

Short Communication

Recent Potential Treatment Approaches for the Management of Uveitis

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Abstract

Uveitis is an inflammatory disease affecting the uveal tract of the eye. Non-infectious uveitis [NIU] is known to be the main cause of blindness in people of all age groups in different parts of the world. NIU can be both due to autoimmune or idiopathic responses causing severe vision-related complications leading to irreversible vision loss. Thus, the treatment of this disease after the rapid diagnosis and evaluation by eminent ophthalmologists and rheumatologists is very important. The primary goal of treatment of uveitis is to limit the inflammation process and prevent recurring responses and hence preserving the vision. The current treatment therapies include corticosteroids as first-line agents followed by more potent drugs including synthetic immunosuppressants like calcineurin inhibitors, antimetabolites, and alkylating agents. However, some patients are reported to be intolerant to these therapies, therefore, biologic agents are adopted as an effective treatment approach in such cases. Anti TNF- α agents have shown promising results in the treatment process. This review enlightens about the current effective treatment approaches that are adopted as potential therapeutic agents preventing NIU.

Introduction

Uveitis, an inflammatory condition of the eye affecting the uvea [blood vessel-rich middle layer of tissue] may lead to slight or complete vision loss. This disease can affect people of any age group mainly between 20 to 60 years of age. It is reported that 24.9 cases per 100,000 persons were affected in a study in the years 2006 and 2007 with a prevalence rate of 57.5 and 58 per 100,000 persons respectively [1,2]. Uveitis is classified as anterior uveitis affecting the iris of the eye, intermediate uveitis affecting the ciliary body, posterior uveitis affecting choroid, and panuveitis affecting multiple areas of the eye. It can also be classified on the basis of severity and progress with time, acute cases that are generally sudden and symptomatic whereas chronic cases that remain asymptomatic for a long duration and are characterized by the relapse of the disease after therapy is discontinued [3]. It can be primary or secondary to some other conditions. Generally, it is known to be associated with some systematic diseased conditions like juvenile idiopathic arthritis but it can be idiopathic too [3,4]. Treatment of uveitis should be carefully implemented

after the prompt diagnosis as if it is not treated in time the chronic state of uveitis may lead to complicated conditions like glaucoma, cataract, keratopathy, macular edema, and irreversible vision loss [3,5]. Since it is known to affect people of all age groups, children diagnosed with it have more chances to develop a higher risk of complications and chronic conditions leading to severe visual impairment during the course of this medical condition. It is also reported that the quality of life of people suffering from uveitis has been noted however, these are not directly correlated with the severe inflammation or complications associated with it [6]. The pathophysiology of ocular inflammation is not very clear and the eye is an organ that is known to not get affected by the conventional immune response like other organs due to the presence of foreign antigens present in that tissue because of the presence of haemato-cellular barriers, immunomodulators like TGF- β , and absence of cell expression of both MHC-I & II in the eye [7]. It is thought that the inflammation in the uveitis is due to the T cells i.e., CD4+ T cells of Th-1 Phenotype. The exact pathogenesis of uveitis is not clearly understood but the presence of cytokines like IL-2, IL-12, IL-17, TNF- α ,

and interferon- γ have been reported in uveitis patients and therefore, they are considered as key contributors in its pathogenesis [8-10]. Therefore, targeting these cytokines might be an effective approach for treating NIU, although it is quite challenging because of the wide range of possibilities in the pathogenesis. Treatment of uveitis is generally established on the basis of the intensity of inflammation and the risk factors accompanied by it. The treatment is initiated using the mild therapeutic agents followed by severe therapeutic agents during the treatment process [3].

Treatment of non-infectious uveitis

The first-line treatment of uveitis includes Corticosteroids that are effective in treating the inflammation in acute conditions. However, in unrestrained conditions, immunosuppressant therapy is adopted including therapeutic agents like antimetabolites-methotrexate, azathioprine, mycophenolate; calcineurin inhibitors-cyclosporine, tacrolimus, and alkylating agents like cyclophosphamide and chlorambucil [11-13]. Current new biological therapies like Anti-Tumour Necrosis Factor- α agents have also emerged as a potential therapeutic approach for treating uveitis in children and adults targeting the immunological pathway involved in the disease [11,12,14].

Corticosteroids

These are considered as the first-line treatment approach for uveitis. Depending on the severity of the diseased condition they are given via topical, periocular, intraocular, or systemic route [11,15]. Generally, 1% prednisolone is given via a topical route or 0.1% dexamethasone. Prednisolone is reported to be the most used and effective corticosteroid drug used in the treatment [16-18]. In severe conditions where all uvea layers including the optic nerve are affected, in such cases i.v. corticosteroids mainly methylprednisolone [30mg/kg] is given three times a week followed by oral corticosteroids [19]. However, these drugs cannot be used in the long run due to the ocular and systemic side effects like cataract, glaucoma, and visual impairment associated with treatment. Treatment of the pediatric population with corticosteroids often requires attention as these drugs have reported causing a delay in growth and puberty development. Therefore, other treatment approaches should be considered [3].

Immunosuppressants based therapies

Immunosuppressant drugs are adopted for treatment to control the disease in cases when corticosteroids fail to inactivate and reduce the inflammatory response or in cases when recurring symptoms are observed with the onset of unusual complications [3].

Methotrexate

It is often the treatment of choice in unmanageable cases of uveitis in pediatric patients [19]. It is administered either via oral route or subcutaneous route at a dose between 10 to 15mg/m². Overall improvement with 95% confidence interval [95% CI, 0.66-0.81] in ocular inflammation in about ¾ of the total subjects has been reported for methotrexate in

unmanageable cases of uveitis in pediatric patients [20]. A randomized multicentre trial on 80 patients [16 years or above] was carried out in which the effect of methotrexate and mycophenolate mofetil was compared. Methotrexate showed better improvement than mycophenolate mofetil 69% and 47% respectively in reducing inflammation during 6 months. Methotrexate was found to be well-tolerated and patients should be examined for liver function tests [LFT] and blood cell count for 3-4 months. The side effects associated with it are usually g.i.t related generally nausea and is treated by prescribing folic acid after one day of treatment with methotrexate [21].

Mycophenolate mofetil and azathioprine: These are antimetabolites that prevent the maturing of B and T lymphocyte cells by inhibiting purine synthesis. The use of azathioprine in a cohort study involving adult patients has resulted in a reduction in ocular inflammation in 59% of patients. Azathioprine is administered at a dose of 1mg/kg per day [Max. dose 100mg per day] and increasing the dose to 3 mg/kg per day with a maximum dose of 250mg per day [22] whereas mycophenolate mofetil is administered at a dose of 600mg twice daily via the oral route. The trial showed that the mycophenolate mofetil is effective in reducing inflammation in uveitis but less effective when compared with methotrexate [23]. In 2007, Schatz et. al reported a follow-up study of forty children with non-infectious uveitis treated with azathioprine and mycophenolate mofetil, and it was found that when both these drugs were combined with corticosteroids the improvement of 61% and 94% were observed with azathioprine and mycophenolate mofetil respectively [24]. Limited data are reported for these drugs in childhood uveitis. The side effects associated with their treatment are usually gastrointestinal related, may enhance the risk of disrupting bone marrow, and also few malignancies are reported when used for long durations [3,25].

TNF- α inhibitors

The next therapeutic approach for the treatment of NIU is biological response modifiers i.e., Tumour necrosis factor - α inhibitors as these TNF- α is a proinflammatory cytokine that is released in the inflammation process of NIU and hence it has become the significant target for the treatment [26,27]. TNF- α is the cytokine that gets binds to the Tumour Necrosis Factor-Receptor [TNF-R] initiating the immunomodulatory and inflammatory response in uveitis. This receptor [TNF-R] exists in two isoforms i.e., p55 also known as TNFr1, and p75 also known as TNFr2, and is either attached to the membrane or present in the soluble forms. TNF- α inhibitors act by preventing the binding of TNF- α ligand to the TNF-R and hence, preventing the inflammatory response in patients. Several patients who are intolerant to the corticosteroid or immunosuppressant therapies can be treated with these biological agents resulting in visual improvement by reversing the vision impairment because of the uveitis [28,29].

Several clinical trials have been conducted on different TNF- α inhibitors as mentioned below and it has been found out that this TNF- α inhibitors showed significant improvement

in treating ocular inflammation and also in preventing the recurrence of symptoms.

Adalimumab, an entire human anti-TNF- α monoclonal antibody approved for the treatment of various immune-mediated inflammatory diseases including non-infectious uveitis [30]. Various clinical trials including randomized placebo-controlled trails VISUAL-I, VISUAL-II & III, and SYCAMORE [31] and ADJUVITE [32] were performed. VISUAL-I study, a phase-III multinational trial where adalimumab was given to treat non-infectious uveitis showed that the extent of treatment failure was declined to 50%. The VISUAL-II, a multicentre randomized trial showed that the adalimumab was effective in reducing the relapsing of uveitis in patients and the treatment failure was observed in 55% patients in the placebo group whereas 39% in the adalimumab group [33]. SYCAMORE trial involved the patients [2 to 18 years] with active juvenile idiopathic arthritis induced uveitis, these patients were kept in the placebo and adalimumab group and were treated with stable methotrexate followed up for 2 years. Results of this trial showed that treatment failure was found to be in 27% of patients receiving adalimumab and methotrexate whereas 60% in patients receiving methotrexate only [3]. In ADJUVITE randomized trial, patients were given adalimumab and methotrexate for two months and it was found that ocular inflammation was decreased in 56% patients and laser flare photometry examination showed improvement in 30% patients with anterior uveitis. The results of these clinical trials showed that adalimumab is effective in treating ocular inflammation and preventing relapses [34,35].

Infliximab, a chimeric monoclonal antibody [25% murine and 75% human] have undergone clinical trials for evaluating its effectiveness in NIU and it has been found that although it shows a sudden onset of action it is of less therapeutic importance as compared to adalimumab as some studies showed its failure after 12 months i.e., 60% of the treatment process [36,37].

A retrospective case study carried out by Maleki et. al showed a reduction in inflammation in 19 out of 23 patients with NIU [38]. Baughman, et al. carried out a study on patients with ocular inflammation and showed improvement in 13 out of 14 patients when treated with infliximab after the failure with usual immunosuppressant therapy [39]. A non-comparative trial conducted by Suhler et. al involved patients with unmanageable uveitis and were treated with infliximab and the results showed clinical improvement in 18 out of 23 patients in the 10th week of the treatment [40].

Golimumab, a complete humanized monoclonal antibody. Tosi. et. al conducted a study on 21 uveitis patients and it has been found that ocular flares were significantly decreased from 128.6 events per 100 patients-year to 24.9 events per 100 patients-year although all patients in that group had received another anti-TNF drug previously [41]. Also, results from Palmou-Fontana, et al. study showed improvement in 4 out of 7 patients when treated with golimumab [42].

Etanercept is a dimeric protein and is known to have a different mechanism of action than other TNF- α inhibitors

[43]. There is not much evidence about the effectiveness of this agent and also, it is no longer prescribed for uveitis due to its low ocular distribution and low effectiveness when compared with adalimumab and infliximab [44].

Certolizumab, a recombinant humanized monoclonal antibody administered at an initial dose of 400mg for one month [4 weeks] and followed by 200mg per week. It is reported having improved distribution in the inflamed ocular tissues than adalimumab and infliximab [45]. A recent study has specified that both golimumab and certolizumab can be effective and safe options for patients with uveitis even if the result with other TNF- α inhibitors have not been efficacious [41].

Other biological therapies

The various other therapies include anti-IL-6 therapies including Tocilizumab as an active therapeutic agent; Secukinumab, an anti-IL-17A monoclonal antibody; Canakinumab, an Anti-IL-1 β ; Anakinra, an IL-1 receptor antagonist; and Rituximab, an Anti CD20 antibody [35].

Anti-IL-6 therapy

Interleukin-6 is a proinflammatory cytokine produced by monocytes, macrophages, B and T cells, and are involved in several immune-mediated diseases. The intraocular concentration of IL-6 is found to be increased in uveitis and retinal vein obstruction [46]. An IL-6 receptor blocker, Tocilizumab [a recombinant human monoclonal antibody] is reported to be effective for the treatment of NIU [47]. The side effects associated with its treatment generally include chest tightness, nausea, fatigue, blisters on limbs and hands, and mild bronchitis [48,49].

Anti-IL-1 therapy

It includes IL-1 receptor antagonist Anakinra, Kineret®, and Canakinumab [Ilaris®], an anti-IL-1 β antibody. The effects of both these anti-IL-1 molecules were examined in a multicentre retrospective study that involved 19 patients with Behcet's disease-associated uveitis. The results showed that both these anti-IL therapies were effective in reducing inflammation in long-lasting and obstinate cases of uveitis [50]. Few mild side effects like headaches and arthralgias have been reported in the case of Kineret® with no major problems, hence these can be considered safe to be used in uveitis [50,51].

Anti-CD20 therapy

Rituximab [Rituxan®], is a human and murine combined monoclonal antibody that binds to the CD20 antigen present on the surface of B-cells [52]. A retrospective study was carried out in which juvenile idiopathic arthritis-associated uveitis patients were treated with it and it was found that all the patients were recovered within 5 months of the treatment and were followed up for the next 44 months [53]. Few mild side effects like flushing, hives, few cases of pneumonia, and herpes zoster have been reported. The results showed long term safe use of rituximab for refractory cases of anti-TNF- α [52].



Anti-CD25 therapy

Daclizumab is a monoclonal antibody that blocks the immune response generated by the activated T-cells by binding to the 2 α subunit of the IL-2 receptor of these T cells. Few mild side effects are reported with its use mainly rashes, herpes zoster infections, palpitations, and some liver-related disorders [35,54].

Anti-IL-17A therapy

Secukinumab is a humanized monoclonal antibody that binds to the IL-17A receptor and neutralizes the immune response [55]. Side effects reported are usually nasopharyngitis and headache. Some cases of recurring uveitis are also reported with its use [56].

Conclusions

The treatment strategies for the management of uveitis follow a stepladder approach starting with corticosteroids, immunosuppressants therapy followed by the biological therapies including anti TNF- α agents. However, acute conditions can be very well treated with the corticosteroids but the severe conditions and long-term therapies cannot be treated with these first-line agents, and hence, a new therapeutic agent is to be adopted. With the available clinical data on the biological therapies and their effectiveness in reducing the recurring inflammatory events and reduction of ocular inflammation, it can be concluded that they may be considered as the new first-line treatment approach for some cases of uveitis. Also, various other therapeutic approaches are likely to emerge as potential treatment therapies for NIU.

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