pediatric-onset IBD is generally well tolerated. A low incidence of SAE was observed, and even when anti-TNF-α discontinuation was necessary, SAEs were mostly not persistent and non-fatal. Infliximab seems to be the anti-TNF-α agent associated with the greatest risk of SAEs in both JIA and IBD patients. Immunologic treatment-related SAEs represent an important subgroup of SAEs in these patients. In particular, the possibility of a specific anti-TNF-α-related lupus-like syndrome, i.e., TAILS, should be kept in mind, since its clinical presentation may be protean, and it may benefit from drug discontinuation. Severe infections may occur more frequently in IBD patients receiving infliximab as compared to JIA patients receiving etanercept; nevertheless all drugs in this class are associated with an increased risk of severe infections, and therefore prompt medical evaluation is always mandatory in case of signs and symptoms suggesting an infectious complication.

Compliance with Ethical Standards

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Conflict of interest Serena Pastore, Samuele Naviglio, Arianna Canuto, Loredana Lepore, Stefano Martelossi, Alessandro Ventura and Andrea Taddio declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this is a retrospective study, formal consent is not required.

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