·Review·

New options for uveitis treatment

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Abstract

• **Uveitis is one of the most important causes of blindness worldwide. Its etiology and pathogenesis are complicated and have not been well understood. The treatment for uveitis is predominantly based on steroids and immunosuppressants. However, systemic side effects limit their clinical application. With the advancement of molecular biology, some intravitreal implants and biologic agents have been used for the treatment of uveitis. Additionally, novel techniques such as gene therapy and RNA interference are being studied for using as uveitis therapy. This paper reviews recent advances in uveitis treatment.**

• **KEYWORDS:** uveitis; intravitreal implants; biologic agents; gene therapy; RNA interference

He Y, Jia SB, Zhang W, Shi JM. New options for uveitis treatment. *Int J Ophthalmol* 2013;6(5):702–707

INTRODUCTION

Uveitis is the most common form of intraocular inflammation caused by multiple agents. It mainly affects the younger patient population and leads to significant vision loss [1]. This disease can be idiopathic or associated with infectious and systemic disorders. In addition to corticosteroids, immunosuppressive drugs such as methotrexate, mycophenolate mofetil and cyclosporine are commonly used to treat patients with severe uveitis[2-4], while serious side effects limit their clinical application. Fortunately, a better understanding of the pathogenesis of uveitis and the development of molecular biology have helped to create more effective treatment approaches [5]. This paper reviews recent advances in uveitis treatment.

EFFECTS OF INTRAVITREAL DRUG ADMINISTRATION

In recent years, intravitreal injection of non-steroidal anti-inflammatory drugs (NSAIDs) has been under clinical investigation and some are commercially available. Baranano *et al* [6] showed that both ketorolac and diclofenac have potent anti-inflammatory effects after intraocular injection but they are rapidly cleared by 48h. In another pilot study of intravitreal injection of diclofenac for the treatment of macular edema of various etiologies, the results suggested that intravitreal diclofenac is effective in improving the visual acuity[7]. Kim *et al* [8] also reported their experience of intravitreal injection of ketorolac in a case series of 10 adult patients with chronic inflammation and/or macular edema who failed to previous treatment or could not tolerate corticosteroids because of adverse ocular effects. They observed that inflammation resolved in 2 of 2 eyes with active intraocular inflammation, and in 4 of 8 eyes with macular edema. They concluded that a 4μg intravitreal injection is safe in ocular disease.

Currently, intravitreal injection of methotrexate has been gradually used to treat uveitis. Hardwig *et al* [9] demonstrated that a dose of 400μg appears to be well tolerated and have positive effects on the preservation of visual acuity. Taylor *et al* [10] conducted a study to investigate the efficiency of intravitreal injection of methotrexate and found that in patients with uveitis and uveitic cystoid macular edema (CME), intravitreal methotrexate can improve their visual acuity and reduce CME, and a further methotrexate injection has similar efficacy for the relapse of inflammation. Furthermore, a study published by Bae and Lee [11] confirmed the efficacy of intravitreal methotrexate in the treatment of refractory retinal vasculitis due to Behcet disease. Seven eyes of seven patients with Behcet disease were enrolled and intravitreal injection of 400μg methotrexate was given monthly until visual acuity and intraocular inflammation were stable. Their results revealed that six patients showed an increase in visual acuity by 3 or more lines, and 4 patients exhibited a decrease in fluorescein leakage. The levels of IL-6 and IL-8 in the aqueous humor were significantly reduced at 4 weeks after intravitreal methotrexate.

Furthermore, a few studies have showed that the intravitreal corticosteroid implant may be an effective treatment strategy for the long-standing uveitis patients [12]. The dexamethasone (DEX) intravitreal implant is a biodegradable sustained-

release intravitreal drug delivery system which will bring high levels of the drug directly to the posterior segment, while minimizing systemic absorption [13]. A single DEX implant has been shown to provide clinical benefits for up to 6 months in eyes with intermediate or posterior uveitis.

Miserocchi et al [14] described their experience in treating recalcitrant and severe cases of noninfectious posterior uveitis with 0.7mg DEX intravitreal implant. Twelve patients were enrolled and followed up for 9 months from injection. Outcome measures included decrease in uveitis activity, improvement in visual acuity, reduction of macular thickness, and occurrence of adverse events. They found that uveitis activity decreased in all the patients after the implant. Best-corrected visual acuity(BCVA) improved from 20/80 to 20/40. The mean central retinal thickness (CRT) improved from 496μm to 226μm. Transient intraocular pressure (IOP) elevation encountered in 3 patients after the implant which was controlled with topical anti-glaucoma treatment. The major adverse event in the study was vitreous hemorrhage but cleared up after 1 month. Taylor et al [15] conducted a retrospective, consecutive case series of patients <16 years of age whom a DEX intravitreal implant was used to treat noninfectious uveitis and demonstrated again that this implant can improve the visual acuity and reduce CME effectively in pediatric uveitis.

Another implant, the fluocinolone acetonide (FA) implant named Retisert, has also been gradually used as an addition to the armamentarium of management of complicated cases of uveitis. FA is a corticosteroid with 1/24 the solubility of DEX in an aqueous solution, allowing steroid release over a much longer time period. The Retisert is a non-biodegradable, 0.59mg sustained-release FA intravitreal implant, designed to continuously release the drug in a linear fashion over a period of approximately 2.5 years. To evaluate the efficacy and safety of the FA intravitreal implant in pediatric patients with intractable noninfectious posterior uveitis. A pilot study was performed by Patel et al [16] on four patients (6 eyes) aged <18 years who have failed to response to conventional treatment with topical and systemic steroids. Inflammation was well controlled in all six eyes and visual acuity improved significantly in 3 eyes. Two patients with IOP spike above 40mmHg ultimately required glaucoma valve placement for adequate IOP control. There were no instances of vitreous hemorrhage, retinal detachment, postoperative infection. Meanwhile, the chart review conducted by Allen et al [17] still shows promising results for the use of the Retisert implant in noninfectious uveitis. They consider the injection of the FA intravitreal implants as a useful therapeutic method in preventing vision loss and recurrence of inflammation. But concerns for development of elevated IOP and cataract remain.

In the same time, Arciune et al [18] compared the safety and efficacy of the FA implant with the DEX implant in cases/patients with noninfectious uveitis. They found that both implants are effective in preventing recurrence of noninfectious uveitis and in improving inflammation and BCVA. The difference lies in each implant's inherent advantages and disadvantages. The DEX implant may need repeated implantation due to the nature of shorter duration of action, but it has lower rates of inducing cataract progression and secondary glaucoma. The FA implant, on the other hand, has the advantage of longer duration of action, but it has higher rates of cataract progression and increasing IOP.

In general, the intravitreal implant represents a valuable approach to uveitis therapy and the use of sustained-release intravitreal corticosteroids delivery system will continue to be an indispensable practice in treating noninfectious uveitis. But prior to planning of clinical trial in humans, the possible risks must be carefully considered with intervention.

OTHER NEW METHODS FOR UVEITIS TREATMENT

Biologic Agents Recently, new drugs that modify the immune system, which emphasize less immunosuppression and seem to be more effective, have been available for treating resistant uveitis [19]. Cytokines play an important role in pathogenesis of uveitis and cytokines antagonists are now increasingly being used in various ocular inflammatory diseases to avoid the side effects of long-term steroid use and to induce remission in chronic disease.

TNF-α Antagonists for Uveitis Tumor necrosis factor-α (TNF-α) is implicated in the early pathogenesis of uveitis and can induce the expression of chemokines and adhesion molecules to prolong inflammation. The use of TNF-α antagonists has represented a significant advance in the treatment of refractory uveitis.

Adalimumab and infliximab are both monoclonal antibodies to TNF-α and have been used successfully in the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. They are effective in treating uveitis related to various autoimmune diseases, systemically or locally.

The systemic use of adalimumab, a fully humanized monoclonal antibody, has shown promising results in controlling intraocular inflammation [20-23]. Furthermore, Díaz-Llopis et al [24] evaluated the efficacy of six monthly adalimumab subcutaneous injections for refractory uveitis in 131 patients. The results showed that adalimumab effectively decreased inflammatory activity in refractory uveitis and may reduce steroid requirement after 6 months of follow-up. However, Androudi et al [25] reported that intravitreal adalimumab showed no efficacy in improving BCVA or in reducing CRT in patients with chronic uveitic macular edema.

Infliximab is a chimeric monoclonal antibody to TNF-α and has been successfully used in treating uveitis related to autoimmune diseases[26,27]. Iwata *et al* [28] reported the efficacy of infliximab systemically combined with methotrexate for suppressing the inflammation in refractory entero-Behcet's disease patients refractory to conventional therapies. They treated ten patients (three men and seven women) with infliximab at 3-5mg/kg body weight every 8 weeks thereafter in combination with MTX. All patients showed improvement of gastrointestinal symptoms and disease- associated complications within 4 weeks and ileocecal ulcerations disappeared in 9 of 10 patients at 12 months. Furthermore, corticosteroid dose was significantly reduced from 22.0mg/d to 1.8mg/d at 24 months. No severe adverse effects were observed during the 24 months of follow-up.

Meanwhile, the technique of intravitreal TNF-α antagonists has also been gradually applied for treating noninfectious uveitis[29].Farvardin *et al* [30] assessed the safety and long-term effects of intravitreal infliximab on chronic non-infectious uveitis. They treated 10 eyes of 7 patients with chronic persistent non-infectious uveitis who were non-responsive to conventional medications. All of the patients were given/administrated intravitreal injection of 1.5mg/0.15mL infliximab and followed up for 6 months. The study showed that intravitreal infliximab is a valuable option for improving the visual acuity and decreasing the central macular thickness but its effect is only temporary. Wu *et al* [31] reported their experience of treatment with intravitreal infliximab in a case series of 7 patients with refractory CME. By 6 months of follow-up, the visual acuity of these patients improved and the macular thickness was reduced. But in another study, Giganit *et al* [32] demonstrated that low-dose (0.5mg/0.5mL) intravitreal infliximab was not well tolerated and was both immunogenic and probably retinotoxic. Pulido *et al* [33] also suspected risks of intravitreal infliximab may outweigh the benefits. Therefore, not only controlled masked studies are warranted to determine the optimal dosage and duration of the treatment, but also its adverse side effects should be carefully monitored. Further data and more clinical trials are still necessary to fully understand their efficacy and potential side effects.

Other Biologic Agents Early studies confirmed that T cells play central roles in immune response. The full activation of T cells demands two special signals, one of which is through co-stimulatory molecules. The characterized co-stimulatory signaling systems, cluster of differentiation-28 (CD28) on T cells and their ligands, CD80 and CD86 on antigen-presenting cells, are critical to T cell activation. Abatacept, a soluble fusion protein which efficiently binds to CD80/CD86 on antigen-presenting cells and blocks the CD28 co-stimulatory signal, can inhibit the interaction between the CD80/CD86 and CD28 and, therefore, result in T cell inactivation. Recent literature increasingly suggests that abatacept may be useful for controlling ocular inflammatory associated with refractory juvenile idiopathic arthritis (JIA)[34-37].

The recent success in treatment of Behcet diseases with rituximab, a chimeric monoclonal antibody directed against the B-cell marker CD20 causingdepletion of CD20-B cells, indicates that B cells may have a much broader role in the pathogenesis of autoimmune uveitis [38,39]. The pathomechanism of JIA-associated uveitis remains complex, but inflammatory cell infiltration in the iris and ciliary body has been reported and was found to be predominantly CD20-B cells. Studies are currently ongoing and have provided further evidence that rituximab against the CD20 antigen may represent a rescue therapy option for severe JIA-associated uveitis refractory to immunosuppression and TNF-α inhibitors[40-42].

Gene Therapy Although the introduction of biologic agents such as TNF-α antibodies provides a new treatment regimen for patients with refractory uveitis, there are still some patients who do not respond to the biological treatment. Gene therapy may be deemed to be a treatment alternative in patients with the most aggressive forms of inflammatory ocular diseases by directly modifying ocular cell genes that encode proteins capable of down regulating the pro-inflammatory cytokine. Ocular gene therapy offers advantages over biologic agents by mediating long term therapeutic gene expression without the potential risk of systemic side effects. Recently, remarkable progress has been made in the development of this new technology in other ocular diseases[43-45].

The cytokines interferon alpha (IFN-α), interleukin (IL)-10 and the IL-1 receptor antagonist (IL-1Ra) have all been demonstrated to have anti-inflammatory effects. A few reports have shown that gene therapy with virus vector encoding the IL-1Ra or IL-10 gene can significantly ameliorate experimental uveitis [46,47]. Furthermore, Tsai *et al* [48] investigated the effectiveness of adeno-associated virus 2 (AAV2)-Mediated Subretinal Gene Transfer of human IFN-α in experimental autoimmune uveoretinitis (EAU), a classic model for human uveitis. They injected into B10RIII mice subretinally at two doses (1.5×10^6 vg, 1.5×10^8 vg). The results showed subretinal injection of both doses significantly attenuated EAU activity, and the higher dose of AAV2. hIFN-α strikingly suppressed lymphocyte proliferation and IL-17 production. In another study they investigated whether subretinal injection of both AVV2. IFN-α and AAV2. IL-4 had a stronger inhibition on EAU activity. They found that AAV2. IL-4 showed a better therapeutic effect when compared with AAV2.IFN-α. The

combination of AAV2. IL-4 and AAV2. IFN-α was not significantly different compared to AAV2. IL-4 alone [49]. IL-27 has been considered to be an effective inhibitor of both Th1 and Th17 responses and may suppress the ongoing process of the inflammatory reaction. Shao *et al* [50] treated EAU in B10RIII mice with subretinal injection of AAV2-murine IL-27p28 vector. The treatment led to positive therapeutic outcomes by decreasing IL-17 expression and increasing IL-10 expression. The transgene showed a sustained high expression from day 14 to 9 months. The experiments suggested that the inhibitory effect on the development of uveitis is mediated *via* a local and not due to a systemic effect. This study suggests that gene therapy is an ideal approach to control EAU in mice which could avoid the possibility of systemic immunosuppressive side effects.

Although gene therapy is a very attractive therapeutic option, gene therapy applied to uveitis remains a challenge, because its success is highly dependent on the gene delivery system and on the stability of transgene expression. Moreover, intravitreal administration of AAV vectors can elicit neutralizing antibodies against the vector capsid which will decrease the efficiency of therapeutic gene transfer. Besides, the results from the animal model cannot be applied directly to human diseases.

RNA Interference RNA interference (RNAi), a powerful tool for gene silencing, is a process within living cells that moderates the activity of their genes. Small-interfering RNAs (siRNAs) bind to the specific messenger RNA (mRNA) molecules and decrease their activity or trigger mRNA degradation to prevent mRNA from producing inflammation proteins. RNAi has become a valuable technique, both in biotechnology and medicine. The first clinical trials of RNAi were directed at the treatment of age-related macular degeneration (AMD) and respiratory syncytial virus infection [51,52]. Nowadays, RNAi has been shown to be of great value in decreasing ocular inflammation.

Choi *et al* [53] applied siRNAs targeting the TNF-α mRNA sequence (TNF-α siRNAs) to inhibit TNF-α function in an *in vivo* Bechet's disease-like (BD) mouse model and demonstrated significant efficacy of intraperitoneal delivery of TNF-α siRNAs to improve inflammatory symptoms by reducing the overall expression of TNF-α. For each mouse, 20mg long TNF-α siRNA in 100mL RPMI media or 100nmol #3TNF-α siRNA was injected intraperitoneally twice with a 1-week interval. To compare the efficacy of TNF-α siRNA versus an anti-TNF-α antibody, symptomatic mice were treated with infliximab which was intravenously injected only once at 150mg/mouse or with etanercept which was injected subcutaneously twice per week at 25mg per mouse. They found that TNF-α siRNA acted more rapidly and more effectively than infliximab in improving BD

symptoms. In TNF-α siRNA group, improvement showed at 9 ±7d after injection and 15 ±4d in infliximab group. The recurrence was late in the siRNA-treated group compared to the infliximab-treated group, but statistically, not different. And the therapeutic efficacy of etanercept was similar to the infliximab but its decreasing capability for the serum levels of TNF-α was delayed more than siRNA or infliximab. These findings highlight the advantages of siRNAs treatment over biologic agents for long term and more effectively therapeutic effects.

Since the inducible co-stimulator (ICOS) is upregulated in experimental autoimmune uveoretinitis (EAU), Hou *et al* [54] treated EAU with intravitreal injection of the recombinant plasmid (pRNAT-U6.1/Neo-ICOS) for the ICOS siRNA. The ICOS gene expression decreased both at the mRNA and protein levels. Moreover, the ocular inflammation decreased remarkably in the treated rats' eyes. They reported that intravitreal injection of the recombinant plasmid pRNAT-U6. 1/Neo-ICOS is sufficient to control the ocular inflammation without any interference with systemic immunosuppression.

Osteopontin (OPN) has been considered to act as a pro-inflammation cytokine to promote the Th1 response, which contributes to the production of IL-12 and IFN-γ. One animal study conducted by Iwata *et al* [55] has shown promising results indicating that OPN-siRNA treatment can be applicable to autoimmune uveitis. They delivered the OPN-siRNA into the EAU mice to down-regulate OPN expression with a modified hydrodynamic transfection method. The plasma OPN levels in the OPN-siRNA-treated group were significantly lower than those in the control group. Furthermore, the cytokines TNF-α, IL-2 and IL-17 in the plasma were also decreased. Accordingly, the clinical and histopathological scores of EAU were significantly reduced in the treatment group. The pilot data will help drive future trials in uveitis.

In conclusion, with the advancement of molecular biology, more and more therapeutic agents and approaches have been applied and will continue to be developed for controlling ocular inflammation. But there is still a long way until the immunobiology of autoimmune uveitis becomes clear and larger studies are also needed for assessing both the safety and efficacy of these new treatment options. Furthermore, key improvements are required to achieve practical management in the treatment of uveitis in humans. Nevertheless, we firmly believe that the future is very bright and all of the efforts we make will be of great benefit to all patients with uveitis.

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