Adamantiades-Behçet's disease therapy: current treatment options and recommendations with regard to the COVID-19 pandemic

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Abstract

Adamantiades-Behçet's disease (ABD) is a chronic, idiopathic, relapsing immune-mediate disease that may involve multiple organs. It is characterized by recurrent oral and genital ulcers, skin lesions, ocular, gastrointestinal, vascular, neurological and joint involvement. It can lead to significant morbidity and mortality. Due to its heterogeneity in clinical findings and physiopathology, its treatment can be various as ABD manifestations in different organs may differently respond to the same drug. The cornerstone of therapy for inducing remission is systemic corticosteroid, whereas immunomodulatory and immunosuppressive agents such as colchicine, azathioprine, cyclosporine-A, interferon-alpha, and cyclophosphamide are used as steroid-sparing agents and to prevent relapses. For aggressive, refractory or frequently relapsing cases, tumor necrosis factor (TNF) alpha inhibitors (infliximab, adalimumab, etanercept) have been reported beneficial. Herein, we describe our experience of 7 patients treated with TNF-alpha inhibitors with recommendations regarding treatment choice during the COVID-19 era.

KEYWORDS
Adamantiades-Behçet's disease, COVID, therapy, TNF alpha inhibitors

1 | INTRODUCTION

Adamantiades-Behçet's disease (ABD) is a complex autoinflammatory, multiorgan disease characterized by a chronic recurrent relapsing course.[1] ABD impacts severely on the quality of life and can cause mortality.[2] A coordinated multidisciplinary approach is necessary for optimal patients' care. The main goals of the treatment are controlling clinical manifestations, decreasing inflammation, suppressing the immune system, and preventing secondary organ damage.[3] Overall, therapy should be based on patients' characteristics (gender, age, comorbidities) as well as on the heterogeneity of the clinical manifestations (organ involvement, severity, natural course) considering the three major ABD phenotypes, notably the mucocutaneous and articular phenotype, the extra-parenchymal neurological and peripheral vascular phenotype, and the parenchymal neurological and ocular phenotype.[4] Therapeutic approaches can be difficult especially in case of ocular, gastrointestinal, neurological and vascular involvement.[5] While mucocutaneous and joint involvement are related more to disability and quality of life impairment, ocular-vascular-neurological-gastrointestinal involvement can cause serious morbidities leading even to death.[6] High-dose systemic corticosteroids and immunosuppressive therapies (see Appendix) are considered first line treatments and generally result in good responses. However, their long-term use is limited by side effects and possible contraindications. Furthermore, although disease manifestations may improve over time, it is still not clear how long treatments should be given to patients with inactive ABD. Recommendations and treatment guidelines have been developed by the European League Against Rheumatism (EULAR).[7] In the appendix to this article, treatments are summarized according to symptoms and organ involvement in a dedicated table.

New therapeutic strategies, such as targeted treatments, are increasingly used in the management of ABD with short- and long-

term efficacy and positive benefit/risk ratio. The most commonly reported drugs are tumor necrosis factor - alpha inhibitors (TNFi), such as infliximab and adalimumab, followed by etanercept especially for mucocutaneous manifestations.[8] These target therapies allow tapering steroids and maintaining medium/long term remission with good safe profile. Preliminary results confirm efficacy in combination with other immunomodulatory agents, although large randomized trials are missing due to the low incidence of ABD.[9] In this worldwide health emergency of COVID-19 outbreak, therapeutic options and management of ABD should be developed considering particularly the risk of infection and its serious course.

In the present article, we report our experience on the use of TNFi in a series of 7 patients diagnosed with ABD and treated during pandemic.

2 | CASE SERIES

From 2015 to 2021, 7 patients diagnosed with ABD according with "The International Criteria for Behçet's Disease (ICBD)"[10] were treated with TNF alfa inhibitors at the Dermatology Department of the University Hospital of Trieste, Italy. Patients signed an informed consent allowing the use of their data for scientific reports. Demographical and clinical data are summarized in Table 1. In short, the cohort of patients included 6 women and 1 man (median age 51.5 years, range 27–71). Three out 6 women presented comorbidities, which included thyroiditis and optical neuritis in one patient, alopecia areata, cataract and intestinal polyposis in another and diabetes in the last one. Prior to TNFi, all patients received immunosuppressive/modulatory treatments which encompass systemic corticosteroids ($n = 7$), colchicine ($n = 7$), rebamipide, thalidomide ($n = 4$), azathioprine ($n = 7$) and cyclophosphamide ($n = 1$). Most frequent clinical manifestations were oral and genital aphthosis. Skin lesions were diagnosed in all patients and included erythema nodosum and pseudofolliculitis. Recurrent arthritis was recorded in 6 out 7 patients, while neurological manifestations were detected in 3 patients and consisted mainly of parenchymal with mental changes, such as cognitive dysfunction and multiple sclerosis-like symptoms, without specific MRI findings. Gastrointestinal illness similar to a non-specific inflammatory bowel disease, recurrent lower limbs thrombophlebitis and posterior uveitis were the other clinical manifestations. All patients were positive to Pathergy test, and 4 out 7 tested positive for HLA-B51. Targeted regimen has been TNF-alpha inhibitors combined with anticoagulation therapy in patients with recurrent thrombosis. The choice of the targeted therapy among infliximab, adalimumab and etanercept was made upon availability and experience. The schedule of infliximab administration has been 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks intravenously; subcutaneous adalimumab started with a loading dose of 80 mg once, followed by 40 mg in the following week and 40 mg every 2 weeks thereafter; subcutaneous etanercept has been given either 25 mg twice weekly or 50 mg once weekly. All patients responded to their treatment without consistent side effects. Patients complained mild and self-healing pain in site of injection with etanercept and adalimumab and headaches with infliximab infusion. They did not report infections, namely tuberculosis, autoantibody formation, drug-induced lupus erythematosus, liver function abnormalities, hematological as well as other malignancies. Flares have been controlled by periodic administration of systemic corticosteroids or azathioprine. Patients are still on the same treatment.

3 | DISCUSSION

TNF-alpha inhibitors are the most frequently reported and used targeted therapies in ABD patients.[8,11,12] As confirmed by our observations, they combine great efficacy and safety for all clinical ABD manifestations.[9] Although the exact etiopathogenesis of ABD is unknow, it has been shown that ABD is associated with altered and increased levels of TNF-alpha.[9] Most early data on TNF-alpha inhibitors in ABD refer to the drugs infliximab and adalimumab, and later etanercept.[8,13] Both former are IgG1 monoclonal antibodies, which bind to TNF-alpha, preventing the activation of its receptor. Infliximab is a mouse/human chimeric antibody, while adalimumab is a humanized antibody. Etanercept has been shown to effectively suppress mucocutaneous lesions in ABD patients.[12] It is a fully recombinant molecule consisting of two soluble TNF receptor (p75) subunits fused to the Fc portion of human IgG1.[14]

Up to date only few prospective and retrospective clinical trials have investigated the efficacy and safety of TNF-alpha inhibitors in ABD[9] and most of the current knowledge is based on small observational studies and case series or reports.[9] This is not surprising as for every rare disease, enrollment of a sufficient high number of patients and randomization is difficult to achieve.[6] In our series of 7 patients, 3 patients without ocular involvement were treated with etanercept with good response confirming the findings of Melikoglu et al.[15] who compared etanercept with placebo in suppressing most mucocutaneous manifestations of ABD. Other prospective and retrospective trials have compared anti TNF-alpha with disease modifying antirheumatic drugs (DMARDs) or corticosteroids, mostly in uveitis, gastrointestinal and vascular manifestations confirming efficacy and safety of infliximab and adalimumab.[9] Vallet et al.[8] published in 2015 a retrospective multicentric study including 124 patients with severe and/or refractory ABD treated either with adalimumab or infliximab. They reported an overall response rate of 90%. In detail clinical responses were observed in 96%, 88%, 70%, 78%, 92%, and 67% of patients with severe and/or refractory ocular, mucocutaneous, joint, gastrointestinal manifestations, central nervous system manifestations and cardiovascular manifestations, respectively. Anti-TNF efficacy, regarding infliximab or adalimumab, did not differ with therapy regimen, namely monotherapy or an association with immunosuppressive agents.[8] Notwithstanding, TNF-alpha treatment impacted on flares and relapses and allowed tapering or suspending systemic corticosteroids.[8]

TNF-alpha inhibitors' safety profile has been proven in large studies for international authority drug approval for psoriasis, but its

TABLE 1 Demographic and clinical data of patients with severe ABD submitted to anti - TNF alpha therapy

Pz. Nr	Age at treatment start	Gender	Previous treatments	Median time to relapse (mo)	Organs involved / symptoms	TNFi	Overall cycles (mo of treatment)	Assessment at latest follow up
1	68	F	SC, colchicine, thalidomide, AZA	4	Mucocutaneous, joints, ocular	Infliximab	48	Complete remission, some flares controlled by SC
2	71	F	SC, colchicine, thalidomide, AZA,	5	Mucocutaneous, vascular, ocular, joints	Etanercept	30	Partial remission, association with AZA
3	42	F	SC, colchicine, AZA, rebamipide	6	Mucocutaneous, gastrointestinal, neurological, joints	Infliximab	20	Complete remission, some flares controlled by SC or AZA
4	48	F	SC, colchicine, AZA	4	Mucocutaneous, joints, neurological	Infliximab	40	Partial remission
5	55	F	SC, colchicine, thalidomide, AZA	8	Mucocutaneous, ocular, joints	Etanercept	42	Partial remission
6	35	M	SC, colchicine, thalidomide, AZA, cyclophosphamide	4	Mucocutaneous, ocular, vascular	Etanercept	24	Partial remission, flares controlled by SC or AZA
7	27	F	SC, colchicine, AZA, rebamipide	5	Mucocutaneous, gastrointestinal, neurological, joints	Adalimumab	22	Complete remission

Abbreviations: AZA, azathioprine; F, female; M, male; mo, months; SC, systemic corticosteroid.

efficacy has been confirmed also in ABD. Among one of the most common known side effects are viral upper respiratory infections. With the COVID-19 outbreak, questions about disease-related immunosuppression and treatments in autoinflammatory diseases such as ABD have been posed. Elmas et al.[16] reviewed the recommendations from task force of the American College of Rheumatology, the European League Against Rheumatism and the International Society for Behçet disease stating that there is no reason to discontinue topical treatments, colchicine, and nonsteroidal anti-inflammatory drugs. Systemic steroids should be used at the lowest possible dose if needed and ongoing treatments can be continued unchanged in patients with no suspected or confirmed COVID-19 infection.[16] In patients with COVID-19 symptoms, immunosuppressive and targeted drugs can be temporarily suspended, but the decision should be made on a case-by-case basis considering the potential beneficial effects on the course of COVID-19. Colchicine, pentoxifylline, and dapsone can be indeed considered as safe treatment options in ABD. The therapy with TNF-alpha inhibitors has controversial indications in case of COVID-19 infection, as those drugs increase the risk of infection, but on the other side they inhibit proinflammatory cytokines with potential protective effects against cytokine storm observed in COVID-19.[16] Suggestions on this issue include postponing the initiation of targeted therapy and continuing in case of non-suspected or non-confirmed COVID-19 and evaluating on a case-by-case basis for patients with suspected or confirmed COVID-19.[16]

In our cohort, no patient suspended anti-TNF-alpha treatment and all patients were followed-up in short intervals. Up to date none of them had suffered from COVID-19 infection.

Nowadays, another issue has arisen about COVID-19 vaccines in ABD patients. Currently available COVID-19 vaccines are non-live vaccines, based on mRNA or on protein-based or on non-replicable viral vectors. Because of their features, they have been considered safe also in patients with immune-mediated diseases and in patients on immunosuppressant therapy, therefore the EULAR task force declared that there is no reason to withhold these vaccines from those patients. The published suggestion is to give vaccine, when possible, during a quiet phase of the disease and to vaccinate before planned immunosuppression, because usually the efficacy of a vaccine is lower when patients are immunosuppressed.[17]

4 | CONCLUSIONS

In conclusion, ABD is a complicated multi-organ syndrome and its treatment is challenging as different organs respond differently to the currently available drugs. Despite the involvement of different organs, disease activity and severity, failure to previous treatments, co-morbidities as well as drug availability, related costs and tolerance play a role in the most adequate therapeutic decision. Novel treatments, in particular targeted agents such as TNF-alpha inhibitors, represent new therapeutic options either alone or in combination with the potential to positively impact on the prognosis of ABD. Based on current knowledge they appear safe even during the COVID-19 pandemic era.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study conception and design: Sara Trevisini, Giusto Trevisan, Serena Bonin. *Acquisition of data*: Sara Trevisini, Giusto Trevisan, Iris Zalaudek. *Analysis and data interpretation*: Sara Trevisini, Giusto Trevisan, Iris Zalaudek. *Drafting of manuscript*: Sara Trevisini, Giusto Trevisan, Serena Bonin. *Critical revision*: Iris Zalaudek.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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APPENDIX A

See Table A1.

TABLE A1 Main therapies for ABD treatment

Topical (mainly for mucocutaneous and ocular manifestations)	
Treatment	**Comment**
Corticosteroids (0.1% triamcinolone acetonide cream or other potent corticosteroid 3–4 times a day) or intralesional corticosteroids (triamcinolone 5–10 mg/ml)[18]	Initial therapy for isolated aphthosis. Overall, for oral aphthae any traumatism should be avoided maintaining proper oral care
Corticosteroids and dilating drops (scopolamine 0.25% or cyclopentolate 1%)	Dilating drops relieve pain due to spasm of the muscles controlling the pupil and also helps preventing the formation of posterior synechiae. If not controlled with topical corticosteroids, a short-term period with systemic glucocorticoids (oral prednisone 40 mg daily tapering over 1 month) can be necessary
Intraocular triamcinolone	May be beneficial for pan-uveitis for 2–6 months[19]
Intravitreal corticosteroid implants	Limited data[20, 21]
Sucralfate 1 g/5 ml	In combination with or as an alternative to topical corticosteroids to reduce pain and healing time[22]
Pimecrolimus	Can improve healing time[23]
Anesthetics (lidocaine 2%–5%, mepivacaine 1.5%, tetracaine 0.5%–1% gel, or mucosal ointments) and silver nitrate	To decrease pain severity in aphthous lesions[3]
Other anti-inflammatory agents (benzydamine hydrochloride, amlexanox, topical prostaglandin E2 gel)	To decrease pain in oral ulcers[3]
Antibiotic and antiseptic mouthwash (minocycline, tetracycline, chlorhexidine)	To reduce the microbial load and pain
Nd:YAG laser	To reduce pain and decrease healing time[24]
Medications for pyoderma gangrenosum—like lesions	Wounds should be cleansed prior to change dressing, which should promote a moist environment without adhering to the wound
Surgery	For pyoderma gangrenosum debridement is suggested only in specific cases where necrotic tissue could give infection, otherwise it should be avoided because of the pathergy phenomenon
Total parenteral, enteral nutrition, surgery	Gastrointestinal involvement
Systemic	
Colchicine 1–2 mg/day in multiple doses (titrated to a dose without gastrointestinal side effects)	For mucocutaneous involvement, it is the first line therapy to prevent recurrent oral and genital ulcers. The effect of colchicine in patients with minor oral ulcers or genital lesions is variable, and generally, it is more favorable for genital ulcers. Comparative studies with cyclosporin showed similar efficacy with safe and cost advantage for colchicine[25-27] It is also suggested for joint involvement[27]
Rebamipide, 300 mg daily	In mucocutaneous involvement, the use of the gastroprotective agent has shown a decrease of aphthae incidence and pain[28]

(Continues)

TABLE A1 (Continued)

Topical (mainly for mucocutaneous and ocular manifestations)	
Treatment	**Comment**
Systemic corticosteroids (SC)	In mucocutaneous involvement, the starting dose of prednisone is 15 mg/day (or the equivalent with other glucocorticoids), tapering to 10 mg/day after 1 week and complete discontinuation over a 2- to 3-week period in case of remission. Some patients may require higher initial doses and patients with recurrent oral aphthae may require longer periods of maintenance treatment with low-dose prednisone (5 mg/day).[29,30] It is also suggested for joint involvement
High dose corticosteroids (prednisone 0.5–1.5 mg/kg daily or intravenous pulse corticosteroids with 1 g methylprednisolone per day for 1–5 days) and immunosuppressive agent: • Azathioprine[15] (AZA), 50 mg daily to 2.5 mg/kg daily depending on tolerance, after performing genetic testing for mutations in the gene for thiopurine methyltransferase if available • Methotrexate • Mycophenolate • Cyclophosphamide • TNF-alpha inhibitor	They are suggested for severe and/refractory mucocutaneous manifestations,[31] joint involvement[31] and gastrointestinal involvement[32] For ocular (posterior uveitis) involvement, the association of corticosteroids to other immunosuppressive agent is recommended[33-36] For neurological involvement, the therapy choice is based upon parenchymal or extra parenchymal involvement, responsiveness to corticosteroids and other previous neurological manifestations Arterial involvement in ABD is uncommon, but it can lead to dilatations and aneurysms.[37,38] A combination of more treatments may be required (medical, surgical and radiological) in such cases. Venous involvement leads to venous thrombosis, mainly secondary to endothelial inflammation. ABD patients with previous venous thrombosis have 34% risk of relapses[39]
TNF-alpha inhibitors In maintenance: infliximab 5 mg/kg every 8 weeks, adalimumab 40 mg every 2 weeks, etanercept 50 mg per week)	**Mucocutaneous manifestations**: Efficacy either in monotherapy or in combination with an oral disease-modifying antirheumatic drug (DMARD), such as azathioprine, to help and prevent the development of potentially neutralizing antibodies[8,11,15] **Joint involvement**[8] **Ocular involvement**: TNF-alpha inhibitors + DMARDs.[11,12,40] The expert panel from the American Uveitis Society recommends initial treatment with TNF-alpha inhibitors because of the observed improvement in ocular manifestations when compared with other treatments.[13,41-46] The choice between infliximab and adalimumab depends largely on patient's comorbidities and preferences (route of administration and frequency of treatment) as well as on the drug availability and clinical experience. Infliximab and adalimumab seem to be more effective than etanercept.[46,47] Reports are limited on the other TNF-alpha agents including golimumab and certolizumab.[47-49] TNFi dosage is the same used in the other ABD manifestations and similar to inflammatory bowel disease or rheumatoid arthritis **Gastrointestinal involvement**: the dosage is the same used in inflammatory bowel disease. It should be combined to azathioprine[50] **Neurological involvement**[4,11,16] **Vascular involvement**[7]
Cyclosporine (2.5 mg/kg–5 mg/kg–10 mg/kg, daily)	Cyclosporine is used for ocular manifestations, but some evidence is supporting its efficacy also for mucocutaneous involvement. Side effects limit its use and its neurotoxicity can be confused with ABD-related neurologic manifestation.[26] It can be combined with glucocorticoids and azathioprine as an alternative to infliximab[51]
Interferon alfa—Interferon alfa-2a and interferon alfa-2b (generally given 3–6 million units three times weekly)	For mucocutaneous involvement (aphthosis, papulopustular lesions and erythema nodosum) with beneficial, but side effects are common and not well-tolerated[52,53] For joint involvement[54] For ocular involvement, it can be useful in patients refractory to previous treatments. Its use is limited by toxicity. High dosage (more than 6 million units three times a week) may be more effective. Relapses are frequent after suspension[53]
Thalidomide (100–300 mg daily)	Beneficial for mucocutaneous manifestations, but neuropathy and teratogenicity limit its use[55]

TABLE A1 (Continued)

Topical (mainly for mucocutaneous and ocular manifestations)	
Treatment	**Comment**
Lenalidomide, 5 mg daily	For mucocutaneous involvement, it is effective in resistant complex aphthosis[56] due to its anti–TNF-α and anti–IL-6 activity For joint involvement it is effective in refractory MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), a rare disease consistent with ABD features with relapsing polychondritis. Its treatment is similar to that of ABD[57]
Mycophenolate mofetil, 2–3 g daily	It is effective in the treatment of mucocutaneous manifestations[58]
Zinc sulfate, 100 mg three times daily	It is effective for mucocutaneous lesions without side effects[3]
Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin	For joint involvement
Methotrexate	For mucocutaneous manifestations,[4] joint involvement, neurological involvement.[4] For optical involvement it can be suitable as a less toxic option for less severe cases[59]
Mycophenolate	For ocular involvement: 500 mg twice daily-1500 mg twice daily may be an alternative, but without consistent data[60] Also for gastrointestinal involvement
Cyclophosphamide	In cases of ocular involvement, it should be limited to severe and refractory disease with respect of treatment risks. Its dosage is similar to those typically used for systemic vasculitis (500 mg/m^2 to 1 g/m^2 of body surface area monthly for 6 months or daily oral cyclophosphamide dosing at 2–3 mg/kg per day). It can be combined with corticosteroids or azathioprine. However, there are no sufficient data to recommend it[61]
Rituximab	For ocular involvement, intravenously at a dose of 1000 mg on days 1 and 15 and repeated every 6 months or as warranted. It has shown benefit in some trials[62]
Sulfasalazine, 2–4 g daily and other 5-aminosalicyclic acid	In gastrointestinal involvement it is mainly used because of its use in inflammatory bowel disease[63]
Subcutaneous low molecular weight heparin, subcutaneous fondaparinux, oral factor X inhibitors (rivaroxaban or apixaban, edoxaban) or unfractionated heparin, direct thrombin inhibitor (dabigatran), vitamin K antagonists (warfarin)	In vascular (venous) involvement, anticoagulation is needed if thrombosis has already occurred. Guidelines of general anticoagulation standard approach should be followed