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REVIEW

A Review of the Landscape of Targeted Immunomodulatory Therapies for Non-Infectious Uveitis

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ABSTRACT

Systemic immunomodulatory therapies are the principal means of managing non-infectious uveitis. This review aims to explore the current landscape of systemic uveitis treatments, including biologic therapies and the advent of biosimilar therapies.

Keywords: Biologics; Biosimilars; Interferon; Interleukins; Non-infectious uveitis; TNFα inhibitors

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INTRODUCTION

Uveitis is a group of diseases characterised by inflammation of the uveal tract and neighbouring structures. Inflammation affecting the posterior segment of the eye involving the choroid, vitreous and retina may lead to secondary damage of photoreceptors and, consequently, loss of vision [35]. Uveitis accounts for 10–15% of bilateral blindness in the developing world, making it the fourth most common cause of bilateral vision loss and the second most common treatable cause [70, 92]. The incidence of uveitis is estimated at 52.4 per 100,000 in the USA and aetiologies are grouped into infectious, non-infectious and a third, less populous group of 'masquerade' syndromes which includes malignancies [28]. Since uveitis typically affects the working age group (20–-60 years of age), not only may quality of life be severely impacted but there may also be profound socioeconomic consequences for affected patients. This impact has stimulated the development of more effective treatment strategies for uveitis [4, 20, 94].

Non-infectious uveitis (NIU) arises from an inappropriate inflammatory response mounted by the immune system against antigens within the uvea and retina [6, 13, 35]. It may manifest as part of an autoimmune syndrome (e.g. Behçet's disease [BD], Vogt-Koyanagi-Harada [VKH] disease, and sarcoidosis) or is termed idiopathic when disease is isolated to the eyes [80]. Since

this article focuses solely on non-infectious causes of uveitis, we will use the term uveitis synonymously with NIU.

The goal of therapy in uveitis is remission of active inflammation, preservation of visual function and prevention of tissue damage to the retina or optic nerve, all with the minimum of side-effects. Up until recently, corticosteroids have been the only globally licensed therapy for uveitis. Although successful in controlling inflammation, their long-term side-effects limit therapeutic application, requiring alternative or additional immunosuppressant or immune-modifying therapies.

Systemic therapies for uveitis may be broadly divided into conventional immunosuppressant agents and newer, targeted immunomodulatory therapies (IMTs). The first immunosuppressant to be used in humans with uveitis was the T-cell inhibitor, cyclosporine, whose efficacy was demonstrated in animal models and a clinical trial [71, 72]. Based upon this success, a range of steroid-sparing agents (in particular, tacrolimus, methotrexate and mycophenolate mofetil) traditionally used in other systemic immune-mediated diseases were adopted over the past 40 years. These have accrued evidence for efficacy through prospective and retrospective studies, but few placebo-controlled or comparative trials [65, 75, 79, 98]. Although the antimetabolites (methotrexate, mycophenolate mofetil and azathioprine) and calcineurin-mediated T-cell inhibitors (cyclosporine and tacrolimus) are accepted as standard of care for NIU, these conventional immunosuppressants fail to adequately control uveitis in up to 40% of cases due to either poor efficacy or side-effects [34, 66, 76]. Moreover, they remain unlicensed by regulatory authorities for use in uveitis [66]. Therefore, there is a great need for more effective corticosteroid-sparing treatment for uveitis with an acceptable side-effect profile.

The discovery that the selective antagonism of TNFα ameliorates joint inflammation in a mouse model of rheumatoid arthritis and its subsequent successful translation into humans using recombinant antibody technology has heralded the growth of therapies that modulate specific cytokine pathways [17, 60]. These treatments target cytokine receptors, cytokines or immune cell surface markers in several inflammatory diseases and are known as biologic therapies because they are generated within living systems. Experimental animal models of uveitis have enabled the translation of TNFα biology to uveitis patients [17, 18]. Interrupting or modulating specific cytokines of the immune system has generated newer, targeted therapies which aim to deliver predictable disease remission without compromising tolerability. In this manner, several potential future therapies are in development which target specific lymphocyte populations or key constituents of the inflammatory cascade.

The landscape of therapeutics for uveitis has undergone substantial change in recent years, partly due to the revolution in biologic therapies but also due to interest in local therapies for treatment of intraocular inflammation [43, 56]. We will present a brief overview of the evolution of uveitis therapies through the lens of key clinical trials, aimed at readers unfamiliar with uveitis therapies and for practitioners requiring an update on therapeutic modalities under current or recent investigation. The focus will be principally on systemic uveitis therapies from 2011 onwards based on a review of published literature and two clinical trial registries (clinicaltrialsregister.eu and clinicaltrials.gov). We will also consider the role of biosimilar drugs since the cost of treatment is an important contributor to the accessibility of therapies to patients.

METHODS

A literature review was conducted through comprehensive searches of five databases (EMBASE via Ovid, MEDLINE, ClinicalTrials.gov, EU Clinical Trials Register, and ISRCTN Registry) from January 2011 onwards. Search strategy and inclusion criteria are detailed in Supplementary Materials. A summary of clinical trials reported in this article are located in Table 1. Unreported clinical trials are summarized in Supplementary Materials. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Table 1 Completed and reported clinical trials in non-infectious uveitis since 2011

Name of study	Study population	*N*	Primary outcome(s)	Duration of follow-up	Primary result
Adalimumab (Humira; AbbVie, IL, USA)					
VISUAL-I					
Jaffe [40] NCT01138657	Active NIU refractive to > 2 weeks of treatment with prednisone	217	Time to treatment failure, defined as: (1) new active, inflammatory chorioretinal or retinal vascular lesions relative to baseline; (2) worsening of best corrected visual acuity (BCVA) by > 15 letters relative to best state achieved; (3) achieving > 0.5 + AC cell grade or > 0.5 + vitreous haze score	80 weeks	(1) In comparison to the placebo treatment, participants receiving adalimumab (80 mg SC baseline loading dose and 40 mg every other week) were 50% less likely to have treatment failure (hazard ratio: 0.50; 95% CI 0.36–0.70; $P < 0.001$). (2) The median time to treatment failure was greater in group 2 (24 weeks) than with the placebo group (13 weeks). (3) The adalimumab treatment group experienced a higher incidence of mild/moderate and serious adverse events than group 2 (1052.4 vs. 971.7 mild/moderate and 28.8 vs. 13.6 serious adverse events per 100 person years)
VISUAL-II					
Nguyen [68] NCT01138657	Quiescent NIU controlled by prednisone	226	Time to treatment failure, defined as: (1) New active, inflammatory chorioretinal or retinal vascular lesions relative to baseline; (2) Worsening of best corrected visual acuity (BCVA) by > 15 letters relative to best state achieved; (3) Achieving > 0.5 + AC cell grade or > 0.5 + vitreous haze score	80 weeks	(1) In comparison to the placebo group, adalimumab treatment (80 mg SC baseline loading dose and 40 mg every other week) exhibited a significantly increased time to treatment failure (> 18 months compared to 8.3 months, respectively). Treatment failure occurred in a greater proportion of the placebo group (55%) than with adalimumab treatment (39%; hazard ratio of 0.57 (95% CI 0.39–0.84; $P = 0.004$), i.e. 43% risk reduction of adalimumab. (2) 40th percentile for time to treatment failure was greater in group 1 (10.2 months) compared to the placebo control group (4.8 months)
SYCAMORE					
Ramanan [78] ISRCTN10065623	Active juvenile idiopathic arthritis (JIA)-associated uveitis refractive to methotrexate treatment	154	Time to treatment failure, defined as: (1) anterior segment inflammatory score; (2) use of concomitant medications; (3) intermittent or continuous suspension of study treatment for a cumulative period longer than 4 weeks	3 years	(1) The group receiving adalimumab (< 30 kg: 20 mg/0.8 mL; > 30 kg: 40 mg/0.8 mL; SC every 2 wk for 18 mo followed by methotrexate alone) exhibited a 75% reduction of treatment failure in comparison to placebo (hazard ratio 0.25; 95% CI 0.12–0.49; $P < 0.0001$). (2) A similar rate of adverse events was reported between the two treatment groups (adalimumab: 88.3%; placebo: 90%)

Table 1 continued

Name of study	Study population	*N*	Primary outcome(s)	Duration of follow-up	Primary result
Certolizumab Pegol (CZP; Cimzia, Brussels, Belgium)					
RAPID-axSpA					
Rudwaleit [81] NCT01087762	Active axial spondyloarthritis	352	Improvement in the following domains: (1) patient's global assessment of disease activity; (2) pain assessment; (3) Bath ankylosing spondylitis functional index; (4) Bath ankylosign spondylitis disease activity index	96 weeks	(1) During the double-blind phase (initial 24 weeks), participants receiving Certolizumab Pegol [400 mg at weeks 0, 2 and 4 (loading dose) followed by either 200 mg every 2 weeks or 400 mg every 4 weeks] exhibited a lower rate of uveitic flares (3.0 per 100 patient years; 95% CI 0.6–8.8) than with placebo treatment (10.3; 95% CI 2.8–26.3)
Secukinumab (Cosentyx; Novartis Pharmaceutical, Basel, Switzerland)					
Letko [51] NCT00685399	Active NIU, posterior uveitis, or panuveitis	37	Percentage of patients with treatment response defined as either: (1) > 2-grade reduction in vitreous haze score or trace of absent vitreous haze in the study eye without an increase in corticosteroid dose and without uveitis worsening; (2) reduction in corticosteroid dosages to pre-specified levels without uveitis worsening	85 days	(1) A greater rate of treatment response was observed with both secukinumab administered 30 mg/kg IV and 10 mg/kg IV when compared with the 300 mg SC doses (72.7% and 61.5% vs. 33.3%, respectively). (2) A similar trend was observed with the rate of remission (27.3% and 38.5% vs. 16.7%, respectively)
SHIELD					
Dick [19] NCT00995709	Behçet's patients with active NIU	118	Rate of recurrent ocular exacerbations during 24 weeks of treatment	24 weeks	(1) There was no difference in primary outcomes between placebo, those receiving secukinumab 300 mg SC every 2 weeks and every 4 weeks ($P = 0.445$ and 0.170, respectively). (2) At week 24, there were statistically significant reductions in composite immunosuppressive medication scores in both secukinumab treatment groups when compared to the placebo group (secukinumab every 2 weeks vs. placebo, $P = 0.034$; secukinumab every 4 weeks vs. placebo, $P = 0.015$). (3) No statistically significant differences were observed in the change from baseline BCVA or vitreous haze score between secukinumab treatment groups and placebo group

Table 1 continued

Name of study	Study population	*N*	Primary outcome(s)	Duration of follow-up	Primary result
INSURE					
Dick [19] NCT01095250	Behçet's patients with quiescent NIU	31	Mean change in vitreous haze grade from baseline to 28 weeks	24 weeks but recruitment was terminated early following analysis of the SHIELD study	No statistically significant differences were observed in primary endpoint between secukinumab treatment groups (2 weeks of secukinumab 300 mg SC weekly followed by 300 mg SC every 2 weeks or 4 weeks) and the placebo group
ENDURE					
Dick [19] NCT01032915	Patients with with quiescent NIU	125	Time to recurrence of active uveitis during 24 weeks of treatment	24 weeks but recruitment was terminated early following first analysis	No statistically significant differences were observed in the primary outcome between the treatment (2 weeks of secukinumab 300 mg SC weekly followed by: 300 mg SC every 2 weeks; 300 mg SC every 4 weeks; or 150 mg SC every 2 weeks) and placebo
Sirolimus (Rapamune; Pfizer Inc., CT, USA)					
SAKURA					
Nguyen [67] NCT01358266	Active NIU	347	Proportion of patients with vitreous haze scores of 0 without use of rescue therapy	24 months	(1) In comparison to intravitreal injection with an active control (44 µg, 10.3%), a greater percentage of the group receiving intravitreal injection with 440 µg sirolimus achieved the primary outcome (22.8%; $P = 0.025$), which was not the case in the group receiving 880 µg (16.4%; $P = 0.182$). (2) While the majority of patients receiving corticosteroids at baseline in the active control group tapered off corticosteroids successfully (63.6%), a greater proportion was observed in the group receiving 440 µg sirolimus (76.9%) and 880 µg (66.7%). However, analysis for statistical significance was not carried out on these data

Table 1 continued

Name of study	Study population	*N*	Primary outcome(s)	Duration of follow-up	Primary result
SAVE-2					
Nguyen [69] NCT01280669	Active NIU	24	Percentage of patients in which vitreous haze scores decreased by > 2		Participants receiving 440 μg of intravitreal sirolimus (administered on day 0, 30, 60, 90, 120 and 150) had a decrease in vitreous haze score of ≥ 2 steps (63.6%) than those receiving 880 μg (50%), but was not statistically significant ($P = 0.695$)
Cyclosporine (Neoral; Novartis, Basel, Switzerland)					
Shalaby [86]	Active NIU	39	Changes in the visual acuity (VA) converted to logarithm of the minimum angle of resolution (logMAR)	12 months	Visual acuity improvement doubled in both groups with insignificant difference in the mean change in vision for the control group (cyclosporine 4 mg/kg/day adjusted to 100–250 ng/ml with placebo) compared with the treatment group (cyclosporine and diltiazem 30 mg BD if < 60 kg and 60 mg for > 60 kg; $P = 0.690$)
Interferon beta (Rebif; Merck-Serono)					
Mackensen [59] NCT00344253	Active NIU and macular oedema	19	Mean change in BCVA on Early Treatment Diabetic Retinopathy (EDTRS) charts at 3 months as compared with baseline	3 months	(1) The interferon-beta treatment group (44 μg SC 3 times weekly) had a greater mean visual acuity improvement (0.31; $P = 0.0435$) in comparison to the control group receiving methotrexate SC 20 mg weekly (0.09). (2) Mean macular thickness decreased in the interferon beta group (206 μm); methotrexate was associated with methotrexate treatment (47 μm; $P < 0.0001$)
Corticosteroid implant					
HURON Lowder [56] NCT00333814	Active NIU	229	Proportion of eyes with a vitreous haze score of 0 at week 8	26 weeks	A greater proportion of eyes with the 0.7-mg and 0.45-mg dexamethasone implant had a vitreous haze score of 0 at week 8 than the sham implant (47% and 36% vs. 12%, respectively; $P < 0.001$)
MUST Kempen [43] NCT00132691	Active NIU	225	Mean change in BCVA (BCVA) from baseline	24 months	Mean improvement in BCVA following fluocinolone acetonide implant of 0.59 mg (+6.0) and systemic therapy (+3.2). A statistically significant difference was not present between the two groups ($P = 0.16$)

TNFα Inhibitors

Of the five available TNFα inhibitors (TNFi) in clinical use, adalimumab (Humira; AbbVie, North Chicago, IL, USA) has USFDA and European Medicines Agency (EMA) approval in adults with uveitis refractory to corticosteroids. Adalimumab is a subcutaneously administered, fully humanised anti-TNFα monoclonal antibody. It is usually given every 2 weeks. Other TNFi include infliximab, certolizumab, golimumab and etanercept.

Infliximab

Infliximab (Remicade, Janssen Biotech Inc., Horsham, PA, USA) is a human-mouse chimeric IgG monoclonal antibody directed at TNFα in both soluble and transmembrane forms. It is administered intravenously and was the first TNFα inhibitor to be used in uveitis. The evidence base for infliximab principally consists of small prospective open-label trials in BD, in which adjunctive use of infliximab led to rapid remission in up to 86% of patients with refractory disease [1, 26], a reduction in ocular inflammation scores comparable with the effect of intravenous corticosteroids, and more rapid resolution of cystoid macular edema [61]. Infliximab is now recommended for sight-threatening ocular disease secondary to BD as a first- or second-line therapy, although it is only licensed for first-line treatment in Japan [52]. For ocular inflammatory diseases as a whole, the efficacy of infliximab has been estimated at 77% overall based on a single prospective trial [90]. Other smaller studies have also reported efficacy with infliximab for juvenile idiopathic arthritis (JIA) uveitis and birdshot retinochoroidopathy [3, 42]. Treatment with systemic infliximab carries a higher adverse event rate than for other TNFα inhibitors, mainly due to infusion reactions which are attributed to immunogenicity of the mouse component of the antibody. Interestingly, a pilot study of intravitreal infliximab for NIU showed limited efficacy with respect to either vitreous haze or resolution of cystoid macular oedema [21]. Therefore, in summary, infliximab's chief application outside BD is usually limited to patients in whom adalimumab therapy has been unsuccessful and potentially, as rescue therapy.

Adalimumab

Within the last 2 years, two international, multicenter, placebo-controlled, randomized controlled trials (RCTs) of adalimumab in adults with uveitis involving the posterior segment (VISUAL I and VISUAL II trials) [40, 68] and one multicenter RCT in children with JIA uveitis (SYCAMORE trial) [78] have been published. All three reached their primary endpoints, but, notably, the SYCAMORE trial was halted at the interim analysis stage due to the clear benefit of adalimumab and methotrexate compared with methotrexate alone (27% vs. 60% treatment failures). VISUAL I studied active uveitis while VISUAL II studied quiescent uveitis which was dependent upon high doses of corticosteroids. Both trials showed that, compared with placebo, treatment with adalimumab was associated with statistically significant increase in median time to treatment failure, a comparative reduction in the number of uveitis treatment failures (28% reduction in treatment failure rate in VISUAL I and 20% in VISUAL II), an approximate halving of the risk of treatment failure and an overall visual quality of life benefit. Adalimumab was well-tolerated overall and the rate of adverse events fell within the expected range. As a result of these studies, adalimumab is now licensed for the treatment of uveitis. In Europe, it is licensed where corticosteroid-sparing is required, or where patients are refractory or intolerant of corticosteroids.

It is worthwhile noting that the VISUAL trials were principally placebo-controlled trials where a small proportion of patients were also treated with conventional immunosuppressive agents. In order to establish its place within the treatment options available, a head-to-head comparison with standard immunosuppression will be necessary. At the time of writing, there is a single phase IV study of the long-term safety and efficacy of adalimumab which is due to report its findings [91].

Regional delivery of adalimumab is also under evaluation following a small pilot study which indicated that four weekly injections of 1.5 mg intravitreal adalimumab was successful in inducing remission in six out of seven patients studied without any safety concern [29]. In contrast, a trial of a topically administered antibody fragment against TNFα for HLA-B27-associated anterior uveitis was terminated prematurely for reasons which were undisclosed (www.clinicaltrials.gov NCT00823173).

Certolizumab Pegol

Certolizumab pegol (Cimzia, UCB Pharma, Brussels, Belgium) is a Fab fragment of a humanised monoclonal anti-TNFα antibody conjugated to polyethylene glycol (PEG) which is administered by subcutaneous injection on a bi-weekly basis. The results of a double-blind, placebo-controlled RCT of certolizumab for anterior uveitis flares associated with spondyloarthropathy showed a lower rate of flares associated with certolizumab, but the result is difficult to interpret because only patients with a past history of uveitis developed uveitis during the trial and, by chance, the placebo group had a greater number of patients with previous uveitis [81].

Golimumab

Golimumab is a fully humanised monoclonal anti-TNFα antibody approved for use in rheumatoid arthritis (Simponi, Janssen Biotech Inc., PA, USA). It has demonstrated potential efficacy in controlling refractory anterior uveitis associated with spondyloarthritis in a small study [8] and the results of an RCT examining its efficacy in preventing ocular inflammation in spondylarthropathy is awaited (www.clinicaltrials.gov NCT01668004).

Etanercept

Etanercept (Enbrel, Amgen Inc., Thousand Oaks, CA, USA) is a recombinant fusion protein of the TNFα receptor and the IgG1 Fc region, acting as a decoy receptor to inhibit TNFα. It is delivered via subcutaneous injection and it has been associated with increased uveitis flares. There is no evidence to support its use in uveitis.

BEYOND ANTI-TNFA AGENTS

Despite a generally high degree of clinical effectiveness of TNFi in the short to medium term, some patients do not respond or may experience declining therapeutic response with successive doses, known as tachyphylaxis. Tachyphylaxis has been attributed to anti-infliximab antibodies which are associated with reduced serum levels and activity of infliximab. This has been observed to occur with prevalence rates between 6.4% and 16% in inflammatory bowel disease (IBD) patients [5, 12, 31, 82] although the rates have not been ascertained in uveitis patients. Antibodies to TNFi have also been observed following treatment with humanised agents, adalimumab (3.8% of treated patients) and certolizumab pegol (12% of treated patients) in IBD and rheumatoid arthritis [83, 84]. Significant adverse events may also necessitate discontinuation of treatment, such as drug-induced lupus-like reaction with infliximab [22, 89] or reactivation of latent tuberculosis (TB) [47]. For these reasons, multiple approaches to control uveitis are essential.

Type I Interferons

Type I interferons (IFN) are naturally occurring cytokines which help to regulate the immune system, including exerting an anti-proliferative effect on T-cells and upregulating the production of regulatory T-cells [54]. Type I IFNs consist of a number of IFNα isotypes and IFNβ. Subcutaneous administration of IFNα2a as a systemic immunomodulatory therapy was first studied in BD in 1986 [95]. IFNα2 has been studied in small non-randomised studies which indicated that it is effective in the management of Behçet's uveitis and may result in long-term

remission following treatment cessation [15]. A small RCT of 19 patients with intermediate uveitis or uveitis associated with multiple sclerosis treated with either subcutaneous IFNβ or methotrexate showed significant reduction in macular oedema and visual acuity with IFNβ but not methotrexate [59]. Unlike TNFi, interferons are not associated with the risk of TB reactivation which is of particular advantage in the treatment of BD in areas of high TB endemicity. It also has a role in the management of patients with macular oedema unresponsive to TNFi. However, one of the practical limitations of using interferons are their side-effects, including flu-like symptoms, risk of depression and, rarely, reports of suicidal ideation [46].

Anti-Interleukin 6

Interleukin 6 (IL-6) is expressed by T-cells, B-cells and monocytes, and potently induces several other inflammatory mediators as well as stimulating production of IL-17-producing helper T-cells (Th17), an important lineage of lymphocytes in the perpetuation of inflammation and tissue injury in many autoimmune diseases [24, 48, 62, 63]. IL-6 has been shown to be responsible for ocular inflammation in the mouse experimental autoimmune uveitis (EAU) model [101]. Cytokine profiling studies have shown serum IL-6 levels to be elevated in a variety of active or chronic NIU [30, 49, 101]. Tocilizumab (RoActemra, Roche AG, Basel, Switzerland) is a humanised mouse monoclonal antibody inhibitor of IL-6 receptor. It is currently licensed for moderate to severe rheumatoid arthritis, which is refractory to TNFi and also recommended for use in systemic JIA [87, 100]. The STOP-Uveitis Study, a 6-month study of 37 patients treated with one of two intravenous doses (either 4 or 8 mg per kg) of tocilizumab for posterior NIU demonstrated that the therapy was well-tolerated and associated with a reduction in vitreous haze and cystoid macular oedema at both doses [85]. Other IL-6 inhibitors are also under development which may become relevant for uveitis in the future [55].

Anti-Interleukin 12 and 23

IL-12 and IL-23 promote differentiation of T-cells into and survival Th17 cells [64, 93]. IL-23 is associated with uveitis in the EAU mouse model and in humans with VKH disease and BD [9, 10, 58]. Ustekinumab (Stelara, Janssen Biotech Inc., Horsham, PA, USA) is a monoclonal antibody directed at a common subunit of IL-12 and IL-23, called p-40, thereby blocking the effects of these cytokines on T-cells and antigen-presenting cells. Studies of ustekinumab for uveitis are at the phase II stage (www.clinicaltrials.gov NCT01647152).

Anti-Interleukin 17

IL-17 has been implicated as a key pro-inflammatory cytokine in autoimmune diseases, including uveitis, and therefore represents a potential target in the treatment of uveitis [7–10, 16, 30, 50, 57, 88]. So far, three randomised phase III trials of subcutaneous secukinumab (Cosentyx, Novartis Pharmaceutical, Basel, Switzerland), a fully human monoclonal antibody against IL-17A, have shown no significant benefit in NIU [19]. However, intravenous delivery of secukinumab in a phase II randomised study suggests that the route of delivery is well-tolerated and response rates are superior to subcutaneous administration [51]. Currently, there are no active phase III trials evaluating the efficacy of secukinumab in NIU.

Anti-Interleukin 1

IL-1β belongs to the IL-1 family of pro-inflammatory cytokines, which is associated with facilitating acute and chronic inflammation, and is secreted by activated macrophages and B-cells [74]. IL-1β is best known for its role in the pathogenesis of disorders involving the inflammasome, such as cryopyrin-associated periodic syndrome (CAPS), but is also implicated in JIA and BD [25, 27, 33, 77]. Gevokizumab (XOMA Corporation, Berkeley, CA, USA) is a recombinant humanised monoclonal IgG2 against IL-1β and inhibits its ability to signal a downstream cascade of inflammatory

events [37]. Several commercially sponsored studies have been withdrawn without completion; in one study at least, the primary outcome was not reached.

Abatacept

The activation of *T*-cells by antigen-presenting cells requires co-stimulation through major histocompatibility complex (MHC), and interaction between *T*-cell CD28 and antigen-presenting cell receptors CD80 or CD86. Abatacept (Orencia; BMS., New York, NY, USA) is a fusion protein of the extracellular domain of cytotoxic *T* lymphocyte antigen 4 (CTLA-4) and the Fc portion of IgG1, which binds CD80 and CD86, thereby inhibiting T-cell activation [36]. Data evaluating the efficacy of abatacept in uveitis is currently limited to case reports of its usage in JIA [2, 45, 102], although an open-label trial is underway (www.clinicaltrials.gov NCT01279954).

BIOSIMILARS

Whether as part of a single-payer system, through insurance or as individuals, the high costs associated with biologic immunomodulatory therapies can impact access. Biosimilar therapies are biological products which are pharmacologically highly similar to an approved biological pharmaceutical 'reference' product, but due to differences which arise from the manufacturing processes, they are not exact copies and, thus, not 'generic' drugs. Biosimilars are cheaper than the innovator molecule, potentially increasing the number of patients who may be treated.

Once approved by a regulatory agency for rigorous demonstration of equivalent pharmacokinetics, effectiveness, safety and immunogenicity to the reference product through an RCT and in vitro studies, a biosimilar acquires the same licensed indications as those of the reference product within a specific regulated region [39]. Of the TNFi biosimilars, CT-P13 (Inflectra or Remsima, Pfizer Inc., New York City, USA), an infliximab biosimilar, is amongst the most widely studied biosimilars and demonstrates a high degree of similarity to the reference product [39]. The adalimumab biosimilar, ABP501 (AMJEVITA, Amgen Inc.), has recently gained regulatory body approval in Europe, having been the subject of RCTs for psoriasis and rheumatoid arthritis [11]. Careful selection of the biosimilar drug and evaluation of safety and clinical efficacy will be necessary to provide the evidence base to demonstrate bioequivalence to biologic reference products in uveitis.

The cost-savings vary between drugs, manufacturers and regions. To illustrate current potential cost savings using infliximab as an example; in the UK the cost of a 100-mg vial of the innovator drug, Remicade (Janssen Biotech Inc., PA, USA), cited in the British National Formulary is £419.62 per 100 mg [41]. In the USA, the Lexicomp database cites the cost of 100 mg of Remicaide as $1401.38 per 100 mg [53]. Inflectra (Pfizer, NY, USA) and Remsima (Hospira, IL, USA) are brands of infliximab biosimilars which costs of £377.66 for a 100-mg vial in the UK and $1135.54 for a 100-mg vial in the USA (Supplementary Materials).

REGIONAL TREATMENTS

Although a detailed description is beyond the brief of this review, the role of regional treatments is the subject of a great deal of interest within the ophthalmic community. The HURON trial demonstrated the efficacy and safety of Ozurdex (Allergan Inc., Irvine, CA, USA), an intravitreal implant which biodegrades to release dexamethasone in a sustained manner [56]. In an RCT of 229 patients, vitreous haze was significantly reduced in eyes receiving 0.7 mg or 0.35 mg of Ozurdex (47% and 36%) in comparison to sham injections (12%). The MUST trial demonstrated equivalence in efficacy between the fluocinolone acetonide implant and systemic therapy at 2 years, as both showed similar improvements in visual acuity (+ 6.0 and + 3.2, respectively) [43]. At the 7--year follow-up, patients on systemic therapy had better visual outcomes than those who received fluocinolone acetonide, principally due to the side-effects of corticosteroids within the eye [43, 44].

A potential future direction for development of regional therapies is the mammalian target of rapamycin (mTOR) inhibitor, sirolimus (Rapamune, Pfizer Inc., New York City, NY, USA). Sirolimus suppresses T-cell proliferation and differentiation [14, 96]. The SAKURA trial demonstrated that intravitreal sirolimus was able to reduce inflammation in NIU without the high rate of adverse events associated with systemic administration [67, 69]. One potential limitation of these studies is the absence of a placebo arm, which prevents accurate quantification of efficacy or adverse events.

CONCLUSION AND FUTURE DIRECTIONS

We have witnessed a rapid growth in the armamentarium available for controlling autoimmune uveitis and, crucially, there are more treatments in the translational and developmental pipeline than at any previous time for uveitis. The expanding landscape of uveitis therapies has grown to encompass not only corticosteroids and conventional immunosuppressants, but also biologic therapies and regional treatments. The successful licensing of the TNFα inhibitor, adalimumab, represents a key milestone in the development of systemic therapies for uveitis as it was the first new drug to be licensed in several global regions for uveitis since corticosteroids in the 1960s. Novel treatments for the near future include inhibitors of IL-6, IL-23 and mTOR, whilst a number of others are in early phase trials. Other potentially exciting developments include complement-directed therapies which are currently at the proof-of-concept stage for uveitis (clinicaltrials.gov NCT01526889) [99]. Signal transduction inhibitors collectively form another emerging class of biologic therapy. These molecules were first developed for haematological diseases such as chronic myeloid leukaemia [73] and myelofibrosis [32, 97], and have had recent success in treating rheumatoid arthritis [23]. This so-called 'small molecule' class of biologic therapies target intracellular signalling enzymes such as those in the Janus kinase/signal transducer activating (JAK/STAT) pathway which mediate the intracellular actions of cytokines within immune cells. The selective JAK1 inhibitor, filgotinib (Galapagos NV, Mechelen, Belgium), is due to be evaluated in an international phase III trial in NIU (www.clinicalTrials.gov NCT02914561).

The rapid developments of novel uveitis therapies have been made possible by a combination of factors, including standardisation of uveitis classification and research outcome measures [38], international collaboration to recruit well-powered studies to conduct clinical trials and the interest of pharmaceutical companies in widening the licensing of new treatments to include uveitis. Optimisation of clinical management will rely upon long-term evaluation of new therapies to monitor safety and disease-specific outcomes. Registry data will be required to capture the incidence of infections and cancer whilst on these newer therapies. The consequence of all of these efforts and closer partnership with patients through clinical trials is that we are progressing towards the aspiration for a range of treatment options which reduce the historical over-dependence on corticosteroids, preserve vision and positively impact quality of life.

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