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Anti TNF-α Use in Pediatric Inflammatory Bowel Disease – Reports from a Romanian Center

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Abstract: Background/Objectives: Treatment armamentarium for inflammatory bowel disease (IBD) has enriched with the advent of anti-tumor necrosis factor (TNF) α molecules, especially infliximab (IFX) and adalimumab (ADA). Besides their incontestable benefits, numerous potential adverse events (AE) are reported to be associated with their use. Our aim was to asses and report the AE for optimal selection and monitoring of patients undergoing these therapies. **Methods**: A retrospective single-center study was conducted on pediatric IBD patients treated with anti-TNF α at "Grigore Alexandrescu" Emergency Hospital for Children in Bucharest, Romania, from January 2015 to October 2024. AE were classified as: non-infectious complications as acute infusion reactions, anti-drug antibodies formation, dermatological effects such as erythema nodosum (EN) and vasculitis, neurologic effects such as Guillain Barré syndrome and infections. AE were assessed according to the administered molecule and described in detail. **Results**: Of 40 patients enrolled, 22 (55%) had CD. Median (IQR) age at diagnosis was 14.8 years [10.8-15.9]. IFX was used in 34 (85%) patients while 6 (15%) patients received either ADA or IFX/ADA sequential therapy. Twenty-seven AE were documented in 19 (47.5%) patients, most prevalent being antidrug antibodies formation, infections and acute infusion reactions. All ADA- treated patients experienced at least one AE, compared to 41.2% in the IFX group, p=.0.01. **Conclusions**: AE affected over half of the patients, with anti-drug antibody formation being most prevalent. ADA treatment was associated with a higher risk of AE compared to IFX. Careful monitoring of patients receiving anti-TNF agents is crucial.

Keywords: inflammatory bowel disease; anti-TNF α; antidrug antibodies; acute-infusion reactions; adverse events

1. Introduction

Inflammatory bowel disease (IBD) primarily consists of two conditions: Crohn's disease (CD) and ulcerative colitis (UC) [1]. Their evolution is chronic and characterized by alternating periods of remission and unpredictable recurrent flares of activity [2]. The precise cause of IBD remains unknown. Nonetheless, it is thought that disruptions in the immune system and/or abnormal interactions with microorganisms contribute to the onset of chronic intestinal inflammation, particularly when specific environmental factors activate genetically predisposed individuals [3].

In the last 30 years, both incidence and prevalence of pediatric IBD have raise, especially in ages less than 5 years. Furthermore, age at diagnosis decreased significantly [4]. Childhood represents the onset time for approximately 25% of the IBD cases. Notably, prevalence increase was highest in the very early onset IBD (VEO-IBD) group, which is reported to be diagnosed in 20% of pediatric patients with IBD [5]. According to a systematic review by Ng *et al*., the prevalence of CD and UC is highest in developed territories like North America and Western Europe with increasing incidence also observed in developing countries [6]. Regarding the geographic distribution, a more recent study by Kuenzig *et al*. note that areas like Northern Europe, Canada and New Zealand have the highest incidence rates. At the opposite end are Southern Europe, Africa, Asia and South America. When compared between the main subtypes, the majority of studies report a 2-3:1 ratio, in favor of CD, especially in Quebec (Canada) and New Zealand [7].

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The therapeutical resources for inflammatory bowel disease (IBD) have enriched significantly over the past few decades. As Burger *et al*. note, treatment options were limited to medication like aminosalicylates (5-ASA), corticosteroids and other immunosuppressive drugs, like thiopurines (azathioprine and 6-mercaptopurine) and methotrexate [8]. Beginning more than 20 years ago, advances in understanding IBD pathogenesis and progress in the field of immunology have led to an expansion of treatment options [9]. This progress shifted treatment strategies towards a "treat-to-target" therapy, a concept that aims both clinical and endoscopic remission [10].

Tumor necrosis factor alfa (TNFα) plays an essential role in the pathogenesis of IBD. It is a pro-inflammatory cytokine that is found in high concentrations within the *lamina propria* of the small intestine and colon of IBD patients [11]. Its role in the IBD-related inflammatory processes, emphasize its potential as a key target for therapeutic interventions [12].

Several monoclonal antibodies have been developed to target TNFα in both its circulating and tissue-bound forms, like infliximab (IFX), adalimumab (ADA), golimumab, certolizumab pegol and etanercept [13]. For pediatric use, IFX and ADA are the only agents that have received approval from both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [11].

IFX is a chimeric monoclonal antibody, containing 25% murine-derived elements, authorized by the FDA in 2006 to treat pediatric CD [14] and then, in 2011 to treat pediatric UC [15]. Its mechanism of action involves binding to both soluble and transmembrane form of TNFα, thereby blocking its biological activity [16]. As outlined by Ruemmele *et al*., IFX typical dose is 5mg/kg, administered by intravenous infusion [17]. However, more recently, Jongsma *et al*. suggest that dose intensification may be necessary in children under 10 years of age in the induction phase due to increased clearance of the drug [18]. The standard therapeutic regimen consists of an induction phase and a maintenance one. During the induction phase, IFX is administered at week 0, 2 and 6. The maintenance phase involves usually administration every 8 weeks, although reduced interval between administrations may be necessary in order to maintain appropriate drug through levels in some patients [19].

ADA is a fully humanized recombinant monoclonal IgG1 antibody, that received FDA approval in 2012 to treat CD in children [20] and more recently, based on evidence derived from the ENVISION I phase 3 study has received the FDA approval for use in pediatric patients with UC [21]. According to European Crohn's and Colitis Organization (ECCO)/ESPGHAN consensus guidelines, ADA is administered subcutaneously with an initial dose of 2,4mg/kg, followed by 1,2 mg/kg at week 2 and 0,6mg/kg every other week for maintenance therapy [17].

As described by Ashton *et al*. therapeutic strategies for pediatric IBD are usually following expert recommendations from specific organizations in the field of pediatric gastroenterology. The usual approach is to gradually increment the treatment plan based on the evolution under previous medications. Current tendencies of stratifying the patients according to associated risks, led to an earlier introduction of biologics in the disease course, also known as "the top-down" approach [22].

Additionally, when choosing a specific medication, it is important to take into account local guidelines and availability regarding different therapies.

Regarding our center, we administered IFX for the first time in 2014 to a patient diagnosed with UC at the age of 5 years and 8 months, who began treatment with a biosimilar IFX molecule in Germany. Concerning the first administration of ADA, we used it in a 16-year-old patient diagnosed with CD, in 2015.

It is widely recognized that anti-TNF agents have dramatically improved the natural course of several autoimmune disorders, including pediatric IBD. Besides their incontestable benefits, numerous potential adverse events are reported to be associated with their use [23]. Given these considerations, it is crucial to carefully selecting [17] and monitoring the patients undergoing these therapies [24].

Data from our country is scarce despite increasing use of these molecules in children with IBD. The aim of this study is to asses and report the adverse events encountered in our practice, in order for better foreseeing, recognition and not ultimately manage these potential shortcomings.

2. Results

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A total of 40 patients were enrolled of whom 22 (55%) were diagnosed with CD. The median (IQR) age at diagnosis was 14.8 years [10.8-15.9] with 4 (10%) patients being classified as very early onset-IBD (VEO-IBD). Characteristics of the patients are described in Table 1.

Table 1. Characteristics of the population. Data are n (%).

	CD *n* = 22	**UC** *n* = 18	**p-value**
Sex [n (%)]			0.055
Male	15 (68.2%)	6 (33.3%)	
Female	7 (31.8%)	12 (66.7%)	
Age at diagnosis [n (%)]			0.110
<10 years	2 (9.1%)	6 (33.3%)	
≥10 years	20 (90.9%)	12 (66.7%)	
Age at inclusion [n (%)]			0.579
<10 years	1 (4.5%)	2 (11.1%)	
≥10 years	21 (95.5%)	16 (88.9%)	
UC extension			
E4		18 (100.0%)	
CD location [n (%)]			-
L1	4 (18.2%)	-	
L2	3 (13.6%)	-	
L3	15 (68.2%)	-	
L4a	7 (31.8%)	-	
P	2 (9.1%)		
CD behaviour [n (%)]			-
B1	12 54.5%)	-	
B2	8 (36.4%)	-	
B3	3 13.6%)	-	
P	7 (31.8%)	-	
IMM associated [n (%)]	12 (54.5%)	12 (66.7%)	0.526
AE [n (%)]			
Acute infusion reactions	2 (9.1%)	4 (22.2%)	0.381
Anti-drug antibodies	4 (18.2%)	8 (44.4%)	0.093
Infections	2 (9.1%)	3 (16.7%)	0.642
Dermatological reactions	1 (4.5%)	1 (5.6%)	1.0
Demyelinating reactions (GBS)	1 (4.5%)	0 (0.00%)	-
Medication administered [n (%)]			0.024
IFX	19 (86.4%)	18 (100%)	
ADA	6 (27.3%)	0 (0.00%)	

ADA, adalimumab; AE, adverse event; CD, Crohn's disease; IFX, infliximab; IMM, immunomodulator; UC, ulcerative colitis.

Throughout the observation period and taking into consideration the interventions for the management of AE as changing the molecule, 34 (85%) patients were treated with IFX only and 6 (15%) patients were treated either with ADA only or both IFX and ADA therapy (IFX/ADA sequential therapy) $p<0.001$. These results are the consequence of switching to IFX from ADA in two patients and from IFX to ADA in one patient, because of AE. In one patient with severe neurological complications, after the occurrence of the AE, biologics were stopped and never resumed. Time from diagnosis to biologics initiation had a median (IQR) of 6.5 months [2.0-16.5] for the entire group with 5.5 months [2.0-13.75] for CD and 7.5 months [1.25-15.75] for UC, $p = 0.989$. Younger patients tend to experience a longer delay in initiating biologic therapy compared to those diagnosed at an older age, ($p < 0.001$, $R^2 = 0.381$). Median (IQR) IFX dose was 5.0 mg/kg/administration [5.0-6.75] for CD while

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for UC were slightly higher 6.5 mg/kg/administration [5.0-10.0], with no statistical difference, *p*=0,182. As for ADA administration, standard and optimized regimes were administered in equal proportions.

Twenty-five patients (62.5%) received combination therapy, 12 (48%) patients with CD, *p*=0.747 highlighting the frequent use of this treatment strategy in our cohort, irrespective of the disease type.

Out of the 25 patients under combination therapy, 12 (48%) patients presented AE from which 8 (66.7%) patients received only IFX and 4 (33.3%) patients received either only ADA or both molecules at consecutive times, *p*=0.248.

We mention the case of a UC patient that at the time of one AE (e.g. antibodies formation) was not under biologic but at her second AE (e.g. Hipersensitivity vasculitis, HV) she was under combination therapy.

Twenty-seven AE were documented in 19 (47.5%) patients, 13 patients (68.4%) were receiving only IFX and 6 (31.6%) received either ADA alone or sequential therapy with both ADA and IFX, p=0.108.

Out of the 27 AE, 20 (74.1%) were as a consequence of IFX administration and 7 (25.9%) were in association with ADA/sequential ADA+IFX therapy, p= 0.01

The 27 AE included: 6 (22.2%) acute infusion-related events of which 5 were classified as severe; 6 (22.2%) infectious episodes were reported in 5 patients: 2 varicella-zoster virus reactivations, one patient developed recurrent *C difficile* infection in association with perianal condilomatosis with *Human papilloma virus (HPV)*, one patient developed severe measles complicated with pneumonia and respiratory failure and one case of bronchopulmonary TB was observed. Two (7.4%) dermatological reactions like EN and hypersensitivity vasculitis (HV). One (3.7%) neurological manifestation (GBS) was noted in an adolescent. Anti-drug antibodies formation was the most prevalent AE, 12 (44.4%). Detailed descriptive statistics for all AE are presented in Table 2. Notably, all 6 patients treated with ADA experienced at least one AE, compared to 14 patients (41.2%) in the IFX only group (n=34), *p*=.0.01. No deaths or malignancies were recorded at the time of completion of this study.

Table 2. Adverse events descriptive analysis. .

AE	Number, % of patients with AE (n=40)	Median duration to reaction (months), IQR
Acute infusion reactions	6 (15)	3.5 (2.4-8.25)
Anti-drug antibodies	12 (30)	13 (9-24.5)
Infections	5 (12.5)	5 (2.5-35)
Demyelinating reactions	1 (2.5)	3
Dermatological reactions	2 (5)	61.5 (3-120)

AE, adverse events; IQR, interquartile.

No statistical differences were observed between IFX and ADA therapy regarding the occurrence of specific AE. The results are summarized (Table 3).

Table 3. Differences in the occurrence of AE in IFX and ADA treated patients.

AE	IFX group (n=34) n, %	IFX and/or ADA group (n=6) n, %	p-value
Acute infusion reactions			0.574

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Present	6 (17.6%)	0 (0%)	
Absent	28 (82.4%)	6 (100%)	
Infections			0.128 (0.154)
Present	3 (8.8)	2 (33.3%)	
Absent	31 (91.2%)	4 (66.7%)	
Drug-antibodies			0.326 (0.341)
Present	9 (26.5)	3 (50%)	
Absent	25 (73.5%)	3 (50%)	
Demyelinating disorders			0.150 (0.150)
Present	0 (0)	1 (16.7)	
Absent	34 (100)	5 (83.3)	
Dermatological reactions			0.255(0.281)
Present	1 (2.9)	1 (16.7)	
Absent	33 (97.1)	5 (83.3)	

ADA, adalimumab; AE, adverse event; IFX, infliximab.

As for the ADA subgroup of patients, there were no significant differences between the standard vs. the optimized treatment strategies in terms of AE occurrence (Table 4).

Table 4. Adverse events according to ADA treatment regimens.

AE	Standard ADA Regimen (n = 3)	Optimized ADA Regimen (n = 3)	p-value
Acute infusion reactions [n (%)]			0.273
No	3 (100%)	2 (66.7%)	
Yes	0 (0%)	1 (33.3%)	
Infections [n (%)]			0.083
No	3 (100%)	1 (33.3%)	
Yes	0 (0%)	2 (66.7%)	
Demyelinating reactions [n (%)]			0.273
No	2 (66.7%)	3 (100%)	
Yes	1 (33.3%)	0 (0%)	
Anti-drug antibodies [n (%)]			0.414
No	1 (33.3%)	2 (66.7%)	
Yes	2 (66.7%)	1 (33.3%)	
Dermatological reactions [n (%)]			0.273
No	3 (100%)	2 (66.7%)	
Yes	0 (0%)	1 (33.3%)	

ADA, adalimumab; AE, adverse events.

Anti-drug antibody formation was observed in 12 patients in our study population. Of these, 8 patients (66.7%) were receiving combination therapy at the time of antibody detection, while 4 patients (33.3%) were on anti-TNF monotherapy, p=0.221.

The occurrence of anti-drug antibodies was similar between patients treated with IFX and ADA when considering combination therapy. In the IFX group, 6 out of 9 patients (66.7%) on combination therapy with IFX developed antibodies, while in the ADA group, in 2 out of 3 patients (66.7%) on combination therapy we observed the same incidence (p=1).

Although patients who developed anti-drug antibodies received higher median (IQR) IFX doses compared to those who did not (7.75 mg/kg/administration [5.75-10.0] vs. 5.0 mg/kg/administration [5.0-7.5], respectively), this difference did not reach statistical significance (p=0.09). The median (IQR) time to antibody formation did not significantly differ between patients on combination therapy and those on monotherapy. For patients on combination therapy, the median time was 13.0 months [10.25-

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23.75], while for patients on monotherapy with anti-TNF molecules it was 13.5 months [9-36.25] (p=0.932).

Infections were observed as an adverse event (AE) in 5 patients during the study period. Of these, 4 patients (80%) were receiving combination therapy, while 1 patient (20%) was on IFX monotherapy. This difference in infection rates between combination therapy and monotherapy approached, but did not reach, statistical significance (p=0.094). When analyzing infections by treatment type, both adalimumab (ADA)-treated patients (100%) who developed infections were receiving combination therapy at the time of infection. In the IFX subgroup, 2 out of 3 patients (66.7%) who developed infections were under combination therapy, while 1 (33.3%) was on monotherapy. The difference in infection rates between ADA and IFX combination therapy groups was not statistically significant (p=1). IFX dosing did not significantly impact infection rates. The median (IQR) dose of IFX was 5.0 mg/kg/administration [5.0-6.25] for the infection-positive group, compared to 5.0 mg/kg/administration [5.0-8.5] for those without any infectious events (p=0.554).

Acute infusion reactions were observed in 6 patients, all of whom were receiving infliximab (IFX). Among these patients, 2 (33.3%) were under combination therapy, while 4 (66.7%) were receiving IFX monotherapy, p=0.386. The median (IQR) IFX dose for patients who developed acute reactions was 5.0 mg/kg/administration [5.0-6.5], compared to 5.0 mg/kg/administration [5.0-9.5] for those who did not experience acute reactions, p=0.526.

Both of the patients with dermatological AE were under combination therapy, one with each molecule. The GBS occurred in an ADA-standard monotherapy patient. The small number of cases precludes further statistical analysis.

3. Discussion

The present study aims to summarize the various AE associated with the use of anti-TNF agents in children with IBD. In our study, there is a statistically significant difference in the use of IFX and ADA between CD and UC patients in our cohort which suggests that the choice of anti-TNF therapy is associated with the type of IBD diagnosis, but this is most probably due to the fact that in our country ADA is only approved for the treatment of CD patients.

These events may lead to intensification of the dose regimen, switching between molecules (whenever is possible) but also can lead to treatment cessation. The most encountered reactions reported in the literature are (but not limited to): infusion reactions, viral, bacterial or fungal infections (including reactivating of some viruses/mycobacterias) but also neurological events, auto-immune disorders, dermatological manifestations and malignancies. Fumery *et al*. report in a recent publication that 76 patients (10.7%) treated with anti-TNF either as the first or second line, experienced adverse reactions to anti TNF molecules, leading to treatment discontinuation [28]. D'Arcangelo *et al*. report the occurrence of adverse events in 67% of the patients treated with anti-TNF molecules [29]. Our observations are closer to their findings. We consider that this higher prevalence found in our study is due to inclusion of anti-drug antibodies formation in the list of AE events.

Li *et al.* reported that the World Health Organization (WHO) VigiAccess database, contained a total number of 1,403,273 AE related to the use of anti-TNF monoclonal antibodies, with ADA accounting for 840,417 of these reports [30]. As observed also in our study, ADA treatment appears to be associated with a higher rate of adverse events compared to IFX, though this may be influenced by the smaller sample size of IFX and/or ADA-treated patients.

Infusion-related reactions are among the most common AE associated with the use of anti-TNF agents. Lichtenstein *et al*. define these events as immediate-type reactions occurring during the drug infusion or shortly after their administration (1-2 hours). The results of their systematic review indicate that IFX was associated with higher rates of infusion-related events compared to other anti-TNF drugs as they occurred in 5-23% of IBD patients [31].

In a study of pediatric patients with IBD and juvenile idiopathic arthritis, Pastore *et al*. identified anaphylactoid reactions as the most frequent serious AE, typically occurring after a median drug exposure of 1.5 months. This study also confirmed the higher incidence of infusion-related

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events associated with IFX compared to other anti-TNF agents [32]. These findings are further reinforced by Li *et al*. who conducted a descriptive analysis of adverse reactions to anti-TNF agents using data from the WHO VigiAccess database [30].

Dan-Nielsen *et al*. described in a cohort of 45 IFX treated pediatric UC patients a range of infusion-related reactions: 7% of patients developed severe infusion-related reactions like anaphylactic shock, angioedema, 3% experienced moderate reactions and 22% presented minor events [33].

Kolho *et al*. observed that acute infusion reactions often occur soon after initiation of therapy but in younger children they may appear over a longer period of time, regardless of associated therapies [34].

Similar to their findings, in our population all six patients with acute infusion-related events were under IFX treatment. Association of azathioprine did not influence the development of these AE. One patient had minor infusion-related reaction that was managed by a gradual increased infusion rate while the other 5 patients experienced moderate to severe reactions like angioedema, bronchospasm in association with angioedema of the face and tachycardia, vomiting and urticaria, that imposed treatment discontinuation. For one CD patient, switching to ADA was possible. All of the patients were receiving IFX with pre-medication – antihistamines and corticosteroids.

A significant concern that can lead to premature discontinuation of biologic treatment in pediatric IBD is secondary loss of response, which may be attributed to increased immunogenicity of anti-TNF agents. Corica *et al*. report that this can result in the formation of anti-drug antibodies, which may neutralize the biologic agent or increase its clearance. The authors also note that antidrug antibodies may appear following dose escalations or in situations like specific low through levels [35].

The first citing about this specific issue was 30 ago by Elliott *et al*. in their study on rheumatoid arthritis patients. They identified antibodies specific to the murine portion of the drug in approximately half of the treated patients [36]. A systematic review by Vermeire et al. reported that the incidence of antidrug antibodies varied widely, with IFX being responsible for a range of 0-65.3% and ADA for 0.3-38% [37]. Furthermore, Thomas *et al*. conducted a meta-analysis focusing on IBD patients, reporting a cumulative incidence of anti-TNF antibodies of 15.8 % (95 % CI 9.6–24.7), with IFX being the most commonly studied agent (14 of 20 trials) [38]. In a recent paper, Winter et al. investigated potential biomarkers for predicting anti-TNF treatment efficacy in both pediatric and adult IBD patients. Their research found that among the pediatric cohort, 17% had detectable targeted anti-TNF antibodies [39].

Current literature recommends the addition of an immunomodulator to IFX therapy in order to prevent or reduce antibodies formation [38, 40]. Although data are conflicting, [41, 42, 43] in a systematic review conducted by Corica *et al*., the authors report that in pediatric IBD patients, there are no significant differences between combination therapy and monotherapy with anti-TNF agents in terms of anti-IFX antibody formation, clinical and endoscopic remission rates or treatment failure rates [35]. However, the debate is ongoing regarding the efficacy of adding immunomodulators to reduce antidrug antibody formation in CD patients treated with ADA [44].

We speculate that the main reason for the higher incidence of neutralizing anti-drug antibodies both in IFX and ADA treated patients, was the reactive measurement of specific drug antibodies, in cases of loss of response. Dose escalation and shortening time interval between administration were main attitudes to overcome the presence of the antibodies; in two cases of CD switching on IFX from ADA was the choice of the consecutive therapy.

GBS is an acute, autoimmune and demyelinating polyradiculoneuropathy. Wachira *et al*. describe the clinical picture of this disease as ascending progressive weakness, associated with diminished or absent reflexes, culminating with a state of acute flaccid paralysis [45].

While GBS has been reported in patients receiving biologic treatments for IBD, these cases are rare and have been primarily documented in adults [46, 47, 48].

To our knowledge, this is the first case that occurred in children. We report the case of a 17-years-old girl treated with ADA in a standard regimen for CD (B2). After three months of therapy, surgery was imposed because of no disease improvement. Terminal ileum resection was performed with

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termino-terminal anastomosis. On discharge, on the 3rd day after surgery, she developed dysphagia and lower limb weakness that progressed rapidly in the next 24 hours requiring mechanical ventilation. The electromyography was suggestive of acute inflammatory polyneuropathy and segmental demyelination, compatible with GBS. Five plasmapheresis courses were performed and five administrations of high-dose intravenous immunoglobulins were administered because of a slowly recovery, marked by persistent swallowing difficulties. After three weeks in the Intensive Care Unit (ICU), she was transferred in the Neurology Department where she slowly completed her recovery. ADA was never resumed (nor any other biologic agent).

It's challenging to establish a causality relation between GBS occurrence and ADA due to potential contributing factors. While GBS has been following surgical procedures, Li et al. note that such occurrences are rare [49]. In our case, we hypothesize a potential link between ADA administration and GBS development. This speculation is based on existing literature, which suggests that post-surgical GBS tends to present more frequently with axonal subtypes rather than the demyelinating subtype observed in our patient [50]. This distinction is in favor of our hypothesis of ADA-related GBS rather than a post-surgical complication.

Multiple studies document the strong correlation between anti-TNF agents' administration and increased rates of infections [32, 51]. Interestingly, Day *et al.* note that with the exception of VEO-IBD cases, IBD patients do not exhibit signs of immune deficiency. This observation suggests that the infectious burden derives primarily from the immunosuppressive drugs utilized to treat these patients, rather than the underlying disease itself [52]. Furthermore, the manufacturer of IFX and ADA have highlighted an increased risk of infections associated with these drugs, particularly when used in combination with other immunosuppressant medication. Of particular concern are TB, opportunistic infections and invasive fungal infections [53, 54]. In 2008, the FDA issued a "Black Box Warning" for anti-TNF agents, following numerous reports of severe bacterial, viral or fungal infections, including disseminated TB [55].

Dulai *et al*. conducted a systematic review evaluating the risk associated with anti-TNF agents in pediatric IBD. The results indicate an absolute rate of serious infections of 352 per 10 000 person-year follow-up, with no evidence that infection rates were higher in children receiving anti-TNF therapy compared to those on IMM alone. However, they noted that corticosteroids use was associated with higher rates of infections in children. Similar findings were observed also when compared with anti-TNF use in adults [56].

Several studies have evaluated infections rates in children with IBD treated with biologics. In the REACH study, which included patients with moderate to severe CD, the overall infection rate was 54.5% [57]. Also, Hyams *et al*. reported in the IMAgINE study that 67% of patients (N=129) experienced infectious events [58].

In a systematic review of literature, Toussi *et al*. examined infectious AE in pediatric IBD patients exposed to ADA or IFX. They found that mild upper respiratory tract infections were the most commonly reported, with incidence rates varying widely from 3% to 77%. Severe infections were less common, with reported rates ranging from 0% to 10%. The authors conclude that these broad ranges may be attributed to several factors, including inconsistent case definitions, varying study designs, and differences in treatment regimens. Additionally, the presence of comorbidities and variations in reporting methods may contribute to this wide range of reported infection rates [59].

In our study, the overall incidence of infections is 12.5 % and includes moderate to severe infections of various etiology. These findings are consistent with previous reports. For instance, Szymanska *et al*. reported a similar infection rate of 12.2% in Polish CD pediatric patients. They primarily note respiratory and digestive infections, as well as one case of oral candidiasis [60]. Our results, although indicate comparable rate of infections, include a broader range of observed infection of different types and severity.

According to Ardura *et al*. the risk of infectious complications associated with the use of anti-TNF agents is not constant over time. The results of their research suggests that patients are most vulnerable during the initial 3-6 months after initiation of anti-TNF therapy. However, the overall risk varies with the type of molecule and the duration of exposure [24].

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Cullen *et al*. reviewed data from rheumatological studies regarding infections associated with anti-TNF use. They reported that viral infections account for 30% of all infections and 11% of serious infections in patients using these biologics. The authors noted that for IBD patients specifically, VZV is a particular concern [61].

Schreiner *et al*. reported that reactivation of VVZ causing herpes zoster is demonstrated in children with IBD, the authors underscoring that differences in incidence are based on gender and IBD subtype [62].

With the use of IFX, the rate of herpes zoster in adolescents with IBD as reported by Veres *et al*. were 3.7%, comparable with the one found in our study (4.8%) [63]. This similarity in incidence rates suggests that our findings are consistent with previously published data on herpes zoster risk in children.

We experienced endogenous reactivation of VVZ in two patients, one UC patient treated with IFX monotherapy with an optimized dose (8mg/kg) and in one CD patient, treated with combination therapy (ADA, optimized regimen in combination with azathioprine for almost 3 years). A great contribution, most probably was represented by the fact that because in our country there is not included in the National immunization Program for VVZ vaccination in children and we witness high incidence rates of infection, especially in children under 9 years of age [64]. Biologic agents and azathioprine were temporary discontinued and resumed after specific antiviral treatment for both patients.

According to Dorhoi *et al*., TNFα has a crucial role in the immune response against *M tuberculosis*. TNFα is essential for granuloma formation which represents aggregations of specialized macrophage and lymphocytes that play a vital role in restricting the dissemination of *M tuberculosis* from different sites [65].

Studies have shown that the use of anti-TNF medications in adults with rheumatological diseases and IBD is associated with an increased risk of TB reactivation. In a report of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) upon the diagnosis and monitoring of infectious diseases in pediatric IBD patients receiving anti-TNF agents, the authors reported that this risk is approximately 4 to 5 times higher in patients receiving anti-TNF therapy compared to those that did not receive these medications. The same paper report that anti-TNF agents independently contribute to this elevated risk. Moreover, the authors noted that combining anti-TNF drugs with other immunomodulators further increases the likelihood of TB reactivation [24].

According to Romania's National Strategy on Tuberculosis Control, Romania holds the highest burden of TB among European Union (EU) members, including pediatric and multidrug resistant (MDR) TB. The report states that Romania accounts for 23,5% of the total TB cases reported in EU, with a pediatric incidence of 12,8%000 in 2019 [66].

There are few reported data upon the risk of developing tuberculosis in pediatric IBD patients receiving anti-TNF agents. Cruz *et al*. reported a decade ago the first two cases of disseminated TB associated with IFX use in children with IBD [67]. More recently, two additional cases have been described: a 13-year-old girl with CD which developed pulmonary TB after sequential treatment with azathioprine, adalimumab and ustekinumab [68] and another 12-year-old girl with CD who was diagnosed with disseminated TB and reactive polyarthritis (Poncet's disease) following treatment with azathioprine, adalimumab and Ustekinumab [69].

Despite the general observation that pediatric patients under anti-TNF treatment are at-risk of developing severe TB, particularly those diagnosed with CD and juvenile idiopathic arthritis [70] a systematic review and meta-analysis by Kedia *et al*. focusing on adult IBD patients treated with IFX or ADA found that TB risk is more closely related to local TB prevalence rather than the associated treatment regimens [71].

In our study we report the case of a 13-year-old girl with refractory CD treated with combination therapy (optimized regimen of ADA both dose augmentation and weekly administration, in combination with azathioprine), despite of a negative IGRA test at baseline and annual screening, which developed severe bronchopulmonary TB 30 months after initiation of ADA treatment.

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Although developing TB is the most prevalent in the first three months of anti- TNF therapy, in our case the disease occurred later most probably because of the recently intensification of her therapeutical regimen. It is difficult to assess whether this was a reactivation of a latent TB (implying a false negative IGRA testing) or a new infection given the fact that the patient, besides the immunosuppressive regimen, experienced repeated hospitalizations and she came from a low socioeconomic environment. Last but not least, the high prevalence of TB in our country must not be out of sight. ADA was interrupted and she received specific tuberculostatic treatment. Biologics were resumed after 2 years, and because of chronic active evolution of her CD with perianal disease even under combo-therapy ADA and azathioprine, IFX was initiated.

Based on current evidence, TB screening at baseline, treatment of latent tuberculosis and yearly follow up assessment of possible *mycobacterium* infection may lower the prevalence of tuberculosis in anti-TNF treated patients, even in high tuberculosis prevalence countries.

Concerning HPV, especially types 6 and 11, is known to cause *condylomata acuminata*, which is typically transmitted through sexual contact [72].

While the increased risk of HPV-associated cancer in IBD patients is well-documented, there is limited research on the prevalence of low-risk HPV infections in this population [73].

Several case reports have suggested a potential link between anti-TNF therapy and the development or exacerbation of genital HPV lesions. For instance, Antoniou *et al*. described a patient diagnosed with psoriasis who experienced worsening of pre-existing HPV lesions shortly after IFX treatment [74]. Similarly, Somasekar *et al*. reported extensive anogenital warts in a 23-year-old man with CD following IFX therapy [75].

Handisurya *et al*. found that the risk of anogenital warts was comparable among IBD patients regardless of their treatment regimen [76]. These last data are supported by those coming from *Elmahdi et al*. who also report that the occurrence of anogenital warts in a Danish IBD cohort was not associated with a specific treatment [77]. Available data on benign HPV infection under anti-TNF are conflicting, but given the fact that our patient developed anogenital warts and concomitant severe *C difficile* associated-diarrhea, under combination therapy (IFX and azathioprine) allow us to speculate that combined iatrogenic immunosuppression may be responsible, in part, for this infectious co-occurrence.

As regards *C difficile* infection, this is a common complication in pediatric IBD patients [78]. Gholam-Mostafaei *et al*. studied 140 patients with IBD and found that combination therapy with anti-TNF agents and other immunosuppressants may increase the risk of *C difficile* infection [79]. Several studies have identified IBD itself as an independent risk factor for *C. difficile* infection, particularly in cases with colonic involvement. Issa *et al*. reported that corticosteroids use increases the risk of *C difficile* infection up to threefold compared to biologics or other immunomodulators [80].

According to NASPGHAN clinical report upon diagnosis and prevention of infectious diseases in IBD patients receiving anti TNF treatment, *C difficile* infection in pediatric IBD is more closely associated with corticosteroids use rather than anti-TNF therapy [24].

Our case of severe and recurrent *C difficile* infection combined with perianal condylomatosis imposed cessation of anti-TNF and immunomodulator treatment and performing a fecal microbiota transplant. The patient was then transferred to an adult care unit because of his age (he turned 18 years); treatment with biologics was resumed with vedolizumab.

Regarding the infectious episodes, we also report a case of a 17-year-old girl with UC under combination therapy IFX and azathioprine who developed severe measles complicated with bronchopneumonia and acute respiratory failure that required prolonged hospitalization, 5 months after IFX initiation and consecutive optimized dose. To our knowledge, this is the first reported case of this occurrence. The measles-mumps-rubella (MMR) vaccine is included in the National Immunization Schedule in our country since 1990, but our patient wasn't vaccinated; moreover, she was under combination therapy with azathioprine, leading to a potentially increased iatrogenic immunologic deficit. Although we recommend specific immunization in children with IBD without immunosuppressive treatment, the severe acute colitis imposed urgent initiation of the specific immune suppression which postponed the vaccination and therefore increased the risk of developing

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various infections that could be prevented. IFX and azathioprine were interrupted and she received specific treatment including immunoglobulins. IFX was restarted after 4 weeks but without azathioprine because of persistent leukopenia. She also developed an acute infusion reaction 2 months after resuming the anti-TNF agent. IFX was stopped and after a period of wash-out, ADA was introduced.

Concerning this particular condition, we found one relevant case in adult population reported by Wichman *et al*. They described the case of a 26 years old female diagnosed with CD who was receiving combination therapy with gut-specific biologic (vedolizumab) and methotrexate. Despite previous MMR vaccination, the patient's measles antibodies became undetectable [81]. This case report is noteworthy as it demonstrates how immunosuppressive therapy can potentially compromise vaccine-induced immunity, thereby indirectly highlighting the risks associated with inadequate/absent immunization encountered in our patient.

Current literature regarding the relationship between infection risk and monotherapy versus combination therapy in IBD patients is conflicting. Toruner *et al*. found that the individual use of steroids, thiopurines or anti-TNF agents increased infection risk with an odds ratio (OR) of 2.9 (95% CI: 1.5–5.3). They noted that concomitant use of two or three of these treatments further amplified this risk (OR14.5, 95%CI:4.9–43) [82]. However, meta-analyses of randomized controlled trials (RCT) suggest that combination therapy does not necessarily increase overall AE rates, including infections. In fact, the studies indicate that combining anti-TNF agents with immunomodulators may result in lower infection rates compared to co-administration of steroids [83, 84, 85].

In the SONIC study, which evaluated the efficacy of combination therapy with IFX and azathioprine in CD treatment, the authors suggested that this combination therapy did not significantly increase the risk of severe infections (including TB) [86]. Completing these observations, The Crohn Therapy, Resource, Evaluation, and Assessment Tool registry indicated that the severity of the disease activity was the primary factor associated with serious infection in individuals with CD (hazard ratio [HR], 2.24; 95% CI: 1.57–3.19) [87].

Our observations are partially discordant with these findings. Adding an immunomodulator to biologic therapy is apparently responsible of a higher percentage of infections in our cohort, but these observations are not sustained by statistical significance, thus limiting our possibility in formulating a clear conclusion, most probably because of small sample size.

HV is a condition affecting small blood vessels that can be triggered by infections, certain medications or have unknown etiology [88]. The histopathological hallmark of HV is leukocytoclastic vasculitis, characterized by neutrophil degeneration due to local immune complex formation. Parra *et al*. analyzed the ongoing dilemmas regarding the pathogenesis of anti-TNF associated vasculitis, suggesting potential mechanisms such as antibody formation against anti-TNF molecules or cytokine ratios disturbances, in favor of Th2 lymphocytes [89]. The diagnosis of anti-TNF associated vasculitis is difficult to establish in cases of IBD, as vasculitis can also occur as an extraintestinal manifestation of the disease itself. Way *et al*. suggest that the timing of symptoms onset in relation to medication administration and assessing the disease activity can help in establishing the etiology [90]. Giorgio *et al*. describe the case of anti-TNF associated vasculitis in a 13-year-old girl with ulcerative pancolitis who developed the condition one year after IFX initiation, persisted under ADA and ustekinumab, prednisone, colchicine, mycophenolate mofetil, azathioprine, before ultimately responding to cyclosporin [91].

Early on the history of biologics use, there is a report by Pastore *et al*. describing four cases (36.4%) of anti-TNF vasculitis in patients with UC, all of them being associated with the use of IFX. The authors noted that vasculitis typically developed within a few months of starting IFX therapy, with onset ranging from 6 to 38 weeks. Importantly, this complication occurred despite adherence to standard administration protocols, including premedication with steroids and chlorphenamine [92].

Our patient developed the condition almost 10 years after the first infusion of IFX. She was in histological remission at the time of vasculitis onset and IFX was administered in a standard regimen. All her immunological work-up was within normal range and the skin of the lower limbs was the only location involved, represented by palpable, nonpruritic purpura. Remarkably, she tolerated IFX

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for 10 years. Moreover, she associates specific anti-IFX antibodies 4 years prior to the dermatological AE. The vasculitis persisted under IFX therapy; the family did not agree to discontinue IFX treatment and initiate steroids administration, thus the purpura persisted. Although this is a longer interval than the ones reported in children, there are reports in literature of similar time-frames in adults. Wu *et al*. describe the case of a man who had been on IFX for 13 years and developed HV, with favorable outcome after treatment cessation [93]. Moreover, the fact that the occurrence of purpura was in a period of inactivity regarding the UC (for at least 2 years), strongly suggests the causality between anti-TNF treatment and the occurrence of HV.

EN is described as a septal panniculitis of the subcutaneous fat tissue resulting from a delayed hypersensitivity reaction [94]. While EN is a recognized extraintestinal manifestation of IBD [95] anti-TNF agents have also been implicated as potential triggers in adult studies [96, 97]. Shivaji *et al*. suggest that the temporal relationship between biologic therapy initiation and EN onset is crucial in distinguishing between disease-related and treatment-induced EN [98]. Intriguingly, Zippi *et a*l. note that anti-TNF agents can serve as a therapeutic option for EN in IBD patients [99].

Our patient developed EN three months after initiation of ADA therapy which was rapidly administered in an optimized regimen and combination therapy because of poor disease control; co-incidental is the occurrence of antibodies against ADA simultaneously with the EN onset. Because of potential poor adherence to periodic admissions for IFX infusions and active disease, the current treatment plan was continued.

Our study has several limitations. First of all, the retrospective nature of data collection may result in missing data or incomplete medical records. The observational nature of the study makes it challenging to establish direct causal relationships between the administered treatment and the reported AE. Moreover, confounding factors not accounted for in the study design may influence these associations. The relatively small sample size in our study limits the statistical power to detect significant associations between the administration of anti-TNF agents and outcomes and also limit the extrapolation of our findings to larger patient populations.

These limitations emphasize the need for larger, prospective studies to confirm our findings and further interpret more accurate the relationship between biologic therapies and AE in pediatric IBD patients. Despite these shortcomings, our study provides valuable observations that can enlarge our knowledge and guide future research in this field of interest.

4. Materials and Methods

This is a retrospective single center study. Pediatric IBD patients diagnosed according to ESPGHAN Porto criteria [25] were recruited from the Department of Pediatric Gastroenterology of "Grigore Alexandrescu" Emergency Hospital for Children in Bucharest, Romania, between January 2015 and October 2024. Anti-TNF treated patients were included. All clinical and laboratory data were collected from the hospital's database. The study was approved by the Ethics Committee of our Institution (reference number 34/7.10.2024).

Age at diagnosis and at inclusion (years) were noted. Disease extension and also behavior were noted for UC respectively CD, as indicated by the ESPGHAN Paris classification for diagnosis of IBD in children [26].

The decision to start anti-TNF treatment was made by the treating gastroenterologist, according to the disease and patients characteristics, with the consent of the patients' parents. Both IFX and ADA were administered according to current ESPGHAN guidelines, in a scheduled manner. Time (months) since the initiation of anti-TNF therapy until AE occurred was noted.

Regarding the administered molecule, median dose/kg/administration and IQR were noted for IFX-treated patient. For ADA, treatment administration was divided in standard or optimized regimen (either dose escalation or weekly administration). Combination therapy was defined as co-administration of an immunomodulator (IMM, azathioprine) for at least eight weeks prior to biologic therapy. Considering the administrated molecule, for the accuracy of statistical processing, patients were divided in "IFX-only" and IFX and/or ADA, sequential therapy".

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AE were categorized for clarity per etiology and systems, according to the available literature in: non-infectious complications as hypersensitivity reactions (acute infusion reactions, anti-drug antibodies formation), dermatological effects such as erythema nodosum (EN) and vasculitis, neurologic effects such as acute demyelinating reactions (Guillain Barré syndrome, GBS) and infections. Minor respiratory infections that were managed locally with the general practitioner were not taken into account. Besides suggestive clinical manifestations, the AE were confirmed on the basis of specific tests: IgM specific antibodies for viral infections, radiology, interferon-gamma release assay (IGRA) and polymerase chain reaction (PCR) assay from sputum for tuberculosis (TB), the detection of *Clostridioides difficile (C difficile)* toxins from stool was possible with an enzyme-linked immunosorbent assay (ELISA) test. Cases of *C difficile* infection identified on glutamate dehydrogenase (GDH) and/or nucleic acid amplification tests (NAATs) testing, without detection of toxins A and/or B were excluded. Moreover, cases that were mild and did not required hospitalization were also excluded.

Skin biopsies were undertaken for EN and vasculitis, cerebrospinal fluid analysis and electromyography for GBS. Anti-drug antibodies were determined by chemiluminescence immunoassay (CLIA). Allergic reactions were divided according to their severity into five severity grades, according to National Cancer Institute [NCI] at the National Institutes of Health [NIH] in the USA. They range from mild: (requiring observation only) through moderate (usually oral intervention is sufficient) and severe (vital organ involved but not life-threatening; usually requires pa medication) to life-threatening (multi-system involvement of vital organs, urgent and critical care required) and death [27].

Statistics

In the context of statistical analysis the following software was used: SPSS v26 and Python v3.12 (scipy.stats module) and R platform. For categorical variables, both the Chi-square test and Fisher's Exact Test were performed. Fisher's Exact Test was preferred in cases where sample sizes were small or where expected frequencies in contingency table cells were below 5, ensuring robustness and accuracy of the p-values. Continuous variables were evaluated for normality using the Shapiro-Wilk test. Given that the data were not normally distributed, the Mann-Whitney U Test (a non-parametric test) was applied to compare medians between groups. A linear regression analysis was conducted to examine the relationship between age at diagnosis and time to therapy initiation. For continuous variables, due to their non-normal distribution, medians and interquartile ranges (IQR) were reported as measures of central tendency and dispersion. A p value < 0.05 was considered as the threshold for statistical significance.

5. Conclusions

Anti-TNF agents, particularly IFX, are widely used in pediatric IBD patients, especially in older children, with a significant proportion of patients receiving combination therapy with azathioprine. Adverse events are protean, affecting over half of the patients, with anti-drug antibody formation being the most prevalent issue. ADA treatment appears to be associated with a higher risk of adverse events compared to IFX. Combination therapy seems to slightly increase the risk of certain adverse events, particularly infections, but may not significantly impact others like acute infusion reactions or antibodies formation. Our findings underscore the importance of watchful monitoring for rare but serious adverse events in patients receiving both combination therapy and monotherapy with anti-TNF agents.

This study highlights the need for careful monitoring of pediatric IBD patients on biologic therapies, especially those on combination therapy or ADA treatment. Further research with larger sample sizes is needed to confirm these findings and to better understand the risk factors for AE in pediatric IBD patients receiving anti-TNF agents.

The fact that biologics offered new and awaited perspectives for IBD treatment since their creation cannot be disregarded. However, prolonged steroid-free remission, better prognosis and improved quality of life come hand in hand with the risk of a wide-range of adverse reactions. One

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must take into account both well proven benefits and possible risks. In an era of rapidly improving therapies, "*Above all else, do no harm*" must be considered with every therapeutical decision. Extension of this research in other centers will improve our understanding regarding possible AE, leading to optimal use of anti-TNF molecules.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Data is contained within the article or supplementary material.

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References

1. Liu, C.; Yu, R.; Zhang, J.; Wei, S; Xue, F.; Guo, Y.; He, P.; Shang, L.; Dong, W. Research hotspot and trend analysis in the diagnosis of inflammatory bowel disease: A machine learning bibliometric analysis from 2012 to 2021. *Front Immunol*. **2022**, *13*, 972079.
2. Fitzgerald, R.S.; Sanderson, I.R.; Claesson, M.J.; Paediatric Inflammatory Bowel Disease and its Relationship with the Microbiome. *Microb Ecol*. **2021**, *82*, 833-844.
3. Kim, D.H.; Cheon J.H. Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies. *Immune Netw*. **2017**, *17*, 25-40.
4. Long, D.; Wang, C.; Huang, Y.; Mao, C.; Xu, Y.; Zhu, Y. Changing epidemiology of inflammatory bowel disease in children and adolescents. *Int J Colorectal Dis*. **2024**, *39*, 73.
5. Arai, K. Very Early-Onset Inflammatory Bowel Disease: A Challenging Field for Pediatric Gastroenterologists. *Pediatr Gastroenterol Hepatol Nutr*. **2020**, *23*, 411-422.
6. Ng, S.C.; Shi, H.Y.; Hamidi, N.; Underwood, F.E.; Tang, W.; Benchimol, E.I.; Panaccione, R.; Ghosh, S.; Wu, J.C.Y.; Chan, F.K.L.; Sung, J.J.Y.; Kaplan, G.G. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet (London, England)* **2018**, *390*, 2769–2778.
7. Kuenzig, M.E.; Fung, S.G.; Marderfeld, L.; Mak, J.W.Y.; Kaplan, G.G.; Ng, S.C.; Wilson, D.C.; Cameron, F.; Henderson, P.; Kotze, P.G.; Bhatti, J.; Fang, V.; Gerber, S.; Guay, E.; Kotteduwa Jayawarden, S.; Kadota, L.; Maldonado, D.F.; Osei, J.A.; Sandarage, R.; Stanton, A.; Wan, M. InsightScope Pediatric IBD Epidemiology Group; Benchimol, E.I. Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review. *Gastroenterology*. **2022**, *162*, 1147-1159.e4.
8. Burger, D.; Travis, S. Conventional medical management of inflammatory bowel disease. *Gastroenterology*. **2011**, *140*, 1827-1837.e2.
9. Lee, H.S.; Park, S.K.; Park, D.I. Novel treatments for inflammatory bowel disease. *Korean J Intern Med*. **2018**, *33*, 20-27.
10. Peyrin-Biroulet, L.; Sandborn, W.; Sands, B.E.; Reinisch, W.; Bemelman, W.; Bryant, R.V.; D'Haens, G.; Dotan, I.; Dubinsky, M.; Feagan, B.; Fiorino, G.; Gearry, R.; Krishnareddy, S.; Lakatos, P.L.; Loftus Jr, E.V.; Marteau, P.; Munkholm, P.; Murdoch, T.B.; Ordás, I.; Panaccione, R.; Riddell, R.H.; Ruel, J.; Rubin, D.T.; Samaan, M.; Siegel, C.A.; Silverberg, M.S.; Stoker, J.; Schreiber, S.; Travis, S.; Van Assche, G.; Danese, S.; Panes, J.; Bouguen, G.; O'Donnell, S.; Pariente, B.; Winer, S.; Hanauer, S.; Colombel, J.F. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*. **2015.**

11. Conrad, M.A.; Kelsen, J.R. The Treatment of Pediatric Inflammatory Bowel Disease with Biologic Therapies. *Curr Gastroenterol Rep*. **2020**, *22*, 36.
12. Hemperly, A.; Vande Casteele, N. Clinical Pharmacokinetics and Pharmacodynamics of Infliximab in the Treatment of Inflammatory Bowel Disease. *Clin Pharmacokinet*. **2018**, *57*, 929-942.
13. Gerriets, V.; Goyal, A.; Khaddour, K. Tumor Necrosis Factor Inhibitors. *StatPearls [Internet]*. **2023**._
14. Goujon, C.; Bachelez, H. Groupe de recherche sur le psoriasis de la Société française de dermatologie. Infliximab [Infliximab]. *Ann Dermatol Venereol*. **2019**, *146*, 483-486.
15. Puthoor, P.R.; Zoeten, E.F. Pediatric ulcerative colitis: the therapeutic road to Infliximab. *Biol Ther*. **2013**, *3*, 1–14.
16. Hanauer, S.B.; Feagan, B.G.; Lichtenstein, G.R.; Mayer, L.F.; Schreiber, S.; Colombel, J.F.; Rachmilewitz, D.; Wolf, D.C.; Olson, A.; Bao, W.; Rutgeerts, P.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. **2002,** *359*, 1541-9.
17. Ruemmele, F.M.; Veres, G.; Kolho, K.L.; Griffiths, A.; Levine, A.; Escher, J.C.; Amil Dias, J.; Barabino, A.; Braegger, C.P.; Bronsky, J.; Buderus, S.; Martín-de-Carpi, J.; De Ridder, L.; Fagerberg, U.L.; Hugot, J.P.; Kierkus, J.; Kolacek, S.; Koletzko, S.; Lionetti, P.; Miele, E.; Navas López, V.M.; Paerregaard, A.; Russell, R.K.; Serban, D.E.; Shaoul, R.; Van Rheenen, P.; Veereman, G.; Weiss, B.; Wilson, D.; Dignass, A.; Eliakim, A.; Winter, H.; Turner, D. European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. **2014**, *8*, 1179-207.
18. Jongsma, M.M.E.; Winter, D.A.; Huynh, H.Q.; Norsa, L.; Hussey, S.; Kolho, K.L.; Bronsky, J.; Assa, A.; Cohen, S.; Lev-Tzion, R.; Van Biervliet, S.; Rizopoulos, D.; de Meij, T.G.J.; Shouval, D.S.; Wine, E.; Wolters, V.M.; Martinez-Vinson, C.; de Ridder, L.; Paediatric, I.B.D.; Porto Group of ESPGHAN. Infliximab in young paediatric IBD patients: it is all about the dosing. *Eur J Pediatr*. **2020**, *179*, 1935-1944.
19. Winter, D.A.; Joosse, M.E.; de Wildt, S.N.; Taminiau, J.; de Ridder, L.; Escher, J.C. Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Infliximab in Pediatric Inflammatory Bowel Disease: A Systematic Review and Revised Dosing Considerations. *J Pediatr Gastroenterol Nutr*. **2020**, *70*, 763-776.
20. Aardoom, M.A.; Veereman, G.; de Ridder, L. A Review on the Use of Anti-TNF in Children and Adolescents with Inflammatory Bowel Disease. *Int J Mol Sci*. **2019**, *20*, 2529.
21. Kapoor, A.; Crowley, E. Advances in Therapeutic Drug Monitoring in Biologic Therapies for Pediatric Inflammatory Bowel Disease. *Front Pediatr*. **2021,** *9*, 661536.
22. Ashton, J.J.; Beattie, R.M. Inflammatory bowel disease: recent developments. *Arch Dis Child*. **2024**, *109*, 370-376.
23. Penagini. F.; Lonoce, L.; Abbattista, L.; Silvera, V.; Rendo, G.; Cococcioni, L.; Dilillo, D.; Calcaterra, V.; Zuccotti, G.V. Dual biological therapy and small molecules in pediatric inflammatory bowel disease. *Pharmacol Res*. **2023**, *196*, 106935.
24. Ardura, M.I.; Toussi, S.S.; Siegel, J.D.; Lu, Y.; Bousvaros, A.; Crandall, W. NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor-α Inhibitors. *J Pediatr Gastroenterol Nutr*. **2016**, *63*, 130-55.
25. Levine, A.; Koletzko, S.; Turner, D.; Escher, J.C.; Cucchiara, S.; de Ridder, L.; Kolho, K.L.; Veres, G.; Russell, R.K.; Paerregaard, A.; Buderus, S.; Greer, M.L.; Dias, J.A.; Veereman-Wauters, G.; Lionetti, P.; Sladek, M.; Martin de Carpi, J.; Staiano, A.; Ruemmele, F.M.; Wilson, D.C.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. **2014**, *58*, 795-806.
26. Levine, A.; Griffiths, A.; Markowitz, J. et al. Pediatric modification of the Montreal Classification for inflammatory bowel disease: the Paris Classification. *Inflamm Bowel Dis*. **2011**, *17*, 1314–1321.
27. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf , accessed on 26th of April 2024
28. Fumery, M.; Dupont, C.; Ley, D.; Savoye, G.; Bertrand, V.; Guillon, N.; Wils, P.; Gower-Rousseau, C.; Sarter, H.; Turck, D.; Leroyer, A. Long-term effectiveness and safety of anti-TNF in pediatric-onset inflammatory bowel diseases: A population-based study. *Dig Liver Dis*. **2024**, *56*, 21-28.
29. D'Arcangelo, G.; Distante, M.; Raso, T.; Rossetti, D.; Catassi,G.; Aloi, M. Safety of Biological Therapy in Children With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr*. **2021**, *72*, 736-741.
30. Li, M.; You, R.; Su, Y.; Zhou, H.; Gong, S. Characteristic analysis of adverse reactions of five anti-TNFα agents: a descriptive analysis from WHOVigiAccess.Front. *Pharmacol*. **2023**, *14*, 1169327.
31. Lichtenstein, L.; Ron, Y.; Kivity, S.; Ben-Horin, S.; Israeli, E.; Fraser, G.M.; Dotan, I.; Chowers, Y.; Confino-Cohen, R.; Weiss, B. Infliximab-Related Infusion Reactions: Systematic Review. *J Crohns Colitis*. **2015**, *9*, 806-15.
32. Pastore, S.; Naviglio, S.; Canuto, A.; Lepore, L.; Martelossi, S.; Ventura, A.; Taddio, A. 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. *Paediatr Drugs*. **2018**, *20*, 165-171.

33. Dan-Nielsen, S.; Wewer, V.; Paerregaard, A.et al. Does infliximab prevent colectomy in acute and chronic active ulcerative colitis*? J Pediatr Gastroenterol Nutr.***2014**, *58*, 768–772.
34. Kolho, K.L.; Ruuska, T.; Savilahti, E. Severe adverse reactions to Infliximab therapy are common in young children with inflammatory bowel disease. *Acta Paediatr*. **2007**, *96*, 128-30.
35. Corica, D.; Romano, C. Biological Therapy in Pediatric Inflammatory Bowel Disease: A Systematic Review. *J Clin Gastroenterol*. **2017**, *51*, 100-110.
36. Elliott, M.J.; Maini, R.N.; Feldmann, M.; Long-Fox, A.; Charles, P.; Bijl, H.; Woody, J.N. Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. *Lancet*. **1994**, *344*, 1125-7.
37. Vermeire ,S.; Gils, A.; Accossato, P.; Lula, S.; Marren, A. Immunogenicity of biologics in inflammatory bowel disease. *Therap Adv Gastroenterol.* **2018**, *11*, 1756283X75035.
38. Thomas, S.S.; Borazan, N.; Barroso, N.; Duan, L.; Taroumian, S.; Kretzmann, B.; Bardales, R.; Elashoff, D.; Vangala, S.; Furst, D.E. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. *BioDrugs.* **2015**, *29*, 241-58.
39. Winter, D.A.; de Bruyne, P.; van der Woude, J. et al. Biomarkers predicting the effect of anti-TNF treatment in paediatric and adult inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. **2024**, *79*, 62-75.
40. Fousekis, F.S.; Papamichael, K.; Kourtis, G.; Albani, E.N.; Orfanidou, A.; Saridi, M.; Katsanos, K.H.; Christodoulou, D.K. The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Ann Gastroenterol*. **2022**, *35*, 1-7.
41. Zitomersky, N.L.; Atkinson, B.J.; Fournier, K. et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. *Inflamm Bowel Dis*. **2015**, *21*, 307–314.
42. Adedokun, O.J.; Xu, Z.; Padgett, L. et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. *Inflamm Bowel Dis*. **2013**, *19*, 2753–2762.
43. Wilson, C.; Huffman, S.; Mcgoogan, K. P-180 YI common factors among children who developed antibodies to infliximab. *Inflamm Bowel Dis*. **2013**,*19*, S98.
44. Löwenberg, M. Is there a beneficial effect of adding azathioprine to adalimumab in Crohn's disease patients? *Ann Transl Med*. **2018**, *6*, 278.
45. Wachira, V.K.; Farinasso, C.M.; Silva, R.B.; Peixoto, H.M.; de Oliveira, M.R.F. Incidence of Guillain-Barré syndrome in the world between 1985 and 2020: A systematic review. *Glob Epidemiol*. **2023**, *5*, 100098.
46. Cesarini, M.; Angelucci, E.; Foglietta, T.; Vernia, P. Guillain-Barrè syndrome after treatment with human anti-tumor necrosis factorα (adalimumab) in a Crohn's disease patient: Case report and literature review. *J Crohn's Colitis.* **2011**, *5*, 619–22.
47. Paquin-Gobeil, M.; Hassard, P.; Gupta G. Guillain-Barré syndrome in ulcerative colitis following treatment with infliximab. *Am J Gastroenterol.* **2012**, *107*, S650.
48. Khodkam, M.; Panahi, D. Guillain-Barré syndrome in remission of ulcerative colitis: A case report. *Neurol Lett.* **2023** ,*2*, 13–15.
49. Li, X.; Zhang, C. Guillain-Barré syndrome after surgery: a literature review. *Front Neurol*. **2024**, *15*, 1368706.
50. Bao, L.; Chen, X.; Li, Q.; Zhang, R.; Shi, H.; Cui, G. Surgery and Guillain-Barré Syndrome: A Single-Center Retrospective Study Focused on Clinical and Electrophysiological Subtypes. *Neuropsychiatr Dis Treat*. **2020**, *16*, 969-974.
51. Raychaudhuri, S.P.; Nguyen, C.T.; Raychaudhuri, S.K.; Gershwin, M.E. Incidence and nature of infectious disease in patients treated with anti-TNF agents. *Autoimmun Rev*. **2009**, *9*, 67-81.
52. Day, A.S.; Gulati, A.S.; Patel, N.; Boyle, B.; Park, K.T.; Saeed, S.A. The Role of Combination Therapy in Pediatric Inflammatory Bowel Disease: A Clinical Report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. **2018**, *66*, 361-368.
53. *Humira [package insert]* North Chicago, IL: Abbott Laboratories. **2009**
54. Remicade [package insert] Malvern, P.A. Centocor Ortho Biotech Inc. **2009**.
55. Zhang, Z.; Fan, W.; Yang, G. et al. Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open.* **2017**, *7*, e012567.
56. Dulai, P.S.; Thompson, K.D.; Blunt, H.B.; Dubinsky, M.C.; Siegel, C.A. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol*. **2014**, *12*, 1443-51, quiz e88-9.
57. Hyams, J.; Crandall, W.; Kugathasan, S. et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. **2007**, *132*, 863–73.
58. Hyams, J.S.; Griffiths, A.; Markowitz, J. et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology*. **2012**, *143*, 365–74.

 doi:10.20944/preprints202412.0778.v1

59. Toussi, S.S.; Pan, N.; Walters, H.M.; Walsh, T.J. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-α inhibitors: systematic review of the literature. *Clin Infect Dis*. **2013**, *57*, 1318-30.
60. Szymanska, E.; Dadalski, M.; Oracz, G. et al. Safety profile of biologic therapy in Polish paediatric patients with Crohn's disease. *Prz Gastroenterol*. **2015**, *10*, 164–168.
61. Cullen, G.; Baden, R.P.; Cheifetz, A.S. Varicella zoster virus infection in inflammatory bowel disease. *Inflamm Bowel Dis*. **2012**, *18*, 2392-403.
62. Schreiner, P.; Mueller, N.J.; Fehr, J.; Maillard, M.H.; Brand, S.; Michetti, P.; Schoepfer, A.; Restellini, S.; Vulliemoz, M.; Vavricka, S.R.; Juillerat, P.; Rogler, G.; Biedermann, L. Varicella zoster virus in inflammatory bowel disease patients: what every gastroenterologist should know. *J Crohns Colitis*. **2020**, *27*, jjaa132.
63. Veres, G.; Baldassano, R.N.; Mamula, P. Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs*. **2007** ,*67*, 1703–1723.
64. Institutul Național de Sănătate Publică. Centrul Național de Supraveghere și Control al Bolilor Transmisibile Analiza evoluției bolilor transmisibile aflate în supraveghere. Raport pentru anul 2019, București, **2022**.
65. Dorhoi, A.; Kaufmann, S.H. Tumor necrosis factor alpha in mycobacterial infection. *Semin Immunol*. **2014**, *26*, 203–209
66. https://sgg.gov.ro/1/wp-content/uploads/2022/09/ANEXA-Strategia-Nationala-.pdf , accessed on the 6th of October 2024.
67. Cruz, A.T.; Karam, L.B.; Orth, R.C.; Starke, J.R. Disseminated tuberculosis in 2 children with inflammatory bowel disease receiving infliximab. *Pediatr Infect Dis J*. **2014**, *33*, 779-81.
68. Renoux, M.C.; Dutronc, S.; Kollen, L.; Theret, S.; Moreau, J. A Case of Disseminated Tuberculosis in a Child with Crohn's Disease After Treatment with Azathioprine, Adalimumab and Ustekinumab. *Arch Bronconeumol*. **2021**, *57*, 552-554.
69. Minotti, C.; Costenaro, P.; Donà, D.; Zuliani, M.; Bosa, L.; Leon, A.; Perilongo, G.; Gaio, P.; Martini, G.; Cananzi, M. Disseminated Mycobacterial Infection With Reactive Polyarthritis (Poncet's Disease) During Immune-suppressive Treatment Including Ustekinumab for Pediatric Crohn's Disease. *Pediatr Infect Dis J*. **2024**, *43*, 543-549.
70. Noguera-Julian, A.; Calzada-Hernández, J.; Brinkmann, F.; Basu Roy, R.; Bilogortseva, O.; Buettcher, M.; Carvalho, I.; Chechenyeva, V.; Falcón, L.; Goetzinger, F.; Guerrero-Laleona, C.; Hoffmann, P.; Jelusic, M.; Niehues, T.; Ozere, I.; Shackley, F.; Suciliene, E.; Welch, S.B.; Schölvinck, E.H.; Ritz, N.; Tebruegge, M. Tuberculosis Disease in Children and Adolescents on Therapy With Antitumor Necrosis Factor-α Agents: A Collaborative, Multicenter Paediatric Tuberculosis Network European Trials Group (ptbnet) Study. *Clin Infect Dis*. **2020**, *71*, 2561-2569.
71. Kedia, S.; Mouli, V.P.; Kamat, N.; Sankar, J.; Ananthakrishnan, A.; Makharia, G.; Ahuja, V. Risk of Tuberculosis in Patients With Inflammatory Bowel Disease on Infliximab or Adalimumab Is Dependent on the Local Disease Burden of Tuberculosis: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. **2020**, *115*, 340-349.
72. Handsfield, H.H. Clinical presentation and natural course of anogenital warts. *Am J Med*. **1997**, *102*, 16–20.
73. Jess, T.; Horváth-Puhó, E.; Fallingborg, J.; Rasmussen, H.H.; Jacobsen, B.A. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. *Am J Gastroenterol*. **2013**, *108*, 1869–76.
74. Antoniou, C.; Kosmadaki, M.G.; Stratigos, A.J.; Katsambas, A.D. Genital HPV lesions and molluscum contagiosum occurring in patients receiving anti-TNF-alpha therapy. *Dermatology*. **2008**, *216*, 364–365.
75. Somasekar, A.; Alcolado, R. Genital condylomata in a patient receiving infliximab for Crohn's disease. *Postgrad Med J*. **2004**, *80*, 358–359.
76. Handisurya, A.; Lázár, S.; Papay, P.; Primas, C.; Haitel, A.; Horvat, R. et al. Anogenital human papillomavirus prevalence is unaffected by therapeutic tumour necrosis factor-alpha inhibition. *Acta Derm Vene- reol*. **2016**, *96*, 494–8.
77. Elmahdi, R.; Thomsen, L.T.; Iversen, A.T.; Allin, K.H.; Kjaer, S.K.; Jess, T. Increased risk of genital warts in inflammatory bowel disease: A Danish registry-based cohort study (1996-2018). *United European Gastroenterol J*. **2022**, *10*, 287-295.
78. Reasoner, S.A.; Nicholson, M.R. Clostridioides difficile Infection in Pediatric Inflammatory Bowel Disease. *Curr Gastroenterol Rep*. **2023**, *25*, 316-322.
79. Gholam-Mostafaei, F.S.; Yadegar, A.; Aghdaei, H.A. et al. Anti-TNF containing regimens may be associated with increased risk of *Clostridioides difficile* infection in patients with underlying inflammatory bowel disease. *Curr Res Transl Med*. **2020**, *68*, 125–30.
80. Issa, M.; Vijayapal, A.; Graham, M.B.; Beaulieu, D.B.; Otterson, M.F.; Lundeen, S. et al. Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol*. **2007**, *5*, 345-51.
81. Wichmann, A. et. all. Measles Vaccine Administered to a Crohn's Disease Patient Receiving Vedolizumab. *Am J Gastroenterol*. **2016**, *111*, 577.

82. Toruner, M.; Loftus Jr E.V.; Harmsen, W.S.; Zinsmeister, A.R.; Orenstein, R.; Sandborn, W.J.; Colombel, J.F.; Egan, L.J. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. **2008**, *134*, 929-36.
83. Deepak, P.; Stobaugh, D.J.; Ehrenpreis, E.D. Infectious complications of TNF-alpha inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis.* **2013**, *22*, 269–76.
84. Lin, Z.; Bai, Y.; Zheng, P. Meta-analysis: efficacy and safety of combination therapy of infliximab and immunosuppressives for Crohn's disease. *Eur J Gastroenterol Hepatol*. **2011**, *23*, 1100–10.
85. Lichtenstein, G.R.; Diamond, R.H.; Wagner, C.L. et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD subgroup analyses across four randomized trials. *Aliment Pharmacol Ther*. **2009**, *30*, 210–26.
86. Colombel, J.F.; Sandborn, W.J.; Reinisch, W.; Mantzaris, G.J.; Kornbluth, A.; Rachmilewitz, D.; Lichtiger, S.; D'Haens, G.; Diamond, R.H.; Broussard, D.L.; Tang, K.L.; van der Woude, C.J.; Rutgeerts, P.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. **2010**, *362*, 1383-95.
87. Lichtenstein, G.R.; Feagan, B.G.; Cohen, R.D. et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of followup in the TREAT registry. *Am J Gastroenterol*. **2012**, *107*, 1409–22.
88. Wu, A.; Brown, D.; Wong, U. A Rare Case of Leukocytoclastic Vasculitis Associated With Infliximab. *Gastro Hep Adv*. **2022**, *2*, 322-324.
89. Parra, R.S.; Chebli, J.M.F.; Chebli, L.A.; Lima Junior, S.Fd.; Lins Neto, M.A.; Medeiros, T.Rd.; Faria, F.M.; Feitosa, M.R.; Nigro, C.M.C.; Féres O. Leukocytoclastic Vasculitis Secondary to Anti-Tumor Necrosis Factor Therapy in Inflammatory Bowel Diseases: A Multicenter Retrospective Cohort Study. *Journal of Clinical Medicine*. **2023**, *12*, 3165.
90. Way, A.; Weinstein, E. A Rare Case of Infliximab-Induced Small Vessel Vasculitis With Renal Involvement. *J Investig Med High Impact Case Rep*. **2023**, *11*, 23247096231188247.
91. Giorgio, V.; Blasi, E.; Rigante, D.; Guerriero, C.; De Simone, C.; Fedele, A.L.; Stella, G.; Gasbarrini, A.; Scaldaferri, F. Anti-TNF-Related Leukocytoclastic Vasculitis in Ulcerative Colitis: A Case Report. *Int J Environ Res Public Health*. **2021**, *18*, 6711.
92. Pastore, S.; Londero, M.; Gortani, G.; Abate, M.V.; Marchetti, F.; Di Leo, G.; Ventura, A. Infliximab-related vasculitis in patients affected by ulcerative colitis. *J Pediatr Gastroenterol Nutr*. **2010**, *51*, 226-8.
93. Wu, A.; Brown, D.; Wong, U. A Rare Case of Leukocytoclastic Vasculitis Associated With Infliximab. *Gastro Hep Adv*. **2022**, 2, 322-324.
94. Porges, T.; Shafat, T.; Sagy, I.; Zeller, L.; Bartal, C.; Khutarniuk, T.; Jotkowitz, A.; Barski, L. Clinical, Epidemiological, and Etiological Changes in Erythema Nodosum. *Isr Med Assoc J*. **2018**, *20*, 770-772.
95. Roth, N.; Biedermann, L.; Fournier, N.; Butter, M.; Vavricka, S.R.; Navarini, A.A.; Rogler, G.; Scharl, M.; Swiss IBD Cohort Study Group. Occurrence of skin manifestations in patients of the Swiss Inflammatory Bowel Disease Cohort Study. *PLoS One*. **2019**, *14*, e0210436.
96. Kudsi, M.; Asaad, W.; Khalayli, N.; Soud Alkousa, H.; Haidar, G. Erythema nodosum after golimumab treatment in ankylosing spondylitis patients: a case report and literature review. *Ann Med Surg (Lond)*. **2023**, *85*, 4633-4637.
97. Rosen, T.; Martinelli, P. Erythema nodosum associated with infliximab therapy. *Dermatol Online J*. **2008**, *14*, 3.
98. Shivaji, U.N.; Sharratt, C.L.; Thomas, T.; Smith, S.C.L.; Iacucci, M.; Moran, G.W.; Ghosh, S.; Bhala, N. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. **2019**, *49*, 664-680.
99. Zippi, M.; Pica, R.; De Nitto, D.; Paoluzi, P. Biological therapy for dermatological manifestations of inflammatory bowel disease. *World J Clin Cases*. **2013**, *1*, 74-8.