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

Edited by Marina Mesquida
Chapter: β Antagonists: Anakinra, Rilonacept, Canakinumab, Gevokizumab

Edited by: Dr. Marina Mesquida

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IL-1β Antagonists: Anakinra, Rilonacept, Canakinumab, Gevokizumab

Maite Sainz de la Maza*
Uveitis Unit, Ophthalmology Department, Hospital Clinic of Barcelona, Barcelona, Spain

*Corresponding author: MaiteSainz de la Maza, Uveitis Unit, Ophthalmology Department, Hospital Clinic of Barcelona, Barcelona, Spain, E-mail: msainz@clinic.ub.es

Introduction

Noninfectious uveitis has a complex and multifactorial etiology that involves the breakdown of the blood-eye and blood-retinal barriers as well as activation of both systemic and intraocular inflammatory components, mechanisms, and processes. Pro-inflammatory cytokines, such as Interleukin-1 Beta (IL-1β), Tumor Necrosis Factor Alpha (TNF-α), and Interleukin 6 (IL-6), play a central role within these ocular inflammatory events. The combined effects of IL-1β or IL-6 along with Transforming Growth Factor beta (TGF-β) induce T helper 17 cells which have demonstrated induction of a neutrophil-associated Experimental Autoimmune Uveitis/Uveoretinitis (EAU) [1-4]. It has also been reported that TNF-α, as well as vascular endothelial growth factor and IL-1β may contribute to the breakdown of the blood-retinal barrier in both, EAU and patients with uveitis. The possible mechanisms are related to opening of tight junctions and increased vesicular transport within the endothelial cells [5].

IL-1β and the Autoinflammatory Disorders

The IL-1 family comprises several members, including IL-1α, IL-1β, and IL-1 Receptor antagonist (IL-1Ra). These cytokines are produced by many cell types, including monocytes and macrophages.

IL-1β is a dominant mediator of inflammatory responses by inducing growth and differentiation of immune competent lymphocytes. IL-1β acts as a messenger to up regulate the innate immune system’s response to infection, injury, and stress [6]. IL-1β expression level and function are tightly regulated by a complex system of IL-1 family members and their receptors.

IL-1β exerts its effects through Interleukin-1 Receptor type I (IL-1RI) and Interleukin-1 Receptor Accessory Protein (IL-1RAcP), which together form the active signaling-complex competent. IL-1β also binds to a second receptor, Interleukin-1 Receptor type II (IL-1RII) which down-regulate the activity of IL-1β.

While IL-1β plays an important role in innate immunity, over expression can be deleterious [7]. Systemic effects from overexpression of IL-1β are the main cause of various autoinflammatory diseases.

IL-1β release is central to the pathogenesis of autoinflammatory diseases, as evidenced by elevation in serum levels of IL-1β, its correlation with disease development and severity, and the effectiveness of anti-IL1β antagonists in treating these disorders [8].

Autoinflammatory disorders are characterized by usually unprovoked recurrent episodes of features of inflammation caused by activation of the innate immune system. A new proposed classification of the immunological diseases with the differences between autoinflammation and autoimmunity is shown in Table 1 [8,9]. Many autoinflammatory disorders are associated with alterations of inflammasomes [10]. Inflammasomes are complex multimolecular structures, which respond to "danger" signals by activation of cytokines. Among these, IL-1 is the key player of the innate immune response and inflammation. Consequently, IL-1 blocking strategies are specific pathway targeting therapies in autoinflammatory diseases such as cryopyrin-associated periodic syndrome, Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), HyperImmunoglobulinemia D Syndrome (HIDS), and Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) [10-12]. This classification is relevant to the clinical situation because innate immune mediated disorders (autoinflammatory diseases) respond better to cytokine antagonism whereas autoimmune-mediated diseases may respond to anti-T and B cell therapies [9].

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MHC: Major Histocompatibility Complex; IL: Interleukin; TNF: Tumor Necrosis Factor;[9]

Table 1: Comparison between autoinflammation and autoimmunity.
Behçet’s disease is a genetically complex disorder, which usually presents first in adulthood but is also observed in children. It is most common among young adults from Eastern Asia and Mediterranean countries, populations spread along the historical silk-road. The etiology is poorly known although there is a familial predisposition and an association with HLA-B51. The disease is characterized by genital and oral ulcerations, papulopustular skin lesions such as pseudofolliculitis, erythema nodosum and pyoderma gangraenosum, arthritis, vasculitis and uveitis. Severe vasculitis may worsen the prognosis by causing potentially life-threatening complications such as thrombophlebitis, arterial aneurysms and occlusion. Because Behçet’s disease shares clinical similarities with autoinflammatory disorders, such as the episodic nature and granulocyte activation in the pathogenesis, it may also be regarded as autoinflammatory disease. However, although IL-1β plays a role in Behçet’s disease and there is a biological response to IL-1 blockade, yet no information exists to suggest which inflammasome might generate the active cytokine[11].

Disregulation in innate immunity has also been found in ankylosing spondylitis, psoriatic arthritis, and Crohn’s disease, diseases often associated with uveitis. This has led to reclassifying these conditions as autoinflammatory conditions[11-13]. T-cell or B-cell targeted therapies such as Abatacept, Alefacept, Efalizumab, and Rituximab have shown only modest therapeutic effects in these diseases, whereas TNF-inhibitors have been found to be very effective[12].

IL-1β in Noninfectious Uveitis

Several animal models of uveitis have demonstrated a relationship between IL-1β and ocular inflammation. Elevated levels of IL-1 have been found in the eyes of mice [14] and rats [15] with experimental endotoxin-induced uveitis. IL-1 messenger RNA levels were markedly elevated in eyes of mice with EAU [16]. IL-1 levels were elevated in the aqueous humor of patients with intermediate uveitis [17-19]. Conversely, knockout mice deficient in IL-1 showed a profound reduction in the severity of immune complex-induced uveitis [20].

Human studies have shown IL-1 elevated levels in the aqueous humor of patients with birdshot chorioretinopathy [21]. In Behçet’s disease patients, IL-1β has been implicated as a mediator in its pathogenesis [22,23], has been found elevated in sera [24], and has been shown to be produced in large amounts by circulating monocytes [25]. Several studies have shown that gene polymorphism is involved in the mechanism of Behçet’s disease, which in turn leads to the increased expression of IL-1β [22].

IL-1β Antagonists

Advances in our understanding that the IL-1β is a key pro-inflammatory cytokine involved in the pathogenesis of uveitis, have increased interest in therapeutic agents targeting it. These therapeutic agents include the monoclonal antibodies Anakinra (Kineret®, Rilonacept (Arcalyst®), Canakinumab (Ilaris®), and Gevokizumab (XOMA 052). Inhibition of IL-1β may be achieved at different levels. Some agents target the IL-1β molecule directly (Rilonacept, Canakinumab, Gevokizumab) while others are antagonists to IL-1RI (Anakinra).

a. Anakinra (Kineret®)

Anakinra (Kineret® Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant form of the naturally occurring human IL-1Ra, which blocks the activity of IL-1β by competitively binding to the IL-1RI. Anakinra has a short half-life of 4-6 hours and therefore needs to be administered daily; usually with an adult dose of 100 mg daily by subcutaneous injection or with a children dose of 1-2 mg/kg daily by subcutaneous injection. It has been used to treat a wide variety of autoinflammatory conditions, including Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)-associated uveitis refractory to anti-TNF therapy, confirming the success in the preclinical experimental autoimmune uveitis model in mice [26]. It has also been effective in treating refractory Behçet’s disease [27]. Serious infections such as pneumonia and infectious cellulitis seem to be more frequent with Anakinra, although there is no increased risk of tuberculosis. Anakinra has reached USA Food and Drug Administration (FDA) approval for the treatment of CINCA and rheumatoid arthritis [28]. It has also been proven to be effective in a number of autoinflammatory disorders such as CAPS [29], SOJIA [30], FMF [31], HIDS [32] and TRAPS [33].

b. Rilonacept (Arcalyst®)

Rilonacept (Arcalyst®, Regeneron Pharmaceuticals, Tarrytown, New York, USA) (IL-1 Trap) is a fully human dimeric fusion protein, which incorporates the extracellular domain of both IL-1 receptor components: IL-1RI and IL-1RAcP. It has a half-life of 67 hours and it is administered once a week with 160 mg subcutaneously. Rilonacept has reached FDA approval for the treatment of familial cold autoinflammatory syndrome (FCAS) [34] and for Muckle-Wells Syndrome (MWS) [35]. Response has also been reported in patients with FMF [36], gout [37], SOJIA [38] and Schnitzler syndrome [39]. To date, no experience has been reported in uveitis.

c. Canakinumab (Ilaris®)

Canakinumab (Ilaris®, Novartis Pharmaceutical Corporation, East Hannover, New Jersey, USA) is a novel fully human IL-1β blocking IgG1 monoclonal antibody. It neutralizes IL-1β, by competing for binding to IL-1RI and therefore blocking signaling by the corresponding antigen-antibody complex. Intravenously or subcutaneously infused, it neutralizes the bioactivity of human IL-1β [40]. The agent has a half-life of 21-28 days and is administered with 150 mg subcutaneously in adults or 2 mg/kg subcutaneously in children once a month. That offers a considerable advantage over Anakinra, which must be injected daily and is often poorly tolerated by patients.

Canakinumab has promising clinical safety and pharmacokinetic properties, and demonstrated potential for the treatment of autoinflammatory disease conditions such as CAPS, MWS, SOJIA, FMF, gout, type II diabetes, TRAPS, and possibly for ocular inflammatory diseases [12,41,42]. Recent reports showed the efficacy of Canakinumab in Behçet’s uveitis refractory to antimetabolites and TNF antagonists [41,42] and in Blau syndrome-related uveitis refractory to antimetabolites and several biologic response modifiers, including TNF antagonists and Abatacept [43].

d. Gevokizumab (XOMA052)

Gevokizumab (XOMA 052, XOMA Corporation, Berkeley, CA, USA) is a recombinant, humanized IgG2 monoclonal antibody that binds IL-1β, reduces affinity to IL-1RI, leaving intact the affinity for IL-1RII. It is a modulating antibody that reduces the affinity for its IL-1RI. IL-1RAC signaling-competent complex [44]. It down-regulates IL-1β activity in cytokine release assays. The monoclonal antibody was humanized using proprietary technology developed at XOMA with the goal of reducing the probability of eliciting anti-drug immunogenic responses. Under physiological conditions where increased levels of IL-1β cause pathology, Gevokizumab neutralizes...
excess IL-1β while potentially allowing continued beneficial signaling in response to local inflammatory stimuli. Therefore, Gevokizumab may allow for better responsiveness of the innate immune system to infection as compared with a complete blockade of IL-1β activity.

Gevokizumab is produced in Chinese hamster ovary cells. Based on pharmacokinetic data from multiple studies, it has a circulating half-life of approximately 22 to 28 days, allowing convenient monthly subcutaneous dosing [45].

Based on its high potency, novel mechanism of action, long half-life and high affinity, Gevokizumab provides a new strategy for the treatment of a number of autoinflammatory diseases in which the role of IL-1β is central to pathogenesis [12].

Clinical Studies

To date, the clinical experience with Gevokizumab includes over 500 subjects who have been treated with the drug in a variety of clinical nonocular autoinflammatory disorders, primarily type 2 diabetes, but also type I diabetes, acne vulgaris, acute gout, cardiovascular disease, FACS, and MWS [7,46].

The emerging clinical safety profile of Gevokizumab supports doses of 30 mg and 60 mg once a month. The safety profile indicates that among over 315 subjects chronically treated with Gevokizumab for at least 6 months, there has been no evidence of increased infections, serious infections, opportunistic infections, chronic infections, hematologic toxicities such as neutropenia or leukopenia, malignancies, or auto-immune phenomena. The laboratory abnormalities with Gevokizumab were mild or moderate, and the majority reflected the disease under study.

An open-label pilot study was performed in patients with resistant Behçet’s disease uveitis [47]. Gevokizumab was administered to seven subjects with acute, vision-threatening posterior uveitis or panuveitis and/or retinal vasculitis resistant to Azathioprine and/or Ciclosporine in the presence of an acute exacerbation. All immunosuppressive agents were discontinued other than baseline oral corticosteroids at 5 to 10 mg per day. Patients were given a single dose of 0.3 mg/kg intravenous (iv) Gevokizumab. Signs of intraocular inflammation began to resolve in all seven subjects from Day 1 to Day 4, with complete resolution of retinal findings achieved in 4 to 21 days (median 14 days). To those who responded to treatment prior to Day 28 and then had a second exacerbation between Day 28 and the end of the study at Day 98 were given a second dose of 0.3 mg/kg (iv) gevokizumab. All subjects had positive response to second infusion and were recurrence-free for a median of 115 days (ranging from 41 to 197 days). All seven subjects who participated in this study elected to receive further treatment in an open-label extension study. The authors reported no treatment-related adverse events. Limitations of this study include its open-label design, the small number of patients, the lack of assessments of the extraocular manifestations, and the short follow-up.

There are two ongoing randomized, placebo-controlled, double-masked study phase III clinical trials studying the safety and efficacy of Gevokizumab in noninfectious intermediate, posterior, or panuveitis. EyeGuardTM-A is for patients currently active in spite of corticosteroids with or without immunosuppressive medications, and EyeGuardTM-C is for patients whose disease is currently controlled with systemic oral corticosteroids (≥ 10 mg/day and < 25 mg/day prednisone equivalent) with or without immunosuppressive medications, but who have experienced active uveitic disease within the previous 12 months.

Concluding Remarks

Autoinflammatory disorders are characterized by usually unprovoked recurrent episodes of features of inflammation caused by activation of the innate immune system. Ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, and Behçet’s disease, disorders often associated with uveitis, have been classified as autoinflammatory disorders. Autoinflammatory disorders are associated with alterations in the activation of the innate immune system. Anakinra, Rilonacept, and Canakinumab have reached FDA and European agencies approval for several systemic diseases. Long-acting IL-1 inhibition using Canakinumab has been successful in several cases with Behçet’s disease resistant to conventional treatment. Gevokizumab has been shown to be effective and safe in Behçet’s disease. Currently there are two randomized, placebo-controlled, double-masked study phase III clinical trials studying the safety and efficacy of Gevokizumab in noninfectious intermediate, posterior, or panuveitis.

Undoubtedly, a lot remains to be learned about the complete network of signal cascades, ranging from signal recognition to the resulting inflammation in uveitis. Increasing knowledge about the specific cytokine production in uveitis will surely develop new opportunities to create molecules that can intervene in this way.

References


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