Editorial

Technology Allows Detection of Target Molecules and Production of Biologic Agents for Treatment of Ocular Inflammatory Disorders

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J Ophthalmic Vis Res 2015; 10 (1): 1-3.

Although the precise pathogenic mechanisms of uveitis remain unknown, cytokines, chemokines and soluble adhesion molecules appear to play a major role in uveitis. They influence the communications between various cell types and alter vascular endothelial properties. Several recent studies have disclosed the beneficial role of aqueous humor samples for investigating involved molecular targets in various diseases leading to uveitis and potentially for specific treatments. Anterior chamber paracentesis for obtaining aqueous humor allows measurement of therapeutic targets and enables investigators to produce specific antagonists.

Three classes of immunosuppressive drugs have been most frequently used for treatment of uveitis; these include antimetabolites, T-cell inhibitors and alkylating agents all of which are slow acting and cause treatment efficacy in up to 76% of cases.[1,2] There are other drawbacks to these class of agents: In autoimmune disease, immunosuppressive therapies affecting one organ or site may not necessarily be effective on another organ/site, even when the inflammation is the manifestation of the same disease in the same individual. Furthermore, treatment with immunosuppressive agents may be complicated by serious side effects.

A new development in uveitis treatment during the recent years is the development of biologic agents. Refractory cases of uveitis with or without retinal vasculitis may benefit from biologic agents of which, interferon-alpha (INF-α), interleukin (IL) 1 blocking agents, and tumor necrosis factor (TNF) blockers have been used successfully in some case reports.

There is strong evidence that aqueous humor levels of many cytokines such as IL-6, IL-10, IL-15, IL-17, IL-23, IL-27, IL-35, TNF-α, transforming growth factor beta (TGF-β), interferon-γ and vascular endothelial growth factor (VEGF) in noninfectious autoimmune uveitis are elevated and the earlier mentioned and upcoming new biologic agents will be increasingly used for treatment of uveitis; however, the question whether the benefits of these agents outweigh their associated risks remains a major concern.

Large clinical trials on the use of these agents in patients with uveitis are lacking and the few published trials do not have sufficient sample size and duration of follow up, thus much of the current evidence stems from observational case series with all their limitations. Due to these limitations, available data, mostly from the field of rheumatology, are used for treatment of uveitis in ophthalmology. Clearly, further research on the involved cytokines and other inflammatory mediators in specific types of uveitis is required to elucidate the role of these proteins in the inflammatory process.

WHERE WE ARE NOW

Biologic therapies use molecular DNA technology to produce a targeted drug on the basis of the pathogenesis of the disorder. They include TNF blockers, monoclonal antibodies against B cells, monoclonal antibodies against IL-6 receptors, antagonist antibodies against IL-1 and soluble receptors blocking the molecule responsible for activation of T cells. In addition to cytokines, biologic therapies can be targeted against adhesion molecules, complements components and cell surface molecules. Therefore, the development of potential therapeutic agents is unlimited and along with growing science, many more targets will be discovered and as

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DOI: 10.4103/2008-322X.156082

a result, more agents will be available for treatment of uveitis [Table 1].[3]

WHERE WE ARE HEADED

In near future, after development of smart slit lamps, we will be able to detect pathogenic cytokines and other inflammatory mediators involved in uveitis in the clinic and measure the levels of these agents in the anterior chamber and vitreous. Smart slit lamps have the ability to transmit all the information and findings to a pharmacologist at the same time to produce a specific inhibitor agent. Then uveitis specialist will be able to apply the provided agent as a topical drug to the eye or by using iontophoresis, these drugs can even be delivered trans-sclerally to the vitreous and retina.

In this issue of Journal of Ophthalmic and Vision Research, Hernández-Garfella et al[4] have addressed changes in aqueous humor levels of interleukins 1-β, 2, 6 and 10 as well as TNF-α and VEGF in a small series of patients (12 eyes) with uveitis of various etiologies before and after treatment with Adalimumab (an anti-TNF-α agent), as compared to a control group of 12 eyes undergoing only cataract surgery. In this study, aqueous humor samples were obtained before initiating adalimumab and on the day after administration of the last dose of adalimumab at month 6. A significant decrease in aqueous humor levels of VEGF and IL-2 occurred after systemic treatment with adalimumab; however, levels of IL-1 β and IL-6 did not change. Interestingly, the aqueous level of TNF-α significantly increased after therapy with adalimumab. The explanation offered by the authors is that TNF-α increases the expression of VEGF factor, and TNF inhibitors exert their anti-inflammatory effect mostly through a decrease in VEGF levels in the aqueous rather than by reducing TNF-α itself.

Another study did not report higher levels of TNF-α in the aqueous humor of patients with uveitis.[5] In contrast,

Table 1. Inflammatory targets and related adhesion drugs

Drug	Target	Target disease(s)
Targeting B cells		
Belimumab	B-cell activating factor antibody	Sjogren's syndrome, systemic sclerosis
Tabalumab	B-cell activating factor antibody	systemic lupus erythematosus, multiple sclerosis
Rituximab	CD20 receptor antibody	Behcet's uveitis, sarcoidosis, granulomatosis with polyangiitis, lymphoma, leukemia, graft-versus-host disease, Graves' ophthalmopathy
Targeting T-cell activation		
Abatacept	B7 co-stimulatory receptor	uveitis, rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, sarcoidosis, granulomatosis with polyangiitis, multiple sclerosis, ankylosing spondylitis, relapsing polychondritis, psoriatic arthritis
Otelixizumab	CD3 receptor	rheumatoid arthritis, Graves' ophthalmopathy
Tofacitinib	SMI: JAK 1/3	rheumatoid arthritis, ulcerative colitis, juvenile idiopathic arthritis, psoriasis, keratoconjunctivitis sicca
Apremilast	SMI: PDE 4	psoriasis, ankylosing spondylitis
Sotrastaurin	SMI: PKC0	psoriasis, cystoid macular edema associated with uveitis
Targeting T-cell migration		
Fingolimod	Sphingosine-1-phosohate receptor antagonist	multiple sclerosis, preclinical for uveitis
Target inflammatory cytokines		
Secukinumab	IL-17 A	uveitis, plaque psoriasis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, psoriasis
Ixekizumab	IL-17 A	psoriasis, rheumatoid arthritis
Brodalumab	IL-17 receptor	psoriasis, psoriatic arthritis, rheumatoid arthritis, asthma, Crohn's disease
Ustekinumab	P40 submit of IL-23 and IL-12	uveitis, ankylosing spondylitis, Crohn's disease, psoriasis
Fezakinumab	IL-22	rheumatoid arthritis
Tocilizumab	IL-6 receptor	uveitis, juvenile idiopathic arteritis, polymyalgia rheumatica, ankylosing spondolitis, relapsing polychondritis, Behcet's uveitis
Sirukumab	IL-6	rheumatoid arthritis, systemic lupus erythematosus
Sarilumab	IL-6 receptor	rheumatoid arthritis, ankylosing spondylitis

IL, interleukin

some other studies have shown elevated levels of different cytokines including TNF-α in uveitis.[6] The question that comes to mind is how does an anti-TNF-α agent such as adalimumab exert its anti-inflammatory effect with no change in the level of TNF-α in the aqueous humor. The answer is that there may be no major contribution of this cytokine above and beyond that of VEGF and IL-6 in uveitis. However, the differences between the results of studies might in part be explained by the complex biologic function of mediators, transient production during the course of the inflammatory process with specific uveitis entities, and medications used at the time of sampling. The relative efficacy of intravitreal injection of adalimumab has also been shown in two uveitis case series[7,8] and it has been reported that anterior chamber cells, vitreous haze, macular edema and vascular staining on fluorescein angiography decreased after intravitreal adalimumab injection.

All of these studies with small sample size must be interpreted very conservatively, given limitations including their retrospective nature, small number of subjects, difference in concurrent immunosuppressive usage, multiple observers and various follow up intervals. Furthermore, treated populations are heterogeneous not only with respect to the form of ocular inflammation and types of systemic association, but also regarding other important variables such as age, gender and race. Additionally, it has been shown that although TNF blockers and immunosuppressive medications may show beneficial effects in given systemic inflammatory diseases, they may not be advantageous for related ocular inflammations.

In summary, a mechanism-based approach is most likely to lead to future breakthroughs in the treatment of uveitis. However, in clinical practice strong evidence is required regarding all of the above mentioned questions. Data that separate and focus on the effects of different agents on various inflammatory targets and various specific diseases with large enough sample size are still pending and future studies should compensate for this defect in the literature. With improvement in the efficacy of molecular science and clinical trial networks, the future is even brighter for patients with ocular inflammatory disorders. Last but not least, the cost of new upcoming biologic drugs is a major concern and should be considered in decision making for patients.

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How to cite this article: Soheilian M. Technology allows detection of target molecules and production of biologic agents for treatment of ocular inflammatory disorders. J Ophthalmic Vis Res 2015;10:1-3.