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REVIEW

Behçet's disease uveitis: is there a need for new emerging drugs?

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ABSTRACT

Introduction: Behçet's disease uveitis (BDU) is a potentially blinding disorder. Systemic treatment with disease-modifying anti-rheumatic drugs (DMARDs) is mandatory in patients with intraocular inflammation involving the posterior segment of the eye.

Areas covered: This article discusses existing systemic treatment with corticosteroids and conventional and biologic DMARDs as well as adjunctive local therapy in BDU. An overview is provided for a wide range of biologic DMARDs that have shown promise or investigated in clinical trials. Most recently introduced biologic DMARDs and targeted synthetic DMARDs are also reviewed for their potential in the treatment of BDU.

Expert opinion: The prognosis of patients with BDU has remarkably improved after the introduction of biologic DMARDs. An expanding therapeutic armamentarium will allow treatment of most refractory cases. The ultimate goal is to provide drug-free remission with preservation of 20/20 vision.

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1. Background

Behçet's disease (BD), first described as a distinct clinical entity by Hulusi Behçet in 1937, is a multisystem disorder of unknown etiology characterized by relapsing inflammation [1]. The disease is significantly more common in the Middle and Far East and the Mediterranean basin corresponding to the old 'Silk Route' [2]. The highest prevalence has been reported from Turkey (420 per 100,000) [3]. It is believed that environmental agents may trigger an enhanced and dysregulated immune response and result in systemic vasculitis in immunogenetically susceptible individuals. A dysregulation of both innate and adaptive immune systems is implicated in its pathogenesis [4,5]. BD affects primarily young adults between 25 and 35 years of age [2]. Although both genders may be affected, the disease has a male predominance especially in series from Turkey, Iran, and Arabic countries [6–9]. Male patients have also a tendency toward ocular involvement, more severe disease course, and poorer visual prognosis [1,6,8–10].

While recurrent oral ulcers, genital ulcers, and skin lesions are the most common manifestations of BD, the eye is the most commonly involved vital organ. Ocular involvement is observed in more than 50% and is bilateral in around 80% of patients. Ocular disease typically occurs within 2–4 years of disease onset and may be the initial manifestation of the disease in 10–20% of cases [1,6,11]. Its classical presentation is a bilateral non-granulomatous panuveitis associated with occlusive and leaky retinal vasculitis affecting vessels of various sizes, especially the veins and capillaries. Other uncommon presentations of ocular disease include episcleritis, scleritis, conjunctival ulcers, keratitis, orbital inflammation, isolated optic neuritis, and extraocular muscle palsies [10]. Among patients with non-infectious uveitis referred to rheumatology clinics in Italy, BD was the most commonly diagnosed entity, comprising up to 35.5% of the cases with systemic inflammatory diseases [12].

The diagnosis of BD is based on clinical findings and there is no specific diagnostic test. Several sets of clinical diagnostic or classification criteria have been developed based on a combination of clinical manifestations in different organ systems. However, as uveitis may be the initial manifestation of the disease and has a blinding potential, it is important to recognize BD uveitis (BDU) as a distinct entity in the absence of systemic manifestations as well [10,13]. Recently, a diagnostic algorithm for BDU based solely on characteristic ocular findings has been described by Tugal-Tutkun et al [13]. Ocular findings highly suggestive for BDU included superficial retinal infiltrates, signs of occlusive retinal vasculitis, diffuse retinal capillary leakage on fluorescein angiography (FA) as well as the absence of granulomatous anterior uveitis (AU) or choroiditis in eyes with vitritis [13].

The frequency and severity of inflammatory attacks determine the visual outcome in patients with BDU. The cumulative damage caused by recurrent inflammatory attacks may lead to macular complications, retinal atrophy, and optic atrophy resulting in irreversible visual loss [8–10]. Therefore, an early and appropriate treatment is of utmost importance in order to prevent poor visual outcome. A multidisciplinary approach to treatment of BDU is essential.

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2. Medical need

The main goals of treatment in BDU include not only the rapid suppression of acute inflammation in order to prevent irreversible tissue damage and regain potential visual acuity, but also the treatment of chronic subclinical inflammation, prevention of recurrences, and achievement of sustained remission, thus preserving vision [14]. Corticosteroids (CSs) are still used to treat sight-threatening acute inflammatory attacks. However, because of their severe systemic side effects and rebound relapses during dose tapering, treatment with long-term high-dose CS and CS monotherapy are no longer accepted in the treatment of BDU [15]. Today, BDU involving the posterior segment is an absolute indication for the use of disease-modifying antirheumatic drugs (DMARDs) in order to attain a CS-sparing effect and to prevent recurrences [10,14–16].

In a large series from Turkey, a better visual outcome was observed in patients who presented in the 1990s compared to those in the 1980s, which was attributed to a change in the management of BDU with a more aggressive approach using conventional DMARDs (cDMARDs), especially the use of cyclosporine A (CSA) [8]. A subsequent study from the same center reported a lower frequency of ocular complications and a better visual outcome in patients who presented in the 2000s compared to the 1990s, explained by the earlier and combined use of cDMARDs and the use of biologic DMARDs (bDMARDs) in the 2000s [17]. Although the use of new and more effective therapeutic agents, especially the targeted bDMARDs improved the visual prognosis of BDU, the risk of severe visual loss was still more than 20% in the 2000s [18–20]. The complete response rate is not 100% for any of the currently available therapeutic options and switching between different bDMARDs has been required in up to one-third of patients due to inefficacy or intolerance [21,22]. Therefore, an unmet need for further therapeutic options in BDU is obvious. A better understanding of immune mechanisms and identification of inflammatory mediators involved in the pathogenesis of BD will allow for the development of new, better targeted, and more effective therapeutic agents.

3. Existing treatment

A multidisciplinary expert committee of the European League Against Rheumatism (EULAR) has recently published updated evidence-based recommendations for the management of BD [16]. Patients with isolated AU can be treated with only topical CS. Systemic cDMARDs such as azathioprine (AZA) may be considered for those with poor prognostic factors, including young age, male gender, and early disease onset, with the anticipation that it may prevent posterior segment involvement. Any BD patient with posterior segment inflammation should be treated with AZA, CSA, interferon-alpha (IFN-α), or anti-tumor necrosis factor-alpha (anti-TNF-α) monoclonal antibodies (mAbs). Systemic CS should be used only in combination with AZA or other systemic cDMARDs and not as monotherapy. Patients presenting with an initial or recurrent acute sight-threatening uveitis attack should be treated with high-dose CS, infliximab (IFX), or IFN-α. Intravitreal CS injection may be used as an adjunct to systemic treatment in patients with unilateral exacerbation [16]. Table 1 shows a summary of existing treatment.

3.1. Corticosteroids

3.1.1. Topical corticosteroids

Anterior segment inflammation is rapidly responsive to topical treatment [14]. Frequent application of potent topical CSs with a slow tapering over a few weeks is usually enough [14,15].

3.1.2. Systemic corticosteroids

High-dose systemic CS treatment has been the most widely used anti-inflammatory therapeutic modality in acute exacerbations of BDU [14,16]. In patients with severe posterior segment involvement and associated complications such as occlusive retinal vasculitis, macular edema, and optic neuropathy, an intravenous (i.v.) pulse methylprednisolone (30 mg/kg/day, maximum 1 g/day, a single dose or for 3 consecutive days) is usually preferred to obtain a rapid anti-inflammatory effect. Oral prednisolone 1 mg/kg/day, maximum 60 mg/day, or its equivalent is then given and slowly tapered to a maintenance dose of 7.5 mg/day or lower after complete resolution of active inflammation [14,15]. A careful dose tapering is crucial in order to prevent rebound inflammation.

3.1.3. Periocular and intraocular corticosteroids

An adjunct periocular or intravitreal CS injection may be considered for the treatment of unilateral severe panuveitis attacks or persistent cystoid macular edema (CME) [15].

Administration of intravitreal triamcinolone acetonide (IVTA) has been shown to result in rapid resolution of intraocular inflammation and improvement of visual acuity without systemic side effects. However, high rates of ocular complications including intraocular pressure (IOP) elevation and cataract development were the main disadvantages [23]. Development of cytomegalovirus retinitis is a rare, but serious risk of IVTA injection [24].

Oh et al. [25] reported that 0.59 mg fluocinolone acetonide intravitreal implant in 8 eyes with BDU led to a significant visual improvement, but also a very high complication rate, including requirement for glaucoma surgery in 6 eyes.

Intravitreal dexamethasone implant is an effective and relatively safer adjunctive treatment, but the duration of its effect is usually limited to 4–6 months [26,27]. It may be used as a bridging therapy, especially in countries where an approval process for the bDMARDs is needed [26].

3.2. Conventional disease-modifying antirheumatic drugs (cDMARDs)

Any posterior segment inflammatory finding, including cells in the posterior vitreous cavity and leakage on fluorescein angiography (FA), is an indication for treatment with DMARDs [10]. cDMARDs have been used for their CS-sparing effect and for the prevention of recurrences [14–18]. The major disadvantage of these agents is their late onset of action. Only AZA and CSA have been proven to be effective in randomized-controlled trials (RCTs).

Table 1. Existing treatment for Behçet's disease uveitis.

	Class	Generic name	Dosage and route	Route of administration	Common side effects	Suggested monitoring
cDMARDs	Corticosteroid	Prednisone Methylprednisolone	1 mg/kg/day 1gr/day (1–3 days) Slow dose tapering	Oral Intravenous	Cushingoid effects, diabetes, hypertension, osteopenia, osteonecrosis, mood changes, cataract, glaucoma	Blood pressure CBC Biochemistries* every 4–6 weeks
	Antimetabolite	Azathioprine	2–2.5 mg/kg/day	Oral	GIS upset, myelosuppression, hepatotoxicity	CBC and Biochemistries every 4–6 weeks
	Antimetabolite	Methotrexate	10–25 mg/week	Oral Subcutaneous Intramuscular	GIS upset, myelosuppression, hepatotoxicity	CBC and Biochemistries every 4–6 weeks
	Antimetabolite	Mycophenolate mofetil	500–1000 mg/BID	Oral	Diarrhea, nausea, neutropenia	CBC and Biochemistries every 4–6 weeks
	Calcineurin inhibitor	Cyclosporine-A	2–5 mg/kg/day	Oral	Hypertension, nephrotoxicity, GIS upset, gingival hyperplasia, hirsutism, neurotoxicity	Blood pressure CBC and Biochemistries every 4–6 weeks, Neurological involvement
	Calcineurin inhibitor	Tacrolimus (FK-506)	0.15 mg/kg/BID increasing to 2–3 mg/BID	Oral	Hypertension, nephrotoxicity, gingival hyperplasia	Blood pressure CBC and Biochemistries every 4–6 weeks
	Alkylating Agent	Cyclophosphamide	1–3 mg/kg/day	Oral Intravenous	Myelosuppression, sterility, hemorrhagic cystitis, alopecia, increased risk of malignancy	CBC and Biochemistries every 4–6 weeks Urine analysis weekly
	Alkylating Agent	Chlorambucil	0.1 mg/kg/day	Oral	Myelosuppression, sterility, increased risk of malignancy	CBC and Biochemistries every 4–6 weeks
bDMARDs	Interferon	Interferon- α2a	3–9 million units once daily–thrice weekly	Subcutaneous	Flu like syndrome, fatigue, depression, leukopenia, elevation of liver enzymes, thyroid antibodies, alopecia	CBC and Biochemistries every 4–6 weeks Thyroid function test, follow the patient's mood
	Anti-tumor necrosis factor-α	Infliximab	5–10 mg/kg infusions at 0, 2,6 weeks and then every 4 to 8 weeks	Intravenous	Infusion reaction, infections, demyelination, lupus-like syndrome	CBC and Biochemistries every 4–8 weeks Rule out infections including TB every 3 months
	Anti-tumor necrosis factor-α	Adalimumab	80 mg loading dose followed by 40 mg at 1st week and then 40 mg every 2 weeks	Subcutaneous	Injection site reaction, allergic reactions, infections, demyelination, lupus-like syndrome	CBC and Biochemistries every 4–8 weeks Rule out infections including TB every 3 months
Intravitreal treatments**	Corticosteroid	Fluocinolone acetonide	0.59 mg (Retisert®) 0.18 mg/0.19 mg (Yutiq/Iluvien®)	Intravitreal implant	IOP rise, glaucoma, cataract, endophthalmitis	IOP measurement Slit-lamp examinations
	Corticosteroid	Dexamethasone implant	0.7 mg	Intravitreal implant	IOP rise, glaucoma, cataract	IOP measurement Slit-lamp examinations
	Corticosteroid	Triamcinolone acetonide	4 mg/0.1 ml	Intravitreal injection	IOP rise, glaucoma, cataract	IOP measurement Slit-lamp examinations
Periocular treatments**	Corticosteroid	Triamcinolone acetonide	40 mg/1 ml	Posterior subtenon injection	IOP rise, glaucoma, cataract, ptosis	IOP measurement Slit-lamp examinations

cDMARDs: Conventional disease-modifying antirheumatic drugs bDMARDs: Biologic disease-modifying antirheumatic drugs
BID:Twice daily CBC:Complete blood count GIS:Gastrointestinal system IOP:Intraocular pressure TB:Tuberculosis
*Liver and kidney function tests, electrolytes, blood sugar
** Local treatments should be considered as adjunct to systemic treatment or when systemic treatment is contraindicated or not tolerated

3.2.1. Antimetabolites

3.2.1.1. Azathioprine (AZA). AZA at a dosage of 2–2.5 mg/kg/day is still a commonly used first-line CS-sparing cDMARD in BDU [14]. In a 3-year double-masked, placebo-controlled trial, AZA was found to be superior to placebo in decreasing hypopyon uveitis episodes, preserving visual acuity, and reducing new eye disease [28]. Reevaluation of the patients 8 years later showed that the beneficial effect of AZA was preserved, especially when it was started early after disease onset [29]. Conversely, this preventive effect on the second eye involvement has not been confirmed by Taylor et al. [19]. In a large retrospective study, 51.6% of BDU patients were complete responders, and patients with retinal vasculitis and severe visual loss at diagnosis were less likely to be complete responders to AZA therapy [30].

AZA is a well-tolerated agent with reversible side effects. Its relatively lower cost and decades of clinical experience are the major advantages of AZA. On the other hand, it fails to control severe BDU.

3.2.1.2. Methotrexate (MTX). MTX is usually not a treatment of choice in BDU [31–34]. In a long-term follow-up study of a large cohort of BD patients treated with MTX, visual acuity improved in only 46.5% [35].

3.2.1.3. Mycophenolate Mofetil (MMF). There is no study specifically investigating the use of MMF in BDU. In a recent RCT comparing MMF and MTX in the treatment of noninfectious uveitis, MMF provided a lower treatment success in patients with posterior or panuveitis [36].

3.2.2. Calcineurin inhibitors

3.2.2.1. Cyclosporine-A (CSA). The efficacy of CSA, a T-cell inhibitor, in treating BDU was first reported by Nussenblatt et al. [37] in 1985. In two early RCTs, high-dose CSA (10 mg/kg/day) was shown to be superior to chlorambucil and colchicine in controlling BDU as well as systemic manifestations of BD [38,39]. In a third RCT, low dose (5 mg/kg/day) CSA provided better results than monthly pulsed cyclophosphamide in the first 6 months of treatment; but there was no significant difference after 2 years [40].

The most common adverse effect of CSA is renal toxicity, especially at higher doses. Low-dose CSA has been safely used in combination with low-dose CS and decreased ocular inflammatory attacks and improved or stabilized visual acuity in patients with BDU [41]. A combination of CSA and AZA is commonly used in patients unresponsive to either agent [14]. It is important to note that a rebound inflammation is not unusual after abrupt cessation or dose reduction of CSA, even when used in combination with CS or AZA. Another important concern is that it may potentiate central nervous system involvement or cause neurotoxicity in patients with BD [42]. Therefore, neurological involvement should be ruled out before initiation of CSA and it should be immediately discontinued at the onset of any neurological symptom.

3.2.2.2. Tacrolimus. Tacrolimus, also known as FK-506, is another calcineurin inhibitor having a similar mechanism of action, but a better safety profile compared to CSA [14]. Data on its use for the treatment of BDU are limited [43,44], and there is no RCT with this agent.

3.2.3. Alkylating agents

3.2.3.1. Cyclophosphamide. In a retrospective study of 64 BDU patients, long-term oral therapy with cyclophosphamide combined with low-dose prednisolone was found to be no better than colchicine alone or no therapy, in maintaining visual acuity or reducing the frequency of inflammatory attacks [45]. Of 198 BD patients treated with cyclophosphamide, mainly for neurological or vascular involvement, 8% developed malignancies and 30% infertility after a median follow-up of 25 years [46].

3.2.3.2. Chlorambucil. Two case series have shown some efficacy of chlorambucil, suggesting even a sustained remission after its discontinuation [47,48]. It had been used only as a last resort because of potentially serious adverse effects.

Neither alkylating agent is recommended anymore for the treatment of refractory BDU due to the availability of more effective and safer bDMARDs [15,16].

3.3. Biologic disease-modifying antirheumatic drugs (bDMARDs)

The introduction of bDMARDs, especially IFN-α and anti-TNF-α mAbs, has significantly improved both the visual prognosis and the quality of life of BD patients [49,50]. Due to the local regulations in most countries bDMARDs are currently used only when BD patients are refractory to cDMARDs. There are no RCTs to guide the management of refractory patients; and the choice of first-line bDMARD is based on local regulations, patient's characteristics, and physicians' experience [16]. A review of the literature revealed similar remission rates with IFX and IFN-α, but IFX had a more rapid onset of action, whereas IFN-α was associated with a higher rate of sustained remission (71% vs 44%) as well as a higher rate of CS cessation (66% vs 33%) [51].

3.3.1. Interferon-alpha (IFN- α)

Both recombinant IFN-α2a and IFN-α2b, have been used as subcutaneous injections for the treatment of BD [52]. In an RCT in 2002, an improvement in the severity and frequency of ocular attacks was reported in 83% of patients with ocular involvement in the IFN-α2a treatment group compared to 33% in the placebo group [53]. Another RCT comparing IFN-α2a and CSA for the treatment of severe BDU was stopped after 37 patients were enrolled, due to slow recruitment; and although there was a tendency toward superiority of IFN-α2a, significant differences could not be shown [54]. While there is a registered RCT in China (NCT03209219), comparing IFN-α2a and CSA for refractory BDU with an estimated completion date of January 2021, the production and marketing of IFN-α2a has been recently stopped in Europe and it is not clear if the trial could be completed in China.

A partial or complete response has been reported in around 90% of patients treated with IFN-α2a for refractory BDU [55–60].

While cDMARDs were stopped immediately before the initiation of IFN therapy in all series, the initial doses of IFN-α2a and systemic CS were quite variable. A stepwise tapering of IFN-α2a was performed according to the clinical response in all cohorts. Inadequate initial clinical response and relapses during dose reduction were mostly managed by increased doses of IFN-α2a. In two studies that showed long-term (4–5 years) follow-up results after drug discontinuation in remission, relapse-free rates were 50% and 76% [57,58]. A lower response rate has been found with IFN-α2b compared to IFN-α2a, especially for ocular manifestations of BD [52].

IFN-α conjugated with a large polyethylene glycol (PEG) molecule (PEG-IFN-α) has slower absorption and longer serum half-life that permits once-weekly dosing [61]. In an RCT in BD patients, the addition of PEG-IFN-α2b to standard care did not significantly reduce the CS dose at 1 year but significantly improved quality of life [62]. In two small case series, PEG-IFN-α2a or PEG-IFN-α2b preserved the remission obtained by IFN-α2a and improved quality of life due to fewer injections [63,64]. On the other hand, there are no data on the use of PEG-IFN-α as induction therapy for BDU; thus, the efficacy or the optimum dose for such use is not known.

The major advantages of IFN therapy in BDU include a high response rate, rapid effect on retinal vasculitis, CME, and retinal or optic disc neovascularizations, and achievement of durable remission after discontinuation of treatment. Most importantly, IFN therapy can be safely used in patients with history of viral infections such as viral hepatitis or in patients with latent tuberculosis. Thus, it has been recommended as the treatment of choice in areas of high tuberculosis endemicity [65].

Practical limitations of IFN therapy have been the frequent occurrence of flu-like symptoms, the risk of depression, and particularly the reports of suicidal ideation [66].

3.3.2. Anti-tumor necrosis factor-alpha (Anti-TNF-α) agents

A recent meta-analysis showed that anti-TNF-α therapy is highly effective, associated with efficient inflammation remission, satisfactory visual improvement, significant central macular thickness (CMT) reduction, and significant CS-sparing effect and had an acceptable incidence of adverse effects in patients with BDU [67]. An expert panel recommended that these agents should be considered as first-line treatment only for BDU [68].

Anti-TNF-α treatment is associated with an increased risk of infection. Patients should be screened for tuberculosis, hepatitis B, hepatitis C, and human immunodeficiency virus infection prior to initiating therapy. Patients should also be watched for drug-induced autoimmune diseases and demyelinating disease. There is also concern about an increased risk of malignancy, especially acceleration of the progression of preexisting cancers [69].

Among the anti-TNF-α agents, there is more experience with IFX in BDU, adalimumab (ADA) seems to be an effective alternative, whereas etanercept is not a treatment of choice for noninfectious uveitis in general or BDU in particular. Previous studies suggested that failure of one anti-TNF-α drug does not predict a poor response to a second one. Thus, switching between IFX and ADA is recommended in patients with primary or secondary failure [16,70].

3.3.2.1. Infliximab (IFX).

IFX, a human-murine chimeric anti-TNF-α mAb, was first shown to control acute inflammation in 24 hours and induce complete resolution in 7 day after a single infusion in 5 BD patients with relapsing panuveitis [71]. The initial open prospective, self-controlled studies confirmed the potent and rapid anti-inflammatory effect of IFX and also showed that repetitive infusions reduced the frequency and severity of ocular inflammatory attacks, improved, or maintained visual acuity, and had a significant CS-sparing effect [72–74]. Afterward, IFX was approved in Japan for the treatment of refractory BDU and has been used as off-label therapy in other countries. The standard dose of IFX is 5 mg/kg given as an i.v. induction regimen at 0, 2 and 6 weeks followed by infusions given every 8 weeks. However, posterior segment involvement in BDU usually requires intervals shorter than 8 weeks in order to prevent recurrences [72,75,76].

There is no RCT comparing efficacy and safety of IFX to cDMARD therapy. Retrospective comparative studies showed that patients treated with IFX had fewer attacks, better visual acuity, fewer ocular and systemic complications, and higher incidence of complete remission than those treated with cDMARDs [77,78] A prospective observational study comparing IFX *versus* high-dose i.v. methylprednisolone or IVTA administered at the onset of acute panuveitis attacks showed a significantly faster resolution in ocular inflammation scores in patients receiving IFX infusion [79].

In a multicenter retrospective study in Japan, long-term IFX therapy has been shown to reduce the frequency of ocular attacks, even though 59% had relapses during treatment [80]. The severity of ocular attacks has also been shown to decrease during IFX therapy [81]. Keino et al. [82,83] reported that IFX was effective not only in reducing the frequency and severity of ocular inflammatory attacks but also the background retinal vascular and disc leakage in refractory BDU. An earlier initiation of IFX therapy led to better outcomes [84,85].

Infusion reactions occur due to the chimeric nature of IFX. The development of neutralizing antibodies with repeated IFX infusions may lead to a decrease in serum concentration of IFX, resulting in recurrence of uveitis and requirement for shortening of infusion intervals [86]. Ueda et al [87] reported shortening of IFX infusion intervals in approximately half of the BDU patients due to loss of efficacy during the second year of follow-up. Concomitant treatment with cDMARDs such as AZA and/or CSA has been recommended to prevent secondary failure [72,75]. However, in a recent study by Fabiani et al [88]. IFX retention rate was high (76%, and 47% at 60, and 120 months, respectively) and not affected by concomitant cDMARDs. While high relapse rates have been reported in earlier studies following discontinuation of short-term treatment [72,73], recent studies have shown that drug-free long-term ocular remission could be obtained after a short- or long-term treatment period [89,90].

In a prospective long-term postmarketing surveillance study of all IFX-treated BDU patients in Japan (the BRIGHT study), the incidence of adverse events and serious adverse events were 32% and 6%, respectively [91]. Infections and

infestations were the most common adverse events (11.9%). Tuberculosis was observed in 0.3%. Infusion reactions were observed in 11% but were not serious. The incidence of lupus-like syndrome, demyelinating disease and malignancies was less than 1% during the 2-year study period [91].

3.3.2.2. Adalimumab (ADA). ADA, a fully humanized anti-TNF-α agent, is currently the only approved bDMARD for noninfectious intermediate, posterior, and panuveitis. VISUAL-1 [92] and VISUAL-2 [93], the two multicenter phase III RCTs led to its approval by the FDA and the EMA in 2016. Around 7% of the study population in these RCTs had BDU. ADA was administered subcutaneously at a loading dose of 80 mg followed by 40 mg every 2 weeks.

Retrospective studies showed that ADA was highly effective and safe for the treatment of BDU including cases that failed IFX [94,95]. In a Spanish multicenter observational study of 177 BDU patients who received IFX (n = 103) or ADA (n = 74) as first-line bDMARD, an improvement in all ocular parameters was observed in both groups after 1 year of therapy [96]. However, a more rapid improvement of anterior chamber inflammation and vitritis was seen in the IFX group, while ADA group had a significantly greater visual improvement as well as a significantly higher drug retention rate. The treatment was discontinued due to inefficacy in 17.5% in the IFX group and 14.9% in the ADA group [96]. Fabiani et al. [97] have also reported high ADA retention rates in BDU patients (76.9% and 63.5% at 12 and 48 months, respectively). Furthermore, long-term control of BDU can be achieved with ADA also in the absence of concomitant cDMARD treatment [98].

Injection site reaction and nonserious allergic reactions are the most common adverse effects of ADA [96,99]. Infections including tuberculosis, demyelination, lupus-like syndrome are the other concerns while using ADA; however, the incidence of adverse events leading to drug discontinuation is low [99]. The main advantages of ADA therapy include a lower risk of developing anti-drug antibodies that limit efficacy, easier subcutaneous administration leading to better patient compliance, and its being the only approved biologic for the treatment of noninfectious uveitis.

Both IFX and ADA have significantly improved the outcome of BDU patients refractory to cDMARDs; however, infusion reactions and secondary failure with IFX and primary failure with ADA at the current dosing regimen seem to limit their efficacy in patients with severe BDU. In a recent meta-analysis of studies focusing on anti-TNF-α treatment of BDU, the pooled inflammation remission rate was 68% [67].

4. Market review

A study from USA reported that mean monthly healthcare costs for noninfectious uveitis were similar or higher than those for diabetes or hypertension patients and similar or lower than those for cancer patients [100]. The average annual healthcare costs of patients with inflammatory eye disease was estimated as 16,300 USD to 38,300 USD in 2016 US dollars [101]. Financial restrictions enforced by healthcare authorities have a major impact on the clinicians' choice between effective but expensive bDMARDs *versus* cheaper cDMARDs. Although CS therapy is cheaper than cDMARDs or bDMARDs, it has been found to associate with increased ocular complications thus additional treatment cost, increased hospital admissions, and emergency room visits and related costs, confirming the importance of CS-sparing therapy in noninfectious uveitis [100]. Patients with noninfectious uveitis involving the posterior segment, as in BDU, also have greater indirect costs associated with increased work disability and absenteeism costs, suggesting an unmet need for more effective treatments [102]. The high annual cost of bDMARDs, often exceeding £100,000 is an important limiting factor in their widespread adoption [103].

Although BD is considered an orphan disease, it causes a considerable economic burden for the healthcare system in countries where the disease has a high prevalence. It accounts for 25% of all uveitis cases and 33% of noninfectious uveitis seen at referral centers in Turkey [7]. Cure of the disease and prevention of blindness will decrease the indirect costs as the disease mainly affects the productive age group. At a multidisciplinary BD clinic in Turkey, drug costs have been found to be the major component (79%) of the total direct cost, and patients primarily treated for ocular involvement had the second highest economic impact following patients with neurological disease [104]. In a 2008 report from France, the estimated annual cost of IFN-α2a, administered at a dose of 3 miU thrice a week, was 4150 Euro and the cost of IFX was 20,200 Euro for a BDU patient of 75 kg body weight receiving 375 mg infusions every 6 weeks [56]. The authors recommended anti-TNF-α agents as a long-term maintenance therapy only for selected patients with severe disease, particularly in case of IFN-α2a failure [56]. Optimization of the dose of expensive bDMARDs is a way of reducing the cost. ADA optimization has been reported to be cost-effective in refractory BDU [105]. A switch to biosimilars may reduce the economic impact of expensive bDMARDS as well.

BDU is one of the most severe forms of noninfectious uveitis and it is considered as a gateway to understanding and treatment of uveitis in general. Both IFX and IFN-α have been first tried in BDU patients. Special attention is being given to its treatment even in countries where the disease is rare, because favorable results obtained with new agents in BDU will be carried over to the general population of noninfectious uveitis, thus a more extensive market.

5. Current research goals

The ultimate goal in the treatment of BDU is cure of the disease; that is achievement of a sustained remission which is durable even after the discontinuation of treatment. A rapidly acting therapeutic regimen with both potent anti-inflammatory and long-term immunomodulatory effects needs to be administered immediately after disease onset in order to prevent irreversible complications and visual loss. Biomarkers need to be identified to predict disease severity and response to various therapeutic agents so that an individualized therapeutic approach can be employed. As there are patients refractory to the currently used cDMARDs and

bDMARDs, alternative therapeutic tools with different modes of action are needed.

Different inflammatory mediators may be involved in the protean manifestations of BD and blocking a certain pathway may not be uniformly effective in different types of organ involvement. Therefore, a therapeutic regimen that is found to be effective in an extraocular manifestation of BD needs to be tested also for its efficacy in BDU.

6. Scientific rationale

Although the description of BD as an autoinflammatory or autoimmune disorder is still debated [4,5], recent immunogenetic findings have confirmed a strong association with HLA-B51 as well as other MHC class I associations and revealed non-HLA susceptibility loci harboring genes involved in both innate and adaptive immune functions [106]. Currently, there is sufficient evidence to support that BD is a multifactorial inflammatory disease associated with an overproduction of inflammatory cytokines such as IL-1, IL-6, and TNF-α by an exaggerated innate immune response to environmental or endogenous stimuli, which in turn leads to a perpetuated adaptive immune response involving predominantly T helper (Th)-1 cells, but also Th-17 and Th-22 cytokine pathways [107]. Impaired production of the anti-inflammatory cytokine IL-10 by regulatory T cells (Tregs) may lead to a defective control of inflammatory responses [108].

We are on track to reach a future where treatment of BDU will be based on specifically targeting the immune and/or inflammatory pathways and cytokines primarily involved in the disease phenotype in individual patients. Clinical, laboratory, genetic, and proteomic biomarkers need to be established for individualized therapy of BDU. A recent study investigating the predictors of sustained clinical response in patients using anti-TNF-α agents for the treatment of BDU, showed that more severe BD activity at baseline was the only clinical parameter to predict early termination of treatment due to lack or loss of efficacy [109]. Ueda et al. [87] reported that patients with higher pretreatment serum levels of IL-2, IL-6, and TNF-α responded better to IFX therapy. Sugita et al. [110] reported that patients who had a high population of Treg cells in peripheral blood had a lower risk of experiencing relapses during IFX treatment.

In search of new biomarkers to determine disease activity, a trial has been designed aiming to investigate the correlation between disease activity and neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, platelet/lymphocyte ratio, and mean platelet volume. (NCT03747354). Another newly designed trial is aiming to determine whether plasma levels of the soluble urokinase plasminogen activator can serve as a blood-based biomarker for diagnosis of BD and if it is correlated with disease activity (NCT04105439). A recent investigation of peripheral blood mononuclear cell proteome profile revealed decreased levels of cytoskeleton-related proteins as well as down-regulation of protein folding and ER stress process proteins in patients with active BD [111]. Liang et al. [112] have found differentially expressed proteins when they compared tear samples from uveitis-relapsed eyes and the contralateral quiescent eyes.

As intraocular inflammation is rarely reflected by systemic laboratory markers unless there is an increased systemic disease activity, ocular clinical biomarkers, including imaging studies still provide more useful information about disease activity and prognosis in BDU [113]. Intraocular fluid sampling may carry the risk of inducing a pathergy-like inflammatory reaction especially in patients with active disease. An objective and precise measurement of aqueous protein by laser flare photometry (LFP) may be used as a surrogate marker of FA leakage [114], which is still the gold standard in monitoring disease activity and treatment response. A LFP value of 6 photons/millisecond or lower is associated with a lower risk of relapses of BDU [114]. A composite score of ocular inflammatory signs, BD ocular attack score 24 (BOS24) has been used to monitor the severity of uveitis attacks [81,115]. Semi-quantitative FA scoring systems have been used to monitor background retinal vascular inflammation [115–117]. Persistent FA leakage in the optic disc and retinal capillaries after IFX therapy was strongly related to ocular attack relapse [118]. Optical coherence tomography (OCT) has been used as a noninvasive tool to monitor CME, CMT, choroidal thickness, and reversible or irreversible changes in retinal layers. Onal et al. [119] have suggested that CMT on OCT was a reliable activity marker in a multimodal imaging study of BDU. Takeuchi et al. [120] have shown that the reconstitution of disrupted outer retinal layers as visualized by OCT led to an improvement of visual acuity during IFX therapy. Perifoveal microvascular changes are best visualized by OCT-angiography [121] and detection of macular ischemia may explain visual loss.

Although several tools are available and used in routine clinical practice, there is an unmet need for standard monitoring of BDU. The definitions of remission, incomplete, or complete response need to be standardized as well. Currently, the absence of leakage on FA, i.e., 'dry angiogram,' seems to be the most reliable outcome measure of complete remission as long as FA imaging is performed in a standard manner.

7. Competitive environment

Table 2 shows a summary of therapeutic agents in clinical trials.

7.1. Anti-TNF-α agents

7.1.1. Golimumab (GOL)

GOL is a fully humanized anti-TNF-α mAb administered subcutaneously at a standard dose of 50 mg every 4 weeks. Even though GOL has been used after failure of other anti-TNF agents in BDU patients, most of the patients were female and had more commonly unilateral involvement and AU, representing a milder disease form [122,123]. The mean time to clinical response was about 5 weeks [122].

There is an ongoing phase II clinical trial that aims to evaluate the efficacy and safety of GOL in the treatment of refractory BDU, to verify its CS sparing effect and to determine whether it can prevent recurrences (NCT04218565).

7.1.2. Certolizumab pegol (CZP)

CZP is a pegylated, humanized mAb Fab fragment that selectively targets and neutralizes TNF-α. It has potential advantages over other anti-TNF-α drugs, including less immunogenicity, increased half-life, and reduced risk of placental transfer in pregnant women. It is administered subcutaneously at an initial dose of 400 mg at weeks 0, 2, and 4 and then 200 mg per week. Data on its use in BDU is scarce [123,124]. A favorable response to CZP was reported by Tosi et al. [123] in a series of noninfectious uveitis, including 5 patients with BDU, 4 of them being female, and 3 having AU. In another series of 13 BD patients with various organ involvement refractory to previous therapies, a satisfactory response was achieved in 54% of patients. Four of them had ocular involvement, but their treatment response was not separately reported [124].

7.1.3. Biosimilars

The availability of biosimilar anti-TNF agents allows reduced drug costs and improved accessibility. Conflicting results have been reported with limited data on the use of IFX biosimilar in BD patients. Cantini et al. [125] reported relapses of Neuro-Behçet and uveitis in 3 patients switched to biosimilar IFX after long-term remission. In another series of 13 BD patients, 10 with BDU, who were switched to biosimilar after a mean period of 106 months, none of them stopped treatment due to uveitis relapse and the overall cumulative survival was 84.6% at 12 months [126]. No difference was found in the frequency of relapses during 12 months before and after switching to biosimilar anti-TNF agents in 37 patients with noninfectious uveitis, including 26 with BDU [127].

7.2. Interleukin (IL)-1 inhibiting agents

IL-1 inhibition has been proposed as an intriguing therapeutic option in BD patients with multi-drug resistant clinical manifestations [128]. It might also be a safer option compared to anti-TNF treatment because IL-1 blockade is less likely to increase the risk of opportunistic infections, including tuberculosis [129]. However, clinical experience with these agents is limited, and the real place of anti-IL-1 agents in the treatment of BD remains unclear.

7.2.1. Gevokizumab (GEV)

GEV is a humanized mAb that binds to IL–1β and inhibits the activation of IL-1 receptors. An open-label pilot study showed an immediate clinical response in 7 BD patients who received i.v. 0.3 mg/kg GEV infusion for the treatment of acute posterior/panuveitis attacks [130]. These results were confirmed by an exploratory phase II open-label multicenter study [131]. On the other hand, a double-masked RCT (EYEGUARD-B) showed no superiority of 60 mg subcutaneous injections of GEV every 4 weeks as compared to placebo in controlling the number and the timing of ocular exacerbations. However, GEV could preserve visual acuity, reduce the uveitis severity, decrease the emergence of macular edema, and have a CS-sparing effect and was well tolerated [132].

7.2.2. Anakinra (ANA)

ANA is the recombinant form of the natural IL-1 receptor antagonist (IL-1Ra), that inhibits both IL-1α and IL-1β. It is administered as subcutaneous injections at a dosage of 100–200 mg/day. In a series of 9 BD patients treated with ANA 100–150 mg/day, three out of four patients with recurrent uveitis showed resolution of ocular inflammation. However, relapses occurred after an average period of 24 weeks [133]. There is a registered phase I/II trial aiming to test whether ANA given at a daily dose of 100 mg with a dose escalation up to 200 mg/day might control all BD manifestations (NCT01441076).)

7.2.3. Canakinumab (CAN)

CAN is a fully human mAb specifically targeting IL-1β. It is administered subcutaneously at a dosage of 150 mg every 6–8 weeks. Vitale et al. [134] have reported complete resolution of BD manifestations with CAN treatment in 3 patients who had failed ANA. Two of them had BDU. A phase II study has been conducted to investigate the efficacy and safety of one-year CAN treatment in BD patients with neurologic or vascular involvement (NCT02756650). There is no registered trial that investigates its efficacy in BDU.

Overall efficacy of IL-1 inhibitors, with no distinction between ANA and CAN, was reported in three retrospective multicenter studies in Italy [135–137]. In a retrospective multicenter study including 30 BD patients, 16 of them with ocular involvement, ANA was the initial line of anti-IL-1 agent in 90% and a switch to CAN was required in 41%. The median time to response was 6 weeks for ANA and 3 weeks for CAN. Eight patients (26%) were shifted to other treatments due to inefficacy or loss of efficacy despite dose adjustments or addition of cDMARDs [135]. In a subsequent report analyzing the role of ANA and CAN in BDU, administered as first-line bDMARD in 37% of 19 BDU patients, a statistically significant reduction of ocular flares during a 12-month follow-up, improvement of retinal vasculitis on FA at 3-month follow-up which was sustained at 12 months, and a significant CS-sparing effect have been observed [136]. In a more recent study, the presence of uveitis was found to be associated with a sustained response to IL-1 inhibitors in BD patients [137].

7.3. IL-6 inhibiting agents

7.3.1. Tocilizumab (TCZ)

TCZ is a humanized anti-IL-6 receptor antibody that prevents the binding of IL-6 with its membrane and soluble receptors. It is used at a standard dose of 8 mg/kg monthly i.v. infusions or 162 mg weekly subcutaneous injections as monotherapy or combined with cDMARDs. In an RCT (STOP-uveitis study), both 4 mg/kg and 8 mg/kg monthly i.v. infusions of TCZ were found to be safe and equally effective in both naïve and previously treated patients with noninfectious uveitis involving the posterior segment [138]. In a multi-center retrospective study of 25 patients with refractory CME secondary to noninfectious uveitis, including 7 patients with BDU, a significant improvement of CMT and visual acuity was obtained after 12 months of TCZ therapy

Table 2. Therapeutic agents in clinical trials (competitive environment).

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
SYSTEMIC THERAPY					
Golimumab	Janssen/ MSD	Human monoclonal antibody	Behçet's disease	Phase II NCT04218565	TNF-α inhibitor
Certolizumab pegol	UCB	PEGylated Fab fragment of a monoclonal antibody	Noninfectious uveitis Behcet's disease	Phase III NCT03020992 C-VIEW	TNF-α inhibitor
Gevokizumab (AIN 457)	XOMA Corporation/ Servier	Recombinant humanized monoclonal antibody	Behcet's disease Noninfectious uveitis	Phase II/IIII NCT01684345 (EYEGUARD A) NCT01965145 (EYEGUARD B) NCT01747538 (EYEGUARD C) NCT02375685 (EYEGUARD X)	Anti-IL-1β antibody
Anakinra	Swedish Orphan Biovitrum	Recombinant human IL-1 receptor antagonist	Behcet's disease Noninfectious uveitis	Phase I/II NCT01441076 Phase II NCT02929251 (RUBI)	IL-1 receptor antagonist
Canakinumab	Novartis	Human IL-1β monoclonal antibody	Behcet's disease	Phase II NCT02756650	Anti-IL-1β antibody
Tocilizumab	Genentech USA, Inc.	Human monoclonal antibody	Behcet's disease Noninfectious uveitis	Phase II NCT01693653 NCT03554161 NCT02929251 Phase II/III NCT01717170 (STOP-UVEITIS) Phase II NCT02929251 (RUBI)	IL-6 receptor antagonist
Sarilumab	Sanofi, Regeneron Pharmaceuticals	Human monoclonal antibody	Uveitis, macular edema	Phase II NCT01900431 SATURN	IL-6 receptor antagonist
Secukinumab	Novartis	Human monoclonal antibody	Behcet's disease Noninfectious uveitis	Phase II/III NCT00995709 (SHIELD) NCT01095250 (INSURE) NCT01090310 (ENDURE) NCT00685399	IL-17A inhibitor
Rituximab	Genentech USA, Inc. Roche	Chimeric monoclonal antibody	Behcet's disease	Phase II NCT00664599	Anti-CD20
Ustekinumab	Janssen	Human monoclonal antibody	Behcet's disease Noninfectious uveitis	Phase II NCT02648581 STELABEC-1 STELABEC-2 NCT02911116 (STAR)	IL-12 and −23 antagonist
Interleukin-2	??	Cytokine	Behcet's disease	Phase II NCT04065672	Expanding and activating regulatory T cells (Tregs)
GSK1070806	Glaxo Smith Kline	Human monoclonal antibody	Behcet's disease	Phase II NCT03522662	IL-18 antagonist
Abatacept	Bristol Myers Squibb	Human recombinant fusion protein composed of CTL-4, CD152 and a fragment of FC domain of human IgG1	Behcet's disease Noninfectious uveitis	Early phase 1 NNCT01279954 Phase II NCT01693640	CTLA4-Ig antagonist
Tofacitinib	Pfizer	Small molecule	Noninfectious uveitis and scleritis	Phase II NCT03580343	JAK inhibitor
Filgotinib	Galapagos	Small molecule	Noninfectious uveitis	Phase II NCT03207815	Selective JAK-1 inhibitor
Apremilast	Celgene	Small molecule	Behçet's disease oral ulcers Noninfectious uveitis	Phase II/III NCT02307513 (RELIEF) NCT00889421	PDE-4 inhibitor
INTRAVITREAL THERAPY					
Infliximab	Janssen Biotech, Inc	Chimeric monoclonal antibody	Behcet's disease	Phase I/II NCT02620618	TNF-α inhibitor

[139]. Ozturk et al. [140] reported significant improvements in visual acuity, LFP values, CMT, and FA scores in 5 patients treated with monthly infusions of TCZ 8 mg/kg for BDU refractory to IFN-α and anti-TNF therapy. On the other hand, the authors noted that a complete resolution of FA leakage could not be obtained in any patient during 5–19 months of treatment period [140]. In a multicenter retrospective study of 11 patients with refractory BDU, TCZ treatment resulted in rapid and maintained improvement in all ocular parameters and complete remission of intraocular inflammation in 8 of them after a mean follow-up of 9.5 months; however, extraocular manifestations could be controlled in only 3 patients [141]. Others have also reported lack of efficacy and even a paradoxical flare of mucocutaneous manifestations in BD patients treated with TCZ [142].

A placebo-controlled RCT of TCZ for the treatment of BD has been terminated due to low recruitment (NCT01693653). An open prospective study investigating the efficacy of TCZ in BDU is still recruiting (NCT03554161).

7.3.2. Sarilumab

Sarilumab is a fully human mAb targeting the IL-6 receptor complex that has shown clinical benefits in posterior segment noninfectious uveitis, especially in the treatment of macular edema, in a phase II multicenter RCT (SATURN Study). There were 58 patients in the trial, 20 with systemic disease associations; however, whether any patient had BD was not reported [143].

7.4. Other bDMARDs

7.4.1. Secukinumab (AIN457)

Secukinumab is a selective, fully human anti-IL 17A mAb neutralizing the downstream signals that lead to activation of neutrophils and macrophages [144]. The multicenter, double-masked RCT (SHIELD Study) did not reveal significant difference between subcutaneous injections of secukinumab and placebo in exacerbations of posterior or panuveitis in 118 BDU patients. However, cDMARDs were significantly reduced in the secukinumab group, suggesting a potential benefit [145]. In a subsequent phase II dose-ranging RCT in patients with noninfectious uveitis involving the posterior segment, intravenous dosing was shown to be more effective than subcutaneous injections of secukinumab [146]. Even though the efficacy and safety of secukinumab has been reported in the treatment of mucosal and articular manifestations of BD in a retrospective multicenter study of 15 patients [147], Dincses et al. [148] have recently reported exacerbation of BD or emergence of *de novo* BD in 2 patients treated with secukinumab for ankylosing spondylitis.

7.4.2. Rituximab (RTX)

RTX is a chimeric mAb against CD20 expressed on B lymphocytes. Although BD is a predominantly T cell-driven disease, in an RCT (NCT00664599) conducted by Davatchi et al in 2010, RTX and MTX combination was found to be more effective than cyclophosphamide–AZA–prednisone combination in improving ocular manifestations; however, all patients in the RTX group relapsed as the B-cell depletion gradually recovered [149].

7.4.3. Daclizumab

Daclizumab is an anti-IL-2Ra (anti-CD25) mAb that inhibits IL-2-mediated responses of activated lymphoid cells. In an RCT, daclizumab did not show any superiority over placebo in terms of ocular attack rates and severity of attacks in 17 patients with refractory BDU. On the contrary, the daclizumab group had a higher rate of uveitis attacks and less reduction of cDMARD score than the placebo group [150]. Consistent with the RCT results, in a retrospective study of 39 patients with noninfectious uveitis treated with daclizumab over an 11-year period, 8 BD cases had the highest number of uveitis exacerbations and least reduction in concomitant medications. Moreover, four patients developed solid tumor malignancies during follow-up [151].

7.4.4. Alemtuzumab (CAMPATH-1 H)

Alemtuzumab is a humanized anti-CD52 antibody leading to rapid and long-term T and B cell depletion. In a pilot study by Lockwood et al. [152], 18 BD patients, including five patients with BDU, received alemtuzumab infusions at an escalating dose for 5 consecutive days after discontinuation of cDMARDs. They reported partial or complete remission in all five cases of BDU at 6-month follow-up. However, after an average of 25 months, relapses were observed in 54% of the whole cohort. In a 20-year follow-up study from the same center, 32 BD patients, 21 with BDU, received 60 courses of alemtuzumab at three different dosing regimens. Relapses were more common in the lowest-dose group. Remission was achieved in all patients with severe eye disease. Infusion reactions occurred in 27% and thyroid dysfunction in 25%. Patients received routine antifungal and antiviral prophylaxis and no opportunistic infection was reported [153].

7.4.5. Ustekinumab

Ustekinumab is a fully human mAb directed against p40, the common subunit of IL-12 and IL-23. It showed favorable results in the treatment of oral ulcers refractory to colchicine [154] but its effect on BDU is not known.

A phase II open-label study that evaluates the efficacy of ustekinumab in subjects with BD having oral ulcers (STELABEC-1) and active posterior or panuveitis (STELABEC-2) finished recruiting patients (NCT02648581). The results of the study have not been reported yet. Another phase II clinical trial (STAR Study) investigating the efficacy and safety of ustekinumab in active intermediate, posterior, and panuveitis, is currently recruiting patients. (NCT02911116).

7.4.6. Abatacept

Abatacept is a recombinant fusion protein of the extracellular component of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It prevents the co-stimulation of T lymphocytes. In a patient with refractory BD and scleritis, short-term remission was obtained after two i.v. infusions of abatacept [155]. A phase II trial evaluating the efficacy of abatacept in vision-

threatening uveitis has been completed, with results still pending (NCT01279954). Another early phase I trial is studying its role for the resolution of mucocutaneous symptoms in BD. (NCT01693640).

7.4.7. Interleukin-2

While high-dose IL-2 activates effector T cells, low-dose IL-2 expands and activates Tregs [156]. In a pilot trial (NCT01988506), Rosenzwajg et al. [156] administered 1miU IL-2 for 5 consecutive days and then every 2 weeks for 6 months in 46 patients with various autoimmune disorders of mild to moderate severity, including 2 with BD. The authors reported Treg activation and expansion as well as significant clinical improvement in all patients, except in those with Crohn's disease [156]. A single-center, open-label, prospective study aimed to explore the clinical and immunological efficacy of low-dose IL-2 in BD is still recruiting patients. (NCT04065672)

7.4.8. Anti-interleukin-18 (GSK1070806)

A phase II study is registered aiming to demonstrate the safety and tolerability of anti-IL-18 (GSK1070806) in the BD population and to evaluate its clinical efficacy. The recruitment status of the study is still unknown. (NCT03522662)

7.5. Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)

tsDMARDs, also known as small-molecule inhibitors, have potential advantages over bDMARDS, including oral administration and low rates of immunogenicity. Based on their small molecular weight and biophysical properties, they can cross cell membranes and target intracellular signaling pathways [157].

7.5.1. Janus kinase (JAK) inhibitors

Tofacitinib, a JAK1/3 inhibitor targeting T cell signaling, was recently used at a dose of 5 mg twice a day orally, in a pilot trial including 13 BD patients with vascular, gastrointestinal, and articular involvement refractory to cDMARDs and/or bDMARDs [158]. A favorable response was observed except in patients with gastrointestinal involvement. Two patients discontinued treatment due to herpes zoster infection. Successful use of tofacitinib has been shown in only a few cases of noninfectious uveitis or scleritis [159,160]. A phase II trial with tofacitinib in uveitis and scleritis is currently ongoing (NCT03580343).

Filgotinib, another selective JAK-1 inhibitor is also being investigated for the treatment of noninfectious uveitis (NCT03207815).

7.5.2. Apremilast

Apremilast, an oral phosphodiesterase 4 inhibitor, modulates both innate and adaptive immune systems by suppressing the functions of Th1, Th17, and M1 macrophages, and enhancing the regulatory functions of IL-10 producing B cells and M2 macrophages [161]. Efficacy and safety of apremilast has been shown in oral ulcers of BD in a phase II trial (NCT00866359) [162] and a subsequent multicenter phase III RCT (NCT02307513, RELIEF study) [163]. In the whole study cohort (n = 207) of the phase III trial, 17% had history of uveitis and none reactivated during apremilast treatment while there were 2 cases of reactivated uveitis in the placebo group [163]. Because of the design of these studies, specifically addressing mucocutaneous BD, any role of apremilast in treating BDU remains unknown.

7.6. Intravitreal non-corticosteroid therapy

Intravitreal administration of anti-TNF-α agents has been investigated in order to avoid systemic adverse effects. Intravitreal IFX at a dose of 1–1.5 mg resulted in improvement in all parameters of intraocular inflammation, visual acuity and CMT in the short term [164,165]. Markomichelakis et al. [164] reported that its effect was not as fast as an intravenous infusion of IFX. The use of intravitreal ADA at a dose of 1.5 mg has been suggested as a potentially effective, practical, and safe adjunctive therapy for the control of breakthrough inflammation in BDU patients maintained on systemic ADA [166].

Intravitreal monthly injection of 400 μg MTX in 7 eyes with BDU has been found to be effective and well tolerated [167]. In BDU with posterior segment involvement, intravitreal MTX provided better control of inflammatory reaction, longer remission, and decreased risk of IOP elevation as compared to retrobulbar triamcinolone acetonide [168].

In phase III multicenter RCTs the administration of intravitreal sirolimus, a cDMARD, every other month has been shown to improve intraocular inflammation in patients with active noninfectious uveitis involving the posterior segment (NCT01358266, SAKURA study) [169]. However, there are no data specifically on BDU.

The use of intravitreal anti-VEGF treatment in CME associated with BDU has shown conflicting results [170,171]. On the other hand, anti-VEGF agents may also be used for the treatment of neovascular complications of BDU.

It is noteworthy that intravitreal drug administration should be considered as an adjunct to systemic treatment or when systemic treatment is contraindicated or not tolerated.

8. Potential development issues

Although the introduction of bDMARDS, particularly IFN-α and anti-TNF-α agents, has revolutionized treatment of BDU, there are still major challenges in the management of this potentially blinding disease:

- ADA is currently the only bDMARD approved for the treatment of noninfectious uveitis, including BDU; and IFX is approved only in Japan for the treatment of BDU refractory to cDMARDs; thus, its first-line use is restricted even in Japan. RCTs comparing the efficacy and safety of IFN-α, IFX, and ADA are still missing; and many questions including which agent to use as initial line or subsequent therapy, at which dosage, and for how long remain to be answered. A prospective randomized, head-to-head study, aimed to compare ADA to ANA and TCZ in refractory noninfectious uveitis; however, the current recruitment status is unknown (RUBI, NCT02929251). Since

results of a trial including various types of uveitis may not be transferable to BDU, the most severe form of uveitis, with possibly a distinct underlying immunopathology, there is an unmet need for RCTs specifically designed to address BDU. International collaboration is essential because of the orphan nature of BD.

- Biosimilars of currently available/approved bDMARDs need to be properly compared to the originator molecules for their efficacy and safety in BDU in order to increase the accessibility of more effective therapeutic regimens, especially in countries where the disease is more prevalent but resources are more limited.
- IFN-α that has been used for the treatment of BDU especially in Turkey, Germany, and France is not available anymore. Experience with PEG-IFN-α is limited and well-designed studies are required to test its efficacy and tolerability.
- BD is a complex disorder with protean manifestations that may not be equally responsive to a given therapeutic regimen. Therefore, studies including a composition of patients with various manifestations may not yield comparable results. BDU phenotype needs to be addressed in a standard manner and therapeutic agents such as apremilast proven to be effective in mucocutaneous manifestations of BD need to be tested specifically in BDU.
- bDMARDs that have failed in RCTs such as secukinumab and GEV might work at higher doses and with a different route of administration. They should not be discarded without further investigation because both agents have shown promising results with i.v. infusions.
- Adequately powered RCTs are needed to evaluate the efficacy and safety profile of bDMARDs, such as IL-1 inhibitors that have shown favorable results in limited clinical cohorts.
- As all patients with BDU do not uniformly respond to any of the available therapeutic regimens, there is certainly a need for an ever-expanding therapeutic toolbox. Ongoing research on new bDMARDs such as ustekinumab, low-dose IL-2, and anti-IL-18 as well as tsDMARDs such as JAK inhibitors may reveal promising results for the treatment of BDU. Long-term follow-up studies will also be required to confirm efficacy and safety of new agents.
- New biomarkers need to be identified to predict treatment response and prognosis. An observational study based on single-cell sequencing technology continues to recruit patients aiming to identify biomarkers and provide new targets for individualized diagnosis and treatment in eye diseases including BDU (NCT04101604).

9. Conclusion

There are no RCTs that indicate the most effective therapy specifically for BDU. The cDMARDs, AZA, and/or CSA, combined with CSs, and the anti-TNF-α agents, IFX, and ADA, constitute the common therapeutic choices. A widely applicable therapeutic algorithm has not been established due to the lack of robust evidence and variable access to anti-TNF-α agents and other bDMARDs with potential beneficial effects. Nevertheless, a more targeted therapeutic approach in the last two decades has remarkably improved the prognosis of patients with BDU. Adequately powered trials with the new bDMARDs and tsDMARDs in the pipeline will shape the future management of BDU.

10. Expert opinion

The clinical course of BDU is characterized by recurrent episodes of acute inflammation, mostly panuveitis, and background leaky retinal capillaritis during apparently quiescent periods. While recurrent episodes of occlusive periphlebitis which may involve major branches or distal veins with or without significant vitreous haze and retinal infiltrates may lead to extensive retinal nonperfusion, a creeping peripheral retinal capillary nonperfusion as well as macular ischemia seem to be more commonly leading to retinal atrophy in the long term. Thus, not only severity and frequency of acute inflammatory episodes and occlusive periphlebitis, but also the magnitude and persistence of background leakage determine the visual prognosis. It is important to note that severity of BDU shows individual variability and also may vary during the course of the disease in a given patient.

Even though head-to-head trials comparing cDMARDs with bDMARDs as first line have not been conducted, there is enough evidence that bDMARDs have much higher efficacy in BDU. A step-wise therapeutic approach, starting with cDMARDs combined with CSs and use of bDMARDs as second line, would not be appropriate in a treatment-naïve patient who presents with severe vitreous haze and inflammatory lesions within the arcades, and/or extensive FA leakage, and bDMARDs (IFX or ADA, since IFN-α is not available anymore) should be considered first-line, as recommended by other experts as well. In other words, any patient who requires high-dose CS therapy would better be treated with bDMARDs early on. A patient who presents with reduced visual acuity due to structural damage caused by treated or untreated previous episodes and presents with active inflammation should also be considered for bDMARDs. On the other hand, patients who present with mild posterior segment inflammation in the form of few peripheral retinal infiltrates and just optic disc staining and/or limited mild peripheral retinal capillary leakage should be placed on cDMARDs that have proven benefits and then should be watched closely. Achievement of a complete and sustained remission is possible with cDMARDs in patients with mild disease and it would be cost-effective.

There is no head-to-head RCT comparing IFX and ADA. High serum concentrations achieved with i.v. infusion of IFX is a major advantage in obtaining a prompt and potent anti-inflammatory effect. On the other hand, ADA seems to be a better choice for long-term control. Standard infusion or injection intervals applied in rheumatology or in other forms of noninfectious uveitis do not usually prevent recurrences in BDU patients and intervals need to be shortened during follow-up. Therefore, there is a need for studies designed to

investigate the outcomes of monthly IFX infusions following induction doses and weekly ADA injections as initial dosing schedule and intervals being increased as a tapering procedure according to the response in BDU patients.

For patients who fail IFN-α, IFX, and ADA, there is almost no evidence guiding the choice between the other anti-TNF agents, GOL and CZP, and TCZ, or IL-1 inhibitors. There seem to be local variations in the physicians' approach to the patients with the most severe disease. Based on experience in other noninfectious forms of uveitis, especially the favorable results obtained in persistent CME, TCZ appears to be a good choice in BDU patients with moderate to severe background leakage and associated CME. Therapeutic agents that rapidly induce complete remission (no recurrent acute inflammation and no background leakage) and have a durable effect after discontinuation would be ideal for the treatment of BDU. Although long-term high retention rate of a drug may indicate a higher efficacy and safety compared to other therapeutic agents, long-term drug-free remission should be the main outcome to show the superiority of any drug to others.

Early data on visual prognosis of BDU have been mostly based on loss of useful vision (visual acuity 20/200 or worse). Our current goal is to preserve 20/20 vision, which is possible in a great majority of patients who are appropriately treated, starting early after onset. An increased knowledge of immunopathogenesis pathways will lead to new entries in the therapeutic armamentarium. An increased awareness of therapeutic options, and most importantly, evidence-based guidelines will improve the quality of care. The challenge is the high cost and off-label use of potentially more effective agents, and also the lack of robust data influencing the regulations of local healthcare systems.

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Declaration of interest

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Reviewer disclosures

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