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REVIEW ARTICLE

Treatment with Biologic Drugs in Pediatric Behçet's Disease: A Comprehensive Analysis of the Published Data

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Abstract

Background and Objective Behçet's disease (BD) is a variable vessel vasculitis. Biologic drugs are increasingly used in the treatment of BD. We aimed to analyze biologic drug use in the treatment of pediatric BD.

Methods MEDLINE/PubMed and Scopus databases were searched from the inception of these databases until 15 November 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only reports presenting data of pediatric patients with BD (BD diagnosis < 18 years of age) treated with biologic drugs were included. The demographic features, clinical characteristics, and data on treatment were extracted from the included papers.

Results We included 87 articles including 187 pediatric patients with BD treated with biologic drugs (215 biologic treatments). Tumor necrosis factor (TNF)-α inhibitors (176 treatments) were the most frequently used biologic drugs followed by interferons (21 treatments). Other reported biologic treatments were anti-interleukin-1 agents ($n = 11$), tocilizumab ($n = 4$), daclizumab ($n = 2$), and rituximab ($n = 1$). The most common indication for biologic drug use was ocular involvement (93 treatments) followed by multisystem active disease (29 treatments). Monoclonal TNF-α inhibitors, adalimumab and infliximab, were preferred over etanercept in ocular and gastrointestinal BD. The improvement rates with any TNF-α inhibitor, adalimumab, infliximab, etanercept, and interferons were 78.5%, 86.1%, 63.4%, 87.5%, and 70%; respectively. The organ-specific improvement rate with TNF-α inhibitors was 76.7% and 70% for ocular and gastrointestinal system involvement. Adverse events have been reported for TNF-α inhibitors, interferons, and rituximab. Six of these were severe [TNF-α inhibitors ($n = 4$); interferons ($n = 2$)].

Conclusions The presented systematic literature search revealed that TNF-α inhibitors followed by interferons were the most frequently used biologic drugs in pediatric BD. Both group of biologic treatments appeared to be effective and have an acceptable safety profile in pediatric BD. However, controlled studies are required for analyzing indications for biologic treatments in pediatric BD.

1 Introduction

Behçet's disease (BD) is a variable vessel vasculitis with a wide range of systemic involvement [1]. Behçet's disease may present with oral and genital aphthosis, inflammatory skin lesions, vasculitis, venous thrombosis, ocular involvement,

Key Points

Tumor necrosis factor-α inhibitors followed by interferons were the most frequently used biologic drugs in pediatric Behçet's disease.

Monoclonal tumor necrosis factor-α inhibitors were preferred over etanercept for ocular and gastrointestinal Behçet's disease.

Tumor necrosis factor-α inhibitors and interferons seem to be effective and have an acceptable safety profile in pediatric Behçet's disease.

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and musculoskeletal, neurologic, and gastrointestinal system manifestations [2–4]. Behçet's disease is mainly a disease of young adults; however, the disease fully manifests during childhood in 7–14% of patients [5, 6]. Pediatric BD differs from adult BD in several aspects. Pediatric patients often present as incomplete cases, not fulfilling the suggested criteria. A family history of BD and neurologic and gastrointestinal system (GIS) involvements are more frequent among children while genital ulcers are more common in adults with BD [7]. Moreover, the disease outcome appears to be worse in adults than pediatric BD [7]. Ocular and vascular manifestations usually determine the morbidity and mortality rates, respectively, both in children and adults [8].

The affected systems and the disease severity determine the treatment strategy in BD. Topical therapeutics and conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) form the standard treatment for mucocutaneous and musculoskeletal manifestations [9]. High-dose corticosteroids and immunosuppressive drugs are usually required in the case of vascular manifestations or major organ involvement [9]. Biologic DMARDs have been increasingly used in the treatment of BD during the last two decades. The introduction of biologic drugs into the treatment of BD has improved the outcome, especially in the presence of ocular involvement and vascular manifestations. [8].

The 2018 update of the European League Against Rheumatism recommendations are the most recent international guidelines for BD treatment [9]. Furthermore, four organ-specific (for neurologic, intestinal, mucocutaneous, and vascular involvements) guidelines from Japan [10–13] and French recommendations [14] for BD treatment were published between 2020 and 2023. However, there are no recommendations addressing the management of pediatric BD in detail. The high-level evidence of biologic drug use comes from a limited number of randomized controlled trials performed in adult patients with BD [15–18]. Although adult BD differs from pediatric BD, indications for biologic drug use in pediatric BD are mainly based on experience in adult BD studies. In this study, we aimed to analyze the data in the literature on the use of biologic DMARDs in pediatric BD.

2 Methods

The MEDLINE/PubMed and Scopus databases were searched using keywords addressing pediatric BD and different biologic DMARDs, from the inception of these databases until 15 November 2022, according to the PRISMA guidelines [19]. The complete list of search terms is provided in the Electronic Supplementary Material (ESM). Two authors (EDB and VC) performed the literature review independently. The controversies between the two authors were resolved by consensus. The search was restricted to English and Spanish articles. Only studies and case reports/series presenting data on pediatric patients with BD (diagnosed with BD before 18 years of age) treated with biologic drugs were included. The reference lists of the systematic reviews were also meticulously hand searched. The protocol of the systematic literature search is presented in Fig. 1. The demographic features, clinical characteristics, and data regarding the previous treatment and biologic treatment (type of biologic drug, treatment duration, response, relapse under biologic treatment, adverse events) were extracted from the included papers.

3 Results

In the systematic literature search, we identified 87 articles including 187 pediatric patients with BD treated with biologic drugs [5, 16, 20–104]. The details of the extracted data from included articles are presented in the ESM. As 18 patients received two different biologic drugs, one patient received three different biologic drugs, and two patients received five different biologic drugs each, the number of biologic treatments was 215 for 187 patients (Table 1).

In the four articles [5, 37, 59, 91], no data were available on pediatric patients with BD except for the number of patients and the type of biologic drug. In the article by Pain et al. [73], the exact number of pediatric patients treated with biologic drugs was not clear although it was understood that one patient was treated with interferons (IFNs), at least one patient was treated with anakinra, and at least ten patients were treated with tumor necrosis factor (TNF)-α inhibitors. These articles are not presented in the ESM although the clear data regarding the number of patients and type of biologic drugs were included in the total numbers. Of note, the total number of pediatric patients with BD treated with biologic drugs was not explicitly indicated in three reports [22, 71, 105]. However, we included the clearly presented part of the data from these articles.

The most frequently used biologic drugs were TNF-α inhibitors (155 patients/ 176 treatments), followed by IFNs (21 patients/ 21 treatments) (Table 1). Previous treatment, which was mentioned for 117 patients, included corticosteroids and conventional synthetic DMARDs in the majority of patients (82.1% and 96.2%, respectively). Ocular involvement was the most common indication for biologic drug use (93 treatments), followed by multisystem active disease (29 treatments) and GIS involvement (19 treatments). The median duration of the biologic treatment was 12 months (data were available for 60 treatments).

Anti-TNF agents were most frequently used for treating ocular manifestations followed by GIS involvement (Table 2). In two patients, anti-TNF drugs were used for

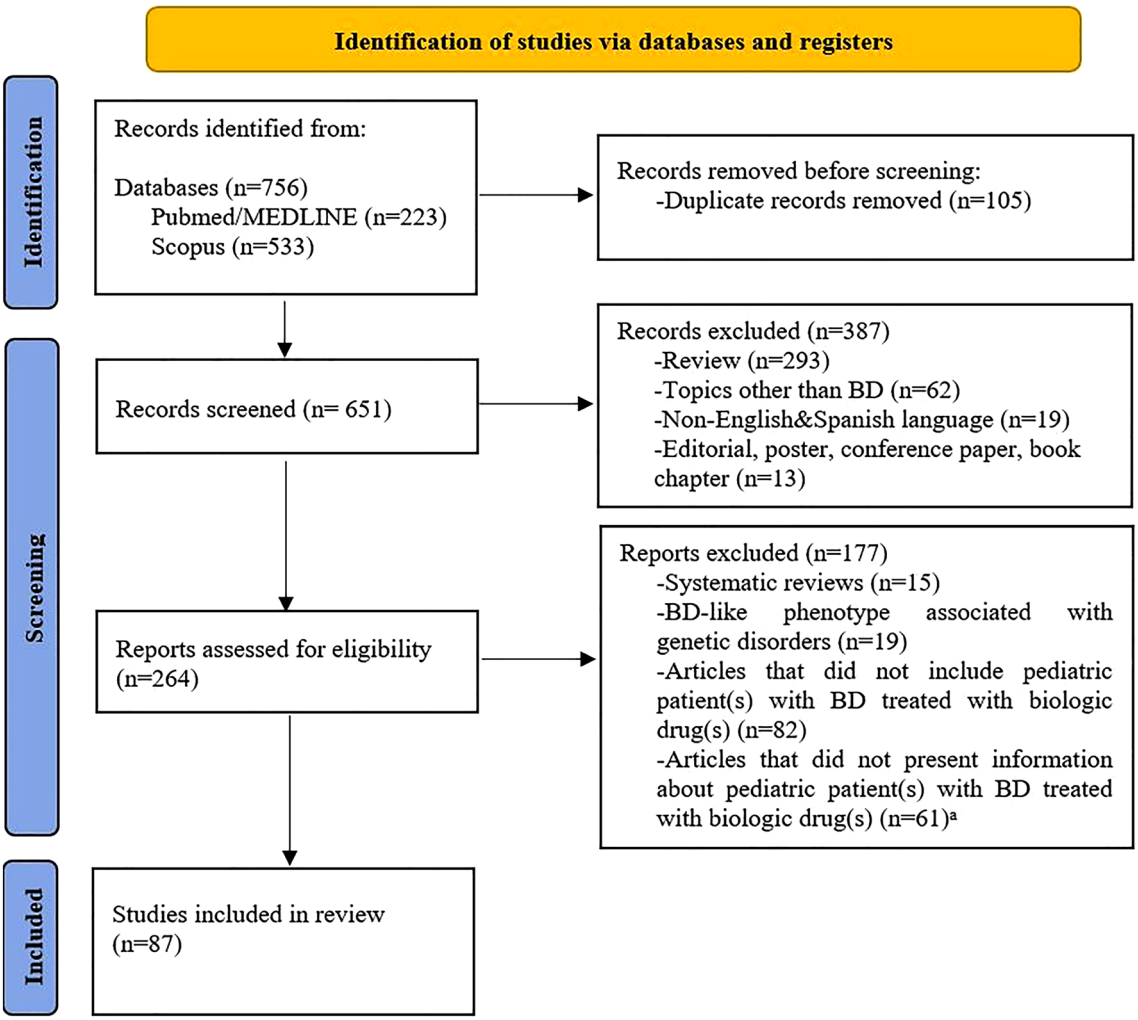

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the literature screening. *BD* Behçet's disease. [a]In 54 of these papers, pediatric BD cases may be present in the cohort; but no data attributed to pediatric patients with BD treated with biologic drugs were presented. In seven of these papers, pediatric patients with BD treated with biologic drugs were included. However, neither the number of these patients nor the type of biologic drug used was indicated

maintenance treatment and the disease remained stable under TNF-α inhibitors. In the rest of the treatment episodes, TNF-α inhibitors were used for treating active disease; improvement was achieved in 84 (78.5%) out of 107 episodes (Fig. 2). Furthermore, corticosteroid tapering was mentioned in 22 out of 84 treatments. The organ-specific improvement rate with TNF inhibitors was 76.7% (46/60) and 70% (7/10) for ocular and GIS involvements, respectively (Table 2). We also analyzed whether pediatric patients with BD experienced a relapse under TNF-α inhibitors during the 84 remedied treatment episodes. These data were available for 47 (out of 84) episodes. The patients had a relapse under TNF-α inhibitors during the follow-up in 10 (21.2%) of 47 treatment episodes (Fig. 2).

The most frequently used TNF-α inhibitor was infliximab (IFX) ($n = 62$), followed by adalimumab (ADA) ($n = 51$) (Table 3). The most common reason for initiating IFX and ADA were ocular involvement followed by thrombosis for IFX, and GIS involvement for ADA. The indications for different biologic drugs are presented in Fig. 3. For etanercept (ETN), multisystem active disease was the most frequent indication. Improvement rates for IFX, ADA, and ETN were 63.4% (26/41), 86.1% (31/36), and 87.5% (14/16), respectively (Fig. 2). The data regarding ETN use was limited ($n = 17$). Relapse rates during treatment were 27.3% and 11.8% for IFX and ADA, respectively. The data regarding relapses under ETN were available for only six treatments with no relapses.

Interferons were used by 21 patients, most frequently for ocular involvement (Table 2). Data regarding IFN responses were available in only ten patients and improvement was noted in seven (70%) (Fig. 2). Of note, three had a relapse

Table 1 The features of pediatric patients in the literature with Behcet's disease using biologic drug(s)

Number of patients, *n*	187
Number of biologic treatments, *n*	215
Age, years, median (minimum–maximum)	15 (1.3–17.7)
Sex, female, *n* (%)	36/86 (41.8)
Indication(s) for biologic treatment, *n* (%)	
Ocular involvement	93/175 (53.1)
Active disease with ≥ 2 systems involvement	29/175 (16.6)
GIS involvement	19/175 (10.8)
CNS involvement	13/175 (7.4)
Thrombosis	9/175 (5.1)
Mucocutaneous involvement	7/175 (4)
Arthritis	2/175 (1.1)
Cardiac involvement	1/175 (0.6)
Maintenance treatment	2/175 (1.1)
Positive pathergy test, *n* (%)	17/30 (56.6)
Positive HLA-B5/51, *n* (%)	26/39 (66.6)
Biologic drugs, *n* (%) (number of patients)	
Anti-TNF agents	155 (72.1)
Infliximab	62 (28.8)
Adalimumab	51 (23.7)
Etanercept	17 (7.9)
Unknown type of anti-TNF agent	35 (16.3)
Anti-IL-1 agents	8 (3.7)
Anakinra	7 (3.3)
Canakinumab	4 (1.9)
Tocilizumab	4 (1.9)
Interferons	21 (9.7)
Interferon-alfa	19 (8.8)
Interferon-beta	1 (0.5)
Interferon-gamma	1 (0.5)
Daclizumab	2 (0.9)
Rituximab	1 (0.5)
Other treatment, *n* (%)	
Corticosteroids	96/117 (82.1)
NSAIDs	14/117 (11.9)
Colchicine	45/117 (38.5)
Salazopyrin	8/117 (6.8)
Azathioprine	39/117 (33.3)
Methotrexate	19/117 (16.2)
Cyclosporine A	16/117 (10.9)
Cyclophosphamide	13/117 (11.1)
Mycophenolate mofetil	7/117 (5.9)
Thalidomide	3/117 (2.6)
Tacrolimus	2/117 (1.7)
IVIG	2/117 (1.7)
Hydroxychloroquine	1/117 (0.8)
Glatiramer acetate	1/117 (0.8)
Mizoribine	1/117 (0.8)
Unknown DMARD	29/117 (24.8)
Any DMARD	103/117 (96.2)
Anticoagulant and antithrombotic drugs	15/117 (12.8)
Surgery	4/117 (2.7)
ASCT	1/117 (0.8)
Duration of biologic treatment, months, median (minimum-maximum)[a]	12 (0.2-93.6)
Adverse event due to biologic drug use, *n* (%)	14/59 (23.7)

ASCT autologous stem cell transplantation, *CNS* central nervous system, *DMARD* disease-modifying anti-rheumatic drugs, *GIS* gastrointestinal system, *HLA* human leukcocyte antigen, *IL* interleukiinterleukin, *IVIG* intravenous immunoglobulin, *NSAID* non-steroidal anti-inflammatory drugs, *TNF* tumor necrosis factor

[a]The duration of biologic treatment was available for 60 biologic treatments

under IFN during the follow-up. The IFN dose was clearly mentioned for 11 patients. One patient received IFN as 5 MIU daily with the indication of ocular involvement. Visual acuity improved with IFN but IFN was later discontinued when the patient experienced a BD relapse with fever and erythema nodosum under IFN. Ten patients received IFN at a dose of 3 MIU three times a week. One of these patients had to stop treatment because of an early severe adverse event, and there was no clinical improvement with IFN in another patient. A clinical improvement was achieved in eight of the ten patients. In one of these patients whose uveitis improved with IFN at a dose of 3 MI three times a week at first, an increment to 6 MIU was required to induce remission when he experienced a uveitis relapse 1.5 years after the cessation of IFN treatment.

Anti-interleukin-1 (anti-IL-1) agents (11 treatments) were most commonly used for treating multisystem active disease followed by ocular involvement. Improvement was achieved in three (50%) out of six treatment episodes. Data about responses to anti-IL-1 treatment were not available in five treatment episodes.

Tocilizumab (four treatments) was used by four pediatric patients with BD for treating ocular involvement in two patients and multisystem active disease in the other two patients. Daclizumab ($n = 2$) and rituximab (RTX) ($n = 1$) were used for refractory ocular BD. No improvement was achieved with daclizumab, while ocular manifestations improved with tocilizumab and RTX.

Twenty-one patients received two or more biologic drugs, and the total number of biologic drug switches was 28. The data regarding biologic drug switches are presented in Fig. 4. The most frequent biologic drug switches were from anti-TNF to anti-TNF drugs ($n = 9$), followed by anti-TNF to tocilizumab ($n = 5$) and IFN to anti-TNF ($n = 5$). In one case, the switch was done for maintenance treatment, and the clinical outcome after the switch was not mentioned in four cases. In the rest of the switches ($n = 23$), clinical improvement was achieved in 74% ($n = 17$).

Table 2 Indications for biologic drugs, treatment responses, and adverse events in pediatric patients with Behcet's disease

Biologic drugs	Number of patients/biologic treatments	Duration of biologic treatment, months, median (minimum-maximum)	Reason for initiating biologic treatment[a]	Response to biologic treatment[a]	Relapse under biologic treatment (among improved)[a]	Adverse events[a]
Anti-TNF agents	155/176	12 (0.2–93.6)	Resistant/recurrent ocular manifestations ($n = 74$)	Improvement ($n = 46$) Corticosteroid tapering mentioned in 10/46 No improvement ($n = 14$) NA ($n = 14$)	10/47 NA = 37	Infusion reaction ($n = 1$) Bacterial endocarditis ($n = 1$) Fever ($n = 1$) Fatigue ($n = 1$) Herpes zoster pneumonia ($n = 1$) Recurrent sinusitis ($n = 1$) Tuberculosis ($n = 1$) Positive autoantibodies ($n = 1$)
			Active disease with ≥ 2 system involvement ($n = 21$)	Improvement ($n = 16$) Corticosteroid tapering mentioned in 4/16 No improvement ($n = 2$) NA ($n = 3$)		
			GIS involvement ($n = 19$)	Improvement ($n = 7$) Corticosteroid tapering mentioned in 3/7 No improvement ($n = 3$) NA ($n = 9$)		
			CNS involvement ($n = 10$)	Improvement ($n = 5$) Corticosteroid tapering mentioned in 2/5 NA ($n = 5$)		
			Thrombosis ($n = 7$)	Improvement ($n = 3$) Corticosteroid tapering mentioned in 1/3 No improvement ($n = 3$) NA ($n = 1$)		
			Resistant/recurrent mucocutaneous findings ($n = 6$)	Improvement ($n = 5$) Corticosteroid tapering mentioned in 2/5 NA ($n = 1$)		
			Refractory arthritis ($n = 2$)	Improvement ($n = 2$)		
			Cardiac involvement ($n = 1$)	No improvement ($n = 1$)		
			Maintenance treatment ($n = 2$)	Stable disease ($n = 2$)		
			NA ($n = 34$)	NA ($n = 34$)		

Table 2 (continued)

Biologic drugs	Number of patients/biologic treatments	Duration of biologic treatment, months, median (minimum-maximum)	Reason for initiating biologic treatment[a]	Response to biologic treatment[a]	Relapse under biologic treatment (among improved)[a]	Adverse events[a]
Interferons	21/21	17 (4.8-54)	Resistant/recurrent ocular involvement ($n = 11$)	Improvement ($n = 3$) No improvement ($n = 2$) NA ($n = 6$)	3/6 NA ($n = 1$)	Depression and agitation ($n = 1$) Major depression ($n = 1$) Elevated liver enzymes ($n = 1$) Retinal venous thrombosis ($n = 1$) Headache and flu-like symptoms ($n = 1$)
			CNS involvement ($n = 3$)	No improvement ($n = 1$) NA ($n = 2$)		
			Thrombosis ($n = 2$)	Improvement ($n = 2$)		
			Active disease with ≥ 2 systems involvement ($n = 2$)	Improvement ($n = 2$) Corticosteroid tapering mentioned in 2/2		
			NA ($n = 3$)	NA ($n = 3$)		
Anti-IL-1 agents	8/11	6 (1-19)	Active disease with ≥ 2 systems involvement ($n = 4$)	Improvement ($n = 1$) No improvement ($n = 1$) NA ($n = 2$)	1/3	None
			Resistant/recurrent ocular involvement ($n = 3$)	Improvement ($n = 1$) No improvement ($n = 2$)		
			Resistant/recurrent mucocutaneous findings ($n = 1$)	Improvement ($n = 1$)		
			NA ($n = 3$)	NA ($n = 3$)		
Tocilizumab	4/4	NA	Resistant/recurrent ocular involvement ($n = 2$)	Improvement ($n = 2$)	NA ($n = 4$)	None
			Active disease with ≥ 2 systems involvement ($n = 2$)	Improvement ($n = 1$) No improvement ($n = 1$)		
Daclizumab	2/2	NA	Resistant/recurrent ocular involvement ($n = 2$)	No improvement ($n = 2$)	NA ($n = 2$)	None
Rituximab	1/1	1	Resistant/recurrent ocular involvement	Improvement Corticosteroid tapering mentioned	No	Conjunctivitis and mild urticaria

CNS central nervous system, *GIS* gastrointestinal system, *IL* interleukin, *NA* not available, *TNF* tumor necrosis factor

[a]*N* for number of biologic treatments

Adverse events were mentioned for only TNF-α inhibitors, IFNs, and RTX in 14 treatments [16, 20, 27, 31, 33, 44, 51, 62, 92, 99] (Tables 2 and 3). In TNF-α inhibitors, the adverse events have been associated with IFX and ETN. However, there was one report of active tuberculosis with TNF-α inhibitors and the type of the TNF-α inhibitor (either

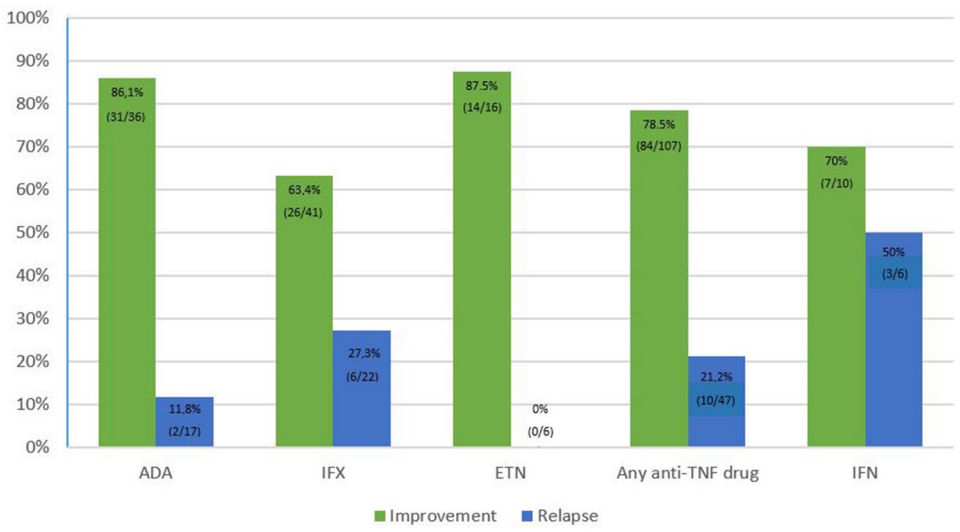

Fig. 2 Improvement and relapse rates with anti-tumor necrosis factor (TNF) drugs and interferons (IFNs) in children with Behçet's disease. *ADA* adalimumab, *ETN* etanercept, *IFX* infliximab

ADA or ETN) was not clear in this report [27]. Severe adverse events have been noted across six treatments, as follows: an infusion reaction that lead to drug discontinuation ($n = 1$; with IFX) [99], bacterial endocarditis ($n = 1$; with ETN) [31], *Herpes zoster* pneumonia ($n = 1$; with ETN) [51], active tuberculosis ($n = 1$; with ADA or ETN) [27], retinal vein thrombosis ($n = 1$; with IFN) [44], and major depression ($n = 1$; with IFN) [44].

4 Discussion

The presented systematic literature search is the most comprehensive analysis on biologic drug use in pediatric BD. Published data accumulate predominantly on TNF-α inhibitors, followed by IFNs as biologic drugs. Resistant ocular disease is the most frequent reason for biologic treatment. Biologic drug use has an acceptable safety profile in most pediatric patients with BD. However, it is not possible to make a fair comparison regarding the efficacy and safety of different biologic drugs based on the presented analysis, as the number of treatments, indications for biologic drugs, previous or concomitant medications, and disease activity were heterogeneous in the included patients.

Biologic drugs are frequently used in the treatment of severe ocular BD. Ocular involvement constitutes one of the major determinants of disease morbidity. Using TNF-α inhibitors or IFNs up-front instead of conventional synthetic DMARDs is recommended for treating sight-threatening uveitis in the 2018 update of European League Against Rheumatism recommendations for BD treatment [9]. Therefore, it is not surprising that severe ocular involvement was the main indication for initiating anti-TNF agents and IFNs in pediatric patients with BD.

Tumor necrosis factor-α inhibitors were most frequently used for ocular involvement followed by multisystem active disease. There was a high improvement rate (~ 80%) with TNF-α inhibitors, while the disease flared in around 20% of patients during anti-TNF treatment. The only randomized controlled trial on TNF-α inhibitor use in BD is with ETN, performed in 2005 [18]. This study showed that ETN was effective in suppressing mucocutaneous lesions in BD. There are two recent meta-analyses showing that TNF-α inhibitors are effective in the treatment of ocular BD and reduce the number of ocular disease recurrences [106, 107]. In the meta-analysis by Hu et al. [107], the inflammation remission rate was 68% and the visual acuity improvement rate was 60%. In a recent multicenter retrospective cohort study on refractory BD uveitis, remission was achieved in 76.5% of patients with IFX [108]. Similarly, the improvement rate was 76.7% in pediatric ocular BD, in our analysis. A recent meta-analysis has claimed an improvement rate of 70% with TNF-α inhibitors in intestinal BD [109]. This was also similar to the results of our analysis, which revealed a 70% improvement rate with anti-TNF drugs in GIS involvement of pediatric BD.

A notable feature in the pediatric BP literature is the preference of the monoclonal antibodies ADA and IFX to ETN in indications of ocular and GIS involvement. This was consistent with the international treatment recommendations for BD [9]. The evidence underlying this comes mainly from studies on ocular and GIS manifestations of other inflammatory diseases. A randomized, double-blind, placebo-controlled trial by Sandborn et al. [110] demonstrated that ETN was not effective for treating active Crohn's disease. There have also been reports of new-onset inflammatory bowel disease with the use of ETN in the treatment of other rheumatic diseases such as juvenile idiopathic arthritis, rheumatoid arthritis, and spondyloarthropathies [111–113]. On the same

Table 3 Indications for anti-TNF agents, treatment responses, and adverse events in pediatric patients with Behcet's disease

Anti-TNF drugs	Number of patients	Duration of biologic treatment, months, median (min-max)	Reason for initiating biologic treatment	Response to biologic treatment	Relapse under biologic treatment (among improved)	Adverse events
Infliximab	62	10 (0.2–72)	Resistant/recurrent ocular involvement ($n = 34$)	Improvement ($n = 15$) Corticosteroid tapering mentioned in 3/15 No improvement ($n = 8$) NA ($n = 11$)	6/22 NA ($n = 4$)	Infusion reaction ($n = 1$) Positive autoantibodies ($n = 1$)
			Thrombosis ($n = 7$)	Improvement ($n = 3$) Corticosteroid tapering mentioned in 1/3 No improvement ($n = 3$) NA ($n = 1$)		
			GIS involvement ($n = 6$)	Improvement ($n = 2$) Corticosteroid tapering mentioned in 1/2 No improvement ($n = 3$) NA ($n = 1$)		
			CNS involvement ($n = 6$)	Improvement ($n = 4$) Corticosteroid tapering mentioned in 1/4 NA ($n = 2$)		
			Resistant/recurrent mucocutaneous findings ($n = 1$)	Improvement ($n = 1$)		
			Cardiac involvement ($n = 1$)	No improvement ($n = 1$)		
			Active disease with ≥ 2 system involvement ($n = 4$)	Improvement ($n = 1$) NA ($n = 3$)		
			Maintenance treatment ($n = 1$)	Stable disease ($n = 1$)		
			NA ($n = 2$)	NA ($n = 2$)		

Table 3 (continued)

Anti-TNF drugs	Number of patients	Duration of biologic treatment, months, median (min-max)	Reason for initiating biologic treatment	Response to biologic treatment	Relapse under biologic treatment (among improved)	Adverse events
Adalimumab	51	17.5 (3–72)	Resistant/recurrent ocular involvement ($n = 29$)	Improvement ($n = 22$) Corticosteroid tapering mentioned in 6/22 No improvement ($n = 4$) NA ($n = 3$)	2/17 NA ($n = 14$)	None
			GIS involvement ($n = 10$)	Improvement ($n = 4$) Corticosteroid tapering mentioned in 2/4 NA ($n = 6$)		
			Resistant/recurrent mucocutaneous findings ($n = 4$)	Improvement ($n = 4$) Corticosteroid tapering mentioned in 2/4		
			CNS involvement ($n = 1$)	Improvement ($n = 1$) Corticosteroid tapering mentioned in 1/1		
			Active disease with ≥ 2 system involvement ($n = 1$)	No improvement ($n = 1$)		
			Maintenance treatment ($n = 1$)	Stable disease ($n = 1$)		
			NA ($n = 5$)	NA ($n = 5$)		
Etanercept	17	12 (6–93.6)	Resistant/recurrent ocular involvement ($n = 3$)	Improvement ($n = 1$) Corticosteroid tapering mentioned in 1/1 No improvement ($n = 2$)	0/6 NA ($n = 8$)	Bacterial endocarditis ($n = 1$) Fever ($n = 1$) Fatigue ($n = 1$) Herpes zoster pneumonia ($n = 1$) Recurrent sinusitis ($n = 1$)
			Refractory arthritis ($n = 2$)	Improvement ($n = 2$)		
			Resistant mucocutaneous findings ($n = 1$)	NA ($n = 1$)		
			Active disease with ≥ 2 system involvement ($n = 11$)	Improvement ($n = 11$) Corticosteroid tapering mentioned in 4/11		

CNS central nervous system, *GIS* gastrointestinal system, *NA* not available, *TNF* tumor necrosis factor

line, studies on uveitis associated with juvenile idiopathic arthritis or ankylosing spondylitis suggest an advantage of monoclonal anti-TNF agents over ETN [114–116]. In monoclonal TNF-α inhibitors, it is challenging to comment on the superiority of IFX or ADA in pediatric BD treatment. There are slightly more data on IFX than ADA use in pediatric BD (62 vs. 51 treatments, respectively), probably because IFX was the first available TNF-α inhibitor. The improvement rate was higher and relapse rates under treatment were lower with ADA than IFX. However, these figures may be biased as it is not possible to compare disease severity at the time of the initiation of biologic drugs. Another problem could be

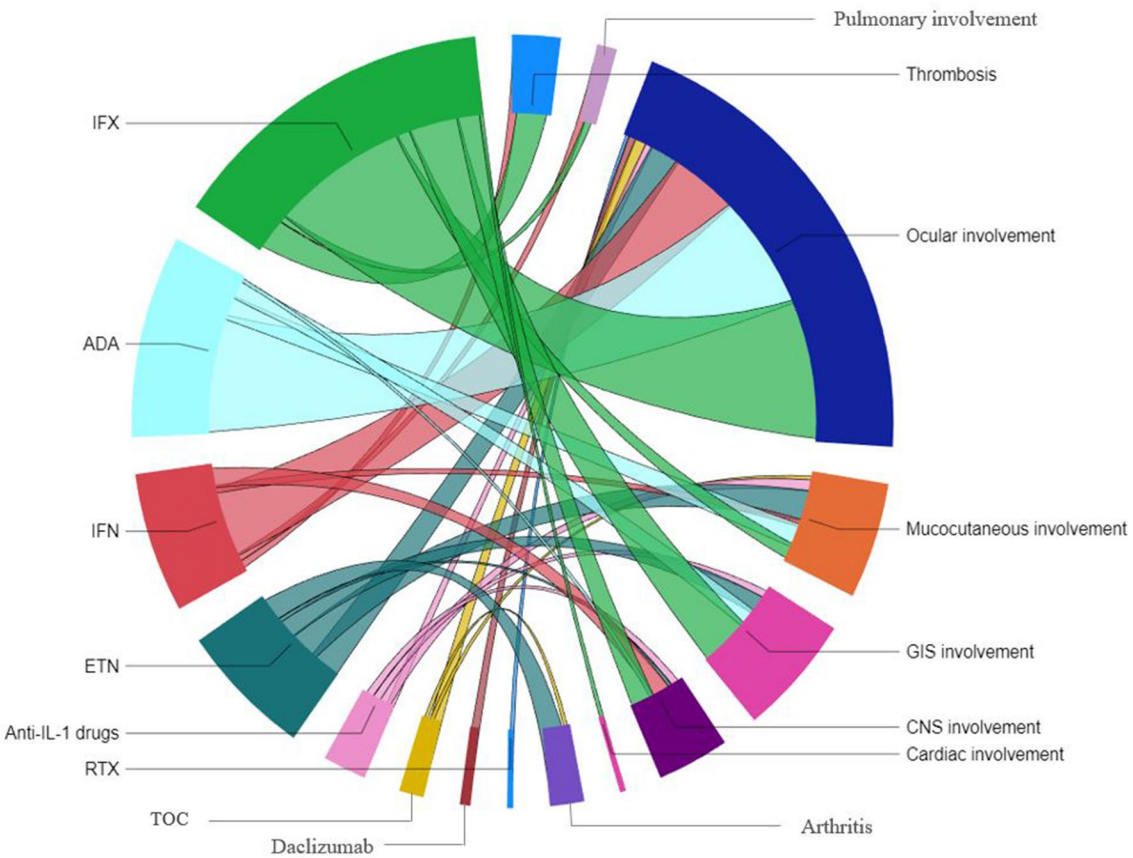

Fig. 3 Chord diagram representing the indications for biologic drug use in pediatric Behçet's disease. *ADA* adalimumab, *CNS* central nervous system, *ETN* etanercept, *GIS* gastrointestinal system, *IFN* interferon, *IFX* infliximab, *IL-1* interleukin 1, *RTX* rituximab, *TOC* tocilizumab

the reporting bias, as authors probably tend to report cases with a refractory disease course and with more striking features. Thus, the improvement rate drawn from these reports could be worse than the real-life situation. Controlled studies in pediatric patients with BD are required to determine the exact improvement and relapse rates with TNF-α inhibitors. Data from adult studies do not point to a clear superiority of IFX or ADA. However, better visual acuity was achieved with fewer drug-related adverse events in the ADA group in a multicenter adult study comparing ADA and IFX in the treatment of refractory ocular BD [117]. The intravenous route of administration (intravenous infusion over 2–3 h) and a higher rate of allergic reactions (because of its chimeric structure) could be the disadvantages of IFX compared with ADA.

Interferons were the second most frequently used biologic drugs in the pediatric BD literature but the data were limited (21 treatments). Interferons were the first biologic drugs to be used in BD treatment. In 2002, a randomized placebo-controlled trial by Alpsoy et al. [15] confirmed the efficacy of IFN-α2a in BD, especially with mucocutaneous involvement. Recently, Qian et al. [118] demonstrated that IFN-α2a was superior to cyclosporine A for treating refractory BD uveitis. One of the important advantages of IFNs over other biologic drugs is that IFN use does not introduce an increased risk for infections [8]. This may be a significant consideration especially during the coronavirus 2019 pandemic. The relatively higher frequency of adverse events such as flu-like symptoms and the risk of decreased efficacy with concomitant glucocorticoid use are the major drawbacks of IFN treatment [8]. Interferon doses significantly vary among different studies in the literature [118, 119]. It was administered at a dose range between 3 and 9 MIU with a frequency of three to seven times a week [118]. Different doses may have different effects on the clinical outcome. In our literature analysis, the IFN dose was similar (as 3 MIU three times a week) in most cases. It is noteworthy that one patient required a dose increment to 6 MIU for remission.

The data on the use of biologic drugs other than TNF-α inhibitors and IFNs are extremely limited in pediatric BD. Anti-IL-1 agents (11 treatments) were reported to be used especially for multisystem active disease and ocular BD. Anti-IL-1 agents are mainly used for treating refractory

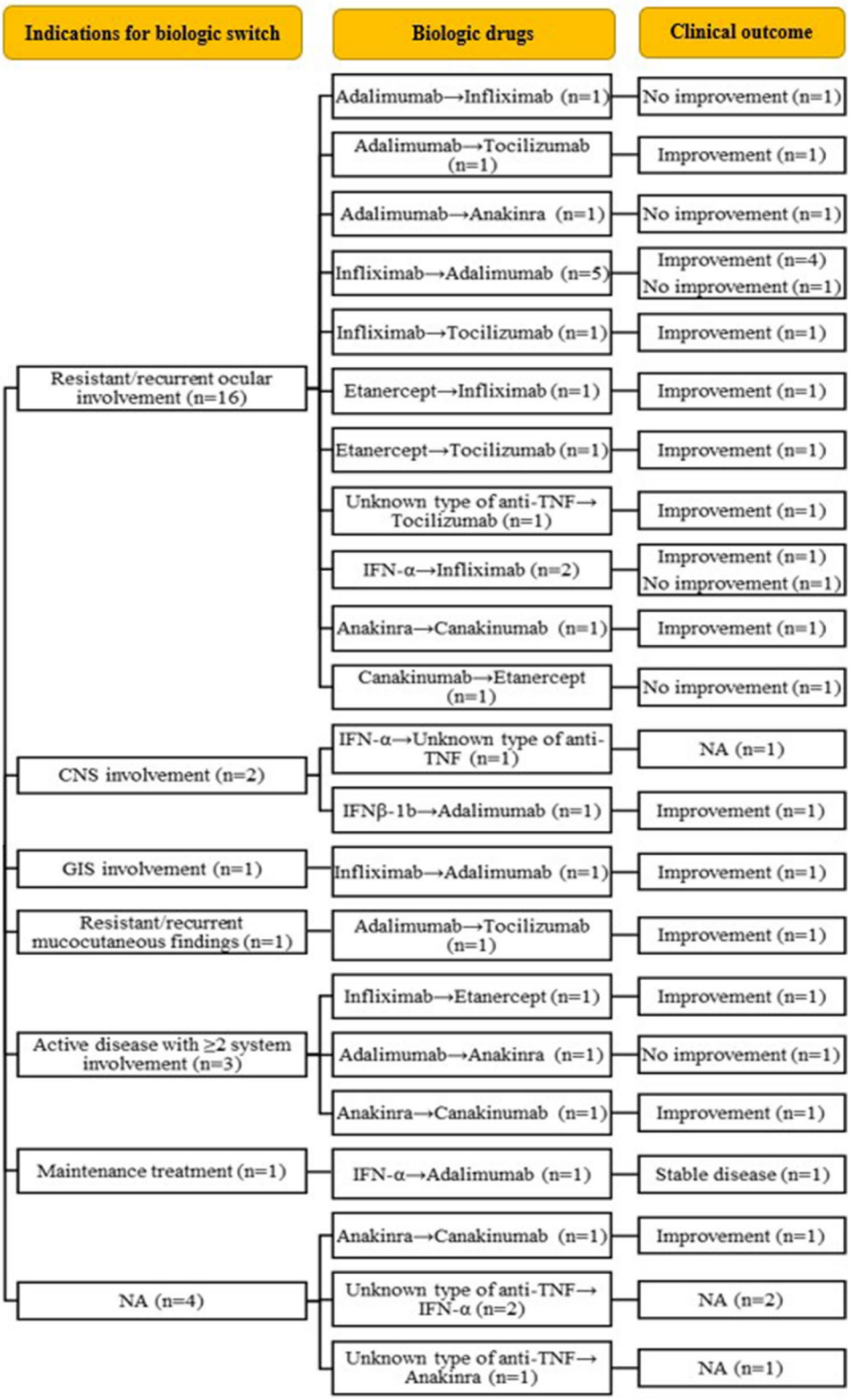

Fig. 4 Switches between biologic drugs in patients with pediatric Behçet's disease (total number of patients: 21; total number of switches: 28). *IFN* interferon, *NA* not available, *TNF* tumor necrosis factor

mucocutaneous and ocular involvement in adult BD [8]. However, the primary efficacy endpoint was not met in the only randomized controlled trial evaluating anti-IL-1 (gevokizumab; monoclonal anti-IL-1 antibody) use in the treatment of BD uveitis [120]. There are fewer than five treatments for other biologic drugs such as tocilizumab (*n*

= 4), daclizumab (n = 2), and rituximab (n = 1). Thus, it was not possible to draw conclusions about the indications or efficacy of these therapeutics. Furthermore, there are other biologic drugs such as drugs targeting the IL-23/IL-17 pathway that could be regarded as promising alternatives in BD [121, 122]. However, there is no previous report on the use of these drugs in pediatric BD.

Biologic therapy appears to be well tolerated in pediatric BD. Adverse events were reported during 14 treatments with TNF-α inhibitors, IFNs, and RTX. The higher frequency of TNF-α inhibitor use compared with other biologic drugs is probably an important factor affecting the frequency of adverse events. The adverse events were generally mild. However, severe adverse events were also reported during six treatments. There was only one report of active tuberculosis under TNF-α inhibitors (ADA or ETN) in pediatric patients with BD [27]. A higher rate of tuberculosis has been reported with monoclonal TNF-α inhibitors, ADA (~three-fold) and IFX (~four-fold), compared with ETN [123]. This may be an important consideration when deciding on the type of TNF-α inhibitor, especially in areas with endemic tuberculosis. It is noteworthy that the prevalence of BD is higher in "Silk Road" countries, where tuberculosis is not uncommon.

5 Conclusions

Biologic drugs, especially TNF-α inhibitors and IFNs, are increasingly used in the treatment of pediatric BD. These therapies had high improvement rates with an acceptable safety profile, and the involved organ systems appear to be the main determinant of the biologic drug use. However, the data come mainly from case reports or case series. The pediatric community needs controlled studies on biologic agents in pediatric BD.

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Declarations

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