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THERAPY REVIEW

Biological therapies for the treatment of Behçet's disease-related uveitis beyond TNF-alpha blockade: a narrative review

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Abstract Intraocular inflammation is one of the more relevant complications of Behçet's disease (BD), which tends to respond poorly to different medications. The ocular histopathologic changes are basically identical to those occurring in other organs and consist in a necrotizing leukocytoclastic obliterative vasculitis, which is probably immune complex-mediated and affects both arteries and veins of all sizes. There are growing evidences showing the potential role of biologic agents other than anti-tumor necrosis factor (TNF)-α agents in the management of ocular-BD, which have been collected in this review, including interleukin-1 and interleukin-6 blockade, secukinumab, ustekinumab, daclizumab, rituximab, and alemtuzumab. Further large studies are needed to fully elucidate and establish the clinical efficacy of these different tools in the refractory ocular manifestations of BD.

Keywords Behçet's disease · Uveitis · Eye disease · Treatment · Biologics

Introduction

Behçet's disease (BD) is a complex and not completely defined systemic inflammatory entity sharing autoimmune and autoinflammatory pathogenetic mechanisms [1], and displaying a heterogeneous clinical spectrum which does not simplify its recognition even among experts [2]. The striking clinical diversity goes beyond the "triple symptom complex" described for the first time by Behçet [3], and several organs may be severely affected, with some of them being life-threatening. For instance, in a 2-decade outcome survey of a cohort reporting 387 patients followed at a dedicated center by Kural-Seyahi et al., major vessel (especially pulmonary artery) and central nervous system complications were the leading causes of mortality [4]. Although ocular-BD (OBD) may not affect mortality, a specific involvement of the eye system has a considerable impact on patients' quality of life. The onset of OBD as well as its most severe damage occur within the first year of disease course, preferentially targeting young males, and indeed, disease severity is more evident in this subpopulation [4].

OBD follows a remitting-relapsing trend with an elevated risk of causing perpetual eye structural damage and even vision loss. Azathioprine (AZA) (2.5 mg/kg/day) combined with corticosteroids (level of recommendation 1b) has been suggested as a first-line choice in OBD involving the posterior segment, while recalcitrant cases with

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severe eye disease settled as a visual acuity drop >2 lines in a 10/10 scale and/or retinal disease (macular involvement or retinal vasculitis) should be treated with either cyclosporine A or infliximab (IFX) associated with AZA and corticosteroids [5]. Anti-tumor necrosis factor (TNF) agents should be employed in intolerant subjects or when the disease is poorly controlled by classic immunosuppressive drugs [6–8]. Strong recommendations indicate adalimumab (ADA) or IFX as the first- or second-line corticosteroid-sparing agents in OBD, with the latter showing a response rate of approximately 90% in several small open-label series. Experience with etanercept is limited, and it should be reserved for cases of intolerance to IFX or ADA. With regard to adverse events, an increased risk of infections and autoimmune disease development has been described during treatment. Invasive opportunistic fungal infections and tuberculosis reactivation are also documented as well as the possibility of developing or exacerbating demyelinating and lymphoproliferative disorders [9].

Despite the handful therapeutic armamentarium, BD management can be hard to handle in refractory cases [10], and a few papers have reported multi-drug resistant OBD cases to help defining a general approach in such cases [11–27]. Increasing knowledge on immunology and molecular biology has also led to the actual expansion of therapeutic agents that specifically bind to distinct cytokines and cell surface molecules in BD.

In this review, we focus on the existing evidences regarding the possible role of biologics other than anti-TNF-α agents in OBD.

An extensive research was conducted via PubMed for papers written in English language using the following items/keywords: “biologics”, “anakinra”, “canakinumab”, “gevokizumab”, “tocilizumab”, “secukinumab”, “ustekinumab”, “daclizumab”, “rituximab”, and “alemtuzumab” each combined with “Behcet’s” and “uveitis”. Given the lack of randomized clinical trials and prospective studies, disease rarity, and therapeutic challenges, single cases and short case series have not been excluded.

The melting plot of ocular signs in Behçet’s disease

Although ocular involvement typically occurs in the second-to-fourth year after disease onset, it can represent the initial manifestation in approximately 10–20% of patients with BD [28], showing a higher frequency in HLA-B51 positive patients [29]. BD-related uveitis has a relapsing trend and tends to be more aggressive than in other types of non-infectious uveitis, such as Vogt–Koyanagi–Harada and HLA-B27-associated disorder. This could be at least partially explained by peculiar pathogenetic findings: a diverse intraocular cytokine profile and specific chemokine expression from intraocular lymphocytes; in addition, it has been found a significant higher production of nitric oxide during the autoimmune process towards retinal autoantigens, such as the S-antigen, which shares common amino acid sequences with the HLA-B51 protein [30]. Nitric oxide production is, in fact, stimulated by interferon-gamma [31, 32], which promotes the cytotoxic effect of $CD8^+$ cells [33, 34], representing the major intraocular infiltrate, while $CD4^+$ cells constitute the most representative component in other types of uveitis. Moreover, a specific subtype of NK cells, identified as $CD8^+$ $CD56^+$, has been found largely increased in the aqueous humour of BD patients compared to other uveal disorders [35]. These distinctive characteristics of OBD justify its more aggressive nature and frequent inclination to relapses [30]. Even though T helper (Th)-1 polarization tends to be predominant, Th-17 cells have also been implicated in the intraocular pathogenesis of non-infectious uveitis [32]. This Th-1 and Th-17 response to environmental triggers working in a specific genetic background is believed to generate a peculiar cytokine pattern leading to neutrophil activation, giving rise to the anatomo-pathological hallmark of BD, i.e., a rich neutrophilic and lymphocytic infiltrate targeting vasa vasorum [36]. Indeed, some authors have classified BD as a ‘’neutrophilic vasculitis’’, and the same have found through immunohistochemical studies a prominent hyperexpression of interleukin (IL)-1α in BD patients with highly active disease [37]. The most frequent complication in case of posterior chamber involvement is optic nerve atrophy. In certain cases, it is possible to find iris and retinal neovascularization that are sometimes followed by intravitreal hemorrhage and tractional retinal detachment. Therefore, it follows that BD can present dramatic sequelae, deriving exactly from a marked ocular inflammatory signature, with a relevant sight-threatening risk [28]. Fortunately, new therapeutic alternatives have provided interesting perspectives, and several promising agents have been developed to improve outcome of OBD.

IL-1 inhibiting agents

IL-1 is the dominant cytokine in a host of local and systemic inflammatory disorders. Its non-constitutional isoform IL-1β, mainly produced by monocytes, macrophages, and dendritic cells, usually leads to the expression of several chemokines and secondary inflammatory mediators [38]. A correlation between BD and IL-1β derives mainly from evidences reporting elevated levels of this key-cytokine in the sera of BD patients [39, 40]. After a meticulous evaluation of the available literature, we found a total of 76 BD patients treated with anti-IL-1 agents [11–20, 41–44]. The first paper which investigated the

role of IL-1 blockade in resistant BD uveitis dates back to approximately 5 years ago, when Gül et al. conducted an open-label pilot study, showing an immediate and sustained clinical response in all patients with OBD. In particular, gevokizumab (0.3 mg/kg) was administered as a single intravenous infusion, and the possibility of an eventual second rescue dose was established in the recurrent cases. Five patients received the second infusion, and as much experienced recurrences of BD-related folliculitis and oral ulcers [17].

In the same period, one case report provided a good clinical response to canakinumab (CAN), with prompt resolution of ocular inflammation and visual acuity [20]. Emmi et al. were the first to employ anakinra (ANA) for resistant BD-related uveitis, demonstrating ANA efficacy in treating vitritis and in restoring retinal-blood barrier in both eyes [13]. One year later, one untreatable BD case complicated by several bilateral panuveitis, retinal vasculitis, and concomitant sacroiliitis was successfully treated with ANA, remaining symptom-free for a prolonged period. The efficacy of ANA expanded to sacroiliitis too, and showed a complete resolution of sacroiliac subchondral bone marrow edema on the magnetic resonance imaging [18]. We recently published a case series of nine patients supporting ANA efficacy. Six patients achieved a rapid overall clinical response within 2 weeks from baseline, and five out of nine with OBD displayed a marked and stable resolution of intraocular inflammation. In line with the previous studies, a poor clinical response of mucocutaneous manifestations was also reported, requiring adjunctive treatment with colchicine [14]. More recently, we described a small case series of three BD patients treated with CAN. Two out of three had OBD, and CAN was effective in controlling uveitis [19]. Accordingly, CAN effectiveness was also reported by Emmi et al. in one patient with bilateral retinal vasculitis [12].

One of the largest experiences with IL-1-blocking agents derives from a multi-center retrospective study carried out to evaluate efficacy and safety profile of ANA and CAN in 30 patients. Sixteen of them had ocular involvement (8 panuveitis, 3 posterior uveitis, 2 anterior uveitis, 1 intermediate uveitis, 1 retinitis, and 1 papillitis): the overall cumulative drug survival at 24 months, as assessed by the Kaplan–Meier plot, was 67.8%. With regard to safety profile, no adverse events for CAN were found, and only four site-injection reactions for ANA. No serious adverse events were recorded [42]. This study has also tried to clarify unresolved issues of previous studies [14], such as the optimal dosage and intervals between doses. Increasing the dose of ANA in cases with low response was a valuable option to consider before switching to other biologic agents. Other solutions included the switch to CAN and, in case of partial or unsatisfactory response, shortening the interval between administrations from 150 mg every 8 weeks to 150 mg every 6 weeks could definitely solve the problem [42]. More recently, the role of the IL-1 inhibitors ANA and CAN in the treatment of BD-related uveitis has been evaluated in a multicenter retrospective observational study. Nineteen patients (31 eyes) were enrolled. At 12-month follow-up, ocular inflammatory flares (OIF) significantly decreased from 200 episodes/100 patients/year to 48.87 episodes/100 patients/year ($p < 0.0001$). The frequency of retinal vasculitis significantly decreased between baseline and 3- and 12-month follow-up visits ($p < 0.0001$ and $p = 0.001$, respectively). Moreover, the systemic steroid dosage was significantly decreased at 12-month visit compared to baseline ($p = 0.02$) [44]. The safety and efficacy of ANA and CAN in BD has been recently confirmed in a Nationwide Multi-Center Retrospective Observational Study on the On-Label and Off-Label Use of the IL-1 Inhibitors in Italy among Rheumatologists and Pediatric Rheumatologists. Fifty-six BD patients were enrolled in the study [45]. ANA has been administered with optimal clinical response even as a first-line biologic in one patient with acute papillitis with a concomitant tuberculosis infection, suggesting its usefulness not only in refractory BD patients [43]. Indeed, blocking IL-1 downstream signaling might be safer than TNF-α inhibition, especially in those areas where tuberculosis is still a social evil [46]. All these findings also support the major role of IL-1β in OBD, and its neutralization has shown to induce a remarkable disease control not only in refractory cases but also as a first-line biologic agent [17, 42–44].

Table 1 lists agents targeting interleukin-1 in the treatment of OBD.

IL-6 inhibiting agents

IL-6 is a mainstay cytokine secreted by monocytic lineage, synovial fibroblasts, and T lymphocytes in response to pathogen-associated molecular patterns and damage-associated molecular patterns by Toll-like receptor signaling. This cytokine drives multiple actions, including induction of acute-phase reactants, B lymphocyte differentiation, and induction of $CD8^+$ cells into cytotoxic T cells. It has another very important effect on a T lymphocyte subset: in fact, IL-6 pursuits a pivotal role in $CD4^+$ Th cell differentiation into Th17 cells [47], which have been found to be actively implicated in the pathogenetic routes of many immune-mediated disorders [48]. Precisely, to activate its receptor, IL-6 necessitates the assembly of a hexameric complex structured by two molecules each of IL-6, IL-6 receptor, and gp130 [49], the last being crucial to the downstream cascade of Janus kinase and signal transducer and activator of transcription three pathways [50].

Table 1 Anti-IL-1 inhibition in Behçet's disease with ocular manifestations

First Author (year, reference)	Biologic agent and dosage	Eye involvement (number of patients)	Outcome measures	Mean follow-up period	Safety concerns
Emmi (2014, [12])	CAN 150 mg/8 weeks	1/2 (bilateral RV)	Resolution of symptoms	6 months	–
Emmi (2013, [13])	ANA 100 mg/die	1 (bilateral RV, bilateral vitritis)	BCVA, FA	12 months	No adverse reactions
Cantarini (2015, [14])	ANA 100 mg/die ANA 150 mg/die (case 1) CAN 150 mg/8 weeks	5/9 (1 RV, 1 bilateral panuveitis and papillophlebitis, bilateral panuveitis, 1 panuveitis on the right eye, 2 anterior uveitis)	Ophthalmologic evaluation (case 1, 4, 5, 9) and resolution of symptoms	7.6 months	No sAE, 3 out of 9 patients with mild itchy skin rashes at the site-injection
Gül (2012, [17])	Gevokizumab 0.3 mg/kg as a single intravenous infusion with a second dose (0.3 mg/kg) in case of relapse	7	Ophthalmological examination followed by fundus photography, laser flare photometry for anterior chamber flare scored by SUN working group grading scheme and Ben Ezra et al. scoring system for retinal findings	115 days after the second infusion without the need for a second medication (range 41–197)	No AE
Caso (2014, [18])	100 mg/die	1 (severe bilateral panuveitis with RV)	Resolution of symptoms	6 months	No AE
Vitale (2014, [19])	CAN 150 mg every 6 weeks	2/3 (AU in one patient and PanU right eye in the other)	Resolution of symptoms	9 months	No AE
Ugurlu (2012, [20])	ANA (no response) CAN single dose of 150 mg	1 (bilateral panuveitis with hypopyon, especially in the left eye, RV)	Visual acuity	8 weeks	None reported
Emmi (2016, [42])	ANA 100 mg/die ANA 150 mg/die CAN 150 mg/8 weeks CAN 150 mg/6 weeks	16/30 (8 PanU, 3 PU, 2 AU, 1 retinitis, 1 papillitis, 1 intermediate uveitis)	Resolution of symptoms	24 months	No sAE and no AE for CAN, no sAE and 4 injection-site reactions for ANA
Emmi (2016, [43])	100 mg/die subcutaneously	1 (acute papillitis)	BCVA	Ophthalmologic evaluation every 2 months for 12 months	No AE (no tuberculosis reactivation)
Fabiani (2017, [44]	ANA 100 mg/die CAN 150 mg every 6 week in 3 patients, 150 mg every 8 weeks in 1, 150 mg every 4 weeks in 1 and 300 mg every 6 weeks in 1	19 refractory uveitis (10 Panuveitis, 6 RV, 1 PU, and 2 AU)	Ophthalmologic evaluation for uveitis flare, BCVA, macular thickness on OCT, FA	12 months	No AE

ANA anakinra, *CAN* canakinumab, *PanU* panuveitis, *PU* posterior uveitis, *AU* anterior uveitis, *RV* retinal vasculitis, *BCVA* best corrected visual acuity, *OCT* optical coherence tomography, *FA* fluorescein angiography, *AE* adverse events, *sAE* serious adverse events

Some authors have demonstrated increased levels of IL-6 in the vitreous fluid of patients affected by chronic uveitis, not only idiopathic, but also as part of systemic inflammatory diseases, like sarcoidosis, Vogt–Koyanagi–Harada syndrome, and BD, suggesting a possible beneficial treatment via IL-6-inhibition in refractory uveitis [51, 52]. In this regard, Deroux et al. reported the largest study dealing with refractory BD and treatment with tocilizumab (TCZ). Three out of four patients presented an important eye disease (relapsing posterior uveitis, bilateral posterior uveitis, and bilateral panuveitis), dramatically responding to TCZ. In addition, this drug seemed to influence significantly the necessity for corticosteroid treatment, consenting a remarkable corticosteroid-sparing effect [26]. Other authors have demonstrated similar results when dealing with recalcitrant BD cases, mostly if complicated with ocular involvement [21, 22, 53–55]. Hirano et al. published the first case of refractory BD successfully treated with TCZ, which provided not only uveitis attenuation, but also silenced other clinical manifestations as well [53]. A severe neuro-BD case with concomitant severe eye disease treated with IFX high-frequency regimen, who showed an initially optimal response and unfortunately developed IgA nephropathy, was then treated with TCZ to obtain total remission of each clinical manifestation after the second infusion [54]. An interesting case of refractory BD coexisting with pemphigus foliaceus, reported for the first time by Caso et al., exhibited a striking response to TCZ in terms of symptom-free period and inflammatory markers, which returned within the normal range [21]. On a multicentre study carried out over 124 BD cases, complicated by non-responsive uveitis and treated with IFX or ADA, 7 patients had to switch to other biologics due to intolerance or inefficacy, with 2 of them treated with TCZ. After 1 year of follow-up, a satisfactory clinical outcome was obtained in all cases [22]. An interesting BD case with the previous iridocyclitis and complicated by renal amyloidosis was then treated with TCZ, given its hypothetical direct effect on the glomerular filtration barrier [55]. Calvo-Rio et al. documented the favorable response to TCZ, without any adverse events, of two OBD patients refractory to anti-TNF-α agents, providing further evidence for TCZ therapy [23]. However, refractory OBD is not always responsive to TCZ, as described by Papo et al., during the study of 8 consecutive patients suffering from non-infectious uveitis [56]. Moreover, the other side of the coin is characterized by TCZ relative inefficacy on BD mucocutaneous signs, as described by several experts [24, 57, 58]. Diamantopoulos et al. illustrated a bipolar aphthous deterioration in 1 patient and the recurrence of painful genital ulcers in the other, both treated with TCZ [57]. The worsening of mucosal lesions in BD during TCZ treatment might be explained by the critical role played by IL-6 on skin regeneration and wound healing [59]. To advocate the above-mentioned clinical experience, two recent cases of paradoxical mucocutaneous flares were recorded with worsening of bipolar aphthous lesions [58] and reoccurrence of oral ulcers after the first infusion [24].

BD may be rarely associated with relapsing polychondritis, configuring the so-called "mouth and genital ulcers with inflamed cartilage" (MAGIC) syndrome. TCZ was recently employed for the first time in this rare disorder, though with poor results. The patient presented with a predominant mucocutaneous involvement, which is the less likely responsive to TCZ [60]. Therefore, the subgroup of patients who would mostly take advantage from IL-6 inhibition is yet to be determined.

Secukinumab

IL-17A secreted by Th17 cells has been identified as one of the principal proinflammatory cytokines implicated in different immune-mediated diseases [61], and Th17 represent a new subset of Th cells which mainly produce IL-17, IL-22, TNF-α, and IL-6 [62]. A critical role in modulating Th17 and regulatory T cells belongs to IL-21, while IL-17 production has been found to be significantly upregulated in BD patients with active uveitis [63, 64]. A high Th17/Th1 ratio has been demonstrated in BD displaying both uveitis and folliculitis, suggesting how these manifestations are immunologically different from other disease features [65]. These peculiar findings encourage the use of a specific therapy targeting this molecule, and therefore, blocking IL-17A offers the prospective to disrupt a cytokine network in BD [64].

Secukinumab, a selective high-affinity fully human monoclonal antibody that binds to IL-17A, neutralizing the downstream signals that lead to activation of neutrophils and macrophages [66], was rigorously studied to evaluate the efficacy and safety profile in three randomized clinical trials. Particularly, the SHIELD study investigated 118 BD patients with active uveitis to assess several endpoints. Unfortunately, the primary endpoint did not meet statistical significance; on the contrary, the secondary endpoints identified as withdrawal or reduction of immunosuppressive medications reached a significant difference between secukinumab and the placebo group. However, the authors pointed out different limitations of the study, such as the small sample size, the difference in disease severity, the peculiar interplay between cytokines in individual patients, as well as potentially confounding effects of concomitant immunosuppressive medications [61]. Since IL-17B and IL-17C are also correlated with TNF-α production, it should be possible to target specific isoforms of IL-17 to obtain potentially the desirable therapeutic results [67, 68].

Ustekinumab

IL-23 is a heterodimeric cytokine structured by two subunits, p40 and p19, and is a key-factor for Th17 differentiation, giving rise to the production of IL-17, IL-17F, IL-6, and TNF [69]. Given the upregulated levels of IL-23 in BD [63], ustekinumab, a fully human monoclonal antibody directed against the common shared p40 subunit of IL-12 and IL-23, inhibiting their binding capacity to 12Rβ1 receptor and consequently obstructing their downstream molecular signaling, would provide a satisfactory outcome in BD [70]. Only one BD case in the current medical literature has been treated with ustekinumab so far. Among the cardinal BD manifestations, anterior uveitis was present in combination with psoriasis and hidradenitis suppurativa. This rare triple combination was properly controlled with ustekinumab with the following posologic scheme: 45 mg subcutaneously at week 0, 4, and then every 12 weeks. The patient remained symptom-free and relapse-free for at least 36 months without the need of parallel immunosuppressive drugs. Even though being a single case, the striking therapeutic success suggested to consider this drug as a valid alternative to the actual more consolidated experience with other biologic agents [71].

Daclizumab

Daclizumab, a humanized monoclonal antibody acting against the α-subunit-CD25 of the IL-2 receptor, has the potential to restore homeostasis in dysregulated immune systems, recognizing the high-affinity protein Tac-p55 of IL-2 receptor and inhibiting IL-2 signaling on activated T cells [72]. In addition, it shows an interesting pharmacodynamic effect on $CD56^{bright}$ NK cells by expanding this subpopulation to simultaneously promote autotolerance [73]. Serum levels of soluble IL-2R have been found to be significantly higher in BD patients with active disease [74]. Another study showed that IL-2 gene polymorphisms might be susceptibility factors for both BD and ocular involvement in BD [75]. Despite the above-mentioned considerations, results on daclizumab effectiveness in OBD are conflicting. In a double-blind randomized study aimed to assess safety and efficacy, daclizumab did not manifest any superiority (in terms of ocular attack rates and severity of attacks) over placebo in treating ocular complications of BD [72]. Wroblewski et al. reported the largest series of patients on daclizumab for non-infectious ocular inflammation and used different therapeutic regimens: 8 out of 39 enrolled subjects were diagnosed with BD and represented the group that experienced the highest number of flares [76], highlighting the aggressive nature of BD uveitis. As one patient with BD developed a cerebellar herniation due to abrupt discontinuation of the drug, it was suggested caution when considering cessation of this therapy. Of particular concern were the solid neoplasms developed during a long follow-up period. In particular, four malignancies were detected: skin squamous cell carcinoma, vulvar carcinoma, renal cell carcinoma, and esophageal cancer. However, since the small increased risk did not exceed the estimated therapeutic profits, the decision-making on treating ocular inflammation was not influenced [77]. The most frequent adverse events were of dermatologic nature: eczema, fibrosis, folliculitis, and psoriasis. In their long-term retrospective study, it was concluded that daclizumab stabilized visual acuity and prevented uveitis exacerbations [76].

Table 2 lists all agents targeting interleukin-6, -17, -23, and -2 for the treatment of OBD.

Rituximab

Although BD is a predominantly T cell-driven disease, B cells seem somehow involved. Findings such as overexpression of B lymphocyte stimulator [78, 79] and expansion of oligoclonal B lymphocytes in the synovial fluid of BD patients support a potential pathogenetic role for B cells [80]. Rituximab (RTX), a chimeric monoclonal antibody against CD20, has been used off-label in four BD patients and in one randomized study [27, 81–84]. In two reports, eye involvement was consistently affecting patients' visual prognosis [27, 81]. Sadreddini et al. were the first to use RTX in one case of BD complicated with retinal vasculitis, obtaining a complete remission of ocular inflammation and a marked corticosteroid-sparing effect [81]. Kidd et al. reported a severe resistant neuro-BD with concomitant occlusion of a branch retinal vein: the vision improved to 6/12 in this patient [27]. In a randomized single-blinded control trial, RTX in association with methotrexate was found to be more effective than the combination cyclophosphamide–AZA–prednisone in ameliorating ocular manifestations, with a significant improvement of total adjusted disease activity index. However, the authors concluded that further studies are needed to investigate the best posologic regimen, as they noticed relapses in all patients after a certain period of time, when B cell depletion vanished, suggesting that RTX had to be maintained for a desirable prolonged remission [84]. Several T cell-mediated disorders have been managed with RTX, thus indicating how interfering with the complex T and B cell interplay may allow RTX efficacy also in disorders lacking of a clearly demonstrated autoantibody production. This fact shows also how RTX mechanisms of action are still far from being fully understood [81, 85].

Table 2 Anti-IL-6, -17, -23, and -2 inhibition in Behçet's disease with ocular manifestations

First author (year, reference)	Biologic agent and dosage	Eye involvement (number of patients)	Outcome measures	Mean follow-up period	Safety drug-related concerns
Caso (2013, [21])	TCZ 480 mg i.v./monthly	1 uveitis	Resolution of symptoms	14 months	Well tolerated
Santos-Gómez (2016, [22])	TCZ (not reported)	2 uveitis	SUN Working Group recommendations for intraocular inflammation, OCT for macular thickness and Snellen test for BCVA	1 year	Well tolerated
Deroux (2016, [26])	TCZ 8 mg/kg every 4 weeks	3/4 (1 bilateral posterior uveitis and retinal vasculitis, 1 bilateral panuveitis, 1 relapsing posterior uveitis)	BDCAF, VA, inflammatory grading score for anterior chamber, vitreous haze, FA	12.67 months	No AE/sAE
Hirano (2012, [53])	TCZ 8 mg/kg every 4 weeks	1 uveitis	SF-36, BDCAF, and VA	12 months	Increase of serum LDL
Shapiro (2012, [54])	TCZ 8 mg/kg i.v. every 4 weeks	1 chronic bilateral uveitis	Resolution of symptoms	7 months	–
Papo (2014, [56])	TCZ 8 mg/kg every 4 weeks	1 (bilateral panuveitis and retinal vasculitis)	BCVA, tonometry, slip-lamp examination, funduscopy, FA	6 months	–
Calvo-Río (2014, [23])	TCZ (8 mg/kg every 4 weeks)	2/3 (1 uveitis and the other patient with vitritis, retinal vasculitis and cystoid macular oedema)	BCVA, OCT	7.33 months	No AE/sAE
Redondo-Pachón (2013, [55])	TCZ 8 mg/kg monthly	Iridocyclitis	Resolution of symptoms	1 year	No AE/sAE
Baerveldt (2013, [71])	Ustekinumab 45 mg subcutaneously at week 0.4 and then every 12 week	1 anterior uveitis	Resolution of symptoms	36 months	–
Dick (2013, [61])	Secukinumab 300 mg subcutaneously (s.c.) at baseline, week 1, and week 2 (loading phase); then every 2 weeks, 300 mg s.c. at baseline and week 2 (loading phase); then monthly	79/118 (intermediate uveitis, posterior uveitis, or panuveitis)	Slit-lamp biomicroscopy (anterior chamber cell grade), ophthalmoscopy (vitreous haze grade), BCVA, OCT, FA, and fundus photography	24 weeks	Exacerbation of the disease measured by BDCAF, uveitis, and folliculitis
Buggage (2007, [72])	Daclizumab 1 mg/kg daclizumab infusions given via an intravenous drip over 30 min every 2 weeks for 6 weeks (4-dose induction), then once every 4 weeks for a minimum of 24 months following randomization	9/17 uveitis	BCVA, anterior chamber cells and flare, vitreous haze, dilated fundus examination, FA and fundus photography and quality-of-life issues as measured through the NEI-VFQ25 questionnaire	15 months	Mild infections, primarily upper respiratory and gastrointestinal

Table 2 (continued)

First author (year, reference)	Biologic agent and dosage	Eye involvement (number of patients)	Outcome measures	Mean follow-up period	Safety drug-related concerns
Wroblewski (2011, [76])	Daclizumab 3 different regimens[a]	8 BD panuveitis/39 non-infectious intermediate and/or posterior uveitis	BCVA, anterior chamber cells and flare, vitreous cells and haze, a dilated fundus examination and FA	40.3 months	Dermatologic AE: eczema, fibrosis, psoriasis, folliculitis; abnormal liver function tests; lower extremity edema; upper extremity neuralgia; lymphadenopathy; upper respiratory infections; gastrointestinal infection; 4 malignancies

IL interleukin, *TCZ* tocilizumab, *BCVA* best corrected visual acuity, *BDCAF* Behçet's disease current activity form, *SF-36* short form-36, *NEI-VFQ* National Eye Institute-Item Visual Function Questionnaire-25 (VFQ-25), *OCT* optical coherence tomography, *FA* fluorescein angiography, *AE* adverse events, *sAE* serious adverse events, *VA* visual acuity

[a] (1) I.V. (1 mg/kg) every 2 weeks for 1 month followed by monthly 1 mg/kg dosages, (2) s.c. induction dose of 2 mg/kg IV (limit 200 mg) every 2 weeks for 1 month, followed by maintenance therapy of 1/mg/kg (limit 100 mg) s.c. monthly, (3) high-dose regimen: the initial induction regimen of IV daclizumab, 8 mg/kg on day 0 followed by a second IV dose of 4 mg/kg on day 14, 1 day [participants who showed improvement without serious adverse events and who did not experience a 3 line drop (15 letters) in visual acuity during the induction treatments had the option to receive extended treatments of 2 mg/kg s.c. daclizumab treatments at 4-week intervals for up to 1 year]

Alemtuzumab

Alemtuzumab (CAMPATH-1H) is a humanized monoclonal IgG_1 antibody that binds to CD52, and its effects on $CD52^+$ cells are well-recognized: within a few minutes, after its infusion, there is a considerable T and B cell depletion via antibody-dependent cytolysis and complement-dependent cytolysis. $CD8^+$ T cells are renewed after 31 months, while $CD4^+$ T lymphocytes reach a full repopulation in about 60 months [86]. Perez-Pampin et al. recently reported one patient with BD refractory to different drugs, but responsive to repeated doses of alemtuzumab [25]. Alemtuzumab efficacy may be most likely based on its ability to induce long-term lymphopenia, and considering the non-negligible risk of infections, careful attention should be used for this agent which should be reserved to multi-drug failure cases. Lockwood et al. explored the therapeutic response to lymphocyte depletion in 18 BD patients: 12 out of 18 patients had uveitis and among them, 4 had active ocular inflammation at baseline; after staring alemtuzumab, 2/4 patients were in disease remission at the 6-month follow-up, while the other 2 exhibited a partial disease remission. Overall, a long-term disease remission was accomplished in the majority of patients (13/18); nevertheless, a close monitoring of lymphopenia should be warranted [87]. Another group of refractory BD patients was studied to assess safety and efficacy of alemtuzumab in three different regimens: all patients with severe eye disease (21/33) achieved remission; regarding adverse events, the most frequent were infusion reactions, followed by the onset of symptomatic thyroid disease (4 patients with thyrotoxicosis, 3 with hypothyroidism, and 1 autoimmune thyroiditis) [88]. Other studies have also revealed the association between alemtuzumab and thyroid dysfunctions [89, 90]. A close monitoring of thyroid function may simplify early diagnosis of this potential complication. Other adverse events consisted in infections, including pneumonia and colitis due to *Clostridium difficile*, autoimmune hemolytic anemia, and esophageal carcinoma. The overall response rate was impressive and results were encouraging in terms of corticosteroid-sparing effect [88].

Conclusive remarks

We have herein summarized all current experiences and the most recent evidence regarding the novel approaches with biological drugs other than TNF-α blockers in BD-related uveitis, providing a valuable addition to the actually available therapeutic armamentarium. Nevertheless, our search strategy has some limitations, since only manuscripts written in English language and indexed in PubMed were taken into consideration. Therefore, we might have missed some

potentially valuable studies in other languages. In the current era of evidence-based medicine, physicians fluctuate in a constant therapeutic impasse, especially when dealing with rare diseases, for which the best evidence derives from undersized and, as a result, potentially biased studies. However, the continuous evolution of biotherapy with more refined and specific targeted molecules has led to greatly encouraging results, more than ever in aggressive and unpredictable sight-threatening episodes of occlusive retinal vasculitis in OBD [91, 92]. Indeed, a special attention should be paid to BD-related uveitis, since this is a leading cause of blindness, especially in the younger age. In conclusion, BD and its ocular involvement can be successfully treated with anti-TNF agents, which are currently recommended as a first-line biotherapy: nevertheless, promising outcomes can be obtained with different non-TNF-targeted biologics in the refractory and multi-resistant cases.

Compliance with ethical standards

Conflict of interest All the authors declare that there is no conflict of interest regarding the publication of this paper.

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