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Behçet disease: from pathogenesis to novel therapeutic options

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ABSTRACT

Behçet disease (BD) is a complex, multi-systemic inflammatory condition mainly hallmarked by oral and genital ulcers which can also affect the vessels, gastrointestinal tract, central nervous system and even the axial skeleton. Without a clear classification among autoimmune or autoinflammatory conditions, BD has been recently classified as a MHC-I-opathy. BD aetiology is still obscure, but it is thought that certain microorganisms can elicit an aberrant adaptive immune response in the presence of a permissive genetic background. Altered T-cell homeostasis, mostly Th1/Th17 expansion and Treg impairment, could lead to an overactivation of the innate immunity, which underlies tissue damage and thus, signs and symptoms. Immunosuppression and/or immunomodulation are central to the BD management. A complex armamentarium ranging from classical synthetic disease-modifying antirrheumatic drugs to new-era biologic agents or small molecules is available in BD, with different therapeutic outcomes depending on disease manifestations. However, the precise

disease mechanisms that underlie BD symptoms are not fully deciphered, which may limit their therapeutic potential and add a significant layer of complexity to the treatment decision-making process. The aim of the present review is to provide an exhaustive overview of the latest breakthroughs in BD pathogenesis and therapeutic options.

Key words: Behçet disease; therapy; pathogenesis; apremilast; IL-17

Introduction

Behçet disease (BD) is a primary systemic vasculitis of unknown etiology that affects the small and large vessels of the venous and arterial systems [1]. It is currently included among the auto-inflammatory disorders [2,3], but only Crohn's disease is sufficiently similar to BD to justify this inclusion [4] and novel insights into pathogenesis have challenged this notion. The most common and frequent clinical feature of BD are oral aphtae and mucocutaneous ulcers, but also ocular involvement and vascular outcomes. Gastrointestinal and/or central nervous system (CNS) manifestations (neuro-BD) can occur the most severe cases. At the clinical level, there are two clusters of BD: the first is the cluster of superficial vein thrombosis, deep vein thrombosis (DVT), and dural sinus thrombi [5], while the second cluster include acne, arthritis, and enthesitis. One-third of BD patients have thrombophlebitis of the deep or superficial veins (usually of the lower extremities), whereas arterial disease is less common (occurring in <5% of cases), but still a serious cause of morbidity and mortality, especially when it involves the pulmonary arteries [6–9].

The aim of this review was to provide an update about novel insights into BD pathogenesis and the potential effect of immunomodulatory and immunosuppressive drugs used to treat BD patients, in order to better understand the action of the new biological agents.

Pathogenesis

The exact pathogenic picture of BD is far from being clear. Whether it should be classified as an autoimmune or an autoinflammatory condition had been extensively debated. Early theories pointed to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals, innate and adaptive immune

mechanisms playing a role in the chronification of disease pathogenesis and tissue damage [10], although conflicting results have been reported thereafter. Then, important differences with 'classical' autoimmune conditions are observed in BD patients, and BD does exhibit important similarities with autoinflammatory conditions, hence suggesting that is may be too simplistic to describe BD as either autoimmune or autoinflammatory disorder [11], and it is accepted that BD does not fit into the strict sense of autoimmunity. [12] In fact, although autoantibodies can be found in BD [12], their prevalence is relatively low and, more importantly, these are largely unspecific autoantibodies that can be found in several scenarios. Them, it may be hypothesized that autoimmune phenomena in BD may be secondary events to immune overactivation, probably contributing to specific disease manifestations but not leading disease pathogenesis by themselves as per a classical autoimmune model. As a result, BD has been proposed to lie on an immunological disease continuum represented by an inflammatory response against self, in which extremes of innate and adaptive immunity (or a variable interaction between both) underscore the full spectrum of non-infectious inflammatory diseases, under the so-called MHC-I-opathy concept [12]. According to this concept, the MHC-I-associated disorders can be considered as intermediate between the innate and adaptive immune diseases. This elegant concept also brings the opportunity to explore the similarities between BD and other related syndromes, such as spondyloarthropaties (SpA) [13].

The unique geographic distribution of BD supports the existence of a strong genetic determinant(s). As a consequence, the involvement of the major histocompatibility complex (MHC) class I locus HLA-B51 was documented [14]. Importantly, this genetic association strengthen similarities with the SpA continuum under the umbrella of MHC-I-opathy [13]. Although this allele is the most abundant risk factor in areas along the 'Silk Route', it is only present in a fraction of local BD patients (approximately in a 60%), hence stressing the participation of other genetic variants [15]. These can also explain the occurrence of BD in other geographical areas, with distinct genetic backgrounds, as well as the occurrence of sporadic forms of BD by spontaneous mutations in other genes. Moreover, the existence of a polygenic substrate highlights the similarities with the classical autoimmune conditions, although different loci seem to be involved.

Although other loci within the MHC region have been proposed, including MICA genes and other non-classical MHC genes such as TNF gene variants, these results must be interpreted with caution due to the strong linkage disequilibrium that exists within the MHC region [16]. The results of genome-wide association studies (GWAS) have demonstrated an association between BD and ERAP1 polymorphisms [17,18]. More importantly epistatic interactions with some HLA class I alleles have been found, thus delineating a link among antigen loading and presentation to T-cells. Recent meta-analyses confirmed the role of other non-MHC loci in the susceptibility to BD, such as variants in IL12, IL23R, IL12A or IL12Rb [19]. Furthermore, risk alleles were also found in genes related to the interferon pathway (IFI16) [20], KIR genes [21], TLR [22], chemokine receptors [23], inflammasome [24] or STAT [17]. Taken together, these findings not only explain the HLA-B51-negative BD genetic substrate but also highlight the broad alteration of immune circuits in this condition. Moreover, recent studies have documented the involvement of rare variants in genes related to auto-inflammatory syndromes in BD susceptibility [25]. Although a lower effect has been reported, these studies may explain, at least in part, the pathogenic and clinical overlap with these disorders. Moreover, heterogeneous usage of these variants and epistatic interactions with other loci have been reported [25]. Further studies are warranted to evaluate whether genetic determinants may be useful to stratify or reclassify BD patients into distinct pathogenic subsets.

Like in most of autoimmune conditions, the genetic component does not suffice to explain disease occurrence. Rather, environmental triggers seem to play a crucial role. Actually, studies have demonstrated an intermediate risk for individuals from endemic areas after immigrating to other regions, compared to their local non-immigrating counterparts [1]. Although far from being clear, current evidence points to infectious agents as environmental triggers for BD. Then, different microorganisms have been postulated to elicit a self-reactive immune response in genetically predisposed individuals due to the presence of conserved motifs or high homology with human proteins (molecular mimicry) [26–28]. This cross-reaction has been attributed to a wide range of organisms, from streptococci species, *Helicobacter sp.* or mycobacteria to even herpex virus or parvovirus [14,29]. Large differences among these groups keep away the possibility of a single, specific aetiology trigger, and reinforce the hypothesis of

conserved peptides that may be loaded in the HLA-B51 molecule with different affinities and presented to T-cells.

An infectious agent is possibly required to trigger the innate-derived inflammation, but an adaptive response might also be sustained through autoantigen-activated antigen-presenting cells [11]. Activation of the adaptive immune response upon this cross-reactivity mechanism is supported by the emergence of antibodies against several microorganisms, such as streptococci or mycobacterium but also against self-antigens. Moreover, most of these microorganisms are able to induce T-cell activation in BD via antigen presentation to both helper or cytotoxic T-cells. CD4+-mediated T-cell responses seem to be skewed towards a Th1 profile in BD [30,31], which is in line with the involvement of IL-12 at the genetic level, as well as to an exacerbated Th17 response, also in line with the involvement of IL-23-related genetic variants, and supported by the increased serum levels of Th17-polarizing cytokines in BD, such as IL-1, IL-6 or IL-23 [32,33]. Interestingly, some studies have failed to demonstrate higher IL-23 serum levels [34] despite raised IL-17 levels, thus calling attention to potential IL-23-independent IL-17 production in BD. Moreover, Th17/Th1 cytokines have been related to the JAK1/STAT3 activation in BD [35]. Additionally, regulatory T-cell (Treg) function seems to be impaired in BD patients, which has been related to parallel the excessive Th17 response [36]. Whether this finding could be attributed to a cell plasticity mechanism under a Th17-polarizing milieu as observed in other autoimmune conditions has not be fully elucidated, but emerging evidence is supportive [36,37]. Due to the relevance of this feature for disease chronification as well as for treatment decision-making, T-cell plasticity in BD warrants further studies. Surprisingly, despite the genetic determinants (HLA class I and ERAP1 variants) strongly pointing to a central role for CD8+ T-cell responses, the role of cytotoxic mechanisms has received less attention. Higher activation of CD8+ T-cells have been observed in BD compared to their CD4+ counterparts [38]. Although a potential role via enhanced IFNg production may be conceived, it has not been confirmed in functional studies [37]. On the contrary, CD8+ T-cells from BD patients are major sources of IL-8 and GM-CSF, both being central to neutrophil biology and thus providing a central link between adaptive and innate continuum [39,40]. Moreover, CD8+ T-cells have been confirmed to largely contribute to the IL-17 secretion [41], as observed in other SpAs [42]. Taken together, CD8+ T-cell responses in BD may also amplify the magnitude,

extent and chronicity of both innate and adaptive immune responses via IL-17, rather than by conventional cytotoxic pathways. Finally, γδ T-cells are gaining ground as key disease players. In fact, γδ T-cells are not MHC-restricted and they are known to be activated by a broad range of antigenic molecules beyond peptides, thus underlining a potential role in the very early stages of the disease across disease phenotypes. γδ T-cells are known to produce IFNg and TNFa in BD patients, which may contribute to the dysregulation of the Th1 response [29,43,44]. Furthermore, their regulatory properties seem to be impaired [45,46], which resulted in a weakened regulation of their homeostatic properties [47]. Importantly, γδ T-cells have also been reported to be able to produce IL-17 by IL-23–dependent and –independent mechanisms [42], thus emphasizing the role of the IL-23/IL-17 axis. In sum, T-cell responses lead to a broad release of several cytokines, including IFNg, TNFa, GM-CSF, IL-17 and IL-8, which can in turn activate innate populations such as macrophages and neutrophils. IL-8-dependent autocrine loops may be involved in the perpetuation of innate responses (Figure 1).

The overproduction of cytokines, enzymes and oxidative stress mediators by innate subpopulations lead to tissue damage and ultimately to clinical signs in BD. Moreover, auto-antibodies and immune-complexes are thought to play a role in this scenario [15,29]. Therefore, it is important to note that immune-mediated endothelial activation and vascular damage may not only prompt ulcer or aphthae occurrence, but loss of endothelial homeostasis may underlie vascular events, hypercoagulability/enhanced thrombosis or blood-brain barrier alterations, thus accounting for major disease manifestations such as cardiovascular disease or neuro-BD.

Therapy

Immunossuppression and/or immunomodulation are central to BD therapy. A vast and quickly evolving drug armamentarium is available for BD management. However, different drugs need to be prescribed based on disease manifestations, severity and background conditions in BD. An exhaustive revision is provided in the following section, together with a comparative summary (Table 1).

Conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Colchicine

Colchicine is an alkaloid derived from *Colchicum autumnale* (autumn crocus). It is one of the oldest drugs still used in modern days, and it has been widely used in gout and familial Mediterranean Fever (FMF) [48], other than in chronic inflammatory conditions such as recurrent pericarditis [49]. Its mechanism of action is still unknown. However, the primary mechanism seems to be the tubulin disruption, which leads to the down-regulation of multiple inflammatory pathways and modulation of innate immunity, following by other mechanisms including inhibition of inflammasome and stimulation of dendritic cell maturation and antigen presentation [50]. Moreover, the drug has anti-fibrotic activities and various effects on endothelial function [51], the main reason why colchicine is used in the therapeutic management of the mucocutaneous (particularly oral and genital ulcers) and joint involvement of BD.

A recent systematic review [51] evaluating four randomized clinical trials (RCTs) in order to assess the efficacy of colchicine on oral ulcerations in BD reported that the role of colchicine as treatment for idiopathic or secondary recurrent oral ulcers is still controversial, and further standardized RCTs and crossover trials are needed. In particular, the first RCT performed by Aktulga et al [52] (n=28), in which subjects were randomly assigned to receive either a 0.5 mg dose of colchicine (3/day) or placebo, after a follow-up period of 6 months, showed no difference in terms of severity or frequency of oral ulcers. The double-blind trial including 96 patients subdivided in two groups, one receiving colchicine at the dose of 1 mg/day and one receiving 10 mg/kg/daily of cyclosporine, for 16 weeks [53], reported an improvement in oral ulcerations in the latter. The study conducted by Yurdakul et al [54] enrolled 96 patients, comparing 1-2 mg/day of colchicine and a similar dose of placebo. By evaluating as primary outcome the absence of oral ulcerations and the difference in the number of oral ulcers as the secondary outcome, it showed no difference between the two groups regarding any of the outcomes, while it had a beneficial effect on genital ulcers and arthritis. A multicenter RCT conducted in Iran involving 169 patients [55] in which subjects were randomly assigned to receive either colchicine 1 mg/daily or placebo for 4 months, then switched to the other arm for another 4 months, showed significantly better scores in the Iran Behcet's Disease Dynamic Activity Measure (including the presence of oral and genital aphthosis, pseudofolliculitis and erythema nodosum) in colchicine-treated

patients. Nevertheless, the authors underlined that there was a difference in number of patients involved and in the follow-up period, which prevented them to draw precise indications on colchicine efficacy in BD. In conclusion, the lack of confirmation of colchicine's efficacy for treatment of mucocutaneous lesions could be related to relative lack of power of the studies or to inappropriate study design. In light of this issue, the Europe League against Rheumatism (EULAR) recommendations stated that colchicine should be used as the first drug for preventing recurrent mucocutaneous lesions such as erythema nodosum or genital ulcers and joint involvement [56].

Azathioprine

Azathioprine (AZA) is an immunosuppressant of the family of the purine analogue, which is widely used in the treatment of several immune-mediated conditions as well as in the prevention of transplant rejection. AZA is used in BD as first-line treatment in ocular involvement and it can be used for the management of DVT, severe gastrointestinal involvement, neurological and joint manifestations [56].

A RCT conducted by Yazici et al [57], including 73 patients with ocular involvement, randomized to receive either AZA or placebo plus glucocorticoids with a follow-up of two years, showed that AZA was superior to placebo for preventing the development of eye involvement in patients without previous history of eye disease, for decreasing the occurrence of uveitis and for preserving visual function in patients with prior eye disease. A follow-up study of seven years also highlighted that AZA-treated patients were less likely to develop new eye disease [58]. Moreover, a study involving 157 patients with posterior uveitis or panuveitis treated with AZA combined with prednisolone demonstrated a 93% partial or complete response [59]. The efficacy of AZA in other BD manifestations, like central nervous system, gastrointestinal tract and vessels has not been studied in RCTs. However, AZA can be used in the treatment of BD vasculitis based on data from of the above RCTs, in which less vascular disease in AZA-treated patients was found. Furthermore, a study conducted in Turkey on 33 patients with entero-BD treated with AZA showed a complete remission in 67% of them after more than three years of follow-up [60].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid (MPA), an inhibitor of inosine-5'-monophosphate dehydrogenase. MPA depletes guanosine nucleotides

preferentially in T- and B-cells and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation. The efficacy of MMF in BD mucosal manifestations was assessed in one trial that was stopped due to lack of efficacy in the first six patients [61]. A case series including 4 patients with neuro-BD treated with 2 g/day MMF, showed no relapse in a follow-up period of 3-7 years of treatment [62]. Taken together, based on these data it is difficult to draw a firm conclusion on the efficacy of MMF in BD.

Cyclosporine A

Cyclosporine (CsA) is a potent immunomodulatory agent with an increasing number of clinical applications. Its major mechanism of action is the inhibition of cytokine involved in the regulation of T-cell activation. In particular, CsA inhibits the transcription of IL-2. In BD, CsA is mainly used to treat ocular manifestations based on the results of three RCTs.

The first RCT conducted in 1988 comparing CsA with conventional therapy (represented at that time by corticosteroid or chlorambucil), and it demonstrated a beneficial effect of CsA on visual acuity [63]. The second RCT compared colchicine to CyA and showed a reduced frequency of ocular attacks in the CsA group [53]. CsA was also compared to cyclophosphamide, thus showing a significant improvement in the first six months of treatment [64]. Currently, CsA is considered one of the therapeutic options for eye disease, although the risk of neurotoxicity limits its use to refractory or severe eye disease. As demonstrated by a study on 454 BD patients treated for uveitis with with CyA or other immunosuppressants, the frequency of parenchymal neurological manifestations was significantly higher in the CsA-treated patients, including seizures and new lesions on MRI [65]. In addition, a meta-analysis of observational studies using CsA in BD patients demonstrated an increased risk in the development of CNS symptoms with a relative risk of 12.6 in CsA-treated patients [66]. In light of its neurological side effects, the EULAR guidelines recommend to avoid using CsA in BD patients with CNS involvement [56].

Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating agent, which prompts nucleic acid cross-linkings and leads to protein synthesis inhibition.

Even if currently there are no RCTs that addressed the effect of CYC on vasculitis, this drug is recommended by the EULAR guidelines in the treatment of major vascular involvement, mainly represented by pulmonary artery aneurysms and aortic and peripheral artery aneurysms, as first-line treatment [56]. CYC is usually used as monthly intravenous pulses, followed by high doses of prednisone. The results of two retrospective studies, one in 1994 [67] and more recently in 2004 [68], found a decrease in mortality in patients with pulmonary artery treated with monthly pulses of CYC. In 2012, a retrospective case series involving 40 patients with severe neuro-BD were treated with cyclophosphamide 600 mg/m2 of body surface area, with a sustained clinical improvement [69]. Also, peripheral artery aneurysms can be treated with a combination of CYC and glucocorticoids at high doses. Regarding DVT, CYC is recommended alongside other immunosuppressants such as cyclosporine, but its use may be reserved for patients with extensive thrombosis due to its side effects.

Biologic drugs

Tumor Necrosis Factor inhibitors

TNF is an essential part of the inflammatory pathways that lead to the different clinical manifestations of BD, so its inhibition was considered a relevant therapeutic target to control symptoms. Current BD management often includes the use of TNF inhibitors (TNFi), particularly for ocular involvement and resistant mucocutaneous manifestations, but also to treat major organ involvement such as vasculitis and CNS manifestations. Although only one RCT was performed, the evidence from the literature and real-world data led to the inclusion of these drugs in the latest guidelines [56].

Recently, van der Houwen et al [70] conducted a systematic review on the use of TNFi in BD. Without a meta-analysis due to the heterogeneity of the studies included, 11 comparative studies (four prospective and seven retrospective studies) were compared. Among retrospective studies, five compared TNFi with csDMARDs, while two compared different starting timeframes of infliximab. Only one trial compared TNFi with placebo, hence finding a significant decrease in nodular lesions and oral ulceration in the TNFi-treated group [71]. Regarding the effectiveness of TNFi compared to corticosteroids, a study enrolled a total of 71 patients with BD and intestinal ulceration showed that the frequency of patients achieving remission was higher in TNFi-treated

patients. The addition of corticosteroids to this treatment did not provide an additional benefit [72].

Etanercept

Etanercept is a soluble fusion protein that binds specifically to the TNF receptor, leading to its inhibition. Among TNFi, it is the only one studied in a RCT [71], thus showing that the frequency of oral ulcers, papulopustular lesions and joint symptoms was reduced after four weeks. Regarding ocular disease, its efficacy was only demonstrated in only two case reports [73,74].

Infliximab

Infliximab (IFX) is widely used in the treatment of various manifestations of BD, including ocular disease, entero-BD, neuro-BD, vasculitis and arthritis. Even if no RCTs were conducted regarding ocular manifestations, data from open label trial [75–77], case report and case series [78–81] demonstrated that IFX-treated patients with uveoretinitis showed a reduced frequency of uveitis attacks and relapses, even if not improving the vision of irreversible retinal damage. In 2011, an analysis on a large number of IFX-treated BD patients with ocular involvement revealed that combination therapy with AZA and CsA was found to be superior to monotherapy for inducing sustained ocular remission [82]. Similarly, a positive effect was demonstrated in patients with refractory uveitis in large-scale long-term post-marketing studies, hence showing that IFX was associated with reductions in ocular attacks as well as with preservation of visual acuity during the period of follow up [83].

IFX is mainly used using endovenous infusions, but a study evaluating intravitreal injection of IFX in 15 patients with unilateral relapsing posterior uveitis found a beneficial effect on visual acuity and eye inflammation, thus suggesting that this route of administration could be effectively used [81].

Regarding vessels disease, a recent retrospective study enrolled 27 DMARD-refractory (mostly (AZA, CYC and corticosteroids) BD patients with vascular involvement (pulmonary aneurysms, arterial involvement and venous thrombi) [84]. Patients started 5 mg/kg IFX treatment at 0, 2 and 6 weeks followed by an infusion every 8 weeks in 24 patients, while adalimumab (ADA) was given at the dose of 40 mg every other week in 3 patients. After 3 months, most of the patients (88%) reached remission. It was noted

that more patients treated with concomitant immunosuppressive drugs reached remission compared to TNFi monotherapy, despite not reaching statistical significance. Also, the main dose of corticosteroid therapy was reduced due to the control of symptoms, with a mean dose of 4 mg of methylprednisolone after 3 months. Two patients treated with IFX and one with ADA experienced a relapse, represented by a new onset renal artery involvement, aortic involvement and DVT. After a follow-up period of 14 months, 23 patients were still treated with TNFi, whereas safety was deemed acceptable (one case of pneumonia, two cases of allergic reactions with IFX and a latent TB reactivation). The authors concluded that TNFi were a viable option for remission-induction of BD patients with refractory vascular involvement. A smaller cohort of patients with vascular BD (aortic involvement, recurrent venous and arterial thrombosis and retinal vasculitis) was described by Adler et al [85]. Improvement in symptoms were seen as long as some days after the induction regimen in all patients included in the observation arm.

Regarding entero-BD, one prospective study on 10 patients with severe intestinal involvement were treated with 3-5 mg/kg IFX. An improvement in gastrointestinal symptoms was demonstrated in all patients in 4 weeks, with sustained remission of mucosal ulcerations in 12 months [86].

Regarding neuro-BD, only case reports have been described in the literature [87–89]. The neurological involvement in BD was also treated with IFX in combination with other csDMARDs, with favorable effects being reported on signs and symptoms. Joint involvement was also improved in patients treated with IFX in a cohort of 369 patients with other disease manifestations [82], while mucocutaneous seemed to be also ameliorated in a series of studies [90,91].

Adalimumab

Adalimumab (ADA) is a completely humanized monoclonal anti-TNFα antibody. Similarly to IFX, it has been mainly studied in ocular disease, gastrointestinal, vascular and CNS involvement.

A study by Emmi et al compared the efficacy of ADA to that of csDMARD therapy in a retrospective cohort of 70 patients with BD and venous thrombosis [92]. A significant improvement in venous thrombosis, both in clinical and in imaging evaluations after 25 months of follow-up was associated to ADA treatment. A number of case reports and

case series also showed improvements in mucosal ulceration, ileocolitis, vasculitis of the CNS and pulmonary aneurisms [93–97].

ADA efficacy on ocular disease was evaluated in 2010 in a study that showed an improvement in visual acuity in 17 o 21 eyes included after 4 weeks, with a considerably lower dose of corticosteroid that had to be used as co-medication [98]. Regarding refractory uveitis, ADA and IFX were also compared in an uncontrolled open label study (n=177) [99]. After 24 months of therapy, the improvement was noted in both groups, but ADA had better results in vitritis and best-corrected visual acuity. Another study comparing ADA and IFX was performed by Fabiani [100] in 107 patients with uveitis, posterior uveitis and panuveitis, with no statistically significant differences between the two groups [100]. Although there are reports in the literature of the successful treatment of intestinal BD using ADA, RCTs are yet to be undertaken.

Tocilizumab

Due to the role played by IL-6 in BD pathogenesis, its inhibition using tocilizumab (TCZ) might be considered as a valid therapeutic option, in line with other inflammatory diseases. TCZ is a humanized monoclonal antibody against the IL-6 receptor. Unfortunately, only a limited number of case report and small case series evaluated the effects of this drug in BD.

A recent systematic review identified a total of 47 patients with BD treated with TCZ [101]. All patients were refractory to conventional immunosuppressive therapy and other biologic agents, including TNFi and daclizumab. TCZ was mainly used for mucocutaneous manifestations, articular and eye disease and, in a smaller number of patients, for gastrointestinal, neurological and vascular involvement. The mean follow-up period was 11 months, with TCZ therapy administered intravenously in every patient at the dose of 8 mg/kg/4 weeks except for one patients that was treated with 162 mg subcutaneously. The majority of patients were treated in combination with other csDMARDs while six patients were treated in monotherapy. TCZ improved clinical manifestations in eye inflammation and in neurological and vascular involvement, both arterial and venous. Furthermore, TCZ ameliorated the clinical manifestation of a patient with secondary amyloidosis and consequent nephrotic syndrome, in which it was able to decrease the level of proteinuria. Moreover, patients using TCZ were able to gradually reduce the dose of glucocorticoids, with 11 patients reaching glucocorticoid-

free remission. In contrast, TCZ failed to improve mucocutaneous manifestations such as oral and genital ulcers, skin lesions, articular symptoms, and gastrointestinal involvement. In addition, it seemed to worsen ulcers and skin lesions such as pseudofollicolitis in a small percentage of patients. Regarding safety, the adverse events reported were infrequent and generally mild. Nonetheless, further studies are needed to assess the efficacy of IL-6 blockade in BD, even if it has promising results limited to ocular disease, neuro-BD and vasculitis, or if specific clinical subsets may experience a better outcome.

Ustekinumab

Ustekinumab is a humanized monoclonal antibody against IL-12 and IL-23 shared p40 unit, strongly linked to the activation of Th1 and Th17 responses. An important difference compared to other biologic agents is that ustekinumab targets the polarizing cytokine (IL-12/23) instead of the effector cytokine (TNF, IL-17, etc), which may account for crucial differences in therapeutic outcomes and pharmacokinetic properties.

A prospective study carried out in France between 2014 and 2018 included a total of 30 patients with BD and oral ulcers despite colchicine treatment [102]. Patients were treated with 90 mg of ustekinumab at weeks 0 and 4 and then once every 12 weeks, in addition to stable doses of prednisone, colchicine, and other immunosuppressive co-therapies. Patients were evaluated at week 12 to assess the efficacy on oral ulcers and other BD manifestations as evaluated by means of the Behçet Syndrome Activity Score (BSAS). At 12 weeks, 18 patients were evaluated to have reached a complete response, 9 a partial response and 3 no response at all, with a median number of oral ulcers that was reduced from 2 to 0, a number that decreased progressively also at the 12-months follow-up. Additionally, genital ulcers decreased from 8 to 2, and an improvement in arthralgias was also registered. The mean BSAS decreased from 70 to 10 at week 24. The drug was well tolerated, with mild adverse events reported only in seven patients. Then, authors concluded that ustekinumab can be considered as effective in BD, representing a valid option for treatment of oral ulcers and joint involvement.

Secukinumab

Secukinumab is an IL-17 blocker that has indication for the treatment of psoriasis, SpA and psoriatic arthritis. As previously discussed, based on the similarity between the

pathogenesis of seronegative SpA and BD, the IL-17 blockade may be regarded as a promising therapeutic option.

A small pilot study conducted in Italy on 5 patients with mucocutaneous and articular manifestations of BD showed encouraging results in a patient treated with secukinumab 300 mg/month, while patients treated with 150 mg/month took a longer time to achieve remission and experienced relapse [103]. On this basis, the same authors conducted a multicentric retrospective study to investigate the effectiveness and safety profile of secukinumab in patients with BD, in particular with mucocutaneous and articular manifestations [104]. The study enrolled 15 patients between November 2016 and November 2019 that had shown a lack of response to colchicine, other immunosuppressive agents and at least one TNFi. Patients with a polyarticular phenotype were given a dose of 300 mg/month, while other patients started with 150 mg/month that were successively augmented in case of worsening symptoms. Concomitant treatment with stable doses of csDMARD was permitted. At the 3-months evaluation, 66.7% of patients achieved a partial or complete control in the mucosal symptoms, defined as no oral ulcers or a significant reduction of them, in the 28 days before the visit, and a response in the articular symptoms, assessed by the Disease Activity Score-28 (DAS28). At 6 months, the proportion increased to 86.7%, while after the complete follow-up of 24 months, all the patients reached a clinical response, with 11 patients experiencing a sustained clinical remission. Regarding oral ulcers, their number decreased as long as three months, and the trend was maintained at 6, 12 and 24 months. A significant decrease was also shown for genital ulcers at 3 months and confirmed in successive evaluations. DAS28 also decreased at three months and remained low even after the 24-months follow-up period. A relapse was registered in nine patients, two in the 150 mg group that were successfully treated increasing the dose to 300 mg. Authors also considered the effect on other clinical manifestations, noting a decrease in the axial symptoms, as shown by the decrease in the value of the Bath Ankylosing Spondylitis Activity Index (BASDAI), which was observed to decrease at 3, 12 and 18 months. Moreover, secukinumab treatment could improve abdominal pain and diarrhea in patients with gastrointestinal symptoms, with a concomitant decrease in fecal calprotectin, an index of gastrointestinal inflammation, in four patients. Notably, secukinumab allowed a reduction in the daily dose of prednisone, with a statistical significance observed at 3 months. The adverse events reported in the population of the

study were represented by two cases of *Candida* infection and one case of vertigo and mild mood disorders. In spite of the retrospective nature of the study and the small number of patients, these encouraging results have led the authors to point at secukinumab as a safe and effective treatment for oral ulcers and peripheral arthritis in BD, with potential beneficial effect also on genital aphtosis, axial arthritis and intestinal symptoms. Taken together, these results reinforce the relevance of IL-23/Th17 targeting in BD.

Small molecules

Apremilast

Apremilast is a small molecule that selectively inhibits phosphodiesterase 4, which is involved in the production of pro-inflammatory mediators. Despite being one of the most promising emerging treatment for oral ulcers in BD, only two double blind, multicentre, RCT have been conducted to assess the efficacy of apremilast until date.

A phase II trial was carried out in 2015 on a total of 111 patients in 3 university hospital in Turkey and 3 in the United States [105]. BD patients had at least 2 oral ulcers within 28 days before screening and 2 oral ulcers at the time of the randomization. Patients were randomly assigned to receive either apremilast at the dose of 30 mg twice daily or placebo for 12 weeks, and then all switched to active treatment with apremilast. After 12 weeks, the mean number of ulcers was significantly lower in the apremilast group, with a median number of 0 oral ulcers in the apremilast group and 2 in the placebo group. This difference was sustained in the complete follow-up phase (24 weeks). A complete response in oral ulcers was achieved in 71% of patients treated with apremilast and 29% in patients treated with placebo. In addition, also the oral ulcer pain was reduced to a higher extent in the apremilast group at week 12. Furthermore, ten patients who presented genital ulcers at baseline and were treated with apremilast experienced a complete remission at week 12, in comparison to 3 in 6 placebo-treated patients. The drug was well tolerated and the number of adverse events was low and similar in the two groups.

A phase III, double-blind RCT [106] was conducted in 2019 involving 53 centers in 10 countries. A total of 204 BD patients with active oral ulcers that occurred at least 3 times in the previous 12 months before screening were randomly assigned to receive apremilast or placebo for 12 weeks, after which all patients were given active treatment

with apremilast for 64 weeks. The primary efficacy endpoint was the reduction in the total number of oral ulcers during the 12-week placebo-controlled period, and it included multiple secondary endpoints, such as pain from oral ulcers, improvement in genital ulcers, change in BSAS, change in Behçet Disease Current Activity Form (BDCAF), and change in Behçet Disease Quality of Life score.

At week 12 the number of oral ulcers over time was found to be lower in the apremilast-treated group compared to placebo. Furthermore, the mean reduction from baseline in the pain associated with oral ulcers was greater in the apremilast group compared to that of the placebo. Beneficial effects were also registered in the mean change in the BSAS and BDCAF scores. The proportion of oral ulcers-free patients by week six and remained without ulcers for at least six more weeks was also higher in the apremilast group. Regarding genital ulcers, non-significant differences were observed between groups. Similar proportions of adverse events were reported in the two groups, but mild symptoms including nausea, diarrhea and headache occurred at a higher percentage in patients receiving apremilast. Data from the extension phase of these studies showed that changes in oral ulcers and disease indices were sustained [107]. Notably, patients previously treated with placebo that were switched to apremilast showed improvement similar to that of seen in patients originally treated with apremilast. Additional retrospective and prospective studies showed a favorable effect of apremilast in patients with oral and genital ulcers refractory to conventional or biological therapies [108–110], clinical responses being observed at 12 and 24 months.

On the basis of these results, apremilast was indicated in the latest EULAR guidelines for treatment of BD as a valid therapeutic option in patients with oral ulcers and mucocutaneous manifestations refractory to colchicine treatment [56]. Regarding other manifestations of BD, it is unclear if apremilast may have a beneficial effect on other organs. In the phase II and phase III studies discussed above, the treatment was associated with improvements of overall disease as measured by disease activity and quality of life scores, but the design of the studies did not permit to assess the efficacy in manifestations other than oral ulcers. Moreover, patients with major organ involvement were excluded from these trials. A recent literature review suggested that apremilast treatment should not be recommended in BD manifestations other than oral ulcers unless further studies are conducted [111].

JAK inhibitors

JAK inhibitors (JAKi) are small molecules that abrogate Jak/STAT signaling and thus represent a robust immunomodulatory therapeutic approach. BD pathogenesis is strongly associated with BD, since genetic variants of Stat genes have been related to BD susceptibility and Jak/STAT expression bas heen observed to hallmark CD4+ T-cells and monocytes from BD patients [35,112]. Therefore, JAKi may be a relevant therapeutic target in BD. In a mouse model of experimental dry eye disease, JAK inhibitors have shown to decrease leukocytes' corneal infiltration and to decrease cytokine levels in the conjunctive [113]. The efficacy of tofacitinib, an anti-JAK1-JAK3 agent, has been reported to control refractory ocular inflammation [114] and macular edema [115]. Miserocchi et al. [116] have recently reported four cases of JAK inhibitor efficacy in Juvenile Idiopathic Arthritis (JIA). Three patients had pan-uveitis, one had anterior uveitis and all the patients had macular edema. All patients have been previously treated with anti-TNF-α drugs, three with tocilizumab and three with abatacept. One patient received tofacitinib, one received baricitinib (anti-JAK1-JAK2) as monotherapy and two received baricitinib with methotrexate. They observed an efficacy for all patients, both on ocular inflammation and macular edema. Furthermore, Lij et al. in a recent pilot study reported the efficacy and safety of tofacitinib in BD patients, with active vascular/cardiac, gastrointestinal and articular involvements despite receiving combination of corticosteroids, multiple immunosuppressants and biologic drugs [117]. All these data suggests a new options for treating ocular involvement and refractory form of BD.

However, although current evidence about JAKi use in BD is available, it mostly come from indirect evidence (JAKi use in uveitis or ocular inflammation) or small studies, which limits the evaluation of the actual role of JAKi treatment in BD.

Conclusion

Despite the current advances in basic, translational and clinical research, a number of questions remain unsolved in the field of BD (Table 2). BD is unique among immune-mediated diseases because of its geographical variation, not only in prevalence but also in disease expression. The identification of different genetic substrates and environmental triggers have broadened our understanding of the disease and put into question whether it should be classified as a single condition or if, on the contrary, BD

can be considered a common umbrella for different but related subsets, or even a continuum of disease manifestations of a complex syndrome. The proposal of the term MHC-I-opathy, and the consequent similarities with SpA strengthen this notion. How this new classification may impact disease management and even pharmacological interventions remain unclear.

Immunopathogenesis in BD is a rapidly evolving field, although the exact picture is yet to be fully established. However, recent breakthroughs have shed new light on novel cell mediators and cytokine axes, which have provided novel treatment rationale. Overall, a shift from general drugs to highly specific agents has occurred in recent years. Among them, the IL-23/IL-17 axis is emerging as a pivotal disease player, but further research is needed. Elucidating the connections among the recent discoveries on T-cell polarization, cytokine networks and novel agents will pave the ground for innovative therapies and clinical management in BD for the coming years.

Current evidence seems to confirm that different drugs may be useful for treating different disease manifestations. Matching immune alterations to the mechanism of action of the different drugs will be key to ensure a maximal clinical benefit. Therefore, unravelling the connections between the different immune alterations and disease manifestations represent an upmost scientific priority in BD management, in order to stratify patients for the treatment decision-making process.

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CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The funders had no role in study design, data analysis, interpretation or decision to publish.

REFERENCES

[1] T. Sakane, M. Takeno, N. Suzuki, G. Inaba, Behçet's Disease, N. Engl. J. Med. 341 (1999) 1284–1291. https://doi.org/10.1056/NEJM199910213411707.

[2] Y. Yazici, S. Yurdakul, H. Yazici, Behçet's Syndrome, Curr. Rheumatol. Rep. 12 (2010) 429–435. https://doi.org/10.1007/s11926-010-0132-z.

[3] A. Gul, Behçets Disease as an Autoinflammatory Disorder, Curr. Drug Target - Inflammation Allergy. 4 (2005) 81–83. https://doi.org/10.2174/1568010053622894.

[4] H. Yazici, I. Fresko, Behçet's disease and other autoinflammatory conditions: what's in a name?, Clin Exp Rheumatol. 23(4) (2005) S1-2.

[5] R. Tunc, Cerebral venous thrombosis is associated with major vessel disease in Behcet's syndrome, Ann. Rheum. Dis. 63 (2004) 1693–1694. https://doi.org/10.1136/ard.2003.018515.

[6] N. Kabbaj, G. Benjelloun, F. Gueddari, R. Dafiri, Imani F, Vascular involvements in Behçet disease. Based on 40 patient records, J Radiol. 74 (1993) 649–56.

[7] G. Tomasson, P.A. Monach, P.A. Merkel, Thromboembolic disease in vasculitis, Curr. Opin. Rheumatol. 21 (2009) 41–46. https://doi.org/10.1097/BOR.0b013e32831de4e7.

[8] N. Ceylan, S. Bayraktaroglu, S.M. Erturk, R. Savas, H. Alper, Pulmonary and Vascular Manifestations of Behçet Disease: Imaging Findings, Am. J. Roentgenol. 194 (2010) W158–W164. https://doi.org/10.2214/AJR.09.2763.

[9] Y. Koc, I. Gullu, G. Akpek, T. Akpolat, E. Kansu, S. Kiraz, F. Batman, T. Kansu, F. Balkanci, S. Akkaya, H. Telatar, T. Zileli, Vascular involvement in Behcet's disease, J. Rheumatol. (1992).

[10] H. Yazici, E. Seyahi, G. Hatemi, Y. Yazici, Behçet syndrome: A contemporary view, Nat. Rev. Rheumatol. 14 (2018) 107–119. https://doi.org/10.1038/nrrheum.2017.208.

[11] H. Direskeneli, Autoimmunity vs autoinflammation in Behcet's disease: do we oversimplify a complex disorder?, Rheumatology. 45 (2006) 1461–1465. https://doi.org/10.1093/rheumatology/kel329.

[12] C. Mendoza-Pinto, M. García-Carrasco, M. Jiménez-Hernández, C. Jiménez Hernández, C. Riebeling-Navarro, A. Nava Zavala, M. Vera Recabarren, G. Espinosa, J. Jara Quezada, R. Cervera, Etiopathogenesis of Behcet's disease. Autoimmun Rev. 9 (2010) 241-5. doi: 10.1016/j.autrev.2009.10.005

[13] D. McGonagle, S.Z. Aydin, A. Gül, A. Mahr, H. Direskeneli, 'MHC-I-opathy'—unified concept for spondyloarthritis and Behçet disease, Nat. Rev. Rheumatol. 11 (2015) 731–740. https://doi.org/10.1038/nrrheum.2015.147.

[14] A. Greco, A. De Virgilio, M. Ralli, A. Ciofalo, P. Mancini, G. Attanasio, M. de Vincentiis, A. Lambiase, Behçet's disease: New insights into pathophysiology,

clinical features and treatment options, Autoimmun. Rev. 17 (2018) 567–575. https://doi.org/10.1016/j.autrev.2017.12.006.

[15] G. Mazzoccoli, A. Matarangolo, R. Rubino, M. Inglese, A. De Cata, Behçet syndrome: from pathogenesis to novel therapies, Clin. Exp. Med. 16 (2016) 1–12. https://doi.org/10.1007/s10238-014-0328-z.

[16] S. MARSHALL, Behçet's disease, Best Pract. Res. Clin. Rheumatol. 18 (2004) 291–311. https://doi.org/10.1016/j.berh.2004.02.008.

[17] M.J. Ombrello, D.L. Kastner, E.F. Remmers, Endoplasmic reticulum-associated amino-peptidase 1 and rheumatic disease, Curr. Opin. Rheumatol. 27 (2015) 349–356. https://doi.org/10.1097/BOR.0000000000000189.

[18] Y. Kirino, G. Bertsias, Y. Ishigatsubo, N. Mizuki, I. Tugal-Tutkun, E. Seyahi, Y. Ozyazgan, F.S. Sacli, B. Erer, H. Inoko, Z. Emrence, A. Cakar, N. Abaci, D. Ustek, C. Satorius, A. Ueda, M. Takeno, Y. Kim, G.M. Wood, M.J. Ombrello, A. Meguro, A. Gül, E.F. Remmers, D.L. Kastner, Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1, Nat. Genet. 45 (2013) 202–207. https://doi.org/10.1038/ng.2520.

[19] L. Ortiz-Fernández, F.-D. Carmona, M.-A. Montes-Cano, J.-R. García-Lozano, M. Conde-Jaldón, N. Ortego-Centeno, M.J. Castillo, G. Espinosa, G. Graña-Gil, J. Sánchez-Bursón, M.R. Juliá, R. Solans, R. Blanco, A.-C. Barnosi-Marín, R. Gómez de la Torre, P. Fanlo, M. Rodríguez-Carballeira, L. Rodríguez-Rodríguez, T. Camps, S. Castañeda, J.-J. Alegre-Sancho, J. Martín, M.F. González-Escribano, Genetic Analysis with the Immunochip Platform in Behçet Disease. Identification of Residues Associated in the HLA Class I Region and New Susceptibility Loci., PLoS One. 11 (2016) e0161305. https://doi.org/10.1371/journal.pone.0161305.

[20] L. Ortiz-Fernández, J.-R. García-Lozano, M.-A. Montes-Cano, M. Conde-Jaldón, N. Ortego-Centeno, F.-J. García-Hernández, G. Espinosa, G. Graña-Gil, J. Sánchez-Bursón, R. Blanco, A.-C. Barnosi-Marín, R. Solans, P. Fanlo, M. Rodríguez-Carballeira, T. Camps, S. Castañeda, A. Núñez-Roldán, J. Martín, M.-F. González-Escribano, Variants of the IFI16 Gene Affecting the Levels of Expression of mRNA Are Associated with Susceptibility to Behçet Disease, J. Rheumatol. 42 (2015) 695–701. https://doi.org/10.3899/jrheum.140949.

[21] Á. Castaño-Núñez, M.-A. Montes-Cano, J.-R. García-Lozano, N. Ortego-Centeno, F.-J. García-Hernández, G. Espinosa, G. Graña-Gil, J. Sánchez-Bursón, M.-R. Juliá, R. Solans, R. Blanco, A.-C. Barnosi-Marín, R. Gómez de la Torre, P. Fanlo, M. Rodríguez-Carballeira, L. Rodríguez-Rodríguez, T. Camps, S. Castañeda, J.-J. Alegre-Sancho, J. Martín, M.-F. González-Escribano, Association of Functional Polymorphisms of KIR3DL1/DS1 With Behçet's Disease, Front. Immunol. 10 (2019). https://doi.org/10.3389/fimmu.2019.02755.

[22] G.G. Song, S.J. Choi, J.D. Ji, Y.H. Lee, Toll-like receptor polymorphisms and vasculitis susceptibility: meta-analysis and systematic review, Mol. Biol. Rep. 40 (2013) 1315–1323. https://doi.org/10.1007/s11033-012-2175-x.

[23] F. Atzeni, L. Boiardi, B. Casali, E. Farnetti, D. Nicoli, P. Sarzi-Puttini, N. Pipitone, I. Olivieri, F. Cantini, F. Salvi, R. La Corte, G. Triolo, D. Filippini, G.

Paolazzi, C. Salvarani, CC chemokine receptor 5 polymorphism in Italian patients with Behcet's disease, Rheumatology. 51 (2012) 2141–2145. https://doi.org/10.1093/rheumatology/kes238.

[24] S. Burillo-Sanz, M.-A. Montes-Cano, J.-R. García-Lozano, L. Ortiz-Fernández, N. Ortego-Centeno, F.-J. García-Hernández, G. Espinosa, G. Graña-Gil, J. Sánchez-Bursón, M. Rosa Juliá, R. Solans, R. Blanco, A.-C. Barnosi-Marín, R. Gómez De la Torre, P. Fanlo, M. Rodríguez-Carballeira, L. Rodríguez-Rodríguez, T. Camps, S. Castañeda, J.-J. Alegre-Sancho, J. Martín, M.F. González-Escribano, Mutational profile of rare variants in inflammasome-related genes in Behçet disease: A Next Generation Sequencing approach, Sci. Rep. 7 (2017) 8453. https://doi.org/10.1038/s41598-017-09164-7.

[25] S. Burillo-Sanz, M.-A. Montes-Cano, J.-R. García-Lozano, I. Olivas-Martínez, N. Ortego-Centeno, F.-J. García-Hernández, G. Espinosa, G. Graña-Gil, J. Sánchez-Bursón, M.R. Juliá, R. Solans, R. Blanco, A.-C. Barnosi-Marín, R. Gómez de la Torre, P. Fanlo, M. Rodríguez-Carballeira, L. Rodríguez-Rodríguez, T. Camps, S. Castañeda, J.-J. Alegre-Sancho, J. Martín, M.F. González-Escribano, Behçet's disease and genetic interactions between HLA-B*51 and variants in genes of autoinflammatory syndromes., Sci. Rep. 9 (2019) 2777. https://doi.org/10.1038/s41598-019-39113-5.

[26] T. Ergun, M. Nce, E. Ekiolu-Demiralp, H. Direskeneli, O. Grbz, L. Grses, F. Aker, T. Akolu, HSP 60 expression in mucocutaneous lesions of Beh?et's disease, J. Am. Acad. Dermatol. 45 (2001) 904–909. https://doi.org/10.1067/mjd.2001.117728.

[27] H. Direskeneli, G. Saruhan-Direskeneli, The role of heat shock proteins in Behçet's disease., Clin. Exp. Rheumatol. 21 (n.d.) S44-8. http://www.ncbi.nlm.nih.gov/pubmed/14727460.

[28] E. Birtas-Atesoglu, N. Inanc, S. Yavuz, T. Ergun, H. Direskeneli, Serum levels of free heat shock protein 70 and anti-HSP70 are elevated in Behçet's disease., Clin. Exp. Rheumatol. 26 (n.d.) S96-8. http://www.ncbi.nlm.nih.gov/pubmed/19026123.

[29] G. Emmi, E. Silvestri, D. Squatrito, M.M. D'Elios, L. Ciucciarelli, D. Prisco, L. Emmi, Behçet's syndrome pathophysiology and potential therapeutic targets, Intern. Emerg. Med. 9 (2014) 257–265. https://doi.org/10.1007/s11739-013-1036-5.

[30] A.M. Dalghous, J. Freysdottir, F. Fortune, Expression of cytokines, chemokines, and chemokine receptors in oral ulcers of patients with Behcet's disease (BD) and recurrent aphthous stomatitis is Th1-associated, although Th2-association is also observed in patients with BD, Scand. J. Rheumatol. 35 (2006) 472–475. https://doi.org/10.1080/03009740600905380.

[31] S. Hirohata, H. Oka, Y. Mizushima, Streptococcal-related antigens stimulate production of IL6 and interferon-γ by T cells from patients with Behcet's disease, Cell. Immunol. 140 (1992) 410–419. https://doi.org/10.1016/0008-8749(92)90207-6.

[32] B. Terrier, G. Geri, W. Chaara, Y. Allenbach, M. Rosenzwajg, N. Costedoat-

Chalumeau, P. Fouret, L. Musset, O. Benveniste, A. Six, D. Klatzmann, D. Saadoun, P. Cacoub, Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis, Arthritis Rheum. 64 (2012) 2001–2011. https://doi.org/10.1002/art.34327.

[33] K. Hamzaoui, Th17 cells in Behçet's disease: a new immunoregulatory axis., Clin. Exp. Rheumatol. 29 (n.d.) S71-6. http://www.ncbi.nlm.nih.gov/pubmed/21968241.

[34] S.Y. Na, M.J. Park, S. Park, E.S. Lee, Up-regulation of th17 and related cytokines in behçet's disease corresponding to disease activity, Clin. Exp. Rheumatol. 31 (2013).37 (2018) 2797–2804. https://doi.org/10.1007/s10067-018-4049-7.

[35] A.Tulunay, M.G.Dozmorov, F.Ture-Ozdemir, V.Yilmaz, E.Eksioglu-Demiralp, F.Alibaz-Oner, G.Ozen, J.D.Wren, G.Saruhan-Direskeneli, H. Sawalha, H.Direskeneli, ctivation of the JAK/STAT pathway in Behcet's disease. Genes Immun 16 (2015) 170-5. doi: 10.1038/gene.2014.64.

[36] C. Sonmez, A.A. Yucel, T.H. Yesil, H. Kucuk, B. Sezgin, R. Mercan, A.E. Yucel, G.Y. Demirel, Correlation between IL-17A/F, IL-23, IL-35 and IL-12/-23 (p40) levels in peripheral blood lymphocyte cultures and disease activity in Behcet's patients, Clin. Rheumatol. 37 (2018) 2797–2804. https://doi.org/10.1007/s10067-018-4049-7.

[37]

J. Shimizu, K. Takai, N. Fujiwara, N. Arimitsu, Y. Ueda, S. Wakisaka, H. Yoshikawa, F. Kaneko, T. Suzuki, N. Suzuki, Excessive CD4+ T cells co-expressing interleukin-17 and interferon-γ in patients with Behçet's disease, Clin. Exp. Immunol. 168 (2012) 68–74. https://doi.org/10.1111/j.1365-2249.2011.04543.x.

[38] H. Yasuoka, Y. Yamaguchi, N. Mizuki, T. Nishida, Y. Kawakami, M. Kuwana, Preferential activation of circulating CD8+ and gammadelta T cells in patients with active Behçet's disease and HLA-B51., Clin. Exp. Rheumatol. 26 (1991) S59-63. http://www.ncbi.nlm.nih.gov/pubmed/1902611.

[39] C. Mantas, H. Direskeneli, D. Oz, S. Yavuz, T. Akoglu, IL-8 producing cells in patients with Behçet's disease., Clin. Exp. Rheumatol. 18 (n.d.) 249–51. http://www.ncbi.nlm.nih.gov/pubmed/10812500.

[40] M. Keller, Z. Spanou, P. Schaerli, M. Britschgi, N. Yawalkar, M. Seitz, P.M. Villiger, W.J. Pichler, T Cell-Regulated Neutrophilic Inflammation in Autoinflammatory Diseases, J. Immunol. 175 (2005) 7678–7686. https://doi.org/10.4049/jimmunol.175.11.7678.

[41] P.K. Dagur, A. Biancotto, E. Stansky, H.N. Sen, R.B. Nussenblatt, J.P. McCoy, Secretion of interleukin-17 by CD8+ T cells expressing CD146 (MCAM)., Clin. Immunol. 152 (n.d.) 36–47. https://doi.org/10.1016/j.clim.2014.01.009.

[42] D.G. McGonagle, I.B. McInnes, B.W. Kirkham, J. Sherlock, R. Moots, The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies, Ann. Rheum. Dis. 78 (2019) 1167–1178. https://doi.org/10.1136/annrheumdis-2019-215356.

[43] J. Freysdottir, L. Hussain, I. Farmer, S.-H. Lau, F. Fortune, Diversity of gammadelta T cells in patients with Behcet's disease is indicative of polyclonal activation, Oral Dis. 12 (2006) 271–277. https://doi.org/10.1111/j.1601-0825.2005.01185.x.

[44] P.M. Van Hagen, H. Hooijkaas, M.W.M. VD Beemd, G. Verjans, G.S. Baarsma, T-γδ Receptor Restriction in Peripheral Lymphocytes of Patients with Behçet's Disease, in: 2004: pp. 267–268. https://doi.org/10.1007/0-306-48382-3_53.

[45] A. Clemente Ximenis, C. Crespí Bestard, A. Cambra Conejero, L. Pallarés Ferreres, A. Juan Mas, J.L. Olea Vallejo, M.R. Julià Benique, In vitro evaluation of γδ T cells regulatory function in Behçet's disease patients and healthy controls, Hum. Immunol. 77 (2016) 20–28. https://doi.org/10.1016/j.humimm.2015.10.001.

[46] G. Parlakgul, E. Guney, B. Erer, Z. Kılıcaslan, H. Direskeneli, A. Gul, G. Saruhan-Direskeneli, Expression of regulatory receptors on γδ T Cells and their cytokine production in Behcet's disease, Arthritis Res. Ther. 15 (2013) R15. https://doi.org/10.1186/ar4147.

[47] B. Tong, X. Liu, J. Xiao, G. Su, Immunopathogenesis of Behcet's Disease, Front. Immunol. 10 (2019). https://doi.org/10.3389/fimmu.2019.00665.

[48] C. Cerquaglia, M. Diaco, G. Nucera, M. Regina, M. Montalto, R. Manna, Pharmacological and Clinical Basis of Treatment of Familial Mediterranean Fever (FMF) with Colchicine or Analogues: An Update, Curr. Drug Target - Inflammation Allergy. 4 (2005) 117–124. https://doi.org/10.2174/1568010053622984.

[49] M. Imazio, M. Bobbio, E. Cecchi, D. Demarie, F. Pomari, M. Moratti, A. Ghisio, R. Belli, R. Trinchero, Colchicine as First-Choice Therapy for Recurrent Pericarditis, Arch. Intern. Med. 165 (2005) 1987. https://doi.org/10.1001/archinte.165.17.1987.

[50] Y.Y. Leung, L.L. Yao Hui, V.B. Kraus, Colchicine—Update on mechanisms of action and therapeutic uses, Semin. Arthritis Rheum. 45 (2015) 341–350. https://doi.org/10.1016/j.semarthrit.2015.06.013.

[51] B.N. Cronstein, Y. Molad, J. Reibman, E. Balakhane, R.I. Levin, G. Weissmann, Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils., J. Clin. Invest. 96 (1995) 994–1002. https://doi.org/10.1172/JCI118147.

[52] E. Aktulga, M. Altac, A. Muftuoglu, Y. Ozyazgan, H. Pazarli, Y. Tüzün, B. Yalçin, H. Yazici, S. Yurdakul, A double blind study of colchicine in Behcet's disease, Haematologica. (1980).

[53] K. Masuda, A. Urayama, M. Kogure, A. Nakajima, K. Nakae, G. Inaba, DOUBLE-MASKED TRIAL OF CYCLOSPORIN VERSUS COLCHICINE AND LONG-TERM OPEN STUDY OF CYCLOSPORIN IN BEHÇET'S DISEASE, Lancet. 333 (1989) 1093–1096. https://doi.org/10.1016/S0140-6736(89)92381-7.

[54] S. Yurdakul, C. Mat, Y. Tuzun, Y. Ozyazgan, V. Hamuryudan, O. Uysal, M.

Enocak, H. Yazici, A double-blind trial of colchicine in Behçet's syndrome, Arthritis Rheum. (2001). https://doi.org/10.1002/1529-0131(200111)44:11<2686::AID-ART448>3.0.CO;2-H.

[55] F. Davatchi, B. Sadeghi Abdollahi, A. Tehrani Banihashemi, F. Shahram, A. Nadji, H. Shams, C. Chams-Davatchi, Colchicine versus placebo in Behçet's disease: randomized, double-blind, controlled crossover trial, Mod. Rheumatol. 19 (2009) 542–549. https://doi.org/10.1007/s10165-009-0200-2.

[56] G. Hatemi, R. Christensen, D. Bang, B. Bodaghi, A.F. Celik, F. Fortune, J. Gaudric, A. Gul, I. Kötter, P. Leccese, A. Mahr, R. Moots, Y. Ozguler, J. Richter, D. Saadoun, C. Salvarani, F. Scuderi, P.P. Sfikakis, A. Siva, M. Stanford, I. Tugal-Tutkun, R. West, S. Yurdakul, I. Olivieri, H. Yazici, 2018 update of the EULAR recommendations for the management of Behçet's syndrome, Ann. Rheum. Dis. (2018) annrheumdis-2018-213225. https://doi.org/10.1136/annrheumdis-2018-213225.

[57] H. Yazici, H. Pazarli, C.G. Barnes, Y. Tüzün, Y. Özyazgan, A. Silman, S. Serdaroğlu, V. Oğuz, S. Yurdakul, G.E. Lovatt, B. Yazici, S. Somani, A. Müftüoğlu, A Controlled Trial of Azathioprine in Behçet's Syndrome, N. Engl. J. Med. 322 (1990) 281–285. https://doi.org/10.1056/NEJM199002013220501.

[58] V. Hamuryudan, Y. Özyazgan, N. Hizli, C. Mat, S. Yurdakul, Y. Tüzün, M. Şlenocak, H. Yazici, Azathioprine in Behçet's syndrome. Effects on long-term prognosis, Arthritis Rheum. 40 (1997) 769–774. https://doi.org/10.1002/art.1780400425.

[59] D. Saadoun, B. Wechsler, C. Terrada, D. Hajage, D. Le Thi Huong, M. Resche-Rigon, N. Cassoux, P. Le Hoang, Z. Amoura, B. Bodaghi, P. Cacoub, Azathioprine in severe uveitis of Behçet's disease, Arthritis Care Res. (Hoboken). 62 (2010) 1733–1738. https://doi.org/10.1002/acr.20308.

[60] G. Hatemi, Y. Yazici, H. Yazici, Behçet's Syndrome, Rheum. Dis. Clin. North Am. 39 (2013) 245–261. https://doi.org/10.1016/j.rdc.2013.02.010.

[61] Y.D. Adler, U. Mansmann, C.C. Zouboulis, Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behçet's disease, Dermatology. (2001). https://doi.org/10.1159/000051781.

[62] E. Shugaiv, E. Tüzün, M. Mutlu, A. Kiyat-Atamer, M. Kurtuncu, G. Akman-Demir, Mycophenolate mofetil as a novel immunosuppressant in the treatment of neuro-Behçet's disease with parenchymal involvement: Presentation of four cases, Clin. Exp. Rheumatol. (2011).

[63] D. BenEzra, E. Cohen, T. Chajek, G. Friedman, S. Pizanti, C. De Courten, W. Harris, Evaluation of conventional therapy versus cyclosporine A in Behcet's syndrome, Transplant. Proc. (1988).

[64] Y. Ozyazgan, S. Yurdakul, H. Yazici, B. Tuzun, A. Iscimen, Y. Tuzun, T. Aktunc, H. Pazarli, V. Hamuryudan, A. Muftuoglu, Low dose cyclosporin A versus pulsed cyclophosphamide in Behcet's syndrome: a single masked trial., Br. J. Ophthalmol. 76 (1992) 241–243. https://doi.org/10.1136/bjo.76.4.241.

[65] G. Akmar-Demir, O. Ayranci, M. Kurtuncu, E.N. Vanli, M. Mutlu, I. Tugal-

Tutkun, Cyclosporine for Behçet's uveitis: Is it associated with an increased risk of neurological involvement?, Clin. Exp. Rheumatol. (2008).

[66] I. Kötter, I. Günaydin, M. Batra, R. Vonthein, N. Stübiger, G. Fierlbeck, A. Melms, CNS involvement occurs more frequently in patients with Behçet's disease under cyclosporin A (CSA) than under other medications—results of a retrospective analysis of 117 cases, Clin. Rheumatol. 25 (2006) 482–486. https://doi.org/10.1007/s10067-005-0070-8.

[67] V. HAMURYUDAN, S. YURDAKUL, F. MORAL, F. NUMAN, H. TÜZÜN, N. TÜZÜNER, C. MAT, Y. TÜZÜN, Y. ÖZYAZGAN, H. YAZICI, PULMONARY ARTERIAL ANEURYSMS IN BEHÇET'S SYNDROME: A REPORT OF 24 CASES, Rheumatology. 33 (1994) 48–51. https://doi.org/10.1093/rheumatology/33.1.48.

[68] V. Hamuryudan, T. Er, E. Seyahi, C. Akman, H. Tüzün, I. Fresko, S. Yurdakul, F. Numan, H. Yazici, Pulmonary artery aneurysms in Behçet syndrome, Am. J. Med. 117 (2004) 867–870. https://doi.org/10.1016/j.amjmed.2004.05.027.

[69] E.H. Ait Ben Haddou, F. Imounan, W. Regragui, O. Mouti, N. Benchakroune, R. Abouqal, A. Benomar, M. Yahyaoui, Neurological manifestations of Behçet's disease: Evaluation of 40 patients treated by cyclophosphamide, Rev. Neurol. (Paris). 168 (2012) 344–349. https://doi.org/10.1016/j.neurol.2011.09.006.

[70] T. van der Houwen, J. van Laar, Behçet's Disease, and the Role of TNF-α and TNF-α Blockers, Int. J. Mol. Sci. 21 (2020) 3072. https://doi.org/10.3390/ijms21093072.

[71] M. Melikoglu, I. Fresko, C. Mat, Y. Ozyazgan, F. Gogus, S. Yurdakul, V. Hamuryudan, H. Yazici, Short-term trial of etanercept in Behçet's disease: A double blind, placebo controlled study, J. Rheumatol. (2005).

[72] I. Miyagawa, K. Nakano, S. Iwata, S. Nakayamada, K. Saito, K. Hanami, S. Fukuyo, S. Kubo, A. Kawabe, Y. Miyazaki, Y. Tanaka, Comparative study of corticosteroid monotherapy, and TNF inhibitors with or without corticosteroid in patients with refractory entero-Behcet's disease, Arthritis Res. Ther. 21 (2019) 151. https://doi.org/10.1186/s13075-019-1933-8.

[73] V. Curigliano, M. Giovinale, C. Fonnesu, C. Cerquaglia, E. Verrecchia, S. Turco, C. Manganelli, R. Manna, Efficacy of etanercept in the treatment of a patient with Behçet's disease, Clin. Rheumatol. 27 (2008) 933–936. https://doi.org/10.1007/s10067-008-0857-5.

[74] P.P. Sfikakis, Behcet's disease: a new target for anti-tumour necrosis factor treatment, Ann. Rheum. Dis. 61 (2002) 51ii – 53. https://doi.org/10.1136/ard.61.suppl_2.ii51.

[75] A.A. Okada, H. Goto, S. Ohno, M. Mochizuki, Multicenter study of infliximab for refractory uveoretinitis in Behçet disease, Arch. Ophthalmol. (2012). https://doi.org/10.1001/archophthalmol.2011.2698.

[76] T. Handa, H. Tsunekawa, M. Yoneda, D. Watanabe, T. Mukai, M. Yamamura, M. Iwaki, M. Zako, Long-term remission of ocular and extraocular manifestations in Behçet's disease using infliximab, Clin. Exp. Rheumatol.

(2011).

[77] F. Cantini, Niccoli Laura, Nannini Carlotta, Kaloudi Olga, CassarÃ Emanuele, Susini Massimo, Lenzetti Ivo, Efficacy of infliximab in refractory Behçet’s disease-associated and idiopathic posterior segment uveitis: a prospective, follow-up study of 50 patients, Biol. Targets Ther. (2011) 5. https://doi.org/10.2147/BTT.S27343.

[78] H. Keino, A.A. Okada, T. Watanabe, W. Taki, Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behcet's disease on infliximab therapy, Br. J. Ophthalmol. 95 (2011) 1245–1250. https://doi.org/10.1136/bjo.2010.194464.

[79] M.J. Capella, C.S. Foster, Long-Term Efficacy and Safety of Infliximab in the Treatment of Behçet's Disease, Ocul. Immunol. Inflamm. 20 (2012) 198–202. https://doi.org/10.3109/09273948.2012.670360.

[80] S. Muñoz-Fernández, V. Hidalgo, J. Fernández-Melón, A. Schlincker, E. Martín-Mola, Effect of infliximab on threatening panuveitis in Behçet's disease, Lancet. 358 (2001) 1644. https://doi.org/10.1016/S0140-6736(01)06677-6.

[81] J.M. Benitez-del-Castillo, J.M. Martinez-de-la-Casa, E. Pato-Cour, R. Méndez-Fernández, C. López-Abad, M. Matilla, J. Garcia-Sanchez, Long-term treatment of refractory posterior uveitis with anti-TNFα (infliximab), Eye. 19 (2005) 841–845. https://doi.org/10.1038/sj.eye.6701689.

[82] A. Arida, K. Fragiadaki, E. Giavri, P.P. Sfikakis, Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients, Semin. Arthritis Rheum. 41 (2011) 61–70. https://doi.org/10.1016/j.semarthrit.2010.09.002.

[83] S. Ohno, I. Umebayashi, M. Matsukawa, T. Goto, T. Yano, Safety and efficacy of infliximab in the treatment of refractory uveoretinitis in Behçet's disease: a large-scale, long-term postmarketing surveillance in Japan, Arthritis Res. Ther. 21 (2019) 2. https://doi.org/10.1186/s13075-018-1793-7.

[84] A. Aksoy, A. Yazici, A. Omma, A. Cefle, F. Onen, U. Tasdemir, T. Ergun, H. Direskeneli, F. Alibaz-Oner, Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: A multicenter observational study of 27 patients and a review of the literature, Int. J. Rheum. Dis. 23 (2020) 256–261. https://doi.org/10.1111/1756-185X.13778.

[85] S. Adler, I. Baumgartner, P.M. Villiger, Behçet's disease: Successful treatment with infliximab in 7 patients with severe vascular manifestations. A retrospective analysis, Arthritis Care Res. (Hoboken). 64 (2012) 607–611. https://doi.org/10.1002/acr.21557.

[86] S. Iwata, K. Saito, K. Yamaoka, S. Tsujimura, M. Nawata, K. Hanami, Y. Tanaka, Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease, Mod. Rheumatol. 21 (2011) 184–191. https://doi.org/10.1007/s10165-010-0370-y.

[87] H. Kikuchi, K. Aramaki, S. Hirohata, Effect of infliximab in progressive Neuro-Behçet's syndrome, J. Neurol. Sci. 272 (2008) 99–105. https://doi.org/10.1016/j.jns.2008.05.002.

[88] N. Pipitone, I. Olivieri, A. Padula, S. D'angelo, A. Nigro, G. Zuccoli, L. Boiardi, C. Salvarani, Infliximab for the treatment of Neuro-Behçet's disease: A case series and review of the literature, Arthritis Rheum. 59 (2008) 285–290. https://doi.org/10.1002/art.23345.

[89] A. Giardina, A. Ferrante, F. Ciccia, M. Vadalà, E. Giardina, G. Triolo, 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, Rheumatol. Int. 31 (2011) 33–37. https://doi.org/10.1007/s00296-009-1213-z.

[90] W. Chan, H. Lee, Combination therapy with infliximab and methotrexate in recalcitrant mucocutaneous Behçet disease, Cutis. 89 (2012) 185–90.

[91] N.E. Aikawa, C. Gonçalves, C.A.A. Silva, C. Gonçalves, E. Bonfá, J.F. de Carvalho, Late response to anti-TNF-α therapy in refractory mucocutaneous lesions of Behçet's disease, Rheumatol. Int. 31 (2011) 1097–1099. https://doi.org/10.1007/s00296-009-1276-x.

[92] G. Emmi, A. Vitale, E. Silvestri, M. Boddi, M. Becatti, C. Fiorillo, C. Fabiani, B. Frediani, L. Emmi, G. Di Scala, M. Goldoni, A. Bettiol, A. Vaglio, L. Cantarini, D. Prisco, Adalimumab-Based Treatment Versus Disease-Modifying Antirheumatic Drugs for Venous Thrombosis in Behçet's Syndrome, Arthritis Rheumatol. 70 (2018) 1500–1507. https://doi.org/10.1002/art.40531.

[93] S.W. Lee, S.Y. Lee, K.N. Kim, J.K. Jung, W.T. Chung, Adalimumab treatment for life threatening pulmonary artery aneurysm in Behçet disease: A case report, Clin. Rheumatol. (2010). https://doi.org/10.1007/s10067-009-1272-2.

[94] C. De Cassan, B. De Vroey, C. Dussault, E. Hachulla, S. Buche, J.F. Colombel, Successful treatment with adalimumab in a familial case of gastrointestinal Behcet's disease, J. Crohn's Colitis. (2011). https://doi.org/10.1016/j.crohns.2011.03.006.

[95] D. Perra, M.A. Alba, J.L. Callejas, M. Mesquida, R. Ríos-Fernández, A. Adán, N. Ortego, R. Cervera, G. Espinosa, Adalimumab for the treatment of behçet's disease: Experience in 19 patients, Rheumatol. (United Kingdom). (2012). https://doi.org/10.1093/rheumatology/kes130.

[96] I. Olivieri, P. Leccese, S. D'Angelo, A. Padula, A. Nigro, C. Palazzi, G. Coniglio, L. Latanza, Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab, Clin. Exp. Rheumatol. (2011).

[97] F. Atzeni, P. Leccese, S. D'Angelo, P. Sarzi-Puttini, I. Olivieri, Successful treatment of leg ulcers in Behçet's disease using adalimumab plus methotrexate after the failure of infliximab, Clin. Exp. Rheumatol. (2010).

[98] A. Bawazeer, L.H. Raffa, Nizamuddin, Clinical experience with adalimumab in the treatment of ocular Behçet disease, Ocul. Immunol. Inflamm. (2010). https://doi.org/10.3109/09273948.2010.483314.

[99] B. Atienza-Mateo, J.L. Martín-Varillas, V. Calvo-Río, R. Demetrio-Pablo, E. Beltrán, J. Sánchez-Bursón, M. Mesquida, A. Adan, M.V. Hernández, M.

Hernández-Garfella, E. Valls-Pascual, L. Martínez-Costa, A. Sellas-Fernández, M. Cordero-Coma, M. Díaz-Llopis, R. Gallego, J.L. García-Serrano, N. Ortego-Centeno, J.M. Herreras, A. Fonollosa, Á.M. Garcia-Aparicio, O. Maíz-Alonso, A. Blanco, I. Torre-Salaberri, C. Fernandez-Espartero, V. Jovaní, D. Peiteado, E. Pato, J. Cruz, C. Férnandez-Cid, E. Aurrecoechea, M. García-Arias, S. Castañeda, M.A. Caracuel-Ruiz, C.A. Montilla-Morales, A. Atanes-Sandoval, F. Francisco, S. Insua, S. González-Suárez, A. Sanchez-Andrade, F. Gamero, L.F. Linares Ferrando, F. Romero-Bueno, A.J. García-González, R.A. González, E.M. Muro, C. Carrasco-Cubero, A. Olive, Á. Prior, J. Vázquez, O. Ruiz-Moreno, F. Jiménez-Zorzo, J. Manero, S. Muñoz Fernandez, C. Fernández-Carballido, E. Rubio-Romero, F.A. Pages, F.J. Toyos-Sáenz de Miera, M.G. Martinez, D. Díaz-Valle, F.J. López Longo, J.M. Nolla, E.R. Álvarez, M.R. Martínez, J.J. González-López, P. Rodríguez-Cundin, J.L. Hernández, M.A. González-Gay, R. Blanco, Comparative Study of Infliximab Versus Adalimumab in Refractory Uveitis due to Behçet's Disease: National Multicenter Study of 177 Cases, Arthritis Rheumatol. 71 (2019) 2081–2089. https://doi.org/10.1002/art.41026.

[100] C. Fabiani, A. Vitale, D. Rigante, G. Emmi, A. Bitossi, G. Lopalco, J. Sota, S. Guerriero, I. Orlando, S. Gentileschi, F. Iannone, B. Frediani, M. Galeazzi, L. Vannozzi, G.M. Tosi, L. Cantarini, Comparative efficacy between adalimumab and infliximab in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis: a retrospective observational study of 107 patients, Clin. Rheumatol. 38 (2019) 407–415. https://doi.org/10.1007/s10067-018-4228-6.

[101] M. Akiyama, Y. Kaneko, T. Takeuchi, Effectiveness of tocilizumab in Behcet's disease: A systematic literature review, Semin. Arthritis Rheum. 50 (2020) 797–804. https://doi.org/10.1016/j.semarthrit.2020.05.017.

[102] A. Mirouse, S. Barete, A. Desbois, C. Comarmond, D. Sène, F. Domont, B. Bodaghi, Y. Ferfar, P. Cacoub, D. Saadoun, Long-Term Outcome of Ustekinumab Therapy for Behçet's Disease, Arthritis Rheumatol. 71 (2019) 1727–1732. https://doi.org/10.1002/art.40912.

[103] G. Di Scala, A. Bettiol, R.D. Cojan, M. Finocchi, E. Silvestri, G. Emmi, Efficacy of the anti-IL 17 secukinumab in refractory Behçet's syndrome: A preliminary study, J. Autoimmun. 97 (2019) 108–113. https://doi.org/10.1016/j.jaut.2018.09.002.

[104] F. Fagni, A. Bettiol, R. Talarico, G. Lopalco, E. Silvestri, M.L. Urban, P.A.J. Russo, G. Di Scala, G. Emmi, D. Prisco, Long-term effectiveness and safety of secukinumab for treatment of refractory mucosal and articular Behçet's phenotype: a multicentre study, Ann. Rheum. Dis. 79 (2020) 1098–1104. https://doi.org/10.1136/annrheumdis-2020-217108.

[105] G. Hatemi, M. Melikoglu, R. Tunc, C. Korkmaz, B. Turgut Ozturk, C. Mat, P.A.

Merkel, K.T. Calamia, Z. Liu, L. Pineda, R.M. Stevens, H. Yazici, Y. Yazici, Apremilast for Behçet's Syndrome — A Phase 2, Placebo-Controlled Study, N. Engl. J. Med. 372 (2015) 1510–1518. https://doi.org/10.1056/NEJMoa1408684.

[106] G. Hatemi, A. Mahr, Y. Ishigatsubo, Y.-W. Song, M. Takeno, D. Kim, M. Melikoğlu, S. Cheng, S. McCue, M. Paris, M. Chen, Y. Yazici, Trial of Apremilast for Oral Ulcers in Behçet's Syndrome, N. Engl. J. Med. 381 (2019) 1918–1928. https://doi.org/10.1056/NEJMoa1816594.

[107] G. Hatemi, A. Mahr, M. Takeno, D. Kim, D. Saadoun, H. Direskeneli, S. Cheng, S. McCue, M. Paris, M. Chen, Y. Yazici, EFFICACY OF APREMILAST FOR ORAL ULCERS ASSOCIATED WITH ACTIVE BEHÇET'S SYNDROME OVER 64 WEEKS: RESULTS FROM A PHASE III STUDY, Ann. Rheum. Dis. 78 (2019) 148–149. https://doi.org/10.1136/annrheumdis-2019-eular.1651.

[108] M. Takeno, Y. Tanaka, H. Kono, S. Sugii, M. Kishimoto, S. Cheng, S. McCue, M. Chen, M. Paris, H. Dobashi, Efficacy of Apremilast for Oral Ulcers Associated with Active Behçet's Syndrome over 64 Weeks: Long-term Results from the Japanese Subgroup in a Phase III Study, Arthritis Rheumatol. Rheumatol. 71 (2019). https://acrabstracts.org/abstract/efficacy-of-apremilast-for-oral-ulcers-associated-with-active-behcets-syndrome-over-64-weeks-long-term-results-from-the-japanese-subgroup-in-a-phase-iii-study/.

[109] G. De Luca, A. Cariddi, C. Campochiaro, D. Vanni, N. Boffini, A. Tomelleri, G. Cavalli, L. Dagna, Efficacy and safety of apremilast for Behçet's syndrome: a real-life single-centre Italian experience, Rheumatology. 59 (2020) 171–175. https://doi.org/10.1093/rheumatology/kez267.

[110] B. Atienza-Mateo, J.L. Martín-Varillas, J. Loricera, V. Calvo-Río, J. Graña, G. Espinosa, C. Moriano, T. Pérez-Sandoval, M. Martín-Martínez, E.D. Alvarez, M.D. García-Armario, E. Martínez, I. Castellví, P. Moya, F. Sivera, J. Calvo, I. de la Morena, F. Ortiz-Sanjuán, J.A. Román-Ivorra, A.P. Gómez, S. Heredia, A. Olive, Á. Prior-Español, C. Díez, J.J. Alegre-Sancho, D. Ybáñez-García, Á. Martínez-Ferrer, J. Narváez, I. Figueras, A.I. Turrión, S. Romero-Yuste, P. Trénor, S. Ojeda, S. Castañeda, M. Calderón-Goercke, D. Prieto-Peña, I. González-Mazón, L.S. Bilbao, M.Á. González-Gay, R. Blanco, SAT0215 APREMILAST IN REFRACTORY ORAL AND/OR GENITAL ULCERS IN BEHÇET'S DISEASE. MULTICENTER STUDY OF 49 CASES IN CLINICAL PRACTICE, in: Saturday, 15 June 2019, BMJ Publishing Group Ltd and European League Against Rheumatism, 2019: pp. 1182.2-1183. https://doi.or**g/10.1136/annrheumdis-2019-eular.4945.**

[111] M. Takeno, Positioning of apremilast in treatment of Behçet's disease, Mod. Rheumatol. 30 (2020) 219–224. https://doi.org/10.1080/14397595.2019.1696504.

[112] A. Puccetti, P.F.Fiore, A.Pelosi, E.Tinazzi, G. Patuzzo, G. Argentino, F. Moretta, C.Lunardi, M.Dolcino, Gene Expression Profiling in Behcet's Disease Indicates an Autoimmune Component in the Pathogenesis of the Disease and Opens New Avenues for Targeted Therapy. Immunol Res actions (2018) 2018:4246965. doi: 10.1155/2018/4246965.

[113] W. Stevenson , Z. Sadrai, J.Hua, S. Kodati, J.Huang, S.K. Chauhan, R. Dana,

Effects of Topical Janus Kinase Inhibition on Ocular Surface Inflammation and Immunity. Cornea. 33 (2014;) 177-183. doi: 10.1097/ICO.0000000000000019.

[114] M. Paley, H. Karacal, P.K. Rao, T.P. Margolis, J.J. Miner, Tofacitinib for refractory uveitis and scleritis. Am. J. Ophthalmol. Case Rep. 13 (2019) 53-55. doi: 10.1016/j.ajoc.2018.12.001.

[115 P. Bauermann , A. Heiligenhaus, C. Heinz, Effect of Janus Kinase Inhibitor Treatment on Anterior Uveitis and Associated Macular Edema in an Adult Patient with Juvenile Idiopathic Arthritis. Ocul. Immunol. Inflamm. 27 (2019) 1232-1234. doi: 10.1080/09273948.2019.160545.

[116] E. Miserocchi, C. Giuffrè, M.Cornalba, I. Pontikaki, R. Cimaz, JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. Clin. Rheumatol. 38 (2020) 847-851. doi: 10.1007/s10067-019-04875.

[117] J. Liu, Y. Hou, L. Sun, C. Li, L. Li, Y. Zhao, X. Zeng, F. Zhang, W. Zheng, A pilot study of tofacitinib for refractory Behcet's syndrome. Ann Rheum Dis. 79 (2020) 1517-1520. doi: 10.1136/annrheumdis-2020

TABLES

Table 1: Therapeutic agents and BD manifestations. Green cells represent positive effects, yellow cells represent controversial effects and red cells represent worsening or lack of efficacy on the different disease manifestations (columns). Empty cells mean lack of evidence based on the current literature.

	Mucocutaneous	Ocular	Articular	Neurological	Gastrointestinal	Vascular	Axial
Colchicine							
AZA							
MMF							
CsA							
CYC							
TNFi							
TCZ							
Ustekinumab							
Secukinumab							
Apremilast							

Table 2: Research agenda in BD

Research agenda in BD
1. Can BD be considered as a common umbrella of different clinical subsets? 2. Can different immunotypes be distinguished within BD? Can immune circuits inform disease taxonomy? 3. Which are the main events in the connection between adaptive self-responses and activation of innate responses in BD? 4. Which are the main players (T-cells, innate subsets and cytokines) in the impairment of endothelial homeostasis in BD? 5. What is the relative importance of IL-23–dependent and –independent mechanisms for Th17 polarization in BD? 6. Do the different immune cell populations play a distinct role in the different disease manifestations? 7. Which are the main determinants of axial involvement in BD? 8. What is the actual effect of TNFi on axial involvement in BD? 9. What is the added value of IL-17-targetting drugs in BD? Is there an additional advantage compared to TNFi?

FIGURES

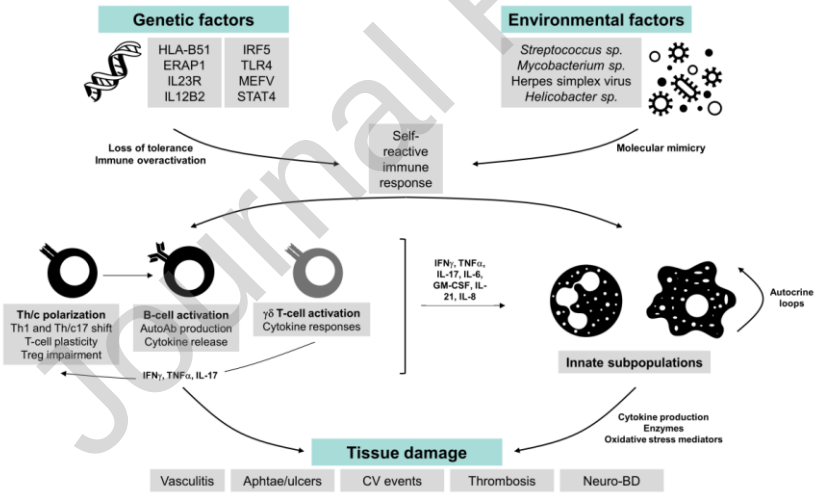

Figure 1: Pathogenesis of BD. According to the current evidence, an integrated model of immunopathogenesis of BD is depicted. BD is triggered by various environmental factors in genetically predisposed individuals. The concurrence of these aetiology factors lead to the activation of adaptive responses and innate mediators, which fuels disease perpetuation by cytokine-mediated, complex immune networks. Activation of innate mechanisms seems to underlie tissue damage and thus, development of clinical features in BD.

HIGHLIGHTS

- Behçet disease (BD) is a complex, multi-systemic immune-mediated-disease
- Instead of autoimmune or autoinflammatory, it is considered as a MHC-I-opathy
- Loss of T-cell homeostasis plays a central role in disease pathogenesis
- Different agents seem to be useful for treating different disease manifestations
- Biologic drugs helped to better understand some underlying disease features