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Review

Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçet's disease

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ABSTRACT

Behçet's disease (BD) is a multi-systemic disorder of unknown etiology characterized by relapsing oral–genital ulcers, uveitis, and involvement of the articular, gastrointestinal, neurologic, and vascular systems. Although the *primum movens* of this condition remains unknown, a tangled plot combining autoimmune and autoinflammatory pathways has been hypothesized to explain its start and recurrence. In-depth analysis of BD pathogenetic mechanisms, involving dysfunction of multiple proinflammatory molecules, has opened new modalities of treatment: different agents targeting interleukin-1 have been studied in recent years to manage the most difficult and multi-resistant cases of BD. Growing experience with anakinra, canakinumab and gevokizumab is discussed in this review, highlighting the relative efficacy of each drug upon the protean BD clinical manifestations. Safety and tolerability of interleukin-1 antagonists in different doses have been confirmed by numerous observational studies on both large and small cohorts of patients with BD. In particular, the potential for *Mycobacterium tuberculosis* reactivation and tuberculosis development appears to be significantly lower with interleukin-1 blockers compared to tumor necrosis factor-α inhibitors, thus increasing the beneficial profile of this approach.

Contents

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1. Introduction

Behçet's disease (BD) is unanimously recognized as a chronic multisystem inflammatory disorder at the crossroad between autoimmune and autoinflammatory diseases [1]. It is clinically characterized by the "triple symptom complex", consisting of recurrent oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis [2]. Pathogenically, the disease is associated with multiple hereditary and environmental risk factors that work as key-determinants involved in its onset and recurrence [3]. The cause of BD is believed to rely in misdirected immune processes triggered by some microbial agents (such as herpes simplex virus-1 and *Streptococcus sanguis*) or their antigens in genetically predisposed individuals. In this regard human leukocyte antigen (HLA)-B51 allele, located in the major histocompatibility complex locus, represents the strongest risk factor for the development of BD [4–7]. More recently, other putative BD-related genes have been identified [8,9].

Multiple cytokines may contribute to the pathological scenery of BD [10], and interleukin (IL)-1 seems to play a decisive role. Notably, IL-1 has been found to be increased in the serum [11] and synovial fluid [12] of patients with BD, and furthermore the time of disease onset has been correlated with IL-1 gene specific single nucleotide polymorphisms [13,14]. In addition, monocytes of patients with BD display an increased expression of the purinergic P2 × 7 receptor, a nucleotide-gated ion channel, chiefly involved in the inflammatory response triggered by the release of adenosine triphosphate from damaged cells, which in turn promote the inflammasome-driven IL-1β secretion, suggesting the role of innate immunity in BD [15].

Similar to what has been observed in other conditions with unexplained pathogenesis, there have been continuous efforts to characterize BD from a nosological viewpoint. Firstly, Yazici has considered the disease as a seronegative spondiloarthritis, but over the years the concept of BD as an autoimmune disease has continued to gather some support [16,17]. More recently, the combination of clinical features, lack of autoantibodies, and beneficial effects derived from IL-1 inhibition has reinvigorated the consideration of BD as an autoinflammatory disease [18–27].

2. Clinical manifestations and treatment strategies

BD is largely heterogeneous in terms of clinical signs. Recurrent oral and genital ulcers, cutaneous lesions, and uveitis are the most common disease manifestations [2,28], though many other organs, including the vascular, gastrointestinal, and neurological systems as well as the musculoskeletal system can be affected. On the basis of EULAR recommendations for the management of BD [29], treatment should be tailored according to the extent and severity of clinical manifestations. Tumor necrosis factor (TNF)-α antagonists (infliximab, etanercept, adalimumab) have represented a cornerstone in the therapeutic approach to severe cases of BD mucocutaneous and joint involvement, refractory eye disease, and gastrointestinal or neurological complications [30–33], while until today the employment of anti-IL-1 agents has not yet been envisaged despite their encouraging efficacy on some disease manifestations.

2.1. Mucocutaneous disease

Mucocutaneous features are the most common symptoms of BD, and may precede by many years the onset of other more complex signs [34–36]. Oral aphthae are mandatory in the international classification criteria of BD [28]. Minor aphthous ulcers (<10 mm in diameter) are the most frequent type, while major or herpetiform ulcers are less common (Fig. 1). Genital ulcers usually occur on the scrotum in males and on the major and minor labia in females. The most frequent skin manifestations are pseudofolliculitis, papulo-pustular lesions, and erythema nodosum-like lesions (Fig. 2). The pathergy reaction is a nonspecific hyper-reactivity of the skin to trauma, and according to the International Study Group (ISG) it is a major criterion required for the diagnosis [2,28].

To treat mucocutaneous lesions, in agreement with the EULAR recommendations, colchicine should be preferred when the dominant lesion is erythema nodosum, while azathioprine, interferon-α, and TNF-α antagonists may be considered in resistant cases [29].

2.2. Eye disease

Ocular involvement occurs in approximately half of patients with BD and may cause significant morbidity, rapidly compromising the visual function. It consists of a chronic, relapsing, bilateral uveitis involving the anterior segment, the posterior segment, or both (panuveitis) [2,37].

Retinal vasculitis, retinal vein occlusion, and optic neuritis represent other less frequent eye manifestations (Fig. 3). Recurrent exacerbations of posterior segment and retinal vasculitis might lead to the loss of central vision [38]. Azathioprine or local and systemic corticosteroids rapidly suppress the eye inflammation. In resistant cases cyclosporine or infliximab in combination with azathioprine and corticosteroids, interferon-α alone or with corticosteroids may be considered [29].

2.3. Gastrointestinal disease

Gastrointestinal involvement is characterized by nonspecific symptoms, including anorexia, vomiting, dyspepsia, diarrhea, and abdominal pain, often mimicking the clinical manifestations of chronic inflammatory bowel diseases. Deep penetrating ulcers, ischemic perforation, and thrombosis are the pathological findings, mostly located in the terminal ileum, ileocecal region, and colon [2,39,40]. Treatment is largely based on expert opinions and observational studies: sulfasalazine, corticosteroids, azathioprine, TNF-α antagonists or thalidomide can be tried, except in emergencies requiring surgical procedures, such as ileocolectomy or hemicolectomy [29,41].

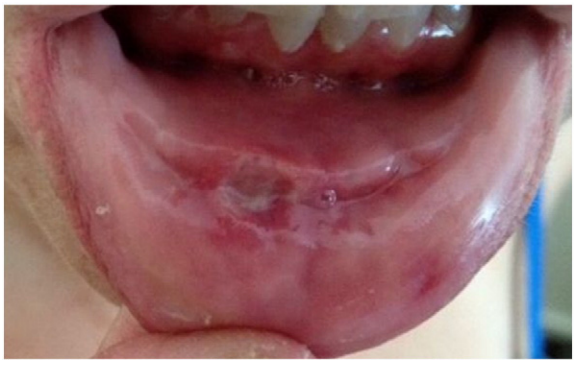

Fig. 1. Typical mucosal lesions in Behçet's disease (two painful minor aphthous ulcers, <10 mm in diameter, surrounded by an erythematous halo in the internal surface of the lip).