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Literature Review

Biologic treatments in Behçet's disease

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Abstract

Behçet's disease (BD) significantly increases morbidity and mortality, especially in young men. While vascular involvement is the most frequent cause of mortality, ocular involvement, which can cause visual loss, is the most important cause of morbidity in BD. Immunosuppressive treatment is the mainstay for major organ involvement. However, despite optimal immunosuppressive treatment, relapses and disease-related damage develop in a subgroup of patients, especially among those with ocular or vascular involvement. With the recent understanding of the immuno-pathogenesis, biologic treatments targeting potential pathogenic cells, cytokines or pathways are better optimized in BD. Data from large series showed that tumor necrosis factor-α inhibitors and interferon-α are effective and safe treatment options for the treatment of refractory and major organ involvement, such as ocular, neurologic, vascular, and gastrointestinal. Anakinra and ustekinumab also seem to be promising agents for refractory mucocutaneous disease. IL-1 inhibitors and tocilizumab may be alternatives for the treatment of patients with refractory eye involvement. Still, randomized controlled trials of biologic agents, especially for the treatment of major organ involvement, are insufficient, and further prospective, long-term follow-up studies are needed to clarify the efficacy, safety, and optimal treatment duration of biologic agents in BD.

Keywords: Behçet's disease, treatment, biologic agents

Introduction

Behçet's disease (BD) is a chronic, multisystemic, inflammatory disease characterized by recurrent attacks of oral-genital ulcers and ocular, musculoskeletal, vascular, central nervous system (CNS), and gastrointestinal (GI) involvement. BD has a disease course with remission and relapses; complete remission is observed in at least 60% of patients at 20 years.[1] BD significantly increases morbidity and mortality, especially in young men. While vascular involvement is the most frequent cause of mortality, ocular involvement, which can cause visual loss, is the most important cause of morbidity in BD.[2]

The pathogenesis of BD is poorly understood, but there are increasing data on the major determinants of the genetic and immune system abnormalities. Triggering infectious factors are believed to participate in the onset of BD in genetically predisposed patients.[3,4] The major genetic risk factor for BD is the human leukocyte antigen (HLA)-B*51. Recent studies have expanded the list of genetic loci, which now also include interleukin(IL)-10, IL-23R, HLA-A*26, chemokine receptor type 1, signal transducer and activator of transcription (STAT) 4, endoplasmic reticulum amino peptidases (ERAP) 1, ubiquitin-associated domain containing protein 2, HLA-Cw6, GTPase of immune associated protein, toll like receptor 4 and familial Mediterranean fever-associated genes.[5-11] Oral microorganisms associated with dental/periodontal diseases are implicated as the environmental causes of BD.[12] Inflammation in BD can be triggered by autoimmune responses resulting from inappropriate adaptive immune activation and broken self-tolerance against local autoantigens such as mucosal or retinal proteins.[13] Although HLA-B*51 is a class I HLA molecule activating cytotoxic T cell/NK cell responses, recent genetic studies mentioned earlier have also clearly linked hyperactive innate immune mechanisms to BD risk, supporting an autoinflammatory contribution to its pathogenesis.[14,15]

BD is thought to be a disease located between autoimmune and autoinflammatory syndromes.[16] Numerous pathogenetic evidences support the autoinflammatory hypothesis, especially the role of the primed state of neutrophils. IL-1 has been found significantly higher in patients with both active and inactive BD compared with healthy controls.[17] However, adaptive immune cells (B- and T-cells) are also activated.[18-21] Increased IL-17, IL-22, and IL-23 expressions are observed, expanding the immune spectrum to Th17-type responses.[22,23] IL-21 production causes an increase in Th17 responses and leads to the suppression of regulatory T cells.[24]

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Inflammatory cells activated in BD included mostly neutrophils, Th1 and Th17, cytotoxic CD8+, and γδ T cells.[25] Nonspecific hyperreactivity, such as "pathergy" (skin reaction to simple trauma), is possibly associated with pro-inflammatory cytokine responses such as IL-1 and IL-6. Increased γδ T cells secreting tumor necrosis factor (TNF)-α and interferon (IFN)γ in tissue infiltrates are also consistent findings suggesting the role of innate immunity.[26,27] Therefore, biologic treatment options targeting potential pathogenic cells, cytokines or pathways can be alternative options for BD.[28,29]

Treatment decisions in BD are mainly based on clinical manifestations, especially major organ involvements.[30] While colchicine, nonsteroidal anti-inflammatory agents, and topical treatments are often sufficient for mucocutaneous and joint involvement, immunosuppressive (IS) agents are required for major organ involvement. However, despite optimal immunosuppressive treatment, relapses and disease-related damage develop in a subgroup of patients, especially in those with ocular and vascular involvement. With recent available data to understand the pathogenesis of BD, it seems that biologic treatment options targeting potential pathogenic cells, cytokines or pathways can be alternative options for BD.

Clinical and research consequences

Interferon-α

Data reporting the efficacy of IFN-α in 3 BD patients were first published in 1986.[31] Since then, the efficacy of IFN-α has been well established in BD, with the data coming from case series, especially in sight-threatening ocular manifestations.[32-37] In a randomized controlled trial (RCT), mucocutaneous manifestations of BD were significantly improved in patients treated with IFN-α compared to those treated with placebo.[38] Case reports also stated the efficacy of INF-α in neuro BD.[39,40] In a literature review, IFN-α was found very effective for all manifestations of BD, especially the ocular involvement. Almost all (94%) patients with eye involvement achieved partial or complete remission within 2 to 4 weeks of IFN-α treatment. The rate of complete remission was higher in patients treated with higher IFN-α dosages. There were no association between the complete remission rate and longer treatment duration.[41] INF-α is used subcutaneously in a range of dosages between 3 and 9 million units (generally 3 times a week). IFN-α can show antagonistic effect via NFκB in concomitant usage with glucocorticoids. Therefore, glucocorticoids should be used in the lowest possible dose when used together with IFN-α.

In long-term follow-up of 53 patients (96 eyes), 52 (98.1%) responded to IFN-α. IFN-α could be stopped when the disease was in remission in 47 patients (88.7%). About half of these 47 patients (n=20, 42.6%) needed a second treatment course during a median follow-up of 6.0 years. Visual acuity improved or remained stable in 91 eyes (94.8%). Ocular disease was still in remission in 50% of the patients after 46 months.[42] In another long-term follow-up study, it was found that 76% of patients remained in remission after 5 years following discontinuation of IFN-α.[43] An indirect retrospective comparison found no difference between azathioprine (AZA) plus colchicine and IFN-α2a treatment in BD uveitis regarding remission and relapse rates.[44] The only prospective head-to-head RCT with a biologic agent compared IFN-α and cyclosporine (Cs)-A. IFN-α was found to be better than Cs-A in the number of patients who achieved ocular remission, visual acuity, and a posterior uveitis score.[45] An open trial of AZA plus IFN-α in 10 male BD patients with retinal involvement had to be stopped because of additive hematologic toxicities.[46] In a recent prospective study of 33 patients with deep venous thrombosis (DVT), the relapse rate was lower and recanalization rate was higher in patients treated with IFN-α compared with AZA (12% vs 45% and 86% vs 45%). IFN-α seems to be a promising option for BD patients with DVT.[47]

There is also some data showing that pegylated IFN-α may be effective in BD.[48-50] In the studies on IFN-α for BD, side effects consisted of fever at the initiation of IFN-α treatment (80%), leukopenia (40%), depression (8%), alopecia (10%), arthralgia/fibromyalgia (10%), weight loss (10%), redness at the site of injection (10%), and development of autoantibodies (16%). Some patients also manifest autoimmune diseases (mostly thyroiditis) and psoriasis (4%-6%).[51] Unlike other biologic treatments, INF-α does not cause an increased risk of infections.[52] However, other adverse effects are seen frequently. The flu-like syndrome occurs in almost all patients, but paracetamol is generally enough to treat this. IFN-α is an important therapeutic option for other manifestations of BD also. IFN-α has been shown to allow sustained remission after cessation of the treatment in ocular involvement.

Inhibition of cytokine signaling

TNF-α inhibitors

Etanercept is the only TNF-α inhibitor studied with an RCT in BD. In this small study, oral ulcers and erythema nodosum were significantly lower in the etanercept group compared with the placebo group.[53] Most of the current data with TNF-α inhibitors consists of usage for refractory ocular involvement of BD. In the first prospective biologic study in BD uveitis (63 patients), uveoretinitis improved with infliximab (IFX) treatment in 92% and remained unchanged at the end of 12 month.[54] Generally, IFX has been used in published open studies and case series. IFX treatment led to a significant decrease in relapse rate and glucocorticoid dosage in patients with ocular involvement.[55-58] An observational multicenter study reported the results of IFX (62%) and ADA (38%) use in 124 BD patients with refractory uveitis. At 1 year, complete remission was achieved in 84/124 (68%). IFX was found effective for macular thickness as well as intraocular inflammation and visual acuity.[59] Two RCTs with ADA reported the efficacy of ADA in patients with non-infectious uveitis.[60,61] However, these studies included few patients with BD and the data for BD patients were not reported separately. The large studies with both INF[62] and ADA[63] also reported the long-term efficacy and safety of TNF-α inhibitors for the ocular involvement of BD. In a retrospective study, comparison of IFX and ADA regarding efficacy and safety in uveitis showed equivalent results.[64] An open study of 177 patients with BD with ocular involvement compared the efficacy of infliximab (IFX) versus ADA as a first-line biologic drug. In this study, ADA had better ocular outcomes and drug retention than IFX after 1 year of follow-up.[65] Keino et al[66] and Guzelant et al[67] also reported an earlier initiation of INF in BD uveitis led to better outcomes for ocular involvement in BD.

In a study including 70 patients with DVT or superficial thrombophlebitis, retrospective comparison was made between ADA and

Main Points

- Data from large case series confirm the efficacy and safety of tumor necrosis factor-α inhibitors and interferon-α for the treatment of refractory major organ involvement in Behçet's disease.
- Anakinra and ustekinumab seem to be promising treatment options for refractory mucocutaneous disease.
- Interleukin-1 inhibitors and tocilizumab seem alternative options for patients with refractory ocular involvement.
- Further prospective, controlled, long-term follow-up studies are needed for the assessment of efficacy, safety, and optimal treatment duration of biologic agents.

conventional ISs including AZA, Cs-A, and cyclophosphamide. During a mean follow-up of 25.7±23.2 months, ADA-based treatment regimens achieved significantly higher vascular response (complete or partial, 34/35, 97%) compared with conventional ISs treatments (23/35, 66%) (P = .001). The mean corticosteroid dosage at the last follow-up visit was significantly lower in ADA-based regimens (P = .002). Significantly lower vascular relapse was observed in ADA-based regimens compared with conventional ISs group (9% vs 40%).[68] In two retrospective case series, Desbois et al[69] (n=18) and Aksoy et al[70] (n=27) reported that clinical remission was achieved in 89% and 80% of patients with BD, respectively, with vascular involvement (mainly arterial) refractory to conventional ISs treatment.

Retrospective case series and open studies also confirmed that INF and ADA were quite effective and safe options for mucocutaneous, articular and other major organ involvement).[70-79] An analysis of published data of TNF-α inhibitor usage in BD patients refractory to conventional ISs showed that IFX achieved clinical response in 90%, 89%, 100%, and 91% of patients with mucocutaneous, ocular, GI, and CNS involvement, respectively, during a median follow-up of 16.2 months.[80]

There are sparse data showing the efficacy of golimumab and certolizumab for BD.[81-83] If the first TNF inhibitor fails, the patient can be switched to another TNF inhibitor. Monoclonal antibodies (IFX and ADA) were reported to be more effective than etanercept, especially in ocular involvement.[84,85] The quick start of efficacy and significant decrease in corticosteroid dosage are important advantages of TNF inhibitors. However, long-term, continuous treatment is needed to achieve sustained remission. There are limited data reporting that the concomitant usage of immunosuppressive agents such as CsA, AZA or methotrexate with TNF inhibitors may prevent anti-TNFα antibody production and may be more effective compared to monotherapy with TNF inhibitors.[55,65,86]

Anti-IL-1

Anakinra and canakinumab, which are IL-1 blocking biologic agents, were reported as effective for different manifestations of BD in retrospective case series.[87-91] In an open-label pilot study and a randomized phase 2 trial, XOMA 052 (gevokizumab), a recombinant, humanized, anti-IL-1β antibody achieved rapid treatment onset and decreased ocular inflammation in BD patients refractory to conventional treatments with no new safety alerts. However, gevokizumab did not reach its primary end point in a phase-3 trial.[92-94] An open, prospective phase-2 study reported that anakinra might be effective in the treatment of refractory oral and genital ulcers of six patients. All patients were treated with anakinra 100 mg/day. The dose had to be increased from 100 mg to 200 mg/day in partial responders after 1 month and to 300 mg after 6 months. Two of the six patients achieved the primary outcome defined as no ulcers. Five of the six patients had improvement in the number and severity of ulcers. Increasing the dose to 300 mg did not lead to further improvement in the ulcers.[95]

Anti-IL-6

Tocilizumab, a humanized, anti-IL-6 receptor antibody, was used in a small case series for both mucocutaneous and major organ involvement in BD.[96] But there is controversy over its effects on mucocutaneous findings because of reports showing no response and even paradoxical exacerbation.[97-101] According to current retrospective data, mucocutaneous manifestations seem to respond mildly or even worsen in BD.[102] In contrast, there are increasing retrospective data showing the efficacy of tocilizumab in refractory ocular and neurologic involvement.[103-106] In a recent retrospective case series of seven vascular BD (arterial involvement in all, venous involvement in 2), tocilizumab was found effective in the treatment of refractory vascular BD in combination with corticosteroid and ISs.[107]

Anti-IL-17

Secukinumab, an IL-17 inhibitor, was studied in five patients with mucocutaneous and joint involvement. All patients were refractory to at least one TNF-a inhibitor. Two of the five patients achieved complete remission at month 6.[108] Interestingly, Barrado-Solís et al[109] reported that BD developed in two patients a few weeks after starting secukinumab therapy for psoriasis. Secukinumab failed to meet the primary end points in BD uveitis in an RCT including 118 patients.[110] A recent retrospective study of 15 patients with mucocutaneous and articular involvement suggested that secukinumab may be safe and effective for the long-term treatment of patients with BD.[111]

Ustekinumab

In two open-label prospective studies, Ustekinumab, a humanized monoclonal antibody targeting IL-12/IL-23, appears to be effective in the treatment of oral ulcers in BD resistant to colchicine.[112,113]

Lymphocytes-targeted therapies

Anti-CD-20

Rituximab (RTX) is a monoclonal antibody selectively targeting the B-cell-specific surface molecule CD20 and depleting the B cells. RTX was given as 1000-mg intravenous infusions separated by 2 weeks with 6 months intervals. It was reported as effective in the refractory ocular involvement in BD in a 6-month RCT.[114] There are few case reports showing the efficacy of RTX for neurologic involvement in BD.[115-117]

Anti-CD-52

Alemtuzumab, an anti-CD-52 antibody which depletes T cells, was reported in two series in 18 and 32 patients with BD that was poorly controlled by conventional therapies. In one series, the majority (72%) of patients entered remission, and 33% could discontinue their treatment.[118] Alemtuzumab as remission induction therapy was effective in 84% (partial/complete remission), and sustained remission was achieved in 69% at 12 months. Lymphocyte depletion, infusion reactions, and symptomatic autoimmune thyroid disease were the most common adverse effects.[119]

Anti-CD-25

Daclizumab is a humanized monoclonal antibody against CD25. In an RCT with 17 patients, daclizumab had no beneficial effect compared with placebo in patients with BD with severe ocular involvement.[120]

Conclusion

Data from large case series confirm the efficacy and safety of TNFα inhibitors and INF-α in the treatment of refractory BD with major organ involvement such as ocular, neurologic, vascular and GI. The results are quite promising with anakinra and ustekinumab in refractory mucocutaneous disease. IL-1 inhibitors and tocilizumab also seem alternative options in patients with refractory ocular involvement. However further randomized controlled studies with biologic agents are needed for the assessment of efficacy, safety, and optimal treatment duration in BD.

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