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REVIEW ARTICLE / DERLEME MAKALE

TREATMENT OF BEHÇET'S DISEASE AND CURRENT APPROACHES

BEHÇET HASTALIĞININ TEDAVİSİ VE GÜNCEL YAKLAŞIMLAR

Gözde YENİCE ÇAKMAK[1*], Ahmet Özer ŞEHİRLİ[2]

[1] Trakya University Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 22030, Edirne, Turkey, e-mail: gozdeyenice@trakya.edu.tr

[2] Near East University, Faculty of Dentistry, Department of Pharmacology, 99138, Nicosia-6 Turkish Republic of North Cyprus, e-mail: ahmetozer.sehirli@neu.edu.tr

ABSTRACT

Objective: *Behçet's Disease (BD) is a multisystemic inflammatory disease which courses with relapses and characterized by four major symptoms of oral aphthous ulcers, genital ulcers, skin lesions and ocular lesions; and five minor symptoms including joint involvement, gastrointestinal ulcers, epididymitis, vascular lesions and neurological involvement. Treatment in BD varies according to the clinical course of age at which the disease begins, gender, the organs involved and the clinical course of the disease; therefore, it should be performed according to the person and the symptoms. While empirical treatment of BD is still continuing; recently, effective protocols have been implemented due to the pathogenesis of the underlying disease that is better defined and many broad-spectrum therapeutic agents have been presented for the treatment. This review is presented to bring together the specific treatment procedures applied during the progression of the disease.*

Result and Discussion: *Although there is no specific treatment strategy for BD, which is an inflammatory disease characterized by local and systemic involvements, treatment procedures range from local corticosteroids to monoclonal antibodies, determined by the type and severity of symptoms. Studies are still continuing on diseases affecting the vascular and gastrointestinal system in BD. Conventional immunosuppressive agents, including corticosteroids, colchicine and azathioprine, and cyclosporine are used in the treatment of BD. Recently, tumor necrosis factor (TNF) inhibitors have become available for a variety of rheumatic diseases, and published data indicate that TNF inhibitors represent a significant therapeutic advance for patients with severe and resistant disease as well as those with contraindications or intolerance to these therapies.*

Keywords: *Behçet's Disease, glucocorticoids, anti-TNF-α, mucocutaneous ulceration, major organ involvements*

ÖZ

* **Sorumlu Yazar / Corresponding Author:** Gözde Yenice Çakmak
e-mail / e-posta: gozdeyenice@trakya.edu.tr, **Phone / Tel.:** +905396393552

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Amaç: *Behçet Hastalığı (BH), nükslerle seyreden, oral aft, genital ülser, deri lezyonları ve oküler lezyonlar olmak üzere dört majör bulgu ve eklem tutulumu, gastrointestinal ülserler, epididimit, vasküler lezyonlar ve nörolojik tutulum dahil olmak üzere beş minör bulguyla karakterize multisistemik inflamatuar bir hastalıktır. BH' de tedavi hastalığın başladığı yaşa, cinsiyete, tutulan organlara ve hastalığın klinik seyrine göre değişir; bu nedenle tedavi kişiye ve semptomlara göre yapılmalıdır. BH' nin ampirik tedavisi halen devam ederken; son zamanlarda altta yatan hastalığın patogenezinin daha iyi tanımlanması nedeniyle etkili protokoller uygulanmış ve tedavi için birçok geniş spektrumlu terapötik ajan sunulmuştur. Bu derleme, hastalığın progresyonu döneminde uygulanan spesifik tedavi prosedürlerini bir araya getirme hedefiyle ortaya koyulmuştur.*

Sonuç ve Tartışma: *Lokal ve sistemik tutulumlar ile karakterize inflamatuar bir hastalık olan BH'nin belirli bir tedavi stratejisi olmamakla beraber; tutulumlara yönelik tedavi, semptomların tipi ve şiddetine göre belirlenen lokal kortikosteroidlerden monoklonal antikorlara kadar değişir. BH' de görülen vasküler ve gastrointestinal sistemi etkileyen tutulumlar üzerinde halen çalışmalar devam etmektedir. BH tedavisinde kortikosteroidler, kolşisin ve azatiyoprin ve siklosporin dahil olmak üzere geleneksel immünosupresif ajanlar kullanılmaktadır. Son zamanlarda, tümör nekroz faktörü (TNF) inhibitörleri, çeşitli romatizmal hastalıklar için kullanılabilir hale gelmiş ve yayınlanmış veriler, TNF inhibitörlerinin, ciddi ve dirençli hastalığı olan hastaların yanı sıra bu tedavilere karşı kontrendikasyonları veya intoleransı olan hastalar için önemli bir terapötik ilerlemeyi temsil ettiğini göstermektedir.*

Anahtar Kelimeler: *Behçet Hastalığı, glukokortikoidler, anti-TNF-α, mukokutenoz ülserasyon, majör organ tutulumları*

INTRODUCTION

Behçet's Disease (BD) is a chronic, multisystem inflammatory disease with an involvement both arteries and veins of all sizes. The unknown aetiology of the disease is characterized by manifestations such as oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, and others.

Pathophysiology

It is thought that both genetic and environmental triggers play a role in mediating the development of the disease. In recent studies, the immunogenetic findings have shown a clue to the development and progression of the disease, albeit the pathogenesis of the disease is still unknown.

Genetic Factors

As the strongest genetic factor, human leukocyte antigen (HLA)-B51 was extensively identified about half century ago. Recently, additional independent factors in the major histocompatibility complex class I region have been identified; HLA-B*15, -B*27, -B*57 and -A*26 as risk factors, and HLA-B*49 and -A*03 as protectives. MHC class I related gene (MIC) and tumour necrosis factor (TNF) genes, located in the MHC locus, are thought to play a role in the pathogenesis of BD. According to recent studies, the relationship between BD and genes encoding common variants of interleukin (IL) -10, interleukin-23 receptor (IL23R) and encoding interleukin 12 receptor beta (IL12RB2) outside the MHC locus has been identified. IL-23, an inflammatory cytokine, plays a key role in stimulating the proliferation of T-helper 17 (Th17), which is also responsible to produce other inflammatory cytokines triggering the formation of disease involvements. IL-10 exerts anti-inflammatory effects and regulates the release of a few pro-inflammatory cytokines [1].

Environmental Factors

Environmental factors that trigger BD are both viral infectious agents, including herpes simplex virus I, hepatitis viruses and parvovirus B19, and bacterial factors, including mycobacter, Borrelia burgdorferi, Helicobacter pylori, and various streptococcal agents [2]. Heat shock proteins (HSP) appear to be the common feature in different infectious agents, and it is assumed that their similarities with human homologues may trigger the immune response by causing cross-reactions [3].

Immunologic Factors

T cells, neutrophils, and antigen-presenting cells (APCs) have a crucial role in the pathogenesis of BD. APCs are responsible for enhancing the response of the T helper 1 (Th1) with cytokines by stimulating neutrophil hyperactivity. In addition, specifically in acute symptoms, the essential role of Th17 and interleukin (IL) -17 pathways have been revealed in the pathogenesis of disease. Elevated neutrophile activation in BD, causes neutrophil and lymphocyte infiltration in the affected organs of patients. Certain levels of TNF-α, interferon-γ, IL-1, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-18, IL-17, IL-21 and IL-23 have been reported in the sera of patients of BD and has been associated with the disease [1, 3].

Toll-like receptors (TLRs) are key proteins of the innate immune system. The detection of elevated TLR2, TLR3, TLR4, and TLR8 expression levels in patients suffering from BD suggests that TLRs may be associated with immunopathogenesis of BD [1, 3].

Another finding of neutrophil hyperactivity and the increased levels of proteins such as myeloperoxidase, superoxide dismutase and nitric oxide in BD patients suggests that they may play a role in the pathogenesis of the disease [4].

Generally, the main goal of the treatment is to relieve the symptoms, to suppress the inflammation, to prevent or reduce the tissue damage, to decrease frequency and severity of the attacks, and to avoid the future complications for the disease [3].

Treatment

Treatment in BD varies according to the age of onset, gender, the organs involved, and the clinical course of the disease; therefore, it should be performed according to the patient and the symptoms. For instance, the treatment procedure quite aggressive in a male patient with BD from an early age, who has severe eye disorders, vascular, neurological, and gastrointestinal manifestations, while the treatment of a patient with oral and mucosal involvements is more conservative. Recently, effective protocols have been implemented due to the pathogenesis of the underlying disease that is better defined and many broad-spectrum therapeutic agents have been presented for the treatment. However, none of these methods provides complete cure of the disease [5]. The following table (**Table**

1) lists BD's treatment procedures based on the manifestations of the disease.

Table 1. Organ based therapy procedures in the management of BD [6].

Manifestation		**Treatment**
Mucocutaneous manifestations	-Oral aphthae and genital ulcers	Initial Treatment • Triamcinolone acetonide cream (0.1 % Orabase), 3-4 times/ day [7] • Topical corticosteroids (for genital ulcers) or/ and Topical sucralfate (1g/5mL 4 times/ day as a mouthwash) [8] Recurrent Oral and Genital Ulcers • Colchicine (1-2mg/ day in divided doses) • Apremilast (10 mg/ day for six days for up-titration, then 30 mg twice daily) • Systemic glucocorticoids (prednisone, initial dose of 15 mg/ day in the first week; then 10 mg/ day until discontinuation of the drug for two to three weeks) • Azathioprine (50 mg/day as starting dose, increasing by 50 mg every 4 weeks until the target dose of 2.5 mg/kg/day is reached) • TNFα inhibitors (infliximab, adalimumab, or etanercept) [9-11] • Cyclosporine (10 mg/ kg/ day in divided doses) [12] • Interferon alfa (3-6 million units 3 times, weekly) [13] • Thalidomide (limited use due to neuropathy and teratogenicity adverse effects) [14]
	Cutaneous lesions	• Colchicine (1-2 mg/ day in divided doses, for mild lesions) • Prednisone (up to 40 mg daily as starting dose for colchicine-resistant symptoms)
Arthritis		• Colchicine 1-2 mg/day in divided doses • Nonsteroidal Antiinflammatory drugs (NSAIDs) (for pain management) For severe symptoms, • Azathioprine and/or TNF-α inhibitors • Interferon-α/ methotrexate • Apremilast (in symptoms unresponsive to colchicine)
Ocular disease	Anterior uveitis	• Topical corticosteroids and drops including scopolamine (0.25%) or cyclopentolate (1%). For refractory symptoms • Systemic corticosteroids (prednisone 40 mg/day as an initial dose, might be discontinuated within a month)
	Posterior uveitis	Initial Therapy • Azathioprine and glucocorticoids [15-17] • Azathioprine and TNF-α inhibitors (for sight- threatening uveitis) More severe cases • Prednisone 1 mg/ kg/ day for a month • Methyprednisolone (1 g/ day for three days) (for sight- threatening uveitis) [18- 21] • Triamcinolone (for panuveitis, for 2-6 months) [22] • Systemic glucocorticoids • Azathioprine (initial dose 50 mg/day, increasing by 50 mg every four weeks up to 2.5 mg/kg/day)

Table 1 (*continued*). Organ based therapy procedures in the management of BD [6].

Manifestation		**Treatment**
Ocular disease	Posterior uveitis	• TNF-α inhibitors (In cases inadequate or unresponsive to azathioprine, or in refractory cases) [23-25] o Infliximab (5 mg/kg at 0, 4, 8, 16, and 24 weeks or 0, 2, 6, and every 8 weeks) o Adalimumab (80 mg as a loading dose, 40 mg after one week, and 40 mg following every two weeks) • Cyclosporine (2-5 mg/ kg/ day) may be combined with azathioprine and corticosteroids [26- 31]. • Interferon alfa-2a (3-6 million units 3 times, weekly) [32- 37] • Cyclophosphamide (500 mg/ m^2 to 1 g/ m^2 of body surface area (BSA) monthly/ 6 months or 2-3 mg/ kg/ day orally.) • Methotrexate (15 mg/ week as an initial dose, increasing up to 25 mg/ week) • Mycophenolate mofetil (500 mg twice daily, after a few days the dose is increased to 1000-1500 mg twice daily) • Rituximab (1000 mg on 1^{st} and 15^{th} days, and repeated every six months) [38] • Intravitreal glucocorticoid implants [39-41]
Gastrointestinal disease		• Glucocorticoid combined with azathioprine (prednisone 0,5-1 mg/ kg/day as an initial dose, azathioprine starting with 50 mg daily, in every four weeks it increased by 50 mg up to 2,5 mg/ kg/day) [42] • TNF-α inhibitors combined with azathioprine o Infliximab (5mg/kg on weeks 0, 2, and 6, then 5 mg/kg every 8 weeks.) • TNF-α inhibitors combined with sulfasalazine • Mycophenolate and methotrexate
Renal Disease		There is no specific treatment regimen for mild nephritis. AA (secondary) amyloidosis • Colchicine 1-1.2 mg/day
Vascular Disease		Large artery disease • High-dose glucocorticoids combined cyclophosphamide [19] Venous thrombosis • Glucocorticoids plus immunosuppressive agent (same procedure used in posterior uveitis)
Neurological Disease		• Azathioprine (commonly used) • Mycophenolate mofetil • Methotrexate • Cyclophosphamide • TNF-α inhibitor (Infliximab)

Topical Treatment

Patients suffering only from skin, mucosal and joint involvement can be treated with topical corticosteroid applications in cream, mouthwash, or spray form. The treatment procedure is determined by the severity and frequency of the lesions and the perceptions and preferences of the patients. Topical sucralfate suspension is also an alternative treatment for aphthous ulcerations.

Similarly, genital ulcers also respond to topical corticosteroid medication. However, long-term use of these drugs causes skin atrophy. Larger (major) oral and genital ulcerations can be treated by intralesional triamcinolone acetonide injection. Lidocaine gel, chlorhexidine mouthwash, silver nitrate rod, amlexanox, and tetracycline mouthwashes are other topical agents have been found beneficious in the treatment of oral ulcers. For mild eye involvements, the use of topical mydriatic agents, and eye drops with corticosteroid may be effective [43].

Systemic Treatment

Glucocorticoids (GC)

Glucocorticoids (GC) are the most preferred group of drugs for the therapy regimens of many inflammatory and immune diseases. Although corticosteroids successfully reduce acute inflammation, they often fail to prevent relapses alone. Therefore, glucocorticoids are combined with other immunosuppressive agents such as colchicine, interferone-α (IFN-α), cyclosporine or azathioprine (AZA) in treatments [44, 45]. Additionally, combined treatment regimens cause to reduce the total dose of corticosteroids [45].

Corticosteroids are preferred in the treatment of moderate to severe manifestations of BD. Intravenous corticosteroids are frequently used in acute relapses of mucocutaneous, ophthalmic and neurological involvement, and progressive thrombophlebitis. However, these agents are known to be effective in acute relapses; there is no data of their effect on the control of disease progression [46].

The mechanism of action of GC is manifested by its binding with the glucocorticoid receptor (GR). Following receptor ligand formation, the GR-GC complex is transferred to the nuclear domain to trigger transactivation or transrepression processes of the target gene [46]. Therefore, it reduces the inflammatory response by suppressing various inflammatory cytokines such as IL- 1, IL- 2, IL- 6, IL-8, TNF, and granulocyte-macrophage-colony stimulating factor (GMCSF), as well as interfering with leukocyte migration [47].

Colchicine (COL)

Colchicine (COL) is an anti-inflammatory alkaloid extracted from the Colchicum plant (Colchicum autumn crocus) which inhibits the chemotactic activities of neutrophils by blocking the formation of microtubules. Forming tubulin-colchicine complexes by binding microtubules, inhibits microtubule polymerisation, leading to repress vesicle transport, cytokine secretion, phagocytosis, migration, and the cell division. The activity of colchicine differs at high and low dose concentrations; while it promotes microtubule dissociation at high doses; at low doses, suppresses microtubule growth. The inhibition mechanisms in neutrophils include inhibition of tyrosine kinases and phospholipases as molecules responsible for intracellular signalling, neutrophil chemotaxis, and lysosomal enzyme release

in phagocytosis. It is also reported that colchicine regulates neutrophil deformation and inhibits neutrophil superoxide anion production, NACHT-LRRPYD-containing protein 3 (NALP3) inflammasomes, IL1β processing and release and increases leukocyte cyclic adenosine monophosphate (cAMP) levels. Additional effect of colchicine on the inflammatory-process-has been demonstrated-in recent studies is that mediating it reduces inflammation through the regulation of myeloid inhibitory C-type lectin-like receptor (MICL), expressed by macrophages, monocytes, neutrophils, myeloid and plasmacytoid dendritic cells [48].

Colchicine can both decrease TNF-α receptor expression in macrophages by disrupting vesicular traffic and prevent granule release in mast cells by preventing degranulation. Proinflammatory cytokine levels of IL-1β, IFN γ, IL-18 and IL-6 have been reported to decrease after colchicine use in *in vivo* and *in* vitro studies. Hence colchicine is included in the treatment procedures of many inflammatory conditions. [49].

However its limited efficacy, colchicine is used as the first choice in therapy regimens due to its low cost and safety profile [50]. Colchicine has been found to be particularly effective in the treatment of mild mucocutaneous lesions, and musculoskeletal disorders in BD [43]. Nevertheless, dose adjustment is required in cases where colchicine, a narrow-spectrum drug, has haematological side effects such as cytopenia [51].

Colchicine is often used in combination with other drugs during the attack. Data from studies on the combined use of colchicine and cyclosporine have proven that the frequency of eye attacks is reduced in BD. However, colchicine is not sufficient in the treatment of severe complications due to presence of T-cell abnormalities before neutrophil activation in the pathogenesis of the disease. Accordingly, other treatment agents such as cyclosporine A or anti-TNF-α have been used in the management of more severe involvements [4].

Apremilast

Apremilast, a phosphodiesterase (PDE)-4 inhibitor, has been approved for the treatment of oral ulcers in Behçet's disease, with efficacy demonstrated in phase 2 and phase 3 clinical trials. Studies have shown that patients taking apremilast have lower number of oral ulcers and less severity of pain and significantly better results in complete response rates, overall disease activity and quality of life compared to placebo [52, 53].

Phosphodiesterase enzymes are involved in the degradation of the second messenger molecules of 3', 5'-cyclic adenosine monophosphate (cAMP) which is potent regulator of innate and adaptive immune cell functions. PDE-4, a member of PDE superfamily is expressed in various cells including proinflammatory cells. The inhibition of PDE-4 activity by Apremilast results in increased intracellular

cAMP levels, diminished proinflammatory mediators such as IFN-γ,-TNF-α, IL-12, IL-17, and IL-23, but increased IL-10 levels **[54] (**See **Figure 1**).

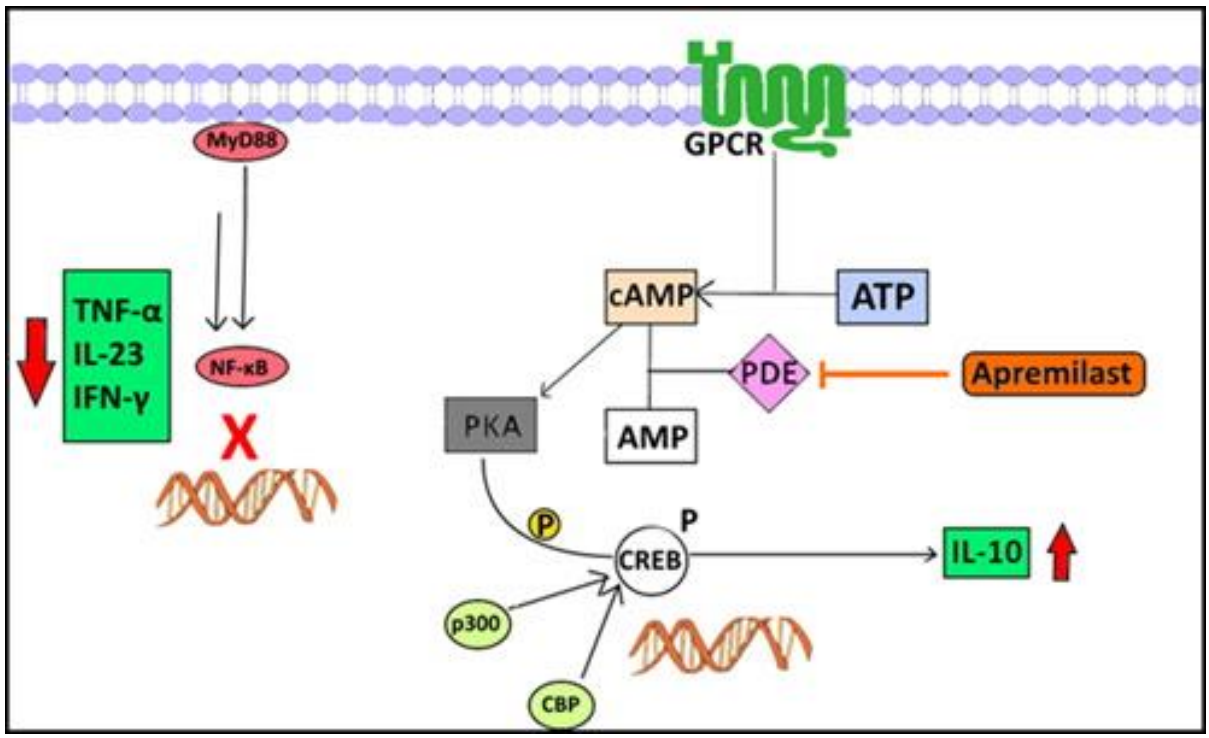

Figure 1. The mechanism of action of a Phosphodiesterase (PDE)- 4 inhibitor, Apremilast. It inhibits the expression of pro-inflammatory mediators by blocking PDE-4. High levels of cAMP modulate the anti-inflammatory effect through activation of protein kinase A (PKA), followed by phosphorylation of the cAMP-response element binding protein (CREB), and by anti-inflammatory cytokine release. Additionally, the activated PKA supresses the Nuclear Factor kappa B (NF- κB) transcriptional activity and NF- κB dependent expression of pro-inflammatory mediators such as Interleukin (IL)- 23, Tumour Necrosis Factor (TNF)-α, and Interferon (IFN)- γ [54].

Azathioprine (AZA)

A synthetic purine analogue of azathioprine (AZA) is an anti-inflammatory drug that has an important role in the treatment of BD [4]. A double-blind placebo-controlled study indicated the incidence of new eye involvements, the frequency / severity of attacks, and less oral / genital ulcers and joint involvements decreased in patients with BD using AZA, when compared with placebo in patients also taking corticosteroids [43]. In addition, administration of AZA in the early stages of therapy has been shown to be better than placebo in preventing the development of deep vein thrombosis [50].

AZA is a prodrug which is converted to 6-mercaptopurine and methylnitroimidazole through non-enzymatically cleavage in the liver after oral ingestion. 6-mercaptopurine is then metabolized to its inactive and active derivatives through a series of further enzymatic pathways. Particularly, 6-thioguanine nucleotides, which are mainly toxic and effective metabolites, inhibit purine nucleotide synthesis and proliferation through de novo pathway. The effect of azathioprine on leukocyte proliferation is thought to be according to the mechanism described over 6-mercaptopurine; and AZA is thought to be responsible for the cytotoxic effects due to the presence of toxic thioguanine nucleotides in the DNA and RNA. The effects of azathioprine, a metabolite of 6-mercaptopurine and mercapto-imidazole on lymphocyte functionality were also evaluated in mice, and the results reported that T cell proliferation, and the nuclear factor of activated T cells (NFAT) followed by activation of T cell receptor are decreased [55].

AZA can be used alone or in combination with other immunosuppressants in the management of posterior uveitis together with glucocorticoids. However, the combination with interferon-α causes severe leukopenia in patients; this treatment should be avoided.

However, the use of interferon-α and AZA combination should be avoided as it causes severe leukopenia in patients. During acute exacerbations of gastrointestinal involvements, disease-modifying agents, AZA or 5-aminosalicylic acid (5-ASA), should be used together with corticosteroids [56].

Cyclophosphamide (CP)

Cyclophosphamide (CP), a fast alkylating, immunosuppressive agent, inhibits DNA replication by binding alkyl radicals to neutrophils. Thus, DNA is not able to be completely separated and replicated during cell division, so cell death occurs. CP suppresses the activity of T-helper cell function and decreases proliferation of T and B cells [57]. As a result, autoreactive, and proliferative immune cell functions are reduced [58].

In a double-blind cross-sectional study, in the treatment of persistent eye involvement, patients using combination therapy with cyclophosphamide and corticosteroids had better results than those using corticosteroid alone [43]. According to The European League Against Rheumatism (EULAR), published in 2018, cyclophosphamide is recommended to be used in the treatment of life-threatening complications such as nervous system and vascular involvement in BD [59]. However, due to its severe toxicity, cyclophosphamide is recommended to use on other treatment-resistant and severe complications [60].

Calcineurin Inhibitors (Cyclosporine A and Tacrolimus (FK506))

Cyclosporine

Cyclosporine is a 11 amino acids cyclic polypeptide from the fungus *Tolypocladium inflatum Gams*. Calcineurin is an enzyme, one of the steps of the signalling cascade initiated by stimulation of the CD4 type T lymphocyte receptor with the Ca^{+2} dependent antigen. Cyclosporine exerts its immunosuppressive and secondary neuronal damage-inhibitory effect by selectively inhibiting this enzyme. Therefore, as a first stage, it is connected to cyclophilin which is the cytoplasmic receptor in the cell. Calcineurin is a dephosphatase enzyme that breaks phosphate groups from the factors called NFAT which are inactive in the cell cytoplasm and transported to the cell nucleus where its site of action. NFAT allows gene transcription by binding to the promoter region of the interleukin-2 gene in the nucleus, thereby producing IL-2. It blocks the pathway at calcineurin level and is therefore responsible for inhibiting IL-2 production. Cyclosporine is generally used for the treatment of many complications of BD, especially for persistent eye involvement [32].

Tacrolimus (FK506)

Tacrolimus, a calcineurin (CaN) enzyme inhibitor like cyclosporine, is a macrolide group antibiotic obtained from *Streptomyces tsukubaensis*. it selectively inhibits T cell lymphocytes. However, according to *in vitro* test results; tacrolimus 50- 100 times more effective than cyclosporine. Although the binding pocket of both drugs is the same, it forms a complex targets a different receptor, FK-binding protein 12 (FKBP-12), instead of cyclophilin. However, there are few controlled studies reporting a reduction in recurrence rate and inflammatory activity in patients with uveitis receiving tacrolimus [61].

Tacrolimus mainly targets T lymphocytes by inhibiting calcineurin- NFAT signalling pathway [19]. Calcineurin is a calcium and calmodulin dependent phosphatase activating T cells of immune system. Signalling through the T cell receptor triggers upregulation of the activity of calcineurin that dephosphorylates the cytoplasmic NFAT. Following dephosphorylation, NFAT is transported to the nuclear domain for transcription of the IL-2 gene. Tacrolimus can supress this process by binding enzyme calcineurin. Thus, NFAT translocation to the nucleus is prevented, and the production of cytokine IL-2 which is necessary for T-cell activation, is blocked [55, 61] (See **Figure 2**).

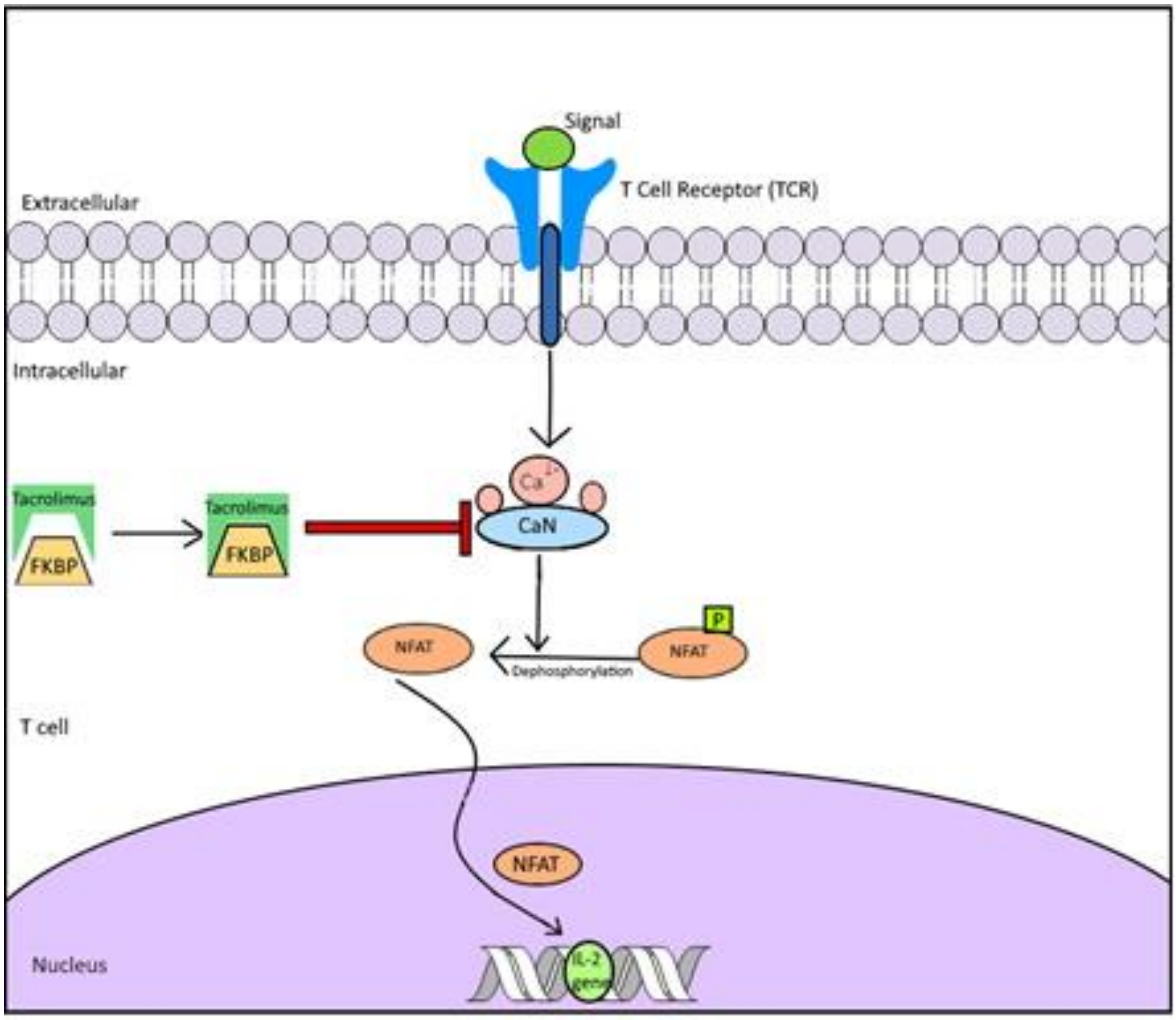

Figure 2. Mechanism of action of Tacrolimus. Upon entry into T cells, Tacrolimus forms a complex with the immunophilin FK506-binding protein (FKBP). This complex suppresses the dephosphorylation of the nuclear factor of activated T-cells (NFAT), consequently reducing the IL-2 transcription required for T cell activation [55].

Dapsone

Dapsone is characterized by both anti-infective and prominent anti-inflammatory properties [62]. It inhibits the increased chemotactic, lysosomal and myeloperoxidase activity of neutrophils. In addition, dapsone, which has an antioxidant activity, can be used as an alternative to colchicine [2, 63]. Neutrophil-induced destruction can be controlled by dapsone in inflammatory diseases.

While the use of dapsone is recommended for the treatment of moderate symptoms; it is not used in the management of the most severe mucocutaneous, ocular and systemic disorders. In a double blind, cross-comparative study of 20 patients, the frequency of oral and genital ulcer episodes,

papulopustular and erythema nodosum findings have been reported to decrease in dapsone users [59]. Other published studies support the effectiveness of dapsone [64].

Although the potency of dapsone in dermatological lesions is unknown; it is thought to have an effect on reducing the level of destruction by preventing neutrophil migration. It acts on neutrophil-induced skin lesions in patients by inhibiting the myeloperoxidase-peroxide halide mediated cytotoxic system. In lesions, dapsone reduces chemotactic lipid levels and controls LTB4 (leukotriene B4)-mediated neutrophil chemotaxis and neutrophil migration. It also reduces the neutrophil adhesions to IgA [65].

Methotrexate (MTX)

Methotrexate (MTX) shows its effect by decreasing the expression of cell adhesion molecules, decreasing endogenous adenosine release, and causing apoptosis in T cells by decreasing cell proliferation [60].

MTX has been reported to be effective in ocular, neurological and mucocutaneous involvements in recent studies [66].

The mechanism of action of MTX has varied according to many cellular mechanisms. Although this mechanism of MTX shows activity on both malignant and non-malignant cells, the anti-inflammatory activity of the drug should also be considered [67]. It affects the de novo synthesis of purine and pyrimidine bases by interfering tetrahydrofolate-dependent processes. As a result, diminished levels of methyl donors as tetrahydrofolate and methyltetrahydrofolate leads to inhibition of lymphotoxic polyamine generations. Inhibition of the enzyme aminoimidazole carboxamido ribonucleotide (AICAR) transformylase results in elevated intracellular levels of AICAR, leading to inhibition of AMP deaminase and adenosine deaminase production in which catabolic processes of adenosine monophosphate (AMP) and adenosine to inosine monophosphate (IMP) and inosine. Thereby, gathered adenosine levels exerts anti-inflammatory effects [68].

Based on the various cell types, the efficacy of MTX is varies. In T cells, it acts by inhibiting the reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4), which is catalysed by the enzyme dihydrofolate reductase (DHFR). The uncoupling of nitric oxide synthase (NOS), following increased levels of reactive oxygen species (ROS) promote the JUN N-terminal kinase (JNK), which leads to protein synthesis responsible for apoptosis and cell cycle processes. Methotrexate activates DNA-dependent protein kinase (DNA-PK) in T cells by unclarified mechanisms, promoting the induction of LincRNA p21, long intergenic noncoding RNA p21 (lincRNA-p21), which inhibits translation of RELA mRNA. Thereby, it increases the proinflammatory transcription factor NF-κB levels and inhibits inflammatory response. Methotrexate also inhibits NF-κB activity in Fibroblast-like synoviocytes by mediating the inhibition of AICAR transformylase (ATIC), elevated adenosine secretion, and activation

of adenosine receptors, which results in inhibition of NF-kB, and ultimately anti-inflammatory effects. In monocytes, inducing apoptosis and increasing the expression of proinflammatory cytokines by an unknown NF-κB-dependent mechanism that has not yet been revealed is thought to be emerged through inhibition of DHFR-mediated reduction of dihydrofolate (DHF) to tetrahydrofolate (TTF) [67].

Treatment Methods Based on Immunopathogenesis in BD

Anti-Tumour Necrosis Factor-α (Anti-TNF-α)

TNF-α acts as the basic cytokine in the generation and maintenance of inflammatory response. Many studies confirm that TNF-α plays a critical role in the pathogenesis of BD. High levels of TNF-α production were detected in aqueous humor and serum of patients. During the active periods of the disease, an increase in the number of cells responsible for producing TNF-α; and the presence of TNF-α was observed in experimental animal models with eye involvement [18].

In the pathogenesis, elevated TNF-α concentrations occur in the inflammation area. Removal of excess TNF-α from these regions has become a target in the treatment. Therefore, agents that may be effective in treatment have designed to reduce the effect of TNF-α. These three anti-TNF-α agents, infliximab, etanercept, and adalimumab, have been investigated in the treatment of ocular disorders [43]. Almost all symptoms have been suppressed by a rapid and apparent response in the treatment with anti-TNF-α of BD. Promising results have been obtained in severe complications, particularly in the presence of persistent mucocutaneous lesions, ocular involvement, gastrointestinal symptoms, arthritis, and cerebral vasculitis. In addition, these drug groups reduce the dose of other immunosuppressants to be used in combined therapy. Anti-TNF-α agents in the patient groups with severe complications of BD-resistant to standard immunosuppressive therapies provide significant therapeutic benefit. However, the route of administration of these drug groups, their costly and toxic side effects and the lack of long-term therapeutic efficacy limit the widespread use of the drug. Based on case reports, it can be suggested that TNF blockade gives good results in individuals with BD who are resistant to or intolerant to severe and standard immunosuppressant therapies [69].

Infliximab

The two known TNF receptors are TNFr1 that binds soluble TNF, and TNFr2 that binds membrane-bound TNF. Infliximab, a chimeric monoclonal antibody, acts by inhibiting the binding of TNF to these two receptors. It reduces the frequency of uveitis attacks. In addition, it has also been reported to be effective in genital ulcers, erythema nodosum, and other skin lesions. According to the data, there is a significant recovery in visual activity and decrease ocular and inflammation within 24 hours after the administration of Infliximab [69].

Data on the effect of the drug on vascular disorders are limited but positive results have been reported [63]. Infliximab is widely used in the treatment of neurological, gastrointestinal and mucocutaneous disorders resistant to conventional treatment in BD [70].

Positive results have been obtained with infliximab in persistent macular oedema and improvement of visual activity, especially in the cases resistant to the combination of azathioprine, cyclosporine and corticosteroids [71]. However, TNF inhibitors are not sufficient to suppress the symptoms of BD alone, but it has been reported that good results can be obtained in long term combined therapies [69].

Etanercept (ETN)

Etanercept (ETN) is an anti-TNF-α agent and differs structurally from its monoclonal antibody constructs of adalimumab and infliximab [63]. ETN is a recombinant human IgG1 TNF-receptor-fusion protein that binds TNF and blocks interactions with its receptor, thus reducing TNF-mediated inflammatory events [72].

ETN is effective in the treatment of mucosal and skin lesions due to BD. In a randomized, double-blind controlled study, it was demonstrated reduced mucocutaneous manifestations in patients with BD treated with etanercept compared to placebo. There are limited reports on the use of ETN in ocular disorders. In addition, good results have been obtained in the treatment of central nervous system disorders of BD [45, 63].

Adalimumab (ADA)

A recombinant, fully humanized monoclonal antibody adalimumab (ADA) acts by binding to human TNF-α–and blocking its interaction with the surface cell receptors p55 and p75, thereby preventing the induction of cytokine-induced inflammatory pathways [73].

After approval by European and US authorities for the treatment of ocular inflammatory disorders, ADA will likely be the first-line choice in the treatment of anti-TNF agents in patients with BD-related uveitis. Although there are promising case reports of the use of ADA in refractory intestinal BD, data from controlled clinical studies are lacking. Additionally, good results were obtained from the studies by using adalimumab in patients with BD in central nervous system (CNS) and vascular involvements [74].

Interferon Alpha (IFN-α)

Interferon alpha (IFN-α) is one of the immunomodulatory cytokines found naturally in the body. Interferons are a family of glycoproteins with antiviral, antitumor and immunomodulatory activities [45].

In the treatment, IFN-α was first used because of its antiviral effects against Herpes simplex virus type-1. The biological effects of IFN-α are the activation of NK cells, inhibition of gamma delta

(ϒδ) T cells, increased expression of HLA-1 from peripheral monocytes, and reduction of T cell adhesion to endothelial cells. Controlled studies published in recent years suggest that IFN-α may be an effective alternative for BD-related mucocutaneous lesions, eye, and joint involvements. Besides, it decreases the frequency of papulopustular lesions, and genital ulcers, and the rate of recurrent attacks of eye diseases. However, all symptoms tend to return to their pre-treatment levels at the end of the treatment [75].

Rituximab (RTX)

Rituximab (RTX), a chimeric murine/ human IgG1k monoclonal antibody, is directly targeted to CD20 surface antigen which is a B cell differentiating marker and regulator of the cell division cycle [63]. By binding, RTX causes B lymphocyte depletion through complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC) [76].

There are case studies investigating the effectiveness of RTX on BD-related manifestations. According to one case report, rituximab has been reported to be effective in remission of the treatment of retinal vasculitis resistant to glucocorticoids, azathioprine and ETA [44, 63]. In addition, a single blind pilot study on the use of RTX in ocular lesions of BD has been published. In this study, 20 patients received RTX or cyclophosphamide. The results show that after administration of methotrexate and prednisolone, patients receiving RTX significantly reduced intraocular inflammation over a 6-month period. [77].

Alemtuzumab (ALZ, Campath 1-H)

Alemtuzumab (ALZ) is a 1-H humanized monoclonal antibody that directly targets CD-52, a surface antigen found on lymphocytes and macrophages [77]. However, the activity of CD52 is not fully known, recently it has been reported that it may be a regulatory function of activated CD4 T cells that express high levels of CD52[78]. After infusion ALZ mainly causes profound CD52 + cell depletion through ADCC and complement-dependent cytolysis (CDC), the recovery time is long and often incomplete [79].

ALZ, which is used in the treatment of many and autoimmune diseases and haematological malignancies, as used after transplantation, will be an effective alternative in the treatment of persistent BD cases [80]. In a 20-year experience study of the use of ALZ in patients with severe BD and refractory to at least one treatment agent. ALZ was used in patients with ocular, central nervous system (CNS), gastrointestinal (GI), and vascular symptoms of BD [77].

Daclizumab (DAZ)

Daclizumab (DAZ), a humanized anti-IL-2Rα (anti-CD25) monoclonal antibody, acts by blocking the activated lymphoid cells IL-2-mediated responses by binding to the CD25 subunit of the high affinity IL-2 receptor [33]. Since IL-2 is the mediator that stimulates and regulates the immune system, success in therapy was aimed by targeting CD25 [81].

Although DAZ was withdrawn from the market after the approval for use in organ transplantation in Europe, there are continuing clinical studies on the safety and efficacy of DAZ in inflammatory bowel disease, uveitis and multiple sclerosis [77].

Tocilizumab

Tocilizumab, a humanized anti-Interleukin -6 (anti-IL-6) receptor antibody, acts by binding to soluble or membrane-bound IL-6 receptors and inhibiting IL-6 signalling competitively [77].

IL-6 is one of the regulators of immune response and inflammatory reactions [82], which also has a critical role in Neuro-Behçet's Disease (Neuro-BD). Therefore, IL-6 signalling inhibited by Tocilizumab reveals a new treatment regimen in Neuro-BD. Several case reports have been published regarding the evaluation of the efficacy of tocilizumab on patients with Neuro-BD [83]. Information from these cases supports the promising results of tocilizumab [84]. Another study investigating the efficacy of the drug on refractory uveitis of BD obtained good responses, suggesting that tocilizumab may be a therapeutic option in the treatment of this manifestation [77, 85].

A small retrospective study of tocilizumab in the treatment of refractory vasculo-Behçet's syndrome between the years 2014 and 2018 was reported [86]. In this study, tocilizumab was added to existing corticosteroid and immunosuppressive treatments of patients suffering from the vascular manifestations. Data conducted from the study suggest that tocilizumab may be effective in combined therapy in the management of refractory vasculo-Behçet's syndrome [77, 87].

Secukinumab (SCM)

Secukinumab (SCM) is a fully human monoclonal antibody, selectively inhibits the IL17A [88, 89]. IL-17A, one of the main proinflammatory cytokines, is particularly produced by Th17 cells and expressed by NK cells, mast cells, and neutrophils [88]. SCM binds directly to IL-17A, blocking its interaction with the receptor, thereby suppressing the downstream inflammatory pathway responsible for the prognosis of the disease [90].

After the approval of SCM use in the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis in the USA, this agent was also evaluated for its effectiveness on BD- related mucocutaneous and articular symptoms. Although the obtained data are promising, there is a need for more adequately

controlled studies on this topic [87]. Additionally, different randomized, placebo-controlled, double-blind clinical studies have been conducted to investigate the effect of SCM on non-infectious uveitis. In one study, it was found that there was no significantly different remission rate between the treatment and placebo groups, resulting with early termination of other studies [77].

Anakinra (ANR)

The recombinant, non-glycosylated human IL-1 receptor blocker Anakinra (ANR) competes with both IL-1α and IL-1β cytokines by binding to IL-1 receptor-1 (IL-1R1). After IL-1 binds to IL-1R1 and forms a receptor-ligand complex; and stimulates IL-1 accessory protein (IL-1AcP). ANR binds to IL-1R1 instead of IL-1, inhibiting the signalling pathway that induces secondary inflammatory mediators such as prostaglandins, cytokines, and chemokines [91].

After ANR has been approved in the treatment of rheumatoid arthritis, there are studies that the off-label use of ANR have an effect on inflammatory conditions [92]. There were case series reporting the effectiveness of ANR in remission of refractory uveitis [93]. Another a pilot open label study of ANR efficacy on refractory oral and genital ulcers. According to the study, in addition to the disappearance of ulcer symptoms in two patients, it was reported that the remaining five patients had signs of partial healing [77].

Gevokizumab

IL-1 is an inflammatory cytokine that has a crucial role in regulating the innate immune response. Gevokizumab, IgG_2 recombinant humanized allosteric monoclonal antibody responsible for IL-1β inhibition; acts by suppressing the bioactivation of IL-1β through its receptor signalling complex [94].

In the first study that tested the efficacy and safety of gevokizumab in patients with treatment-resistant uveitis in BD, it was reported that recurrence of uveitis decreased despite discontinuation of immunosuppressive therapies [95]. Another study was the phase 2 study to evaluate the pharmacokinetic and pharmacodynamic profile as well as clinical and biologic activity of gevokizumab in patients suffered from uveitis [96]. Although the study was terminated because the desired endpoints were not achieved, positive results have been obtained in treatment with gevokizumab [77, 95].

Canakinumab (CAM)

Canakinumab (CAM) is human anti-IL-1β monoclonal antibody. IL-1β is one of the major cytokines involved in many inflammatory diseases, has become the target during the development of the new anti-inflammatory agent [97]. To suppress inflammation, it binds to IL-1 and block interaction with its receptor, thereby inhibiting the signalling pathway [94].

There are published case reports of CAM efficacy on TNF-alpha inhibitors resistant to BD, pediatric BD, and severe and refractory BD with major vascular, ocular, and gastrointestinal symptoms [98]. In order to analyse the effectiveness of CAM in three retrospective cohort studies; patients suffering from refractory BD were given either ANR or CAM. Based on the suggested results by the authors, reduced ocular symptoms occurred with the use of CAM [99].

Golimumab (GLM)

Golimumab (GLM), a new fully humanized anti-TNF-α monoclonal antibody, blocks endogenous TNF-α activity by binding soluble and transmembrane TNF-α and disrupting binding to the TNF-α receptor [100]. Thus, the formed Ab-TNF-α complex inhibits the interaction with the receptor that promotes myriad inflammation cascades [101].

The higher affinity and avidity of GLM for TNF-α than other available anti-TNF-α agents has been reported [100]. Recently, in studies of Golimumab promising results have been showed regarding the effectiveness of non-infectious uveitis and Uveitis of Behçet' s Disease [102, 103].

Certolizumab pegol (CZP)

Certolizumab (CZP) is a humanized recombinant Fab' fragment, which specifically targets human TNF-α and able to neutralize both soluble and membrane-bound forms [104, 105]. Polyethylene glycol (PEG) was attached to its molecular structure in order to improve its pharmacokinetic and pharmacodynamic properties. In addition, since CZP lacks an Fc region in the Fab fragment, Fc-induced effects such as complement fixation and cell lysis are not observed [106]. Another difference between certolizumab and other TNF-α inhibitors (adalimumab, etanercept, and infliximab) is that while certolizumab is bivalent, these agents are univalent [104].

However, in reports that include limited numbers of patients, recent studies have reported that CZP is effective for ocular and other refractory manifestations of Behçet' s disease [77, 102, 107].

Ustekinumab

IL-12 and IL-23 cytokines play an important role in the differentiation and activation of Th17 and Th1 lymphocytes and NK cells, which are involved in the pathogenesis of BD. Ustekinumab, a humanized immunoglobulin G_K (IgG_K) monoclonal antibody, directly targets to those, which regulate inflammatory and immune responses. It binds to the p40 subunits of IL-12 and IL-23, inhibiting their binding to these receptors on the surface of T cells, NK cells and antigen presenting cells [108].

According to the recent studies, the use of ustekinumab for BD patients with colchicine-resistant oral ulcers has shown promising efficacy [109]. The effectiveness of Ustekinumab in the

treatment of BD-like diseases such as psoriasis and Crohn's disease which share Th17 pathway has also been reported [110].

Specific Immune Tolerance Induction

HSPs play a major role in the pathogenesis of BD are synthesized when stimulated by a nonspecific stimulant such as cell, trauma, heat, and infection. Tolerance Induction is the method used in the treatment of autoimmune uveitis in BD [63, 111]. It has been reported that 336-351 peptide, which is subcutaneously administered to HSP-60, reduce the severity and development of uveitis seen in BD, and 336-365 peptide covalently linked to the orally administered recombinant cholera toxin B (CTB) subunit. Moreover, no adverse effects during treatment suggests that tolerization therapy may be one of the effective alternatives in the management of BD [18, 112].

Immunoablation

Autologous hematopoietic cell transplantation and immunoablation have been shown to be effective in the treatment of autoimmune disorders. Myeloablative chemotherapy followed by immunosuppressive drugs and T cell free hematopoietic stem cell transplantation were found to be effective and safe in BD. Especially in cases with resistance to immunosuppressive therapies, immunoablation may be an alternative treatment method in the control of BD [18].

Other drugs

Rebamipide

Rebamipide, a gastroprotective agent, provides inhibition of free radicals and inflammatory cytokines from activated neutrophils. It protects existing cells and shows its efficacy by regenerating the lost tissue [113].

The mucoprotective effects of rebamipide on gastric ulcer lesions are mediated by elevated prostaglandin levels in the gastric mucosal surface by promoting upregulation of cyclo-oxygenase-2 (COX-2) protein, endothelial growth factor (EGF) and EGF receptors. EGF and prostaglandin E2 (PGE2) are normally found in biological secretions, responsible for the healing of impaired mucosal lesions and maintenance of the protective barrier in the epithelium. Rebamipide also regulates the mucus secretion, neutrophil inactivation, and free radical elimination as well as effects on COX-2 and EGF [114].

In a double-blind placebo-controlled clinical study on patients with oral ulceration due to BD; patients after underwent rebamipide for 3-6 months, moderate/ significant improvement in oral ulcers has been reported. Therefore, rebamipide is thought to be effective in the prevention and treatment of attacks in oral ulcers [113].

Mycophenolate Mofetil (MMF)

Mycophenolic acid (MPA) was first identified with its antibiotic effects after being isolated from Penicillium stoloniferum cultures in 1913 [115]. Antibacterial, antifungal, antitumoral, antiviral and anti-inflammatory effects of the compound were described in following decades [116, 117]. After the anti-inflammatory activity of MPA gained interest, the ester form Mycophenolate Mofetil (MMF) was developed due to its improved bioavailability and gastrointestinal (GI) tolerability [117, 118].

MMF is a selective and non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH), an enzyme involved in de novo pathway of purine nucleobases. Generally, many cells in the organism are able to synthesize guanine nucleotides through two different pathways, namely de novo and salvage pathways. However, lymphocytes mainly perform their guanine nucleotide synthesis processes through the de novo pathway, so MPA specifically targets T and B lymphocytes, preventing their proliferation [119]. MMF also disrupts the endothelial cell adhesions and lymphocyte and monocyte recruitment to sites of inflammation [55, 120].

B and T lymphocytes specific inhibitor MMF is generally applied in post-transplant therapies. There is a published clinical study of 4 cases with parenchymal neuro-BD, where used immunosuppressive treatment could not be continued due to intolerance or inefficacy. According to study, it has been reported that these patients have positive results with MMF and remission has proceeded for 3–7-years [121]. In another clinical study, MMF has been administered in combination with prednisolone, but no positive results have been obtained compared with placebo. However, the use of immunosuppressive agents in other autoimmune diseases suggests that it may also be effective in BD [55].

Levamisole

Levamisole, an anthelmintic agent, is also used in the treatment of BD. The mechanism of action of levamisole is not fully known. It is thought that it plays a role in cellular immunity by affecting the T cells in various circles [122].

The anthelmintic effect of levamisole occurs as an agonist of nicotinic acetylcholine receptor. The immunomodulatory properties varied and primarily effects on macrophages and T-lymphocytes. Privilege effect of levamisole on T helper-1 cells following the upregulation of IL-2, IL -12 and IFN-γ was demonstrated. According to the data obtained, inhibition of endogenous immunosuppressive factors and increased B-cell activity indicate low levels of immunoglobulin G, immunoglobulin M and circulating immune complexes. The drug has anti-anergic properties that regenerate depressed immune responses in immunocompetent individuals [123].

According to previous clinical studies, levamisole has been reported to be effective on patients with oral and genital ulcers, arthritis, and uveitis [60].

Sulfasalazine

Sulfasalazine has several effects such as anti-inflammatory, antiproliferative as well as its antibacterial potency. It exerts anti-inflammatory and immunosuppressive effect by inhibiting cytokine release, and leukotriene synthesis and NF- κB transcription. It eliminates T-cell cytokine IL-2 and monocyte macrophage cytokines (IL-1, IL-6, IL-12, and TNF), reduces leukotriene production, and disrupts cell adhesion and function. Sulfasalazin acts by inhibiting endothelial cell chemotaxis and migration of inflammatory cells as neutrophils and reducing superoxide and proteolytic enzyme synthesis. Other considerable in vitro anti-inflammatory effects of sulfasalazine are inhibition of PGE2 synthase enzyme activity, apoptosis of neutrophiles, inhibition of the extracellular release of proinflammatory secretory phospholipase A2 and B-cell suppression and immunoglobulin production. It has been reported to be effective in relieving BD-related gastrointestinal symptoms [124].

Zinc Sulphate

There are studies suggesting that oral zinc sulphate is effective in preventing clinical symptoms with no side effects related to BD [125].

The antioxidant effect of zinc sulphate has a therapeutic effect on BD. Increased zinc levels in serum mediate increased antioxidant effects in BD patients suffering from the detrimental effect of reactive oxygen species leading to immunological events of BD. Further mechanism should be considered is that zinc has an immunomodulatory effect on BD of autoimmune origin that might be useful in the treatment of BD [125].

Pentoxifylline

Pentoxifylline is another agent with anti-TNF activity. The major pharmacological effect of pentoxifylline is the inhibition of several proinflammatory cytokines, particularly TNF-α. CD8 + type T lymphocytes are likely to have a suppressive effect directly on the inhibition of perforin. Furthermore, it reduces the production of free radicals and neutrophil-induced tissue damage [80].

Although a clinical study on pentoxifylline has not been published, anecdotal data suggest that it may be useful in the treatment of oral and genital ulcers in BD [126].

Benzathine Penicillin

According to one study, the use of benzathine penicillin with colchicine was found to be more effective than colchicine alone. It has been reported that this combination reduces the frequency, duration, and prolongation of remission in oral ulcers, genital ulcers, and erythema nodosum attacks in BD [127].

Surgical Treatments

Although there are many medical treatment methods, surgical interventions are performed especially in arterial aneurysms. Surgical treatment may be necessary in patients with recurrent or severe haemoptysis. Endovascular treatment of pseudoaneurysms associated with BD can be an effective option when symptoms are controlled by immunotherapy. Surgical procedures may be the only possible treatment in other serious conditions, such as in gastrointestinal canal perforations, enterocutaneous fistula formation, thrombotic obstructions in large vessels, cardiac involvements, eye complications (such as glaucoma), and vitreous opacities [128].

RESULT AND DISCUSSION

BD is an inflammatory disease with local and systemic involvements. The treatment strategies of these involvement vary from local corticosteroids to antibodies, determined by type and severity of symptoms. In addition, there are controlled studies based on the treatment of vascular, neurological, and gastrointestinal disorders. Colchicine is the primary care agent for the mucocutaneous involvements, as well as apremilast has been shown to be safe in the oral ulcerations. In some persistent manifestations, anti-TNF-α agents may be effective, with the development of biotechnological drugs, positive results have been obtained. But for some; require new treatment strategies. Future research should focus on the study on combined use of immunosuppressive drugs with anti-TNF antibodies, the use and the effectiveness of anticoagulant agents in the treatment of venous thrombosis, and the immunosuppressive treatment in early use in patients who were thought to have high risk in major organ involvements. Additionally, advances in molecular genetics and potentially newly discovered inflammatory pathways (e.g., those related to HLA - B * 51), will have a great impact on us in designing newer and more effective compounds in the management Behçet' s Disease.

AUTHOR CONTRIBUTIONS

Concept: *A.Ö.Ş., G.Y.Ç.;* Design: *G.Y.Ç.;* Control: *A.Ö.Ş.; Sources*: *G.Y.Ç.* Materials: *G.Y.Ç.*; Data Collection and/ or Processing: *G.Y.Ç.; Analysis and/ or Interpretation*: *A.Ö.Ş.*.; Literature Review: *G.Y.Ç.*.; Manuscprit Writing: *G.Y.Ç.*; Critical Review: *G.Y.Ç., A.Ö.Ş.*; Other: *G.Y.Ç., A.Ö.Ş.*

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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