Advances in the Treatment of Noninfectious Uveitis with Biologics: Anti-TNF and Beyond

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Chapter: Emerging Therapies: Fingolimod, Secukinumab and Efalizumab

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Emerging Therapies: Fingolimod, Secukinumab, and Efalizumab

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Introduction

This chapter is intended to provide a short glimpse on recent emerging therapies that could play an important role in the field of non-infectious uveitis in the next years to come. Both secukinumab and fingolimod are quite new therapies that are being examined and analyzed by worldwide physicians, which means controversy has been found regarding its clinical use in ocular inflammation. Efalizumab had a promising starting in the fields of uveitis but unfortunately clinical trials were stopped because of safety concerns. Efalizumab is presented a possible emerging therapy in the new clinical trials to come whenever its safety concerns are resolved. Our aim is to give basic knowledge of these new drugs such as their molecular basis, clinical evidence, and preliminary conclusions.

Secukinumab

Molecular basis

Both affected subjects and experimental models have proven the core role of auto reactive T cells in the pathogenesis of non-infectious uveitis, thus allowing immunosuppressive (IS) medication to become a central therapeutic agent [1,2]. Several molecular agents and cytokines have been described in the proinflamatory reactions involving immune-mediated diseases, and, of them, interleukin-17A (IL-17A), secreted by T-helper (Th) 17 cells, is one of the main ones [3,4]. Increased levels of IL-17A have been described in the peripheral blood of subjects with uveitis such as Vogt-Koyanagi-Harada syndrome and Behçet disease, compared with unaffected subjects (or quiescent uveitis) [5,6]. Moreover, it has already been stated than IL-17A inhibition in animal models of uveitis suppresses disease activity [7]. In addition, from a strategic point of view, agents targeting IL-17A act selectively in the inflammatory cascade at the level of a key cytokine, thereby preserving other immune functions of IL-17A-expressing agents [8]. This selective targeting differs from other therapeutic agents such as IL-23/12 inhibitor therapies that are believed to block both the generation and maintenance of T-helper 1 cells (Th1) and T-helper 17 cells (Th17), thus impacting numerous T-helper activities far beyond IL-17A [8,9] (Figure1). Nowadays, inhibition of IL-17A can be achieved with secukinumab (AIN457, Novartis), a fully human monoclonal antibody that binds selectively and with high-affinity to this cytokine, therefore preventing initiation of the inflammatory cascade and consequent activation of neutrophiles, macrophages, epithelial cells and other inflammatory agents [10,11].

Clinical evidence

Secukinumab was first reported to show clinical efficacy and safety in active chronic non-infectious uveitis by Hueber et al. in 2010 [12], based on the results of an open-label proof-of-concept clinical study. Sixteen patients with non-infectious uveitis refractory to...
corticosteroid therapy received intravenous secukinumab (10 mg/Kg) at baseline and 3 weeks afterwards, and 11 out of 16 patients responded and improved visual acuity, with reduction of intraocular inflammation that allowed stopping corticosteroid therapy. Disease activity was reduced in a similar manner to that achieved with infliximab therapy (antibody against tumor necrosis factor-alpha) thus setting the basis on future clinical trials [13]. Moreover, it was also reported that secukinumab induced clinically relevant responses in patients with other autoimmune diseases such as rheumatoid arthritis and psoriasis [12]. Since then, 3 major clinical trials with secukinumab have been promoted and analyzed, comparing this drug versus placebo in the treatment of non-infectious uveitis [14]. These studies were named SHIELD (patients with Behçet’s disease with posterior uveitis or panuveitis), INSURE (patients without Behçet’s disease and active non-infectious uveitis) and ENDURE (patients without Behçet’s disease and quiescent non-infectious uveitis). Secukinumab was administered subcutaneously in a dosage of 300 mg or 150 mg in a once a week or twice every two weeks regime depending on the trial arm of each study. Primary endpoints were set at the reduction of clinical disease activity (varying from rate of relapses, vitreous haze or time to first reactivation depending on the study) and secondary endpoints at the reduction of concomitant IS medication. In the SHIELD study, no statistically significant differences were observed between either of the secukinumab treatment groups and the placebo group for the rate of uveitis recurrence in the study eye [14]. There was a larger proportion of patients with no recurrences and a smaller proportion of patients with 3 or more recurrences in the secukinumab treatment groups compared with the placebo group, but the differences were not statistically significant. There were also no differences found in the mean duration of exacerbations. However, SHIELD study did show statistically significant reductions in the IS concomitant treatment from baseline with secukinumab versus placebo, a difference that was maintained taking into account events such as differences in the rate or duration of the exacerbations [14]. After completion of the SHIELD trial, having showed insufficient evidence for the efficacy of secukinumab, INSURE trial was terminated early. In the same line, ENDURE and INSURE trials were also terminated early because an interim data analysis did not show sufficient evidence of efficacy.

It can be argued that extended and intensive use of concomitant IS medication in all study groups may have played a role in the results of these studies, not allowing secukinumab to achieve clinical goals in the setting of an already deeply immune modulated subject. Discussion on the promotion of its clinical use in lightly treated patients can be taken into consideration. Moreover, another potential reason for these results is that Behçet’s disease patients were selected using quite aggressive criteria (2 or more exacerbations in the past 6 months and needing IS therapy) thus their outcomes could not be the same that those in patients with milder forms of uveitis or quiescent ones.

Conclusion

Secukinumab is thought to have a role to play in non-infectious uveitis. Being a most favored immune modulatory agent due to its capacity of selectively blocking some IL-17A effects, it seems reasonable to think that more investigation on this promising drug is expected.

**Fingolimod**

**Molecular basis**

Fingolimod (Gilenya™, Novartis) is a drug structurally analogue to sphingosine-1-phosphate (S1P), a natural lysophospholipid that plays an important role in several pathways of immune and vascular biology. It modulates immune cascade by preventing T cells release from secondary lymphoid organs, therefore reducing the population of peripheral T lymphocytes [15]. It has been mainly developed and indicated in the context of multiple sclerosis, with widespread acceptance because of its more tolerable oral dosage regime, although new uses in other autoimmune diseases are being explored. Its active metabolite is fingolimod-phosphate (FP), which acts by binding to isoforms 1-3-4-5 of the S1P receptor, thus inducing internalization and degradation of the S1P1 receptor. Such lymphocytes with the S1P1 receptor, some already sensitized to auto antigens, are therefore withhold within the lymph node and are unable to access peripheral circulation and thus end up not accessing their target tissue to participate in the autoimmune response. Moreover, Fingolimod seems to preferentially suppress a subset of T cells (naïve and central memory), allowing ongoing cell-based immunity to continue undisturbed while modulating the autoimmune activity associated with the target disease [16]. In addition, several studies indicate that S1P activation enhances endothelial barrier integrity through acting on both the cytoskeleton and intercellular junctions [17,18]. This may explain the pathophysiology of fingolimod’s most characteristic ocular adverse event - macular edema-based on that, although FP is a structural analogue to S1P, it behaves biochemically as a functional antagonist due to receptor down-regulation, thus deteriorating endothelial barrier integrity. Regarding adverse events, macular edema is thought to affect 1-4% of fingolimod-treated patients on a dose-depending regime [19]. It commonly resolves when discontinuing the drug. Patients with multiple sclerosis treated with fingolimod and with a history of past uveitis are thought to bare an increased risk to develop macular edema (up to 20%), making patients on a dose-depending regime [19]. It commonly resolves when discontinuing the drug. Patients with multiple sclerosis treated with fingolimod and with a history of past uveitis are thought to bare an increased risk to develop macular edema (up to 20%), making patients on a dose-depending regime [19]. It commonly resolves when discontinuing the drug. Patients with multiple sclerosis treated with fingolimod and with a history of past uveitis are thought to bare an increased risk to develop macular edema (up to 20%), making patients on a dose-depending regime [19].

**Clinical evidence**

Fingolimod’s efficacy in preventing inflammation has been successfully described in diverse conditions including relapsing-remitting multiple sclerosis [21], post transplantation inflammation [22,23] and ocular inflammation [24-26]. Clinical evidence in ophthalmic systems has been mainly based on published studies regarding its efficacy in experimental autoimmune uveoretinitis. These studies have shown that fingolimod-treated specimens had statistically significant less macrophage and T-cell infiltration than untreated ones and, moreover, this reduction was also accompanied by a reduction in early anatomical damage to the analyzed retinas. Regarding these data, authors suggest that oral fingolimod could embrace an important role in the acute treatment of non-infectious uveitis whether as a rescue therapy for patients resistant to other treatments or as an adjunct therapy to prevent structural damage [26].

**Conclusion**

Reported findings in experimental models regarding fingolimod use in autoimmune uveitis provide a solid basis where to develop and promote extensive clinical trials to evaluate its efficacy in non-infective uveitis. Although its benefits being extensively proven in multiple sclerosis studies, given the unique anatomical and structural characteristics of ocular tissues, results from specific designed trials are to be waited and analyzed before general recommendations could be set.
Efalizumab

Molecular basis

Efalizumab (Raptiva; Genentech) is a humanized form of a murine IgG1 antibody targeted against CD11a, a subunit of lymphocyte function-associated antigen 1 (LFA-1) [27]. LFA-1, which expression is increased in memory T-cells, and intercellular adhesion molecule 1 (ICAM-1), expressed on endothelial cells at inflamed sites, are both thought to bear important roles in the pathogenesis of autoimmune diseases; therefore existing studies have shown that inhibition of molecular adhesion function, for example, CD11a, decreases histologic and clinical expression of endotoxin-induced uveitis [28,29]. In the same way, in vitro studies have pointed out that efalizumab is able to inhibit T-cell activation, recruitment and adhesion without decreasing its population [30]. Efalizumab was approved for use in moderate to severe plaque psoriasis in adults [31-33].

Clinical evidence

Based on its approved application for plaque psoriasis and taking into account its uveitis usefulness rationale, an open-label, prospective and non-comparative clinical trial (phase I/II) was carried out to evaluate efalizumab in non-infectious uveitis [34]. The study recruited 6 patients with non-infectious uveitis and cystoid macular edema (CME) who were treated with weekly subcutaneous efalizumab for 16 weeks. No serious adverse events, including serious infections attributable to the study medication, were reported by the patients. All participants showed a reduction in CME (mean reduction of 128.9±105 micrometers), as evidenced by optical coherence tomography, and all patients experienced an improvement in visual acuity (mean best-corrected visual acuity improvement was 6.7±5.2 ETDRS letters (worse eye) and 1.7±5.2 letters (better eye). Three patients were able to reduce their concomitant IS medications by 50%, and 5 out of 6 participants maintained clinical quiescence of their uveitis during the study. Despite its promising results in ocular inflammatory disease, efalizumab was finally taken off the market due to safety concerns: 3 consecutive cases of progressive multifocal leukoencephalopathy were reported in long-term users (older patients using efalizumab for more than a year), none of them suffering from uveitis [34].

Conclusion

Efalizumab had its clinical use slowed down (if not stopped) due to safety concerns despite its promising results in available trials in uveitis. Since these described serious adverse events were limited to non-uveitic long-term users of this drug, decisions would be taken in order to promote clinical trials addressed to a much more selected group of patients. Nonetheless, widespread use of efalizumab for non-infectious uveitis is nowadays not possible.

References


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