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Use of Upadacitinib in Refractory Behcet's Disease: Case Report and Systematic Literature Review

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INTRODUCTION

Behçet's Disease (BD) is a chronic, relapsing and remitting, systemic neutrophilic vasculitis. The syndrome is characterized by recurrent oral aphthous ulcers (98.1%), genital ulcers (76.9%), uveitis (53.7%), and cutaneous lesions (71.9%) such as folliculitis, erythema nodosum and thrombophlebitis.[1] Rarely, there may also be neuro-ocular, gastrointestinal, pulmonary, urogenital, and large vessel involvement that carry high morbidity and mortality.[1]

First described by a Turkish physician, Dr. Huluci Behçet in 1937, the disease is endemic in populations along the ancient "Silk Road" in countries such as Turkey, Iran, Japan, and Korea.[1] While BD can affect men and women of all ages, young males appear to present with the most severe forms of BD, perhaps due to neutrophil-promoting effects of testosterone.[1]

While the etiology of BD is largely unknown, etiology of the disease is likely multifactorial with genetic and infectious components affecting both the innate and adaptive immune systems. The most widely accepted risk factor for BD is the HLA-B*51 MHC-I allele.[2] HLA-B*51 is present in approximately 60% of BD cases with HLA-B*51 positive patients having an increased propensity for oral, genital, and skin involvement.[2] HLA-B*51 has also been reported to affect both the innate and adaptive immune response via its association with CD8+ T cell activation, Th1/Th17 axis, neutrophil dysfunction, and chemotaxis.[2] Cytokine studies have found increased levels of IL-1ß, IL-4, IL-17A, IL-21, IL-22, IL-31, IFN-γ, sCD40L, and TNFα in patients with BD. Further studies have also shown mutations in IL-10, IL-23 receptor, and IL-12 receptor beta genes in patients with BD.[4] Microbial triggers such as streptococcus and herpes simplex virus-1 infections have also been implicated in disease pathogenesis.[5] Molecular mimicry and cross-reaction likely lead to the formation of the anti-endothelial cell autoantibodies seen in BD.[1]

To date, there are no diagnostic laboratory tests or pathognomonic histology features that confirm BD diagnosis. Therefore, BD relies on clinical criteria such as the International Criteria for Behçet's Disease (ICBD).[6] The ICBD ascribes points to the most common signs or symptoms of BD. For example, two points are awarded to a patient for each of the following: ocular lesions, genital aphthosis, and oral aphthosis. Skin lesions, neurological manifestations, vascular manifestations, or a positive pathergy test are each worth one point. BD is diagnosed if a patient score is >4 points.[5]

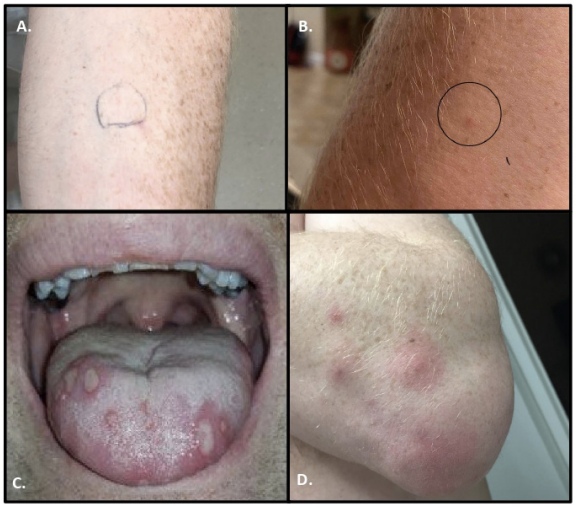
Treatment of BD is widely variable and individualized to treat patient symptom, organ involvement, and severity.[1] Patients with disease limited to skin and mucosa are often treated with topical corticosteroids and colchicine.[1] Ocular, arthritic, gastrointestinal, and serious large vessel involvement is treated with immunosuppressive therapies: cyclosporine, methotrexate, cyclophosphamide, thalidomide and azathioprine and immunomodulatory agents: IFN-γ, apremilast, and anti-TNF agents.[1] Lastly, systemic glucocorticoids may be added for rapid relief of acute flares.[1]

Here, we present a case of a 38-year-old male with refractory BD treated with a JAK inhibitor (JAKi), upadacitinib.

CASE REPORT

Our patient, 38-year-old Caucasian male with no past medical history presented with a 2-year history of recurrent oral and perianal ulcers. He also had episodic joint pain and elbow swelling accompanied by pain in his left heel, headaches, and fatigue. Further, he had recently developed cutaneous acneiform pustules and tender nodules on his back, arms, legs, and genitals. His symptoms followed a remission and relapsing cycle. The patient was negative for HLA-B27 and HLA-B51 as well as ANA, ANCA, CCP, RF, Sjogren's Anti-SS-A, Anti-SS-B antibodies. He had a positive pathergy test on exam and biopsy of a nodule on his posterior neck showed papillary dermal edema and neutrophilic infiltrate in dermis, consistent with BD. Taken together, the patient was diagnosed with HLA-B*51 negative, BD (ICBD Score 6) (Figure 1).

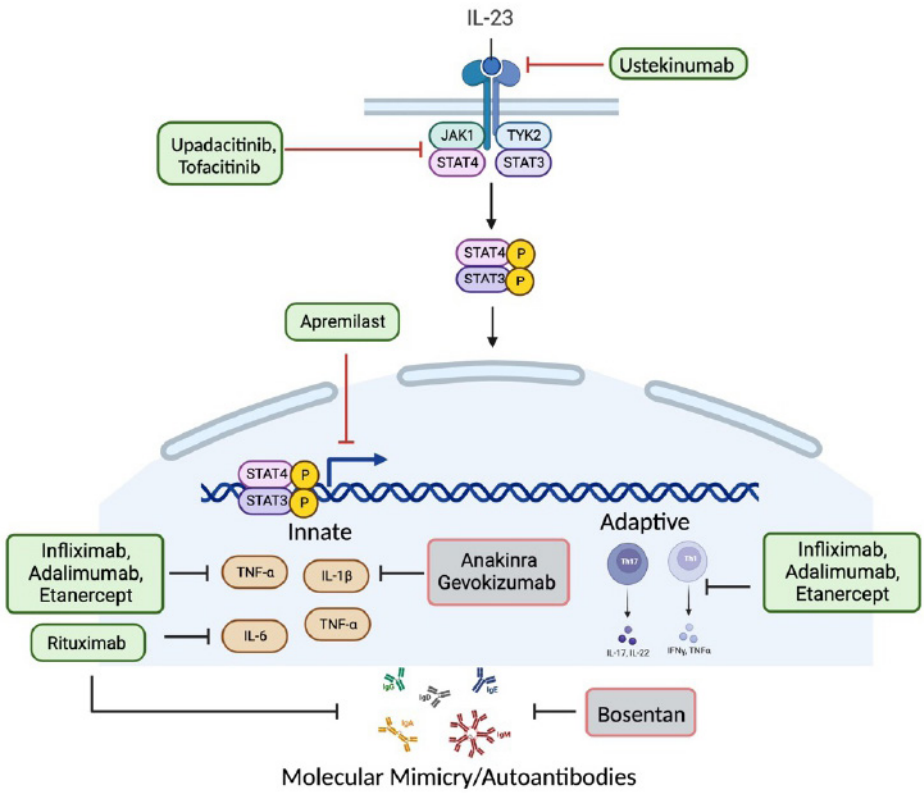
FIGURE 1. Behçet's Disease (6 ICBD points) in 38-year-old male.



At time of presentation, the patient was started on colchicine 0.6 mg daily and adalimumab 40 mg weekly. The patient returned after one month with little improvement presenting with new painful, erythematous nodules on his back, trunk and extremities with multiple aphthosis covering his mouth and tongue. Thus, the patient was increased to colchicine 0.6 mg twice daily, started on apremilast 30 mg twice daily. For 6 months, the patient achieved relative remission reporting only a few episodes of joint pain and oral apthosis. However, 6 months later, the patient presented with new oral and genital ulcers and required a course of high-dose prednisone. He was instructed to stop colchicine and was prescribed rituximab treatment in addition to adalimumab 40 mg weekly and apremilast 30 mg twice daily. Despite concomitant rituximab, adalimumab, and apremilast therapy, the patient continued to have flares requiring prednisone over the next 6 months. In addition, he had contracted COVID-19 4 times attributed to his immunocompromised state.

Over the next few months, the BD continued to flare and failed to respond to trials of mycophenolate mofetil 500 mg daily, 150 mg/month of canakinumab for 2 months, and three 900 mg spesolimab infusions spaced 4 weeks apart. Finally, the patient was switched to upadacitinib 15 mg daily, stopping all other concomitant therapies. Within 48 hours of treatment, the patient reported reduction in ulcer pain with resolution of his ulcers and joint pain by week 10. The patient has remained in remission for the past 6 months. Of note, the patient was hospitalized for 4 days after four months of upadacitinib treatment for bilateral pneumonia. He resumed upadacitinib treatment once he recovered and remains in corticosteroid-free remission for 9 months on JAK inhibition.

FIGURE 2. Therapeutic targets in clinical trials for Behçet's disease



DISCUSSION & REVIEW

Upadacitnib is an oral JAKi with major inhibitory effects on JAK1 and mild inhibitory effects on JAK2, JAK3, and TYK2.[7] The JAK-STAT pathway activates transcription-mediated signaling pathways involved in the pathogenesis of a variety of inflammatory diseases. To date, upadacitinib has been FDA approved for treatment of atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondylarthritis. Implicated in a variety of inflammatory diseases, the JAK-STAAT pathway has also been reported to be upregulated in BD.[8] Further, STAT4 polymorphisms have been reported to confer susceptibility to BD.[9] Our patient's positive response to upadacitinib confirms that the JAK-STAT pathway plays a key role in disease pathogenesis.

In general, colchicine, an anti-inflammatory, is first-line in BD treatment as per the European League Against Rheumatism (EULAR) for management of mucocutaneous and arthritic BD.[10] To date, there have been few clinical trials that have aimed at finding targeted, efficacious treatments for BD. This is likely due to the rarity and heterogeneity of the disease. The heterogeneity of the disease makes quantifying outcomes of disease a challenge with few standardized tools available.

In more than 10 years, there have been few advancements, aside from apremilast, in the field (Table 1). We conducted a systematic review using the following search terms on PubMed: "Behcet Syndrome"[Mesh] AND "treatment" OR "biologic" OR "novel" OR "small molecule" OR "therapy". Following this, we filtered for clinical trials, meta-analysis, randomized controlled trials, humans, and English between the years 2010 to 2023. Our search yielded 64 results, of which we included 27 clinical trials based on novelty and outcome measures. Table 1 displays our results. The majority of clinical trials conducted for BD are open label clinical trials with few randomized, placebo-controlled trials.

Our results suggest that anti-TNF agents and apremilast have the most robust, recent data to suggest their efficacity in BD patients. Apremilast has since been FDA approved for BD. Tofacitinib, a pan-JAK inhibitor, was also shown to lead to BD improvement in 13 patients over 8 months.[11] Other therapies that showed promising results included ustekinumab, rituximab, and mycophenolate sodium. Interestingly, IL-1ß inhibitors did not prove to be successful in larger scale trials for BD (Table 1).

TABLE 1.

Treatment Advances From 2010-2023 for Behcet's Disease

Treatment Target/	Drug	First Author, Year	Title of Study	Type of Study	Type of Behcet's Syndrome	Sample Size	Primary Outcome	Primary Outcome Results	Serious Adverse Events in Treatment Groups	Verdict
Anti-TNFα	Infliximab	Zou et al. (2017)	Mucosal Healing at 14 Weeks Predicts better Outcome in Low-dose Infliximab Treatment for Chinese Patients with Active Intestinal Behcet's Disease	Open Label Clinical Trial	Gastrointestinal/ Mucocutaneous	20	Steroid-Free Remission at Week 30	Low-dose Infliximab (3.5 mg/kg): 40% Remission (4/10 patients) Standard Dose Infliximab (5mg/kg) 60% Remission (6/10 patients)	None	✓
		Mohammed, R. H. A et al. (2023)	The effectiveness of the anti-tumor necrosis factor therapy infliximab in neuro-Behçet's disease	Meta-Analysis	Neurological	64	Hamdy and Woldeamanuel neuro-Behcet's simple response score, 2020) Clinical Response (0-5, 5, excellent, ≥3 good response)	Infliximab Treatment (3-7 mg/kg): 93.7% "good response" (59/64 patients)	Pneumocystis carinii, pulmonary and CNS tuberculosis, Non-Hodgkin's Lymphoma , cardiac insufficiency, pulmonary infection, herpes zoster	
		Markomichelakis, N et al. (2011)	A single infliximab infusion vs corticosteroids for acute panuveitis attacks in Behçet's disease: a comparative 4-week study.	Comparative Study	Ocular	22	Retinal Inflammation	3 Day-High Dose IV methylprednisolone (1g/day) Intra-Vitreal Triamcinolone (4mg) Single IV Infliximab (5mg/kg)	None Cataracts, ocular hypertension None	
		Ida et al. (2021)	An open-label, prospective, single-arm study of switching from infliximab to cyclosporine for refractory uveitis in patients with Behçet's disease in long-term remission.	Open Label Clinical Trial	Ocular	3	Rate of reintroduction of biologics due to relapse of ocular inflammation and extraocular symptoms after IFX withdrawal and CYA administration.	Rate of the Reintroduction of Anti-TNF at 1-year: 0% (0/3 patients)	None None	
		Hibi, T. et al. (2016)	Infliximab therapy for intestinal, neurological, and vascular involvement in Behcet disease: Efficacy, safety, and pharmacokinetics in a multicenter, prospective, open-label, single-arm phase 3 study	Open Label Clinical Trial	All	18	Complete Response at Week 30	Infliximab (5mg/kg): 61% (11/18 patients)	cataracts, worsening of BS	
		Ohno, S et al. (2019)	Safety and efficacy of infliximab in the treatment of refractory uveoretinitis in Behçet's disease: a large-scale, long-term postmarketing surveillance in Japan.	Open Label Clinical Trial	Ocular	656	PGA at 24 months	Infliximab (5mg/kg): 60.7% (378/623 patients evaluated)	pneumonia, cellulitis, gastroenteritis, septic shock, sinusitis, tuberculosis	
		Giardina, A. et al. (2011)	One year study of efficacy and safety of infliximab in the treatment of patients with ocular and neurological Behçet's disease refractory to standard immunosuppressive drugs.	Observational Trial	Ocular/Neurological	21	Clinical Efficacy (total or partial recovery) at Week 54	Infliximab (5mg/kg): Total Recovery 85.7% (18/21 patients); Partial Recovery: 9.5% (2/21 patients)	non-Hodgkin lymphoma	

TABLE 1. (CONTINUED)

Treatment Advances From 2010-2023 for Behcet's Disease

Treatment Target/	Drug	First Author, Year	Title of Study	Type of Study	Type of Behcet's Syndrome	Sample Size	Primary Outcome	Primary Outcome Results	Serious Adverse Events in Treatment Groups	Verdict
Anti-TNFα	Infliximab, Etanercept, Golilumab, Adalimumab	Zhang, Q. et al. (2022)	Efficacy and Safety of Anti-Tumor Necrosis Factor-Alpha Agents for Patients with Intestinal Behcet's Disease	Systematic Review and Meta-Analysis	Gastrointestinal	671	Pooled Rate of Remission	Rate of Remission after anti-TNF treatments: 39% (35/89 pooled patients)	gastrointestinal disorders, tuberculosis, severe pneumonia, interstitial pneumonia, malignancy, autoimmune disease, pancytopenia, worsening of udnerlying disease, cataract, intestinal stricture related	✓
	Infliximab, Adalimumab	Zhang, M. et al. (2022)	The efficacy and safety of anti-tumor necrosis factor agents in the treatment of intestinal Behcet's disease, a systematic review and meta-analysis	Systematic Review and Meta-Analysis	Gastrointestinal	739	Pooled proportions of clinical remission at Months 3, 6, 12, and 24	Months 3: 0.61 (95%CI 0.48-0.78), Month 6: 0.51 (95%CI 0.40-0.66), Month 12: 0.57 (95%CI 0.48-0.67), and Month 24: 0.38 (95%CI 0.16-0.88)	severe infection	
	Adalimumab	Tanida, S. et al. (2015)	Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease	Open Label Clinical Trial	Gastrointestinal	20	% of patients with scores of 1 or lower for GI symptom and endoscopic assessments at week 24	Adalimumab (160 mg at week 0, 80 mg at week 2, then 40mg q2weeks): 9/20 (45%)	infection	
	Adalimumab	Martin-Varillas, J. L. et al (2018)	Successful Optimization of Adalimumab Therapy in Refractory Uveitis Due to Behçet's Disease	Open Label Clinical Trial	Ocular	65	BD Relapse over study period	Adalimumab Optimized Taper (40mg q2 weeks, 40mg q3weeks, 40mg q4weeks, 40mg q6weeks) : 2/23 patient relapses Adalimumab Standard Dose (40mg q2weeks): 4/42 patient relapses	None lymphoma, pneumonia, severe local reaction at the injection site, and bacteremia by Escherichia coli	
PDE-4 Inhibitor	Apremilast	Takeno, M. et al. (2022)	Apremilast in a Japanese subgroup with Behçet's syndrome: Results from a Phase 3, randomised, double-blind, placebo-controlled study	Open Label Clinical Trial	Mucocutaneous	39	Complete Oral Ulcer Resolution at Week 12	Apremilast 30mg BID: 57.9% of patients with complete resolution Placebo: 25.0% of patients with complete resolution	diarrhea, nausea	✓
		Iizuka, Y. et al. (2022)	Beneficial effects of apremilast on genital ulcers, skin lesions, and arthritis in patients with Behçet's disease	Systematic Review and Meta-Analysis	Mucocutaneous, Arthritis	236	Remission Rate of Mucocutaneous Ulcers at Week 12	Apremilast 30mg BID: 45.76% patients complete remission of ulcers at week 12	diarrhea, nausea, infection, neuropsychiatric symptoms	
		Hatemi, G. et al. (2022)	Impact of apremilast on quality of life in Behçet's syndrome: analysis of the phase 3 RELIEF study	Randomized, Double-Blind, Placebo-Controlled, Clinical Trial	All	207	Improvement in Quality of Life using 36-Item Short-Form Health Survey at Week 12	Apremilast 30mg BID: 41.1% at Week 12 noted improvement in "General Health" Placebo: 38.7% at Week 12 noted improvement in "General Health"	none	
		Hatemi, G. et al. (2019)	Apremilast for Behçet's syndrome--a phase 2, placebo-controlled study.	Randomized, Double-Blind, Placebo-Controlled, Clinical Trial	Mucocutaneous	207	Area under the curve for the number of oral ulcers over 12 weeks (AUCWk0-12)	Apremilast 30mg BID: 129.5 Placebo: 222.1	migraine, soft-tissue injury	
		Hatemi, G. et al. (2021)	Apremilast for oral ulcers associated with active Behçet's syndrome over 68 weeks: long-term results from a phase 3 randomised clinical trial.	Extention of Interventional Group in Randomized, Double-Blind, Placebo-Controlled, Clinical Trial	Mucocutaneous	143	Area under the curve for the number of oral ulcers at week 64 (AUCWk0-12)	Effects of Apremilast on Ulcer Count Sustained through week 64	diarrhea, nausea, headache, URI	
1ß-Inhibitor	Gevokizumab	Tugal-Tutkun, I. et al. (2018)	Use of Gevokizumab in Patients with Behçet's Disease Uveitis: An International, Randomized, Double-Masked, Placebo-Controlled Study and Open-Label Extension Study	Randomized, Double-Blind, Placebo-Controlled, Clinical Trial	Ocular	83	% of particpants with ocular exacerbation at endpoint	Gevokizumab 60mg q4weeks: 14 patients (35.0%) Placebo: 15 patients (34.9%)	None None	x
		Tugal-Tutkun, I. et al. (2017)	Safety and Efficacy of Gevokizumab in Patients with Behçet's Disease Uveitis: Results of an Exploratory Phase 2 Study.	Open Label Clinical Trial	Ocular	21	% Patient Responders (response defined as improvements in the index eye without any deterioration from the baseline in either eye: improved vitreous haze score by ≥2 units; ≥15-letter Improvement in BCVA; or resolution of retinal infiltrates or acute signs of retinal vasculitis)	Gevokizumab 30mg or 60mg q4weeks: 100% responded (14/14 evaluated)	None	
		Gül, A. et al. (2012)	Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behcet's disease: an open-label pilot study	Open Label Clinical Trial	Ocular	7	Progression of uveitis from days 0 to 28	Complete resolution of intraocular inflammation in all patients	None	
	Anakinra	Grayson, P. C. et al. (2017)	Treatment of mucocutaneous manifestations in Behçet's disease with anakinra: a pilot open-label study.	Open Label Clinical Trial	Mucocutaneous	6	Complete remission (defined as no ulcers on physical exam for two consecutive monthly visits between months 3 and 6)	Anakinra 100 mg daily: 2/6 patients saw complete remission	Pulmonary hypertension, non-cardiac test pain, pre-syncope	
Anti-IL-12 and IL-23 Antibody	Ustekinumab	London, J. et al. (2022)	Efficacy and safety of ustekinumab in Behçet disease: Results from the prospective phase 2 STELABEC trial.	Open Label Clinical Trial	Mucocutaneous	15	Change in the number of oral ulcers at week 24	Ustekinumab 90mg (weeks 0, 4, and 16): 11 patients responders (73.3% [range, 60.0%-95.7%]), including 9 (60% [range, 35.2%-84.8%]) complete responses and 2 (13.3% [range, 0%-30.5%]) partial responses	None	✓

TABLE 1. (CONTINUED)

Treatment Advances From 2010-2023 for Behcet's Disease

Treatment Target/	Drug	First Author, Year	Title of Study	Type of Study	Type of Behcet's Syndrome	Sample Size	Primary Outcome	Primary Outcome Results	Serious Adverse Events in Treatment Groups	Verdict
JAK Inhibitor	Tofacitinib	Liu, J. et al. (2020)	A pilot study of tofacitinib for refractory Behçet's syndrome.	Open Label Clinical Trial	Vascular, Gastrointestinal, Neurological, Ocular	13	BDCAF score improvement	Tofacitinib 5mg BID: 5 point improvement in BDCAF Score by Month 8	None	✓
ET-1 receptor antagonist	Bosentan	Houwen, T. B. V. et al. (2022)	A pilot study into bosentan (Tracleer®) as an immunomodulating agent in patients with Behçet's disease	Randomized, Double-blind placebo controlled pilot study	Mucocutaneous	10	BDCAF score improvement	No decrease in disease activity in the bosentan group was found	infection	X
Anti-CD20	Rituximab	Davatchi, F. et al. (2010)	Rituximab in intractable ocular lesions of Behcet's disease; randomized single-blind control study (pilot study)	Randomized, Double-Blind, Controlled Trial	Ocular	20	Total Inflammatory Activity Index (TIAI)	Rituximab (two 1000-mg courses with 15-day interaval): (t=3.340, P=0.009) Combination therapy group (CCTG) (pulse cyclophosphamide (1000mg/monthly), azathioprine (2–3mg/kg per day) and prednisolone (0.5mg/kg per day): t=2.241, P=0.052	conjunctivitis, pneumonia, herpes zoster	✓
Vitamin A Derivative	Isotretinoin	Sharquie, K. E et al. (2013)	The therapeutic role of isotretinoin in the management of Behçet's disease: a single-blinded, controlled therapeutic study	Open Label Clinical Trial	All	30	Clinical Manifestation Index (CMI) at Week 12	Stastically significant decrease in CMI score by Week 12 (P=.046), effect was not sustained by week 24	None	X
Immunomodulators	Pegylated interferon-α-2b	Lightman, S. et al. (2015)	Pegylated interferon-α-2b reduces corticosteroid requirement in patients with Behçet's disease with upregulation of circulating regulatory T cells and reduction of Th17.	Randomised, controlled, parallel group, single-blinded clinical trial	All	72	% of patients not requiring more than 10mg of prednisolone per day was required through months 10-12 after initiation of treatment	Peginterferon-α-2b at a dose of 0.3 µg/kg/week for 26 weeks (+Systemic coritosteroids): 66% of patients did not require additional corticosteroids Non-Interferon Group (continued on other immunosuppressants): 62% of patients did not require additional corticosteroids	None	X
Immunosuppressant	Mycophenolate Sodium	Köse, O. et al. (2011)	Mycophenolate sodium in the treatment of mucocutaneous Behcet's diseases.	Open Label Clinical Trial	Mucocutaneous	10	Total Activity Scores (TAS) index at Month 6	Mycophenolate Sodium (720 mg twice daily for 6 months): 6.4 point change in TAS from Month 0 to Month 6 (p<0.05)	None	✓

Our patient saw the most durable remission from his symptoms with apremilast and upadacitinib. This suggests that upstream targets may be most potent in managing BD flares. IL-23 has been implicated in the pathogenesis of BD.[3] IL-23 leads to JAK signaling through JAK1 and TYK2 which then leads to STAT4/STAT3 upregulation and translocation to the nucleus.9 STAT transcription factors subsequently lead to upregulation of innate and adaptive pro-inflammatory pathways[9] (Figure 2). Based on recent literature, it appears that drugs targeting upstream or at JAK/STAT signaling confer stronger BD flare-fighting effects than those that target individual cytokines downstream. Further, this underlines the idea that successful therapies must be able to target both the innate and adaptive inflammatory pathways. Il-1ß is mostly implicated in the innate immune system, which may explain its inefficacy in BD. Anti-TNF agents target both the innate and adaptive systems by blocking the downstream effects of TNF, which is implicated in both systems. Unlike biologics, small molecule inhibitors such as upadacitinib do not harbor the risk of developing anti-drug antibodies. This may help address resistance to anti-TNF agents in patients on long-term use of the medication for flares.

Future studies will be essential to help identify a reliable and effective treatment for patients suffering from debilitating symptoms related to BD. Our patient provides the stepping stone towards larger scale trials for upadacitinib and other JAK inhibitors in this inflammatory disease.

DISCLOSURES

Authors Guénin, Amara, and Patel have no conflicts of interest to declare.

Dr. Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Novartis, Ortho Dermatologics, Regeneron, and UCB, Inc. Dr. Mark Lebwohl is also a consultant for AnaptysBio, Arcutis, Inc., Arena Pharmaceuticals, Aristea Therapeutics, Avotres Therapeutics, BioMX, Boehringer-Ingelheim, Brickell Biotech, Castle Biosciences, Corevitas, Dermavant Sciences, Evommune, Inc., Facilitatation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Hexima Ltd., Meiji Seika Pharma, Mindera, National Society of Cutaneous Medicine, New York College of Podiatric Medicine, Pfizer, Seanergy, SUN Pharma, Verrica, and Vial.

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REFERENCES

1. Yazici H, Seyahi E, Hatemi G, et al. Behçet syndrome: A contemporary view. *Nat Rev Rheumatol*. 2018;14(2):107-119.
2. Maldini C, LaValley MP, Cheminant M, et al. Relationships of HLA-B51 or B5 genotype with Behcet's disease clinical characteristics: Systematic review and meta-analyses of observational studies. *Rheumatology.* 2012;51(5):887-900.
3. Leccese P, Alpsoy E. Behçet's disease: An overview of etiopathogenesis. *Front Immunol*. 2019;10:1067.
4. Morton LT, Situnayake D, Wallace GR. Genetics of Behçet's disease. *Curr Opin Rheumatol.* 2016;28(1):39-44.
5. Greco A, De Virgilio A, Ralli M, et al. Behçet's disease: New insights into pathophysiology, clinical features and treatment options. *Autoimmun Rev.* 2018;17(6):567-575.
6. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD), Davatchi F, Assaad-Khalil S, et al. The International Criteria for Behçet's Disease (ICBD): A collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol* Venereol. 2014;28(3):338-347.
7. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): Results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet.* 2021;397(10290):2151-2168.
8. Puccetti A, Fiore PF, Pelosi A, et al. Gene expression profiling in Behcet's disease indicates an autoimmune component in the pathogenesis of the disease and opens new avenues for targeted therapy. *J Immunol Res.* 2018;2018. ID 4246965.
9. Yang C, Mai H, Peng J, et al. STAT4: An immunoregulator contributing to diverse human diseases. *Int J Biol Sci.* 2020;16(9):1575-1586.
10. Hamuryudan V, Hatemi G, Tascilar K, et al. Colchicine in Behçet syndrome: A long-term survey of patients in a controlled trial. *J Rheumatol.* 2014;41(4):735-738. https://doi.org/10.3899/jrheum.130847
11. Liu J, Hou Y, Sun L, et al. A pilot study of tofacitinib for refractory Behçet's syndrome. *Ann Rheum Dis.* 2020;79(11):1517-1520.

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