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REVIEW ARTICLE

## Biologic Therapy for HLA-B27-associated Ocular Disorders

Julie Gueudry, MD<sup>1</sup>, Jennifer E. Thorne, MD, PhD<sup>2</sup>, Rakesh Bansie, MD<sup>3</sup>, Juergen Braun, MD<sup>4</sup>,  
P. Martin van Hagen, MD, PhD<sup>3</sup>, and Bahram Bodaghi, MD, PhD<sup>5</sup>

<sup>1</sup>Department of Ophthalmology, Charles Nicolle University Hospital, Rouen, France, <sup>2</sup>Department of Ophthalmology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA, <sup>3</sup>Department of Clinical Immunology, Erasmus Medical Center, Rotterdam, the Netherlands, <sup>4</sup>Department of Rheumatology, Rheumazentrum Ruhrgebiet, Herne, Germany, and <sup>5</sup>Department of Ophthalmology, University of Paris, VI Pitié-Salpêtrière Hospital, Paris, France

### ABSTRACT

The treatment of articular and extra-articular manifestations associated with HLA-B27 has undergone dramatic changes over the past two decades, mainly as a consequence of the introduction of biologic agents and in particular anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) agents. Uveitis is known to be the most frequent extra-articular feature in HLA-B27-associated spondyloarthritis. Topical corticosteroids and cycloplegic agents remain the cornerstones of treatment. However, biologic therapy may be effective in the management of refractory or recurrent forms of uveitis. This review gives an update on the management of HLA-B27-associated ocular disorders with biologics, including anti-TNF $\alpha$  agents and non-anti-TNF $\alpha$  biologic modifier drugs. There is an emerging role for newer biologics targeting interleukin-12/23 and interleukin-17 for the treatment of spondyloarthritis but data on their efficacy on anterior uveitis are sparse.

**Keywords:** Anti-TNF $\alpha$ , biologics, HLA-B27, spondyloarthritis, uveitis

Over the past two decades, the introduction of biologic treatments, especially those targeting anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$  agents) has dramatically improved the management of rheumatic diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis (JIA) and the spondyloarthritis (SpA). Anterior uveitis is the most common ocular manifestation in patients affected by SpA. Similarly, anti-TNF $\alpha$  agents have become a valuable addition to the therapeutic armamentarium for patients with associated uveitis that is refractory or intolerant to conventional treatment. Conversely, only few data are available for other biologic agents. The purpose of this review is to summarize current evidence on the use of these drugs, highlighting various possible choices of molecules and treatment strategies in HLA-B27-associated ocular disorders.

### HLA-B27-RELATED DISORDERS

The spondyloarthritis are a group of chronic inflammatory diseases characterized by typical clinical features, such as axial inflammation, enthesitis and extra-articular manifestations associated with the human leucocyte antigen B27 (HLA-B27). Traditionally, the term “spondyloarthritis (SpA)” comprises ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated spondyloarthritis.<sup>1</sup> The Assessment of SpondyloArthritis International Society (ASAS) group has recently developed criteria to classify patients with axial SpA (axSpA) with or without radiographic sacroiliitis, and criteria to classify patients with peripheral SpA. Patients with axSpA can in turn be classified as having ankylosing spondy-

litis, if they have definite structural changes in their sacroiliac joints.<sup>2</sup> There is a strong association of SpA, especially axSpA and AS with the major histocompatibility complex (MHC) class I molecule HLA-B27, which is now also part of the classification criteria for axSpA.<sup>1,3,4</sup> More than half of the patients with axSpA have extra-articular manifestations, such as psoriasis, IBD, and uveitis. The absence of rheumatoid factor was the basis for the SpA group being labeled 'seronegative' – although this is no longer used.<sup>5</sup>

Anterior uveitis is the most common extra-articular manifestation of AS.<sup>6–8</sup> About one-third of the patients with AS have one or more episodes of anterior uveitis. More rarely, intermediate, posterior, or panuveitis may develop, especially in patients with IBD.<sup>9</sup> The typical phenotype of HLA-B27-associated uveitis is an acute unilateral alternating non-granulomatous anterior uveitis, characterized by significant cellular and protein extravasation into the aqueous humor, including occasionally fibrin and even hypopyon in the anterior chamber, with high tendency for recurrences.<sup>10</sup> Each acute episode lasts 4–6 weeks on average. The first episode most commonly occurs between the ages of 20 and 40. The most frequent complications are posterior synechiae, cataract, glaucoma, and the development of chronic anterior uveitis. Sight-threatening posterior segment complications can occur, especially cystoid macular edema (up to 13%).<sup>11–13</sup> Recently, secondary glaucoma was found to be the most common primary cause for irreversible vision loss in patients with HLA-B27-associated uveitis.<sup>14</sup>

The approach is to treat the inflammation aggressively with topical steroids. Nevertheless, systemic treatment with corticosteroids or other immunosuppressive agents has a role in the more severe recurrent or chronic anterior uveitis.<sup>15</sup> Indeed, sulfasalazine may have a beneficial effect in preventing relapses, even though the literature is scarce. Thus, one retrospective study showed that treatment with sulfasalazine can reduce the number of uveitis relapses in spondyloarthritis.<sup>16</sup> Two prospective studies confirmed these results in patients with both spondyloarthritis and idiopathic acute anterior uveitis.<sup>17,18</sup> However, sulfasalazine is known to be effective for peripheral arthritis in SpA, but there is no clear option for the axial manifestations.<sup>19</sup> Otherwise, the use of methotrexate in uveitis associated with SpA is, notwithstanding, controversial with little data in the literature.<sup>20,21</sup> Besides, Kezic *et al.* reported in a murine model resembling spondyloarthritis that interferon gamma (IFN $\gamma$ ) deficiency markedly exacerbates uveitis while ameliorating joint and spine disease, indicating divergent mechanisms that drive diseases in the eye versus joints and spine. Therefore, the clinical response to one specific treatment in one organ does not guarantee a clinical response in another organ.<sup>22</sup>

Episcleritis and scleritis may rarely occur. Finally, reactive arthritis may be associated with conjunctivitis, which may be easily overlooked. For the purposes of this review, we have focused on the treatment outcomes related to HLA-B27-associated uveitis.

## BIOLOGICS

Biologic agents are a class of therapeutic drugs that target different mediators involved in the pathogenesis of human diseases, of which the first biosimilars have been approved by EMA (European Medicines Agency) in 2013,<sup>23</sup> and more recently by the FDA (Food and Drug Administration, USA).<sup>24</sup> Definitions of biologics in common use vary greatly.<sup>25</sup> A proposed definition is: "a biologic is a protein or nucleic acid based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source."<sup>26</sup> In inflammatory diseases, the therapeutic target of a biologic is often a specific protein of the immune system, related to inflammatory processes. This has changed the management of chronic inflammatory diseases in the sense that this approach is much more specific, for example, by directly and rather exclusively targeting TNF $\alpha$  or interleukin 6. Biologics include monoclonal antibodies, soluble receptors, cytokines themselves (such as interferons), and natural cytokine antagonists.<sup>27,28</sup> Monoclonal antibodies can be murine, chimeric (partly murine and human), humanized (only the complementarity determining parts of the variable regions are of mouse-sequence origin), and fully humanized.

An international nomenclature was proposed to establish a common classification.<sup>29</sup> The pharmaceutical company gives usually the prefix and the suffix indicating whether the molecule is a monoclonal antibody (mab) or a soluble receptor (cept). Concerning monoclonal antibodies (mab), the classification also determines the target and the source of production. For example, infliximab is an anti-TNF $\alpha$  antibody used against cells of the immune system (-li-), chimeric (-xi-), and monoclonal (-mab).

The management of anterior uveitis associated with SpA covers both prevention and treatment. There is some evidence on the efficacy of biologics, mainly anti-TNF $\alpha$  agents. This review concentrates on the use of anti-TNF $\alpha$  agents.

### Anti-TNF $\alpha$ Agents and HLA-B27-associated uveitis

#### *Anti-TNF $\alpha$*

Among pro-inflammatory cytokines produced in answer to the stimuli of the innate and adaptive immune system, TNF $\alpha$  plays a key role. Indeed, TNF $\alpha$  is found by diverse methods in the synovial cells of the articular liquid and the synovial membrane it thus constitutes a target of choice to handle the inflammation of SpA. Moreover, there are, currently, substantial data accumulated on the anti-TNF $\alpha$  agents in the treatment of ocular inflammation; particularly, in patients with Behçet disease and JIA, for whom anti-TNF $\alpha$  agents appear to be especially effective. In 2016, EMA and FDA approved adalimumab for

TABLE 1. Anti-TNF $\alpha$  agents currently available.

	Etanercept	Infliximab	Adalimumab	Certolizumab pegol	Golimumab
Year approved for use in the USA	1998	1999	2002	2008	2009
FDA and EMA-approved indications (2016)					
Rheumatoid arthritis	X	X	X	X	X
Juvenile idiopathic arthritis	X		X		
Ankylosing spondylitis	X	X	X	X	X
Psoriatic arthritis	X	X	X	X	X
Plaque psoriasis	X	X	X		
Crohn disease (adult)		X	X	X <sup>a</sup>	
Crohn disease (pediatric)		X	X		
Ulcerative colitis		X	X		X
Hidradenitis suppurativa			X		
Uveitis			X <sup>b</sup>		
Route of administration	SC	IV	SC	SC	SC
Usual posology in adults (mg)	50	3–5 <sup>c</sup>	40	50	400
Usual maintenance dosing interval	1 week	8 weeks	2 weeks	1 month	1 month

IV, intravenous injection; SC, subcutaneous injection.

<sup>a</sup>In 2016, certolizumab pegol had not yet been approved for the treatment of Crohn disease by EMA (European Medicines Agency).

<sup>b</sup>Adalimumab is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

<sup>c</sup>mg/kg body weight.

treating non-infectious intermediate, posterior, and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. These biologics are administered parenterally with intervals ranging from twice a week to every 8 weeks depending on the drug used. There are currently five anti-TNF $\alpha$  agents available (Table 1).

Etanercept is a fusion protein combining two human p75 TNF $\alpha$  receptors extracellular fractions fused to the human Fc portion of IgG1 in order to prolong the half-life. There are substantial data suggesting that etanercept has lower efficacy for treatment of uveitis than anti-TNF $\alpha$  antibodies.<sup>30</sup> It could be explained by the fact that, while both infliximab and adalimumab bind effectively to the soluble and transmembrane forms of TNF $\alpha$ , etanercept forms less stable bonds with TNF $\alpha$ , particularly the transmembrane form.<sup>31</sup> Infliximab is a murine-human chimeric antibody against TNF $\alpha$  and adalimumab is a fully human monoclonal antibody targeting TNF $\alpha$ . Recently, strong recommendations were made to explain that adalimumab and infliximab should be considered as first-line immunomodulatory agents for severe uveitis associated with Behçet disease; and as second-line immunomodulatory agents for the treatment of uveitis associated with JIA and for the treatment of severe posterior uveitis or panuveitis, who failed or are not candidate to immunomodulation with antimetabolite or calcineurin inhibitor.<sup>30</sup>

The most recently approved agents, golimumab and certolizumab pegol, have been used for a shorter period in ocular inflammatory conditions. Golimumab is a fully human anti-TNF $\alpha$  monoclonal antibody. The constant regions of the heavy and light chains of golimumab are identical to those of infliximab in terms of the amino acid

sequence. Since 2011, several case reports and series demonstrated successful control of severe uveitis with golimumab, especially in JIA and Behçet disease.<sup>32–36</sup> Certolizumab pegol consists of a PEGylated recombinant humanized antibody Fab fragment against TNF $\alpha$ . Pegylation of the antibody delays the elimination. Current evidence indicates that certolizumab pegol is an effective option for the treatment of axSpA and PsA.<sup>37,38</sup> The reported experience on the use of certolizumab pegol for treatment of immune-mediated uveitis is currently limited to one retrospective case series (see below).<sup>39</sup>

#### Adverse Events

Anti-TNF $\alpha$  agents carry a specifically increased risk of tuberculosis (TB), usually reactivations of latent disease<sup>40</sup> but also primary infection. Important differences in the risk of latent TB reactivation exist, with the risk being higher with infliximab and adalimumab than with etanercept.<sup>41,42</sup> A recent study showed that tuberculosis incidence rates during infliximab and adalimumab treatment were 2.78 and 3.88 times, respectively, higher than during etanercept treatment in patients with rheumatoid arthritis.<sup>43</sup> Screening for latent tuberculosis and prophylactic anti-TB treatment for all those found positive is recommended for all patients planning to start therapy with anti-TNF $\alpha$  agents. Various and severe non-tuberculous opportunistic infections, especially those with intracellular microorganisms, may develop in patients receiving anti-TNF $\alpha$  treatment. Several demyelinating and neurologic events, including exacerbations of pre-existing multiple sclerosis, were reported in patients receiving anti-TNF $\alpha$  agents.<sup>44–48</sup> There is no conclusive evidence for an increase in risk of solid tumors or lymphoproliferative diseases with anti-TNF $\alpha$  agents,<sup>49,50</sup> except

non-melanoma skin cancer for which anti-TNF $\alpha$  seems to increase the risk.<sup>51</sup> Development of antinuclear antibodies and autoantibodies against double-stranded DNA has previously been reported in response to all anti-TNF $\alpha$  therapies, but may be more common with infliximab. However, “full-blown” anti-TNF-induced lupus or vasculitis are rare.<sup>52</sup> Mechanisms involved in the production of antinuclear antibodies are still unknown.<sup>53</sup> Anti-TNF $\alpha$  may lead to apoptotic cell death and the release of autoantigens that induce antiDNA antibodies in susceptible patients.<sup>54,55</sup> Downregulation of TNF $\alpha$  may be associated with autoantibody production due to the upregulation of IL-10, which activates autoreactive B cells.<sup>53</sup> Local complications at the site of drug administration have been frequently reported. Anti-TNF $\alpha$  agents can induce the formation of neutralizing antibodies, resulting in loss of efficacy and the appearance of infusion reactions.<sup>56</sup> New onset and worsening of congestive heart failure have been reported.<sup>49</sup> A rare and paradoxical adverse event is development of sarcoidosis during anti-TNF $\alpha$  therapy,<sup>57–60</sup> as well as paradoxical occurrence of psoriasis.<sup>61</sup>

The issue of whether anti-TNF $\alpha$  agents cause ocular inflammation remains debated.<sup>62</sup> There are several case reports of uveitis developing in patients treated with anti-TNF $\alpha$  therapy. Most cases have been reported with etanercept.<sup>63–69</sup> However, as etanercept was shown to be less effective than anti-TNF $\alpha$  antibodies to prevent and to control uveitis, does it induce uveitis or does it only fail to prevent their occurrence? Nonetheless, Lim *et al.* reported 26 cases of uveitis presumably associated with anti-TNF $\alpha$ , in which no known condition predisposing to uveitis was identified.<sup>62</sup> However, the authors conceded that there was limited information on the clinical diagnoses available.

### Anti-TNF $\alpha$ Agents for Acute HLA-B27 Uveitis Attack

Actually, in acute HLA-B27-associated uveitis, topical or periocular corticosteroids and mydriatic agents can manage most acute attacks. Nevertheless, oral administration of corticosteroids may be required in cases of recalcitrant inflammation. However, in some patients, steroids use is restricted owing to a lack of response, intolerance, or side-effects. In these situations, infliximab may be effective in treating an acute uveitis attack.<sup>70–72</sup> El-Shabrawi and Hermann described a prospective non-comparative case series of seven consecutive patients with acute onset of HLA-B27-associated anterior uveitis who received a single infliximab infusion of 10 mg/kg body weight. Total resolution of the uveitis was achieved with infliximab as the sole anti-inflammatory drug in all but one patient. The median duration of uveitis was  $8 \pm 12$  days. A relapse was seen in four patients after a median period of  $5 \pm 6.4$  months.<sup>72</sup> Rudwaleit *et al.* reported, in patients with active AS during adalimumab treatment, that the rate of anterior uveitis flares was reduced by 50% in 28 patients with

symptomatic anterior uveitis at baseline ( $p = 0.001$ ) and by 45% in 43 patients with chronic uveitis ( $p = 0.002$ ).<sup>73</sup>

Use of golimumab in a case of refractory HLA-B27 uveitis was recently reported<sup>74</sup> and Faez *et al.* showed that golimumab may be useful for uveitis associated with SpA (three patients).<sup>75</sup> Moreover, golimumab efficacy was noted in three out of four patients with HLA-B27 uveitis, who had inadequate response to previous biologics.<sup>35</sup> Golimumab therapy achieved complete control of inflammation in 12/13 patients (92.3%) after 6 months of treatment in a retrospective study, including patients with PsA (two patients) or AS (two patients).<sup>76</sup> More recently, a multicenter study reported in EULAR (European League Against Rheumatism) Congress 2015 showed that golimumab seemed to be effective and safe in refractory uveitis associated with AS.<sup>77</sup> In this retrospective study, after a mean follow-up of 13 months, 7/9 patients were on remission.

The reported experience on the use of certolizumab pegol for treatment of immune-mediated uveitis is currently limited to one retrospective case series. Seven patients with infliximab and adalimumab refractory and/or intolerant uveitis were treated and five patients achieved quiescence. Four out of the seven patients presented uveitis associated with AS or PsA and two patients showed only a partial response.<sup>39</sup> However, data is too limited to make any substantial comments regarding this agent in HLA-B27-associated uveitis treatment.

As a result, expert panel recommendations published in 2014 concerning spondyloarthritis or HLA-B27-associated uveitis explained that infliximab or adalimumab may be used as corticosteroid-sparing treatment for patients with chronic uveitis resulting from spondyloarthritis.<sup>30</sup>

### Anti-TNF $\alpha$ Agents in Preventing HLA-B27 Uveitis Relapses

The main interest of anti-TNF $\alpha$  agents concerning HLA-B27-associated uveitis lies in preventing relapses of uveitis. A large retrospective study suggested that infliximab and adalimumab reduced the rate of uveitis, while the frequency of uveitis in patients with spondyloarthritis treated with etanercept remained unchanged.<sup>78</sup> In a large meta-analysis, concerning data from four placebo-controlled studies with anti-TNF agents in AS (two with etanercept and two with infliximab) and three open-label studies, infliximab and etanercept therapies seem to reduce the incidence of uveitis versus placebo (6.8 per 100 patient-years and 15.6 per 100 patient-years, respectively). Furthermore, infliximab appeared to be more effective than etanercept, even though the difference between them did not reach statistical significance (3.4 per 100 patient-years and 7.9 per 100 patient-years, respectively) ( $p = 0.08$ ).<sup>79</sup>



Similarly, adalimumab was evaluated from data of 1250 patients with active AS in a prospective open-label study. The anterior uveitis flare rates before adalimumab treatment were 15 per 100 patient-years. Adalimumab achieved an approximately 50% reduction in uveitis flares.<sup>73</sup> Finally, a recent cohort study about 2115 patients indicated that initial adalimumab therapy is associated with a significantly lower risk of developing uveitis compared to initial etanercept therapy in anti-TNF-naïve patients diagnosed with AS and no prior history of uveitis.<sup>80,81</sup>

Furthermore, an open-label, phase IV study investigating the difference in the annual incidence rate of uveitis attacks in participants with AS before treatment and after treatment with golimumab is underway (<https://clinicaltrials.gov>; NCT01668004). Finally, a recent study suggested that certolizumab pegol had an impact on reducing uveitis flares in axial spondyloarthritis. However, the number of patients experiencing uveitis flares was low and there was an imbalance in the number of patients with prior history of uveitis between the placebo and the certolizumab pegol group. Prospective studies are mandatory to confirm or to invalidate these findings.<sup>82</sup>

Hence, the use of infliximab or adalimumab should be considered first rather than using a soluble TNF receptor, in “spondyloarthritis patients” with a history of uveitis, although there are no prospective head-to-head studies. Furthermore, given collective clinical experience in uveitis and other conditions, switching between anti-TNF $\alpha$  therapies appears to be efficient and safe in cases of primary or secondary failure permitting to prolong their use.<sup>83</sup>

It is however necessary to note that a meta-analysis published by Wu et al.<sup>84</sup> from six selected randomized controlled trials<sup>38,85–88</sup> shows contradictory results. In this study, 663 patients “etanercept vs placebo” and 436 patients “monoclonal anti-TNF $\alpha$  antibodies vs placebo” were analyzed. Subgroup analysis showed TNF $\alpha$  receptor fusion proteins to be more efficacious than placebo ( $p = 0.04$ ); whereas monoclonal anti-TNF $\alpha$  antibodies did not significantly differ from placebo. These surprising results compared with previously published studies might be explained by the fact that only randomized controlled trials, with a short follow-up (range: 12–30 weeks) limiting the number of “uveitis events”, were analyzed. It is also important to note that the absence of systematic ophthalmologic evaluation, and the analysis of a study involving certolizumab for which intraocular penetration might be modified due to the addition of a macromolecule to increase its half-life may partly explain the discrepancies.<sup>38</sup>

## Non-anti-TNF Biologic Modifier Drugs and HLA-B27-associated Uveitis

TNF $\alpha$  inhibitors have dramatically improved the treatment of SpA patients. However, as up to 40% of patients do not respond well to anti-TNF $\alpha$  treatment, either due to

adverse reactions and intolerance or due to inefficacy, there is still a need for other and better therapeutic compounds.<sup>89</sup> Are these new molecules going to be effective on treatment and prevention of uveitis flares? Only very few data regarding HLA-B27-associated uveitis management with other biologic agents are available.

## Anti-interleukins (IL)

Anti-interleukins therapies, which could be used in uveitis, are summarized in Table 2. The major interest has recently focused on therapies targeting the IL-23/IL-17 axis, as there is an extensive rationale for targeting this pathway in SpA. First, abnormal withdrawal of the molecule HLA-B27, which cannot migrate correctly and stays in the endoplasmic reticulum, may lead to an inflammatory answer (production of IL-23). Second, cell surface HLA-B27 homodimers may induce stimulation of the innate immunity. These homodimers can interact with KIR3DL2 (killer-cell-Ig-like receptor), expressed by natural killer cells and a minority of lymphocytes T. The rate of cells TCD4 + KIR3DL2 is increased in the blood of the subjects SpA-B27+. These cells, after interaction with HLA-B27 homodimers, produce high quantities of IL-17.<sup>89,90</sup> Third, plasma IL-17 levels are high in patients with AS but not in healthy controls or in patients with rheumatoid arthritis. IL-17 levels in joint fluid are higher in reactive arthritis and undifferentiated spondyloarthritis than in rheumatoid arthritis.<sup>91</sup> Furthermore, several data suggest that IL-17 is implicated in the pathogenesis of uveitis. Indeed, serum IL-17A levels were found to be elevated in uveitis patients, particularly in active patients,<sup>92</sup> and increased IL-17A transcript was detected in retinas of mice during experimental autoimmune uveoretinitis.<sup>93</sup>

### Anti-interleukin-17 Therapy

Secukinumab is a fully humanized, anti-IL-17A monoclonal antibody. Secukinumab reduced clinical or biologic signs of active AS and psoriatic arthritis in phase III studies.<sup>94</sup> There are no reports on its use in HLA-B27-associated uveitis management at present. A prospective study showed its efficiency in the treatment of non-infectious uveitis in 13 out of 16 patients (intravenous secukinumab);<sup>95</sup> however, its efficacy was not confirmed in three clinical trials assessing subcutaneous secukinumab against placebo in management of uveitis associated with Behçet disease and other non-infectious uveitis (unknown HLA-B27 status).<sup>96</sup> In contrast, intravenous secukinumab was reported to be effective and well-tolerated in patients with non-infectious uveitis (unknown HLA-B27 status) who required systemic corticosteroid-sparing immunosuppressive therapy.<sup>97</sup>

### Anti-interleukin-12/23 Therapy

Ustekinumab is a fully humanized monoclonal antibody with high affinity for the common p40 subunits

TABLE 2. Anti-interleukin therapies and HLA-B27 ocular disorders.

Molecules	Structure	Target	Route of administration and maintenance dosing interval	FDA and EMA-approved indications in 2016	Principal side-effects
Anakinra	Receptor antagonist	IL-1 receptor	Daily SC	RA CAPS	Injection site reactions Infections, cellulitis Neutropenia
Canakinumab	Fully human monoclonal antibody	IL-1 $\beta$	Every 8 months SC	CAPS JIA Gouty arthritis <sup>a</sup>	Injection site reactions Infections Neutropenia
Tocilizumab	Humanized monoclonal antibody	IL-6 receptor	Monthly SC or IV	RA JIA (polyarticular and systemic forms)	Infections Injection site reactions Hepatitis cytolytic Neutropenia, thrombocytopenia
Secukinumab	Fully human monoclonal antibody	IL-17A	Monthly SC	Psoriasis Psoriatic arthritis AS	Hypercholesterolemia Gastrointestinal perforation (rare) Infections Hypersensitivity reaction
Ustekinumab	Fully human monoclonal antibody	IL-12/23	Every 12 weeks SC	Psoriasis Psoriatic arthritis	Infections Hypersensitivity reaction including anaphylaxis

of IL-12 and IL-23. There are no reports on its use in HLA-B27-associated uveitis management at present. Recent studies reported a beneficial effect of ustekinumab in the treatment of PsA and axial disease in AS patients.<sup>98–101</sup>

#### Other Anti-interleukin Therapy

Biologic therapies targeting several key proinflammatory cytokines, such as blockade of IL-1 with anakinra<sup>102,103</sup> and inhibition of IL-6 with both tocilizumab and sarilumab (human monoclonal antibody against the interleukin-6 receptor), failed to show clinical efficacy in AS.<sup>104,105</sup> Uveitis flares are not detailed in these studies. On the contrary, tocilizumab was reported with success in case reports and case series about management of refractory uveitis associated with JIA, birdshot retinochoroidopathy, Behçet disease-associated uveitis and idiopathic panuveitis.<sup>106–112</sup> Interestingly, among these studies, only one patient with an associated spondyloarthritis and panuveitis was successfully treated (HLA-B27-positive).<sup>107</sup> On the contrary, Wendling et al. reported a first episode of uveitis in a patient being treated for HLA-B27-positive AS.<sup>113</sup>

#### Other Molecules

cT-cell and B-cell targeted therapies, such as Rituximab (CD20-directed cytolytic antibody)<sup>114</sup> and Abatacept (soluble fusion protein able to block CD-80 and CD-86 present on antigen-presenting cells),<sup>115,116</sup> only showed modest, if any, therapeutic efficacy in SpA. T-cell and B-cell targeting therapies failure might be consistent with the concept that SpA belongs to the class of autoinflammatory rather than autoimmune disorders.<sup>117</sup> No data are available concerning possible associated uveitis in these studies.

### DISCUSSION

The treatment of extra-articular manifestations associated with HLA-B27 has undergone a complete revolution in the past two decades, mainly as a consequence of the introduction of biologic therapies and principally anti-TNF $\alpha$  agents. The current data on the use of biologics in the management of uveitis associated with HLA-B27 are relatively restricted and most of the available data concentrate on the prevention of uveitis flares. Even though, there are no prospective head-to-head randomized comparative studies comparing efficacy of anti-TNF $\alpha$  agents in HLA-B27 uveitis management, infliximab and adalimumab are generally accepted to be more effective than etanercept. Because golimumab requires less frequent injections, it might have potential application in uveitis as well. When patients become refractory to

treatment with anti-TNF $\alpha$  agents, or when there is a formal contraindication for their use, there is a need for the use of new therapeutic options, targeting other cytokines or their proinflammatory pathways. Only very few data are available with other biologic agents, but data from other immune-mediated inflammatory diseases keep a promise for non-infectious inflammatory ocular diseases.

### DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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