Biologics in Uveitis Treatment

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Biological drugs, especially those targeting anti-tumour necrosis factor α (TNFα) molecule, have revolutionized the treatment of patients with non-infectious uveitis (NIU), a sight-threatening condition characterized by ocular inflammation that can lead to severe vision threatening and blindness.

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1. Introduction

Uveitis refers to a heterogeneous group of diseases characterized by inflammation of the uvea, a structure formed by the iris, the choroid, and the ciliary body. They are usually classified depending on their aetiology as infectious or non-infectious, or according to the location of the inflammation (anterior, intermediate, posterior, or panuveitis). Non-infectious uveitis (NIU) has an immune-mediated or idiopathic aetiology and usually occurs in the form of flares [1].

Traditionally, local or systemic treatment with corticosteroids has been the mainstay therapy in patients with NIU. The powerful immunosuppressive effect of corticosteroids makes them highly effective drugs in the control of acute flares; however, long-term treatment can lead to the appearance of adverse effects or other ocular complications, especially in patients with chronic doses of prednisone equivalents over 7.5 mg per day [2]. Therefore, in many cases, it is necessary to associate other immunomodulators that allow for the reduction of the long-term adverse effects of corticosteroids while enhancing their immunosuppressive action [3]. The immunomodulatory drugs commonly used as first-line treatment in NIU are antimetabolites such as methotrexate (MTX), mycophenolate mofetil (MMF), or azathioprine (AZA), calcineurin inhibitors such as cyclosporine, or alkylating agents such as cyclophosphamide. These drugs are also known as “corticosteroid-sparing agents” since corticosteroid doses can be reduced while maintaining good control of ocular inflammation. Although treatment with immunosuppressants has led to substantial improvement in the management of NIU [3], in some cases the ocular inflammation persists. However, biological drugs have emerged in recent years as useful resources in many forms of NIU that do not respond to conventional treatment [4][5].

Numerous studies have confirmed the favourable results both in efficacy and safety of biological drugs, mainly molecules against tumour necrosis factor α (TNFα), in patients with uveitis refractory to conventional treatments. The introduction of these drugs in the treatment of NIU has been possible due to the knowledge gained about the

inflammatory mediators involved in this pathology, thus allowing the use of drugs that act specifically against these molecules [4]. Despite the wide use of various biological drugs including anti-TNFα drugs for the treatment of autoimmune diseases, only adalimumab (ADA) has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (2014 and 2016, respectively) in non-anterior NIU [6]. After the introduction of ADA for the treatment of NIU, better control of inflammation has been achieved, with improvements in visual quality and fewer complications, but there is still a high percentage of patients, around 40%, who present primary treatment failure in the first six months according to the results of VISUAL clinical trials [6][7]. However, results from a recent real-world data study showed higher drug retention rates close to 55% after the first five years, with inefficacy being the main cause of discontinuation [8]. In non-responders, treatment with ADA is not only not beneficial, but it can produce undesired adverse events. This situation highlights the need to identify factors related to treatment response with biological drugs that allow better management of patients with NIU. In this sense, the study of pharmacokinetic (PK) and pharmacogenetic (PG) parameters related to anti-TNFα drugs appears to be promising in the identification of biomarkers for treatment response.

Studies that have evaluated factors related to failure in therapy with anti-TNFα agents in the field of ophthalmology are scarce in comparison with those in immune-mediated rheumatic and gastrointestinal pathologies. This is mainly due to the short course of anti-TNFα drugs in the treatment of NIU, although the low prevalence and high heterogeneity of the disease also contribute. PK studies in other immune-mediated pathologies have revealed a significant inter-individual variability in the systemic concentrations of biological drugs. This has been related to the development of anti-drug antibodies (ADAbs), the use of concomitant immunomodulatory treatments, and alterations in biochemical parameters, among which albumin is one of the most important [9]. This variability together with the difficulty of access of the drug to the site of action may be two relevant aspects of conditioning response to treatment. From a biopharmaceutical point of view, the eye has barriers that limit the passage of high molecular weight molecules. However, the presence of inflammation can facilitate the passage of large molecules such as biologic drugs [10]. The passage of monoclonal antibodies (mAbs) through the ocular barriers toward the eye is a barely studied aspect, but it could have a great impact on the pharmacodynamic aspects of these drugs regarding the treatment of NIU. On the other hand, PG studies in immune-mediated pathologies have provided evidence of the influence of certain genetic polymorphisms in the response to biological drugs, although the relevance of these findings in NIU is currently unknown. Thus far few studies have been conducted aimed at evaluating the clinical relevance of PK and PG aspects in NIU.

Compared with classical drugs such as digoxin, mAbs used as therapeutic proteins have different pharmacokinetic characteristics due to their particular physical characteristics, generally showing a smaller volume of distribution and a longer half-life. Classic drugs are eliminated through hepatic metabolism, renal filtration, and excretion through bile or faeces. In contrast, the clearance of therapeutic antibodies is related to protein degradation and target binding. This phenomenon known as target-mediated drug disposition (TMDD), is also present in small molecules that exhibit non-linear pharmacokinetics, although it is more frequent in therapeutic proteins [11]. Although the pharmacokinetics of classical drugs and therapeutic proteins differ, in both treatment scenarios systemic drug concentrations falling within a specific therapeutic range should be achieved to maximize treatment efficacy and clinical outcomes while avoiding undesired adverse events that may arise from excessively high drug

levels. However, in clinical practice, this is not achieved in all patients due to the inter-individual variability in treatment, which highlights the need for tailored therapy. Therapeutic Drug Monitoring (TDM) is a useful tool to meet this need with which treatment can be personalized to reach therapeutic concentrations.

The introduction of biological therapies has revolutionized the treatment of NIU, especially those targeting TNFα. However, NIU treatment is challenging and current strategies are sometimes insufficient to achieve adequate control of ocular inflammation. Approximately 40% of patients experience early treatment failure (primary non-response, PNR), whereas up to 20% of patients experience an initial clinical improvement followed by a loss of response 12 months after starting treatment (secondary non-response, SNR) [6]. Given the limited repertoire of effective biologic drugs available in NIU, early identification of non-response (PNR) or loss of response (SNR) is of utmost importance in clinical practice.

The therapeutic outcome of biologic drugs in immune-mediated diseases is closely related to serum drug concentration [12][13]. Whilst therapeutic failure to anti-TNFα agents is commonly associated with low or undetectable serum trough drug levels (subtherapeutic), therapeutic success is associated with trough drug levels over a specific threshold, in a range in which maximum favourable outcomes are achieved with minimal or no adverse events [14]. Hence, the implementation of therapeutic drug monitoring (TDM), consisting of measuring trough drug levels and ADAbs, is essential to assess in each patient the performance of a given biological drug and define its optimal dose ranges.

Several approaches are currently available to measure drug and anti-drug antibody concentrations. Enzyme-linked immunosorbent assay (ELISA)-based techniques and radioimmunoassay (RIA) are the most used tests compared to other assays such as Homogenous Mobility Shift Assay (HMSA) and immunological multiparameter chip technology (IMPACT) [15][16]. Each assay format has a different sensitivity, dynamic range, and cut-points, so the results obtained are not equivalent. Therefore, the method of choice to monitor drug levels and anti-drug antibodies should be reported in all studies. All assays have advantages and limitations, some of them are inherent to the specific methodology, but others are related to economic factors, the presence of adequate facilities, or qualified personnel, among others. A detailed description of the available assays, their characteristics, and their main benefits and limitations can be found elsewhere [15][16].

Ideally, anti-TNFα therapy should result in therapeutic concentrations in all patients, but this is not always achieved in clinical practice as evidenced by the large differences observed in the systemic concentration of anti-TNFα drugs [17][18][19][20]. These differences are likely explained by heterogeneous drug bioavailability in patients, which in turn is influenced by PK factors, such as drug immunogenicity [21].

Furthermore, TDM was typically considered advantageous for drugs with a large inter-individual variability in exposure with relatively low intra-individual variation, a significant exposure–efficacy relationship, a narrow therapeutic window, and the availability of a validated bioanalytical assay. It has been postulated recently that this could also represent a useful tool to individualize dosing and optimize treatment using drugs with a wide therapeutic window and high cost [22].

2. Biologics in Uveitis Treatment

A better understanding of ocular inflammation pathways has led to the emergence of biological therapies for the treatment of NIU [3][23] that aim to overcome the 30% failure rate obtained under classical immunosuppressive treatment [24]. Different cytokines such as TNFα, IL-6, IL-17, or IL-23 play a key role in NIU inflammatory process [25], therefore becoming very attractive as potential therapeutic targets. Bearing this in mind, randomized prospective studies have been developed in the last years to evaluate the treatment efficacy of biological drugs in NIU [6][7][26]. In this sense, the main biological drugs used in NIU treatment are depicted in **Table 1**.

Adalimumab: ADA is a fully human monoclonal antibody targeting TNFα, which plays a central role in ocular inflammation via reactive oxygen species, inducing angiogenesis and breakdown of blood–retinal barrier (BRB). The time to reach maximum serum concentration is 56 h, after a 40-mg subcutaneous administration to a healthy adult subject, with an average absolute bioavailability estimated at 64%. The mean terminal half-life is approximately two weeks [27]. The first report about the role of ADA in NIU was in 2008 [28], after which several studies established the effectiveness of ADA in NIU, mainly the VISUAL I and VISUAL II trials. Both were randomised and multicentric clinical trials compared with a placebo, which evaluated the efficacy and safety of ADA in active and inactive NIU [6][7]. Based on the findings of these trials, ADA was approved for its use in NIU and is currently the only biological treatment approved by FDA and EMA for this purpose [1]. Phase III extension study (VISUAL III) has shown that ADA treatment maintains disease control and provides long-term corticosteroid-sparing effects [29]. In addition, a recent meta-analysis of six randomized controlled trials (RCTs) evaluating the efficacy and safety of ADA treatment of NIU has shown that treatment failure is halved compared with placebo, as well as a reduction in visual loss and ocular inflammation [30]. Future research aims to directly compare the efficacy of ADA in monotherapy and in combination with other immunosuppressants [31].

Infliximab (IFX): IFX is a chimeric (human/mouse) monoclonal antibody targeting TNFα has a half-life of up to 9.5 days and is administered intravenously. IFX use in uveitis was first reported in 2001 [32] and has been shown to be effective for NIU in children [33] and for Behçet's disease-associated uveitis resistant to classical immunosuppressive treatment [34], although it may also be effective for the management of other ocular diseases [1][4]. The use of IFX for the treatment of patients with refractory uveoretinitis of Behçet's disease (RUBD) has been approved in Japan in 2007 [35]. Its early use is strongly recommended in patients with vision-threatening ocular manifestations of Behçet's disease and should be considered as second-line therapy in juvenile idiopathic arthritis (JIA) related uveitis [36], proven its efficacy and its safety at doses as high as 20 mg/kg successfully used in these patients [37]. Furthermore, comparable results in terms of efficacy have been reported between IFX and ADA treatments for NIU [38].

Etanercept: Etanercept is a human recombinant fusion protein consisting of the ligand-binding region of the TNF-R2 receptor coupled to the constant region of immunoglobulin G1 (IgG1-Fc), which inhibits the attachment of TNFα to endogenous TNF receptors. Its half-life is around 70 h. Etanercept is approved for use in rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis (PS), ankylosing spondylitis, and polyarticular JIA, whereas its use in NIU is limited to case reports and small clinical trials [4]. Paradoxically, a significant association between

etanercept and the development of uveitis as a drug-associated side effect has been reported compared to ADA or IFX [39]. Therefore, it is strongly recommended that the use of either of these two anti-TNFα agents should be considered before etanercept therapy for the treatment of ocular inflammatory disease [36].

Golimumab: Golimumab, a fully human monoclonal antibody targeting TNFα, with a half-life of about 12 days, has shown potential efficacy in patients with refractory NIU to TNFα blockers [40][41], emerging as a promising therapeutic option in this disease. Nevertheless, all data were obtained from retrospective case series with small sample sizes, so additional studies on its efficacy are required.

Certolizumab: Certolizumab is a PEGylated antigen-binding fragment (Fab') of a recombinant humanized monoclonal antibody to TNFα. The conjugation of the hydrophilic polyethylene glycol (PEG) chains increases the half-life of certolizumab pegol to around two weeks. The clearance of certolizumab differs from that of other biological agents due to the absence of an fc fragment in its structure, which prevents FcRn-mediated recycling. In addition, renal excretion of certolizumab has been described due to the relatively small size of the Fab' fragments [42][43]. Data on the efficacy of certolizumab in the treatment of NIU are limited to case series showing it may be effective in the inflammatory control of refractory NIU [44].

Tocilizumab: Tocilizumab is a humanized monoclonal antibody that inhibits IL-6 signalling by preventing IL-6 from binding to its receptor. A prospective randomized trial evaluated tocilizumab safety and efficacy for the treatment of non-anterior uveitis and observed significant improvement in visual acuity and a reduction of central foveolar thickness [45]. Additionally, tocilizumab has demonstrated efficacy in managing JIA-associated uveitis refractory to anti-TNFα therapy [46], Behçet-associated uveitis [47], birdshot chorioretinopathy [48], and uveitic macular oedema [49].

Rituximab: Rituximab is a B-cell-depleting chimeric anti-CD20 monoclonal antibody. The mean terminal half-life is approximately 22 days. A growing number of reports have supported the use of rituximab in some types of NIU [50][51][52][53][54][55]. A retrospective study in JIA-associated uveitis showed a decrease in uveitis recurrences in patients who have not previously responded to other biologic therapies [50]. Additionally, rituximab treatment resulted in clinical improvement in 14 patients with Vogt–Koyanagi–Harada (VKH) disease-associated uveitis [51][52], 20 patients with severe manifestations of Behçet-associated uveitis [53] and induced remission in 20 patients with refractory ophthalmic Wegener's granulomatosis [54].

Table 1. Monoclonal antibodies used in different types of NIU.

Drug	Target	Structure	Dosage	Uveitis Type	References
Adalimumab [1]	TNF-α	mAb, fully humanized	LD: 80 mg MD: 40 mg every other week	Non-infectious non-anterior uveitis †	[6][7]
Infliximab	TNF-α	mAb, mouse-human chimeric	LD: 5 mg/kg at weeks 0, 4, and 6 MD: 5 mg/kg	JIA-related uveitis, Behçet, VKH, sarcoidosis, pars planitis,	[1][4][33][34][37]

Drug	Target	Structure	Dosage	Uveitis Type	References
			every 4 to 8 weeks Max. dose: 10mg/kg for adults, 20 mg/kg for children every 4 weeks	birdshot retinochoroidopathy, idiopatic uveitis	
Etanercept [2]	TNF-α	Human fusion protein	50 mg weekly	Behçet	[4]
Golimumab	TNF-α	mAb, fully humanized	MD: 50 mg monthly Max. dose: 100 mg monthly	Refractory uveitis	[40][41]
Certolizumab	TNF-α	mAb, fully humanized	200 mg every 2 weeks	Refractory uveitis	[44]
Tocilizumab	IL-6	mAb, fully humanized	4–12 mg/kg every 2–4 weeks	Non-infectious non-anterior uveitis, Behçet, birdshot, JIA-related uveitis	[46][47][48][49]
Rituximab	CD-20	mAb, mouse-human chimeric	LD: 500 or 1000 mg at 0, and 2 weeks. MD: Repeat at 6–12 months if needed	Refractory uveitis, JIA-related uveitis, Behçet, VKH, Wegener's granulomatosis	[50][51][52][53][54][55]

[1] Only biological drug indicated to treat non-infectious intermediate, posterior, and panuveitis. [2] Use of infliximab or adalimumab should be considered before etanercept therapy for the treatment of ocular inflammatory disease. [†] Adalimumab on-label indication. LD: loading dose, MD: maintenance dose, TNFα: tumour necrosis factor-α, IL-6: interleukin-6, CD-20: cluster of differentiation-20, mAb: monoclonal antibody.

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