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Review article

Behçet's disease uveitis

Uvéites associées à la maladie de Behçet

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ABSTRACT

Uveitis in Behçet's disease (BD) is frequent (40% of cases) and is a major cause of morbidity. The age of onset of uveitis is between 20 and 30 years. Ocular involvement includes anterior, posterior or panuveitis. It is non-granulomatous. Uveitis may be the first sign of the disease in 20% of cases or it may appear 2 or 3 years after the first symptoms. Panuveitis is the most common presentation and is more commonly found in men. Bilateralisation usually occurs on average 2 years after the first symptoms. The estimated risk of blindness at 5 years is 10–15%. BD uveitis has several ophthalmological features that distinguish it from other uveitis. The main goals in the management of patients are the rapid resolution of intraocular inflammation, prevention of recurrent attacks, achievement of complete remission, and preservation of vision. Biologic therapies have changed the management of intraocular inflammation. The aim of this review is to provide an update previous article by our team on pathogenesis, diagnostic approaches, identification of factors associated with relapse and the therapeutic strategy of BD uveitis.

Mots clés :
Maladie de Behçet
Uvéite
Vascularite
Biothérapies
Agents anti-TNFα

RÉSUMÉ

L'uvéite associée à la maladie de Behçet est fréquente (40 % des cas) et constitue une cause majeure de morbidité. L'âge d'apparition de l'uvéite se situe entre 20 et 30 ans. L'atteinte oculaire comprend une uvéite antérieure, postérieure ou une panuvéite. Elle est non granulomateuse. L'uvéite peut être le premier signe de la maladie dans 20 % des cas ou apparaître 2 ou 3 ans après les premiers symptômes. La panuvéite est la présentation la plus fréquente et se rencontre plus souvent chez les hommes. La bilatéralisation survient en moyenne 2 ans après les premiers symptômes. Le risque de cécité à 5 ans est estimé à 10–15 %. L'uvéite associée à la maladie de Behçet présente plusieurs caractéristiques ophtalmologiques qui la distinguent des autres uvéites. Les principaux objectifs de la prise en charge des patients sont : (1) la résolution rapide de l'inflammation intraoculaire, (2) la prévention des crises récurrentes, (3) l'obtention d'une rémission complète et (4) la préservation de la vision. Les thérapies biologiques ont modifié la prise en charge de l'inflammation intraoculaire. Le but de cette revue est de fournir une mise à jour sur les approches diagnostiques, l'identification des facteurs associés à la récidive et la stratégie thérapeutique de l'uvéite associée à la maladie de Behçet.

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1. Introduction

Behçet's disease (BD) is a systemic vasculitis at the crossroads between autoimmune and auto-inflammatory diseases that can manifest itself in a variety of clinical manifestations (Fig. 1). Uveitis is one of the most severe complications of BD and progress in biologic therapy has transformed visual outcomes. The current issues in uveitis associated with BD are to better define ophthalmological criteria, and diagnostic algorithm, with improvement of ocular imaging advances, to shorten the delay of induction therapy. The therapeutic challenge is to treat as early as possible to limit visual sequelae and optimize inflammation control. Our aim was to provide up-to-date review on biomarkers, diagnostic approach, identification of factors related to relapse and therapeutic strategy in BD uveitis.

2. Methodology and literature search

We realised an unsystematic narrative review by selecting articles written in English and French from PubMed/MEDLINE database published until March 2023. The keywords used to screen the database were searched in Medical Subject Headings (MeSH) were: (Behçet's disease) and (uveitis) and (diagnosis) or (prognosis) or (therapy) and (Behçet's disease) and (biologics).

3. Epidemiology

Epidemiology shows large geographic variations in BD frequency, with prevalence rates per 100,000 inhabitants of 20–420 for Turkey, 1.5–15.9 for southern Europe, and 0.3–4.9 for northern Europe [2]. Interestingly, ethnic disparities persist among higher-prevalence migrants or their descendants living in lower-prevalence areas [3]. Familial cases account for less than 5% [4]. The incidence in patients under 25 years old is higher [5] and young males have the worst prognosis [6]. BD uveitis occurs in 50 to 60% of patients [7] and may be the first sign of the disease in 20% of cases or it may appear 2 or 3 years after the first symptoms.

Table 1
International criteria for Behçet's disease (adapted of The International Criteria for Behçet's Disease [ICBD]: a collaborative study of 27 countries on the sensitivity and specificity of the new criteria [9]).

Sign/Symptom	Points
Ocular lesions	2
Genital aphtosis	2
Oral aphtosis	2
Skin lesions	1
Neurological symptoms	1
Vascular manifestations	1
Positive pathergy test[a]	1

[a] Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result. Diagnostic of Behçet's disease if score > 4.

4. Prognosis of Behçet's disease uveitis

BD uveitis is responsible for a large amount of blindness in high prevalence countries. In the most recent series, the blindness rate ranged between 11 and 25% [8].

5. Diagnosis of Behçet's disease uveitis

5.1. Diagnosis of systemic Behçet's disease

The diagnosis of BD is based on the presence of clinical diagnostic criteria, established by the International Study Group (ISG) in 1990 and revised in 2013 (Table 1) [9].

5.2. Diagnosis of uveitis associated with Behçet's disease

5.2.1. Ocular clinical presentations

Uveitis may be the initial manifestation, reported in 6–20% of patients [6]. Extra-ophthalmological signs are often overlooked.

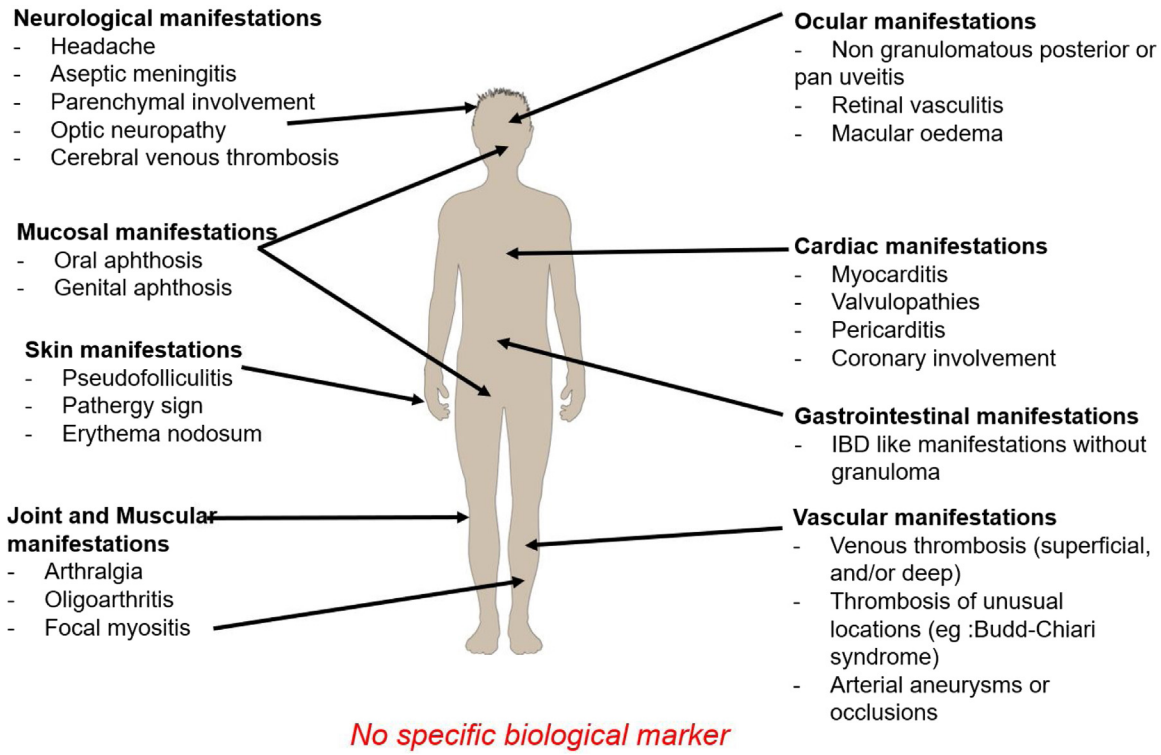

Fig. 1. Summary of clinical manifestations in Behçet's disease (extracted from French recommendations for the management of Behçet's disease. Kone-Paut et al. [2018] [1]).

Panuveitis is the most frequent presentation. Intermediate uveitis in the form of isolated vitritis is more common in early BD than late BD and isolated intermediate uveitis is exceptional [10]. The average age of onset is 25 years. Bilateralization usually occurs on average 2 years after the disease's onset.

Isolated anterior uveitis (AU) affects less than 10% of patients. It presents as a sudden acute onset, with ocular redness, periorbital pain, photophobia, and tearing. It is always non-granulomatous, associated with anterior chamber Tyndall and may be complicated by posterior synechiae. Hypopyon reflects the severity. Recurrence of AU may be complicated by glaucoma. Ocular hypertonia might be the result of angle closure due to anterior synechiae or pupillary occlusion, inflammation, or local or systemic administration of steroids [8].

Posterior uveitis is the most frequent and severe. Posterior involvement can be present by an isolated visual acuity decreasing or be asymptomatic. It may present as hemorrhagic retinitis areas of variable number and distribution or white yellowish. In the case of macular localisation, it may be associated with visual acuity decreasing. Vitreous involvement may limit access to the fundus. Retinal vasculitis is common and mostly venous but can be arterial or both. BD vasculitis is likely occlusive [11]. These peripheral ischemic areas may be complicated by pre-retinal or papillary neovascularization, which may cause retinal or vitreous hemorrhage, retinal ischemia, neovascularization and secondary neovascular glaucoma. Macular edema may occur and affect the visual prognosis. Complications caused by recurrent posterior inflammatory flares include retinal atrophy, vascular sclerosis, optic atrophy, neovascular glaucoma and retinal detachment [12]. Macular holes have also been reported and associated changes involving the vitreomacular interface. Moreover, localized retinal nerve fiber layer defects not associated with a retinochoroidal scar in the absence of glaucoma could guide diagnosis of BD uveitis. They are linked to past foci of retinitis which are transient and resolve without scar formation, and so could be missed.

Besides uveitis, other ophthalmological disorders such as episcleritis, scleritis, conjunctival ulcers, keratitis, orbital inflammation, isolated optic neuritis, and extraocular muscle palsies have been described.

5.2.2. Ocular investigations

5.2.2.1. Fundus photography. Fundus photography can document and monitor the grade of vitreous damage [13].

5.2.2.2. Fundus fluorescein angiography (FA). FA is the gold standard imaging modality for the diagnosis and monitoring. FA is a mandatory tool for the assessment of inflammatory fundus conditions due to posterior uveitis; the leakage on FA identifies retinal vasculitis and is an important marker of BD uveitis activity [14]. Specific signs of inflammatory activity include increased tortuosity of retinal veins, staining of vessel walls, leakage from large and small retinal vessels and from the optic disc. Fern-like capillary leakage is the most characteristic FA finding in BD uveitis and may be present even when the uveitis seems inactive. Even if FA is a challenging assessment to perform in daily care it remains critical to monitor BD uveitis activity.

5.2.2.3. Optical coherence tomography (OCT). OCT is used to diagnose and to monitor macular complications (macular edema, retinal cysts, severe retinal serious detachment, epiretinal membranes, vitreomacular traction, foveal atrophy and macular holes) [15].

5.2.2.3.1. Enhanced depth imaging (EDI) OCT. EDI-OCT provides detailed and measurable images of the choroid [16]. Subfoveal choroidal thickness may reflect macular vasculitis; its measurement may be a non-invasive tool to investigate macular inflammatory activity [16]. However, it should be noted that a study has published with conflicting results, showing no increase choroidal thickening during active BD uveitis [17].

Table 2
Criterias pointing to uveitis in relation to Behçet's disease (extracted from uveitis in Behçet disease: an analysis of 880 patients, Tugal-Tutkun et al. [7] and an algorithm for the diagnosis of Behçet disease uveitis in adults, Tugal-Tutkun et al. [24]).

Demography
Male patient
Mean age at onset of the uveitis: 28.5–30 years old
Originated from Mediterranean basin, the Middle East, and Asia
Characteristics of Uveitis nature
Bilateral uveitis
Rarely isolated anterior uveitis (<10%)
Recurrent flares
Posterior uveitis (with retinal vasculitis or its sequelae and/or retinal infiltrate) or panuveitis
Presence of retinal nerve fiber layer defect
Presence of macular edema (the most common complication)
Presence of diffuse capillary leakage on fluorescein angiography
Association with peripheral occlusive periphlebitis or gliotic sheathing or ghost vessels
Association with retinal vein branch occlusion
Negative signs
Non-granulomatous uveitis
Not associated with choroiditis
Extraophtlamological associated signs of BD
Recurrent oral ulcers, genital aphtosis
Pseudofolliculitis, erythema nodosa
Neurological symptoms
Vascular manifestations
Positive pathergy test

5.2.2.3.2. Optical coherence tomography angiography (OCTA). OCTA is a technique that detects movement in vessels, without contrast injection and provides depth-resolved visualisation of the retinal and choroidal vascularisation [18]. OCTA has been shown to better visualise of microvascular changes in the macular area, such as capillary dropout, increased foveal avascular zone, telangiectasias, shunts, and neovascularisation zone than FA in eyes with active BD uveitis. The deep capillary plexus appears to be more affected than the superficial capillary plexus [18].

5.2.3. Strategy for earlier diagnosis of BD uveitis

BD uveitis has several distinctive clinical features. Tugal-Tutkun et al. suggested a useful diagnosis algorithm for BD uveitis based on ophthalmological criteria [19] although the results need to be validated in larger cohorts. This algorithm was built after collection of multicenter prospective data on 127 patients with BD uveitis and 322 controls and identified ocular findings with a high diagnostic odds ratio (DOR). The study identified 10 items with DOR > 5 [19]. The signs that provided the highest accuracy for the diagnosis of BD uveitis were in patients with vitritis the presence of retinitis foci, signs of occlusive retinal vasculitis, diffuse retinal capillary leakage on FA and [20] the absence of granulomatous anterior uveitis or choroiditis (Table 2). Although, relapsing-remitting course has a high clinical value, this criterion was not relevant in this retrospective evaluation because patients were treated before spontaneous resolution [19]. The parafoveal microvasculature seems also to be affected in BD patients without uveitis [21]; likewise peripapillary microvascular changes could be detected by OCTA in BD patients without clinical ocular involvement [22]. FA is performed to ensure the absence of any vascular leakage or subclinical vasculitis [23]. OCTA appears to be promising. Conventional color retinography and FA are limited in their field of view. Ultra-widefield imaging, which provides 200° angle of photographic, autofluorographic, and angiographic views of the ocular fundus, has recently been introduced in ophthalmology. In the future, it is likely to become an essential tool in the diagnosis, treatment, and follow-up of retinal vasculitis, particularly those associated with BD. The laser flare

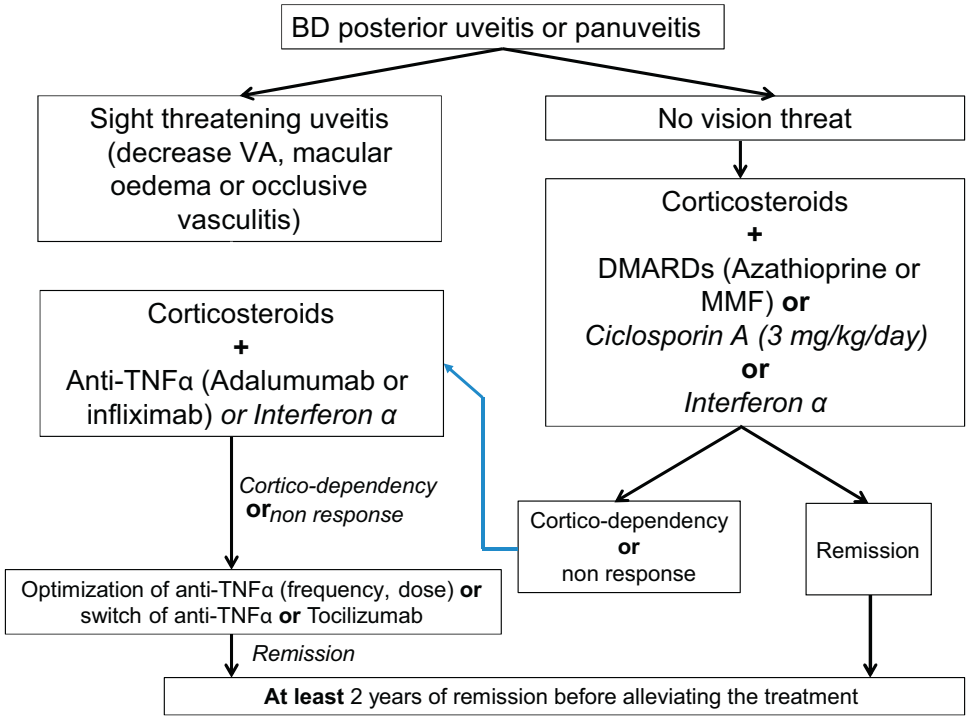

Fig. 2. Management of uveitis in Behçet's disease (extracted from of French recommendations for the management of Behçet's disease. Kone-Paut et al. [1]).

meter can be used to monitor the degree of inflammation, as its values would correlate with the amount of vascular leakage visible on FA [24].

6. Treatment modalities and perspectives

6.1. BD uveitis management recommendations

The goals of therapeutic management are to quickly and effectively control inflammation to preserve visual function and limit irreversible damage and to treat the chronic subclinical inflammation, to prevent relapses and ocular complications, to limit ophthalmological and general adverse effects of iatrogenic causes, and to control systemic manifestations.

European and French recommendations on the treatment of BD were recently updated [1,25] (Fig. 2). In case of posterior segment ocular involvement, systemic immunosuppressive agents such as azathioprine, cyclosporine-A, interferon-α, anti-TNF agents should be used with steroids. Patients presenting with sight-threatening uveitis should be treated with high-dose glucocorticoids and TNF inhibitors as intravenous infliximab, or subcutaneous adalimumab, or subcutaneous adalimumab or interferon-α [1,26] as an alternative. Intravitreal corticosteroid injection could be a therapeutic option in patients with unilateral exacerbation as an adjunct to systemic treatment [1,25].

French recommendations call for the use of corticoids as soon as posterior uveitis is present, whereas EULAR recommends the use of glucocorticoids only in the event of threatened visual impairment [1,25].

During BD uveitis management, decrease of immunomodulating treatment should be considered only after 2 years of remission and after steroids tapering to 5 mg daily or less. However, a study [27] has shown a high rate of relapse after cessation of TNF inhibitors and suggest optimization by spacing the intervals between the doses [27]. The Biovas study [28] has recently shown lower relapse rate of retinal vasculitis and/or cystoid macular edema with infliximab (5 mg/kg) every 4–6 weeks as compared to adalimumab 40 mg/14 days. IFX should be preferred in cases of threatening vasculitis. Finally, with anti-TNF agents, proactive therapeutic drug monitoring, consisting of individualized treatment based on scheduled assessments of serum drug levels, has been shown to be more effective than treatment without therapeutic drug monitoring in maintaining disease control without disease worsening [27].

In case of isolated AU treatment is based on topical corticosteroids. However, systemic immunosuppressants such as azathioprine could be considered, in cases of risk factors of flares, such as young age, early onset of the disease, and male gender [1].

6.2. Screening for relapse

A scoring system for determining the activity of ocular BD termed Behçet's disease ocular attack score 24 (BOS24) has been used to predict visual acuity deterioration. BOS24 consists of a total 24 points divided into 6 parameters of ocular inflammatory symptoms [29]. This score have limitations and cannot replace the FA. Diffuse capillary leakage on FA is an important supportive feature, because retinal vasculitis may not be readily apparent especially during the clinically quiescent periods [30]. A study, demonstrated that FA leakage, particularly of the optic disc and capillary vessels, after IFX therapy was strongly related to the presence of ocular inflammatory relapses in patients with ocular BD. FA is important for predicting visual outcome. Therefore, it should be done in every patient. However, BOS24 may also be a useful alternative when FA is unavailable, such as the limitation of time, cost or machine [31] (Tables 2 and 3). Another study shown that BOS24 scoring system is an objective and quantitative measurement to evaluate the disease activity, but further investigations and accumulation of evidence are warranted to improve these scoring systems [32].

6.3. Peri- or intraocular treatment

Intravitreous corticosteroids infusions could be proposed as adjuvant treatment in addition to systemic treatment for unilateral

Table 3
Factors linked to Behçet's uveitis relapse and should lead to therapeutic escalation (Extracted from: fluorescein angiographic findings and Behcet's disease ocular attack score 24 [BOS24] as prognostic factors for visual outcome in patients with ocular Behcet's disease [33] and the relationship between fluorescein angiography leakage after infliximab therapy and relapse of ocular inflammatory attacks in ocular Behcet's disease patients [34].).

Fundus fluorecesin angiography parameters
Severe posterior pole leakage particularly on the optic disc and capillary vessels
Vitreous haze
Arterial narrowing
If FA is unavailable
BOS24 ≥ 6

outbreak. Intraocular pressure elevation and cataract development are the main side effects, in addition to the limited duration of action and lack of systemic disease control. This option can be used as a bridging therapy pending escalation of therapy or in rare cases of absolute contraindication to some systemic therapies [35].

A first study of 15 patients with BD uveitis treated with intravitreal infliximab showed a significant improvement in best-corrected visual acuity, with significant reductions in macular thickness, retinal vasculitis and retinitis [36]. Another study showed that intravitreal infliximab appeared to be safe and effective in the treatment of uveitis in 20 BD with patients [37]. However, conflicting results have been published in a study of 16 patients. Four eyes developed a severe immunological reaction and failure to control inflammation was described in the majority of eyes [38]. Intravitreal adalimumab was not successful in chronic refractory cystoid macular edema [39]. In this first study, no ocular or systemic adverse effects were observed. In the small population, intravitreal adalimumab was shown to be effective in controlling the inflammation, limiting uveitis flares, reducing macular edema, and improving the visual acuity in noninfectious uveitis including BD uveitis [20,40]. Nevertheless, there are conflicting results regarding the safety of intravitreal adalimumab infusions [33,39,41]. Further studies on the concentration and toxic effects of intravitreal injections anti-TNFα agents are needed, although the efficacy of these injections is not certain.

Intravitreal bevacizumab has been shown to be well tolerated and an effective adjunctive therapy in chronic uveitis, cystoid macular edema and noninfectious uveitis particularly in BD; however, the median duration of effect was reduced [34].

6.4. Conventional immunosuppressants

Ciclosporine and azathioprine are the only treatments that have been tested in randomized controlled trials (RCT). In a large placebo-controlled trial, azathioprine significantly decreased of AU relapses and the development of new ocular disease after 2 years. None of the patients in the azathioprine group experienced serious adverse events whereas one patient in the placebo group died of a pulmonary artery aneurysm [42]. Cyclosporin A was evaluated in 3 RCT [43–45]. Response rates were between 80 and 91%, but safety was poor [43–47]. Cyclosporin A was significantly more effective than cyclophosphamide [48].

A longitudinal study using methotrexate (7.5–15 mg/week) showed improvement or worsening of visual acuity in 46.5 and 37.2% of patients with BD uveitis, respectively [49].

Alkylant agents are not recommended.

6.5. Interferons

Several studies emphasized the efficacy and tolerance of IFN-α2a in patients with BD uveitis [50,51]. Subcutaneous IFN-α2a is effective and safe for the long-term treatment of refractory BD uveitis. Ninety percent of BD uveitis patients had a partial or complete response [52]. It would also allow in some cases long-term remission without treatment [53,54]. IFN-α2a was withdrawn from the market in 2020. Pegylated interferon-α2a (PEG-IFN-α2a), given once a week, is still available. The addition of PEG-IFN-α2a to usual BD treatment with or without ocular involvement did not significantly reduce their cortico-dependence at one year. However, in those receiving corticosteroids at baseline, post hoc analysis demonstrated that the addition of PEG-IFN-α2a reduced the required corticosteroid dose [55]. Small case series have reported the efficacy of INF-α2b or INF-α2a in BD uveitis [56,57], even though INF-α2a was described to be more effective than INF-α2b [58]. The occurrence of influenza syndrome and mental disorders is the main limitation of interferon prescription [53]. Compared with anti-TNFα agents, this treatment does not promote serious infections, especially tuberculosis.

6.6. Anti-TNFα agents

A retrospective study showed that anti-TNFα agents reached earlier ocular inflammation control and better steroid sparing than cDMARD in non-anterior noninfectious uveitis [59].

Infliximab is a murine-human chimeric antibody against soluble and transmembrane forms of TNFα. The usual loading dose is 5 mg/kg given intravenously at weeks 0.2 and 6, and then every 4 to 5 weeks [28,60]. A significant reduction in uveitis flares was achieved in 89%. No trial comparing infliximab and INF-α2a has been published but a meta-analysis showed similar remission rates with a higher sustained remission rate in the INF-α2a group compared to infliximab. Infliximab has a faster onset of action. The rate of discontinuation due to adverse effects was similar [26].

Adalimumab is a fully human monoclonal antibody that binds TNFα, with the advantage of a subcutaneous form (80 mg followed by 40 mg every 2 weeks). The two RCTs vs. placebo evaluated the efficacy and safety of adalimumab in patients with noninfectious uveitis [61,62]. A meta-analysis evaluated the efficacy and safety of anti-TNFα agents in the treatment of BD uveitis in 18 clinical trials with a minimum follow-up of 6 months. The overall uveitis remission rate was 68%, visual acuity improvement rate was 60%, central macular thickness reduction was 112.70 μm with a significant corticosteroid-sparing effect [63]. In the event of failure of a first anti-TNFα agent, switching to another may be useful. In a French multicentre study of 124 BD patients, 31 patients received a second line of anti-TNFα agent because of lack of efficacy and/or side effects or because of patients' choice. In terms of ocular manifestations, complete and partial responses were observed in 67 and 28% of patients, respectively [64]. An observational multicenter study compared the efficacy of infliximab versus adalimumab as a first-line treatment for refractory BD uveitis. In both groups, an improvement in all ocular parameters was observed after 1 year of therapy, with a significant difference in the improvement of anterior chamber inflammation, vitritis and best-corrected visual acuity in adalimumab group compared to infliximab group. However, more rapid improvement in anterior chamber inflammation and vitritis was observed with infliximab, even though patients in the adalimumab group did not receive a loading dose. Drug retention rate was higher in the adalimumab group; 17% of infliximab and 14.9% of adalimumab patients discontinued treatment due to lack of efficacy. There was no significant difference between the two treatments in the improvement of vasculitis and macular edema [65].

The cumulative retention rate of adalimumab in 54 patients with BD uveitis patients as 12- and 48-months of follow-up was 76.9 and 63.5%, respectively. It was not influenced by the concomitant use of DMARDs or by the different lines of biologic agents. The retention rate was not reduced in patients with known negative prognostic factors for BD ocular involvement. Similarly, the

cumulative retention rates of infliximab in 40 patients with BD uveitis patients at 12-, 24-, 60- and 120-months of follow-up were 89.03, 86.16, 75.66 and 47.11%, respectively, and were not modified by the use of concomitant DMARDs or by known negative prognostic factors. At 10-year follow-up, discontinuation was due to: secondary failure (6 patients), primary failure (2 patients), adverse events (4 patients), prolonged disease remission (2 patients) and switching to subcutaneous treatment (1 patient) [66].

If ineffective, the increasing the dose of infliximab or reducing the frequency of administration has been described in the treatment of BD uveitis [65]. Similarly, reducing the dose of adalimumab to weekly has recently been described in uveitis with encouraging results, but not specifically in this indication [67].

Etanercept is a fusion protein, which is a soluble receptor that binds to soluble TNFα and prevents it from binding to target cells. There are substantial data suggesting that etanercept is less effective than anti-TNFα antibodies in the treatment of uveitis [68].

Golimumab is a fully human anti-TNFα monoclonal antibody. The constant regions of the heavy and light chains of golimumab are identical in amino acid sequence to those of infliximab. Several case reports and series have demonstrated successful control of severe uveitis with golimumab, particularly in juvenile idiopathic arthritis and BD [69,70].

Certolizumab-pegol is a pegylated recombinant humanized antibody Fab fragment against TNFα. Pegylation of the antibody delays clearance. The reported experience of using of certolizumab-pegol for the treatment of BD uveitis is currently limited.

Anti-TNFα agents are associated with an increased risk of tuberculosis (TB). Screening for latent TB and prophylactic anti-TB treatment for all those found positive is recommended for all patients planning to start therapy with anti-TNFα agents. Patients receiving anti-TNFα agents may develop a variety of serious opportunistic infections. Several demyelinating and neurological events, including exacerbations of preexisting multiple sclerosis, have been reported in patients receiving anti-TNFα agents [71]. There is no conclusive evidence of an increased risk of solid tumors or lymphoproliferative disorders with anti-TNFα agents [71], except for non-melanoma skin cancer [72]. All anti-TNFα agents can induce antinuclear antibodies, but the development of anti-TNFα-induced lupus is less reported. Local complications at the site of drug administration have been frequently reported. Anti-TNFα agents may induce the formation of neutralizing antibodies, resulting in loss of efficacy and the occurrence of infusion reactions [73]. New onset and worsening of congestive heart failure have been reported [74]. A rare and paradoxical adverse event is the development of sarcoidosis during anti-TNFα therapy, as well as the paradoxical occurrence of psoriasis [68].

6.7. Biologics beyond the anti-TNFα agents

6.7.1. Anti-interleukin-6 agents

Tocilizumab (TCZ) is a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody that inhibits the IL-6 pathway by preventing IL-6 from binding to its receptor. In the prospective STOP-Uveitis study, intravenous TCZ was found to be safe and equally effective in both naïve and previously treated patients with non-anterior noninfectious uveitis, mostly idiopathic, including one BD uveitis in 37 patients [75]. In a retrospective study, TCZ was shown to be effective in 5 cases of BD uveitis refractory to IFN-α and anti-TNFα agents, when administered intravenously at 8 mg/kg [76], and in 11 cases of BD uveitis refractory to anti-TNFα agents [77]. A recent review, which aimed was to summarize the articles published on PubMed and EMBASE up to December 2021 reporting on the use of tocilizumab in BD, showed that tocilizumab was effective in 87% of anti-TNF naive patients and in 80% of anti-TNF experienced patients in 25 articles involving a total of 74 patients [78]. Moreover, a recent retrospective multicenter French study, aimed at analysing the factors associated with response to anti-TNFα agents and tocilizumab in patients with 69 refractory uveitic macular edema showed in multivariate analysis that treatment with tocilizumab was independently associated with complete response of uveitic macular edema, compared to anti-TNF-α agents, so, tocilizumab seems to improve complete response of uveitic macular edema compared to anti-TNF-α agents [60].

6.7.2. Anti-interleukin-1 agents

Three anti-interleukin-1 (IL-1) agents have been studied in BD treatment: anakinra an IL-1 receptor antagonist protein; canakinumab a human anti-IL-1β monoclonal antibody, and the recombinant humanised anti-IL-1β gevokizumab. Their place in the treatment of BD uveitis remains unclear. In a randomised, double-masked, placebo-controlled trial in patients with BD uveitis who had experienced an ocular exacerbation, gevokizumab did not significantly reduce the median time to relapse [79]. However, in an open-label study, a single infusion of gevokizumab resulted in a rapid and sustained reduction in intraocular inflammation in seven patients with resistant BD uveitis [80]. Anakinra controlled ocular inflammation in three out of four BD uveitis patients. However, patients relapse over time [81]. In a case series, of 4 patients with recurrent BD uveitis refractory to anti-TNFα agents, 3 showed a complete resolution of ocular inflammation with anakinra, but relapse of uveitis occurred after a mean of 24 weeks [81]. In a retrospective multicenter study, anakinra and canakinumab were shown to be effective and safe in 73% out of 30 patients, including 16 with BD uveitis. The most common adverse events were local skin reactions [82]. In an observational study, anakinra or canakinumab, were evaluated in 19 BD uveitis and improved retinal vasculitis and reduced the rate of uveitis flares. However, no significant effect in macular thickness or visual acuity was observed [35].

6.7.3. Anti-interleukin-17 agents

Secukinumab, is a fully human monoclonal antibody [83]. It has been tested subcutaneously against placebo in three RCTs. The SHIELD study included 118 patients with non-anterior BD uveitis, the INSURE study analysed 31 patients with non-anterior non-BD uveitis and the ENDURE study analysed 125 patients with quiescent non-anterior non-BD uveitis. In the SHIELD study, as in the other two studies, the primary endpoint, of a reduction in the rate of uveitis recurrence was not met. The secondary efficacy data from SHIELD and INSURE may suggest a potential beneficial effect of secukinumab in reducing the use of concomitant immunosuppressants [84]. Nevertheless, a prospective study suggested the efficacy of intravenous secukinumab in the treatment of active chronic noninfectious uveitis, which requires systemic immunosuppression in 16 patients including one with BD uveitis [85]. Similarly, a subsequent prospective study reported that intravenous secukinumab was more effective and better tolerated than subcutaneous secukinumab in 37 patients without BD uveitis in patients with noninfectious uveitis requiring systemic corticosteroid-sparing immunosuppressive therapy [86]. A retrospective study in 15 patients with BD refractory to colchicine, DMARDs, and at least one anti-TNFα agent reported the efficacy and safety of secukinumab in the treatment of mucosal and articular manifestations. One patient with active anterior uveitis at the time of initiation of secukinumab did not experience an ocular flare during follow-up [87].

6.7.4. Anti-interleukin-12/23 agents

Ustekinumab is a fully humanized monoclonal antibody with high affinity for the common p40 subunit of IL-12 and IL-23, which

appears to play a critical role in noninfectious uveitis [88]. Efficacy data in BD uveitis are not yet available.

6.7.5. Other biologics

Rituximab is a B-cell targeted therapy. Davatchi et al., reported efficacy of rituximab in combination with methotrexate versus a combination of pulse cyclophosphamide and azathioprine in BD uveitis with no significant differences between the two groups [89].

Alemtuzumab is a humanised anti-CD52 monoclonal antibody. A single infusion of alemtuzumab was given to 18 patients including five BD patients with ocular involvement, all of whom were in complete or partial remission, at 6 months [90]. In a retrospective study, twenty-one patients out of 32 BD patients had ocular involvement and all of them achieved remission [91].

Abatacept is a T cell targeted therapy, capable of blocking CD-80 and CD-86 on antigen-presenting cells, which are necessary for their activation. Short-term efficacy has been described in a case report of refractory BD-associated scleritis [92].

Daclizumab, a humanised monoclonal antibody that binds CD25 of the IL-2 receptors was studied in a randomised, placebo-controlled trial in 17 BD and was not superior to placebo in preventing relapses and tapering immunosuppressive drugs [93]. It was withdrawn from the market in 2018 after reports of autoimmune encephalitis [94].

6.7.6. Targeted synthetic disease-modifying antirheumatic drugs

Tofacitinib is an anti-Janus kinase (JAK) 1/3 inhibitor. A study in 13 patients with refractory BD suggested its safety and potential efficacy in vascular and joint involvement. No ocular involvement was described [95]. In a case series of 2 patients, tofacitinib was interesting for refractory, noninfectious idiopathic uveitis or scleritis [96]. Encouraging results have recently been reported in uveitis associated with juvenile idiopathic arthritis [97].

Apremilast, a phosphodiesterase 4 inhibitor, modulates cytokines that are upregulated in BD. Its efficacy has been demonstrated in phase 2 and 3 randomised, placebo-controlled clinical trials in BD oral ulcers and it is now approved for this indication. However, its potential role in the treatment of BD uveitis has not yet been investigated [98–100].

7. Conclusion

Despite diagnostic and therapeutic innovations, BD uveitis remains severe. Clinicians need to be aware of the criteria for uveitis in relation to BD. Improvement in multimodal ocular imaging are likely to improve the assessment of patients. However, there are still cases of BD uveitis that are refractory to the recommended treatment and studies comparing the various existing biologics will help to improve management. The therapeutic armamentarium is expanding and alternatives to anti-TNFα or interferon, especially anti-IL-6 agents are likely to be useful in refractory macular edema. Some questions remains, such as the duration of treatment. Clinicians should pay attention to FA leakage, particularly of the optic disc and capillaries or evaluate BOS24 if FA is not available, when following patients with ocular BD after the initiation of systemic treatment to define the best time for therapeutic escalation and avoid visual impairment and improve prognosis.

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Disclosure of interest

The authors declare that they have no competing interest.

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