Rheumatology International (2019) 39:1107–1112
https://doi.org/10.1007/s00296-019-04300-0

Rheumatology
INTERNATIONAL

CASES WITH A MESSAGE

Adalimumab in the treatment of pediatric Behçet's disease: case-based review

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Received: 5 March 2019 / Accepted: 2 April 2019 / Published online: 11 April 2019

Abstract

Behçet's disease (BD) is a systemic vasculitis affecting prominently the veins, which is usually diagnosed in adulthood, but can occur in children younger than 16 years in about 4–26% of cases. The therapy is based on several immune-suppressive drugs; in case of inadequate control and/or complications, the biologic therapy with anti-TNF drugs has been successfully used in adults. Here, we reported one pediatric case of BD with systemic (persistent/recurrent high fever), skin and mucosal manifestations (recurrent aphthous stomatitis, anal/penile ulcers, erythema nodosum and papulo-pustules), that were unresponsive to the conventional treatment with steroids and colchicine; however, he was successfully treated with adalimumab. Compared to adult patients, the experience with adalimumab in the treatment of pediatric BD is very limited. Indeed, through a systematic search in the medical literature, we retrieved 4 case reports and 2 case series, describing BD pediatric patients treated with adalimumab, in addition to three clinical studies including some BD children. The analysis and discussion of these available clinical experiences may indicate adalimumab as an effective and safe option to treat several forms of BD, in addition to BD-related chronic uveitis.

Keywords Behçet's disease · Adalimumab · Pediatric rheumatology

Introduction

Behçet's disease (BD) is a systemic vasculitis affecting prominently veins, although variable types of vessels can be involved. The main target organs are the oral and genital mucosae, skin and eyes; however, several systems can be affected by the inflammatory process of BD, leading to variable clinical presentations, which can make the final diagnosis challenging, especially in children [1, 2]. Indeed, BD is usually diagnosed in adulthood, with a peak of incidence between 25 and 40 years of age, and rarely occurs in children younger than 16 years, who account for 4–26% of cases. Moreover, the clinical onset is often insidious and the complete syndrome may develop over time. However, children with recurrent oral and genital ulcerations must be assessed for this diagnosis, especially if unusual and/or severe ocular (uveitis), articular, neurological and gastrointestinal manifestations are evident in the clinical history [3–5].

The general therapeutic approach to BD is based on the immunosuppression, ranging from topical/systemic corticosteroids and colchicine up to other immune-suppressive drugs, such as azathioprine, mycophenolate mofetil and thalidomide. In case of inadequate control, the biologic therapy with anti-TNF drugs has been widely described in adults, but much fewer cases have been reported in the pediatric age [6, 7]. Here, we report the successful management of one BD pediatric case by adalimumab and we provide a case-based review of pediatric cases managed in this way so far.

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Fig. 1 Aphthous stomatitis and oral ulcerations before (**a**) and after (**b**) the treatment with adalimumab in the presented pediatric patient affected with Behçet's disease

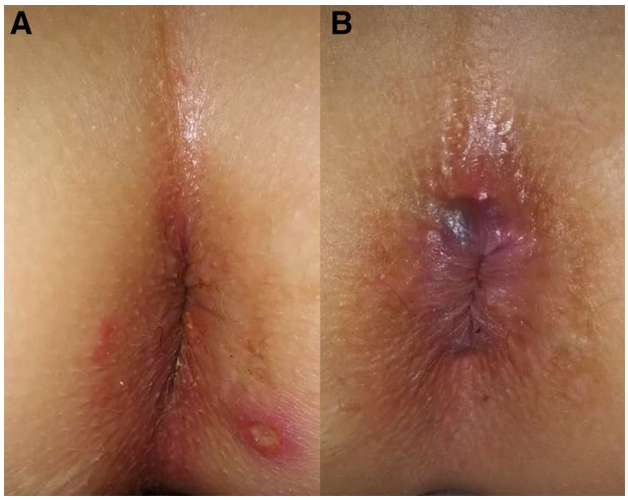

Fig. 2 Anal ulcers and skin lesions before (**a**) and after (**b**) the treatment with adalimumab in the presented pediatric patient affected with Behçet's disease

Clinical description

A 9-year boy (weight = 20 kg, height = 130 cm) was assessed at the Department of Pediatric Rheumatology of the National Research Center for Mother and Child Health (Astana, Kazakhstan), because of persistent illness for more than 3 years. Indeed, the patient reported recurrent aphthous stomatitis, anal/penile ulcers (Figs. 1a, 2a) and skin lesions (e.g., erythema nodosum and papulopustules), along with variable occurrence of high fever and diffuse arthralgia. No vomiting, diarrhea or abdominal pain were reported; occasional headache was referred, but no additional neurological manifestations were noticed. The first-level blood work-up during the acute episode at the admission showed leukocytosis, neutrophilia, thrombocytosis, microcytic anemia [white blood cells = 23,060/mm^3, hemoglobin = 10.8 g/dl, mean corpuscular volume = 74.9 fl, platelet count = 727,000/mm^3, neutrophils = 76.7%, lymphocytes = 15.7%, monocytes = 6.2%, eosinophils = 1%, basophils = 0.4%, ferritin = 34 ng/ml [normal values/n.v. 30–100 ng/ml]), in addition to a moderate elevation of acute inflammatory parameters (C-reactive protein = 41.2 mg/dl [n.v. < 5 mg/dl], erythrocyte sedimentation rate = 30 mm/h, [n.v. < 15 mm/h]). Moreover, an extended panel of microbiological investigations allowed to exclude any concomitant and significant viral and bacterial infection; the patient was even tested for parasite infestation, as he had been previously diagnosed with Ascariasis, although he was treated appropriately. Importantly, the autoimmunity panel resulted to be completely negative, with particular regard to anti-nuclear antibody (ANA), rheumatoid factor (RF), extractable nuclear antigens (ENA) and anti-dsDNA autoantibody. Finally, no serum antibody deficiency was detected and the lymphocyte immune phenotype did not show any abnormalities suggesting immunodeficiency and/or clonal proliferation. Therefore, no bone marrow examination was performed. According to the international diagnostic criteria [5, 8], the patient was diagnosed with BD, due to the presence of oral aphthae recurring more than three times a year, in addition to genital ulcerations and skin lesion. On the ocular examination, no signs of uveitis were found and no further complications were recorded. HLA genetic testing (as regards HLA-B27 and HLA-B51 in particular) was not available in our hospital.

Therefore, considering the acute and febrile illness and the compromised general clinical condition, at the diagnosis he received intra-venous methyl-prednisolone pulses (20 mg/kg/day for three consecutive days) and, then, oral prednisone (1 mg/kg/day), to be tapered over 4 weeks; in the meantime, the treatment with colchicine (1 mg/day) was started as well. However, while tapering the steroid treatment, he relapsed and needed further increases of the steroid regimen, despite the concomitant increase of colchicine dose up to 1.5 mg/day. Due to the unsatisfactory clinical response to the conventional therapy and the poor clinical condition (explained by his long-lasting clinical history before the diagnosis), he underwent the biological therapy with adalimumab (20 mg every other week), in addition to colchicine. After this therapeutic management, the clinical response was outstanding and rapid (within 2 weeks), as the patient was able to restart tapering the steroid therapy until complete withdrawal within 2 months and without any relapse. The skin and mucosal manifestations were completely controlled (as shown in Figs. 1b, 2b) and he is currently free

from any complaints for 6 months. Moreover, the general condition and nutritional status improved a lot: indeed, the patient gained 6 kg in weight after five months of treatment with adalimumab and, importantly, no adverse events were noticed.

Search strategy

In order to discuss the available evidences, we performed a systematic search in MEDLINE/PubMed and Scopus databases [8], retrieving all original publications (case–control study, cross-sectional, and retrospective cohort study, case-reports) on the use of adalimumab to treat pediatric BD. We searched all English-language articles published up to March 2019. The following search terms were used: (adalimumab AND pediatric AND Behçet) OR (adalimumab AND children AND Behçet). The reference lists of included articles were searched manually to identify and extract all potentially relevant articles. Exclusion criteria were review and non-English papers; only articles describing the treatment with adalimumab in patients younger than 18 years, have been considered in our discussion.

Discussion

Recently, Koné-Paut et al. revised 210 pediatric patients diagnosed with BD, in order to provide reliable diagnostic criteria for the pediatric onset of this disease. According to the 2015 PEDBD International classification criteria, the recurrence of oral aphthous lesions for at least three times per year, genital ulcers and typical skin manifestations (e.g., necrotic folliculitis, erythema nodosum, etc.) can be considered as being diagnostic for pediatric BD, regardless of the occurrence of ocular, vascular and neurological complications [9]. Therefore, our patient fulfilled these classification criteria and, importantly, other rheumatic and immune-mediated diseases were ruled out after a careful diagnostic work-up, as previously described.

Due to the long-lasting disease history before the diagnosis of BD, our patient presented very poor general conditions and his response to the conventional therapy was unsatisfactory, as he relapsed even before achieving a significant reduction of the steroid therapy. Several immunosuppressive drugs, including azathioprine and cyclophosphamide, could have been used as steroid-sparing drugs. Unfortunately, the strong systemic inflammatory response with high fever (despite no ferritin increase or other features of macrophage activation), the early relapse during steroid therapy and the poor nutritional condition required a rapid-acting therapeutic management [10, 11]. Therefore, the biological therapy was implemented before any trial with other conventional immunosuppressive drugs, whose full therapeutic action may require weeks or months. In compliance with the local drug availability and national regulatory policy, the patient received adalimumab, as anti-TNF therapy, and the clinical response was rapid, impressive and complete.

The effectiveness of adalimumab in adult patients with BD has been well defined. In 2016, Vallet et al. published the results of a multicenter study showing comparable efficacy of infliximab and adalimumab in severe and refractory BD patients [12]. Similarly, Calvo-Rio et al. obtained positive results with both adalimumab and infliximab in their interventional, open-label, multi-center study about BD uveitis refractory to conventional treatment [13]. Additional cohort studies supported the efficacy of adalimumab in BD patients, including some cases poorly responsive to infliximab [14–16].

Conversely, whereas the use of adalimumab is well described and consolidated in several pediatric rheumatic diseases [17], the experience with this drug to treat pediatric BD is much more limited, due to its rare occurrence in childhood [5, 18].

Through a systematic search in MEDLINE/PubMed and Scopus databases, we retrieved 4 case reports and 2 case series, describing BD pediatric patients treated with adalimumab, as summarized in Table 1 [19–24]. Moreover, three additional clinical studies, including some BD pediatric patients, have been found; unfortunately, only aggregated data were presented in those studies and, therefore, we could not extract any specific information on patients treated with adalimumab [25–27].

Robinson et al. first reported the use of adalimumab to treat a 12-year-old child with neuro-BD, which resulted in the resolution of both systemic and neurologic symptoms [19]. Similarly, Marsili et al. reported the successful treatment of a 15-year-old boy developing sensorineural hearing loss, as a complication of neuro-BD [22]. Lim et al. reported the case of a 5-year-old BD patient developing multiple aseptic splenic abscesses: due to the recurrence of skin, mucosal and gastrointestinal symptoms, he was treated with adalimumab, leading to symptoms resolution and improvement of colon endoscopic findings [23]. Thus, all these patients were successfully treated by adalimumab. Conversely, the 9-year-old male patient described by Pagnini et al. did not respond to adalimumab, despite the concomitant therapy with mofetil-mycophenolate, and he needed to switch to other biologics (e.g., IL-1 antagonists) [21].

Additional experiences with adalimumab have been provided by the following articles including pediatric BD patients, which specifically aimed to investigate this biologic treatment in uveitis. Actually, Interlandi et al. specifically analyzed the effectiveness of adalimumab in their cohort of BD patients, where even three pediatric cases have been included. These three children were reported to

Table 1 Reported cases of pediatric Behçet's disease BD pediatric patients treated with adalimumab [19–24]

Authorship (year, type of article)	Age (years)	Sex	Major organ involvement [indication]	Previous therapy	Adalimumab dose	Concomitant therapy	Clinical response	Side effects	Follow-up	Refs.
Robinson et al. (2010, case report)	12	F	Central nervous system	PDN AZA	40 mg every 2 weeks	–	Complete	None	12 months	[19]
Interlandi et al. (2014, case series)	8 15 16	M M M	Uveitis	DMARDs IFX (first two patients only)	40 mg every 2 weeks	DMARDs	Complete	None	Variable (mean = 21 months)	[20]
Pagnini et al. (2015, case report)	9	M	Skin and systemic symptoms	Colchicine Thalidomide PDN	24 mg/m^2 every 2 weeks	MMF	Incomplete	None	"Few months"	[21]
Marsili et al. (2016, case report)	15	M	Neuro-vestibular system and uveitis	PDN Colchicine	24 mg/m^2 every 2 weeks	–	Complete	None	24 months	[22]
Lim et al. (2017, case reports)	5	M	Skin, abdominal and systemic symptoms	PDN Colchicine IFX	40 mg (first administration), then 20 mg every 2 weeks	–	Complete	None	3 months	[23]
Atienza-Mateo et al. (2018, case series)	16	M	Uveitis	AZA IFX	N/A	AZA	Incomplete	N/A	N/A	[24]

PDN prednisone, *AZA*: azathioprine, *DMARDs* disease-modifying anti-rheumatic drugs, *IFX* infliximab, *MMF* mofetil mycophenolate, *N/A* information not available

obtain a complete clinical response and, interestingly, two of them switched from infliximab because of loss of therapeutic effect [20]. In the study by Atienza-Mateo et al. assessing the efficacy of tocilizumab in refractory uveitis associated with BD, there was a 16-year male who also received (unsuccessfully) adalimumab, before switching to anti-IL-6 biological therapy [24]. Therefore, very few experiences with adalimumab in BD children are available so far: most of them suggested that adalimumab can be an effective and, importantly, safe (as no adverse effect has been reported in this clinical setting, see Table 1) option to treat several clinical forms of BD.

Finally, we retrieved three studies mentioning the use of adalimumab in BD pediatric patients, without any further specifications. Nanthanpisal et al. described the clinical characteristics of 46 pediatric patients with BD diagnosed in a tertiary hospital in UK: among them, 5 patients received adalimumab at some time point of their therapeutic management, but the authors did not report any specific analysis about the response to each specific treatment [25]. Similar considerations can be done for the prospective study by Simonini et al. (including two cases of BD-related childhood refractory uveitis) [26], and the retrospective analysis by Deitch et al. including four BD pediatric patients in a study where both adalimumab and infliximab were used, with no specification about the individual treatments [27].

In conclusion, compared to adult patients, the experience with adalimumab in the treatment of pediatric BD is very limited; however, almost all available reports, including this article, may support the effectiveness and safety of this biological therapy in children with BD. Additional and larger studies are required to establish the exact therapeutic role of adalimumab in this clinical context.

Author contributions DP conceived and wrote the article, and provided contribution to the clinical management; ZM and MA cooperated in the clinical management and provided important intellectual contributions; KD cooperated in the literature search and patient's management.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Informed consent The guardian and the patient provided informed written consent for this publication.

References

1. Seyahi E (2019) Phenotypes in Behçet's syndrome. Intern Emerg Med. https://doi.org/10.1007/s11739-019-02046-y **(Epub ahead of print)**
2. Borlu M, Uksal U, Ferahbas A, Evereklioglu C (2006) Clinical features of Behcet's disease in children. Int J Dermatol 45:713–716
3. Karincaoglu Y, Borlu M, Toker SC et al (2008) Demographic and clinical properties of juvenile-onset Behçet's disease: a controlled multicenter study. J Am Acad Dermatol 58:579–584
4. Yazici H, Ugurlu S, Seyahi E (2012) Behçet's disease, is it one condition? Clinic Rev Allerg Immunol 43:275–280
5. Koné-Paut I (2016) Behçet's disease in children, an overview. Pediatr Rheumatol Online J 14:10
6. Hatemi G, Silman A, Bang D et al (2008) EULAR recommendations for the management of Behçet disease. Ann Rheum Dis 67:1656–1662
7. Emmi G, Bettiol A, Silvestri E, Di Scala G, Becatti M, Fiorillo C, Prisco D (2018) Vascular Behçet's syndrome: an update. Intern Emerg Med. https://doi.org/10.1007/s11739-018-1991-y **(Epub ahead of print)**
8. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417
9. Koné-Paut I, Shahram F, Darce-Bello M et al (2016) Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: pEDBD. Ann Rheum Dis 75:958–964
10. Caso F, Costa L, Rigante D, Lucherini OM et al (2014) Biological treatments in Behçet's disease: beyond anti-TNF therapy. Mediators Inflamm 2014:107421
11. Poddighe D, Cavagna L, Brazzelli V, Bruni P, Marseglia GL (2014) A hyper-ferritinemia syndrome evolving in recurrent macrophage activation syndrome, as an onset of amyopathic juvenile dermatomyositis: a challenging clinical case in light of the current diagnostic criteria. Autoimmun Rev 13:1142–1148
12. Vallet H, Seve P, Biard L et al (2016) Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis: a multicenter study from the French uveitis network. Arthritis Rheumatol 68:1522–1530
13. Calvo-Río V, Blanco R, Beltrán E et al (2014) Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology (Oxford) 53:2223–2231
14. Vitale A, Emmi G, Lopalco G et al (2017) Adalimumab effectiveness in Behçet's disease: short and long-term data from a multicenter retrospective observational study. Clin Rheumatol 36:451–455
15. Tanida S, Inoue N, Kobayashi K et al (2015) Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Clin Gastroenterol Hepatol 13:940–948
16. Martín-Varillas JL, Calvo-Río V, Beltrán E et al (2018) Successful optimization of adalimumab therapy in refractory uveitis due to Behçet's disease. Ophthalmology 125:1444–1451
17. Poddighe D, Romano M, Gattinara M, Gerloni V (2018) Biologics for the treatment of juvenile idiopathic arthritis. Curr Med Chem 25:5860–5893
18. Gallizzi R, Pidone C, Cantarini L et al (2017) A national cohort study on pediatric Behçet's disease: cross-sectional data from an Italian registry. Pediatr Rheumatol Online J 15:84
19. Robinson AB, Gallentine WB, Rabinovich CE (2010) Pediatric neuro-Behçet's disease responsive to adalimumab. Pediatr Neurol 43:291–293
20. Interlandi E, Leccese P, Olivieri I, Latanza L (2014) Adalimumab for treatment of severe Behçet's uveitis: a retrospective long-term follow-up study. Clin Exp Rheumatol 32:S58–S62
21. Pagnini I, Bondi T, Simonini G, Giani T, Marino A, Cimaz R (2015) Successful treatment with canakinumab of a paediatric patient with resistant Behçet's disease. Rheumatology (Oxford) 54:1327–1328

22. Marsili M, Marzetti V, Lucantoni M, Lapergola G, Gattorno M, Chiarelli F, Breda L (2016) Autoimmune sensorineural hearing loss as presenting manifestation of paediatric Behçet disease responding to adalimumab: a case report. Ital J Pediatr 42:81
23. Lim KI, Yang DH, Ryoo E (2017) Behçet's disease with multiple splenic abscesses in a child. Intest Res 15:422–428
24. Atienza-Mateo B, Calvo-Río V, Beltrán E et al (2018) Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behçet's disease: multicentre retrospective study. Rheumatology (Oxford) 57:856–864
25. Nanthapisal S, Klein NJ, Ambrose N, Eleftheriou D, Brogan PA (2016) Paediatric Behçet's disease: a UK tertiary centre experience. Clin Rheumatol 35:2509–2516
26. Simonini G, Taddio A, Cattalini M et al (2013) Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis. Pediatr Rheumatol Online J 11:16
27. Deitch I, Amer R, Tomkins-Netzer O, Habot-Wilner Z, Friling R, Neumann R, Kramer M (2018) The effect of anti-tumor necrosis factor alpha agents on the outcome in pediatric uveitis of diverse etiologies. Graefes Arch Clin Exp Ophthalmol 256:801–808