Special Report
Taiwan J Ophthalmol 2018;8:117-20

Recommendation of using systemic anti-tumor necrosis factor-alpha for the treatment of noninfectious uveitis in Taiwan

De-Kuang Hwang1,2, Yih-Shiou Hwang3,4, Ming-Ling Tsai5,6, Chun-Ju Lin7,8, Wei-Chun Chan9, Yo-Chen Chang10,11, Der-Yuan Chen8,12, Tsu-Yi Hsieh13,14, Shwu-Jiuan Sheu2,15, Chang-Ping Lin16

Abstract:
Noninfectious uveitis is a sight-threatening disease with an autoimmune or autoinflammatory basis. Systemic treatment is required if intraocular inflammation threatens a patient’s vision or cannot be controlled locally and when it is associated with systemic rheumatic diseases. Corticosteroids and immunomodulatory chemotherapy are the conventional initial treatments. However, the various side effects of these therapies increase the burden on patients, not only physically but also mentally. Moreover, uncontrolled inflammation and poor visual outcomes have sometimes been recorded despite the combination of these medications or their high dosage. Antitumor necrosis factor-alpha (anti-TNF-α) and other biologic agents have been widely used to treat rheumatic diseases for >15 years. Randomized controlled clinical trials have demonstrated that anti-TNF-α can reduce and delay episodes of intraocular inflammation not only in patients with active uveitis but also in corticosteroid-dependent patients with inactive uveitis. The Taiwan Food and Drug Administration approved the use of adalimumab, an anti-TNF-α agent, for treating nonanterior noninfectious uveitis (NANIU) in 2017. This report provides a recommendation and a proposed stepladder approach for using anti-TNF-α agents to treat NANIU in Taiwan.

Keywords:
Adalimumab, immunomodulatory, noninfectious, treatment, tumor necrosis factor, uveitis

Introduction

Uveitis is a sight-threatening disease, and intraocular inflammation in uveitis involves the iris, ciliary body, and choroid.[1] Reports have noted that 5%-20% of legal blindness in developed countries can be attributed to uveitis.[2] The disease is associated with more than 60 etiologies, either infectious or noninfectious.[3] Antipathogenic agents that focus on the specific pathogen are the definitive treatment for infectious uveitis, whereas the regional or systemic administration of anti-inflammatory drugs is the main treatment for noninfectious uveitis.[4,5]

Anterior uveitis involves intraocular inflammation that affects the iris only, and it represents 78% of new uveitis cases in Taiwan. Compared with nonanterior uveitis, iritis can be easily controlled using topical
medications only. Conversely, nonanterior uveitis, including intermediate uveitis, posterior uveitis, and panuveitis, usually requires systemic immunomodulatory therapy (IMT) and is more commonly associated with ocular complications or poor visual outcomes. To date, oral corticosteroids remain the mainstay of systemic treatment for noninfectious uveitis. Various conventional immunomodulatory therapy (IMT) agents, including cyclosporine, tacrolimus, methotrexate, azathioprine, mycophenolate, leflunomide, chlorambucil, and cyclophosphamide, are used as steroid-sparing agents or for systemically reducing exposure to high-dose corticosteroids. Two large multicenter randomized clinical trials in 2016 proved that adalimumab, a humanized monoclonal anti-TNF-α antibody, is effective in controlling nonanterior noninfectious uveitis (NANIU) and providing a potential steroid-sparing effect. Accordingly, the Taiwan Food and Drug Administration approved its use for the treatment of NANIU.

Antitumor necrosis factor-alpha (anti-TNF-α) has been used for the treatment of systemic rheumatic diseases since 1999. To date, it has been approved for the treatment of up to 14 indications globally. Various studies and case series have already demonstrated the effectiveness of anti-TNF-α for treating refractory uveitis. Two large multicenter randomized clinical trials in 2016 proved that adalimumab, a humanized monoclonal anti-TNF-α antibody, is effective in controlling nonanterior noninfectious uveitis (NANIU) and providing a potential steroid-sparing effect. Accordingly, the Taiwan Food and Drug Administration approved its use for the treatment of NANIU.

Owing to Taiwan’s universal insurance reimbursement policy, a general consensus of the timing and application of anti-TNF-α agents for treating uveitis should be reached. Thus, in this paper, we propose a stepladder approach for using adalimumab to treat NANIU in Taiwan based on the literature and the recommendations of uveitis specialists and rheumatologists.

Methods

To reach a consensus and provide recommendations for using adalimumab to treat NANIU in Taiwan, on March 11, 2017, two expert rheumatologists and eight uveitis specialists met and discussed the usage and time point of systemic therapy using biologic agents including anti-TNF-α for treating uveitis. Studies relevant to the use of biologic agents for treating uveitis were searched and reviewed before the meeting. Topics including “clinical indication of anti-TNF-α in uveitis,” “general first-line therapy for NANIU,” “timing of anti-TNF-α in the induction (acute) phase of uveitis,” “evidence-based definition of disease activity in uveitis,” “timing of anti-TNF-α in the maintenance (nonacute) phase of uveitis,” “timing of discontinuing current anti-TNF-α agent if the treatment fails,” “timing of discontinuing or tapering anti-TNF-α agent if the patient is stable,” “recommended treatment of recurrence,” and “exceptional disease entities” were discussed. Based on the consensus reached on these topics, a stepladder approach was proposed for using adalimumab to treat NANIU in Taiwan.

Results-Recommendations

The proposed stepladder approach is described as follows and is illustrated in Figure 1:

a. Before biologics, systemic corticosteroids and conventional IMT should be used as the first-time therapy in patients with NANIU before biologics. The recommended initial dosage of systemic corticosteroids is 1 mg/kg/day. The treatment response of patients to the conventional therapy should be evaluated at 1 month after initial treatment.

b. The treatment effect should be evaluated based on changes in the activity and severity of intraocular inflammation. Based on studies with a high level of evidence, three critical indicators for “active uveitis” were defined: “anterior chamber cells ≥2+ based on the Standardization of Uveitis Nomenclature criteria,” “vitreous haze Grade ≥2+ based on the National Eye Institute criteria,” and “new chorioretinal or retinal vascular lesion.” The presence of any of these signs indicates that the uveitis is still active in the patient. If the uveitis is effectively controlled by conventional therapy, systemic corticosteroids should be gradually tapered to ≤7.5 mg/day within 3 months to avoid their systemic side effects. However, if the uveitis cannot be controlled by conventional therapy or if maintenance on a moderate-to-high dosage of systemic corticosteroids (>7.5 mg/day) is required, an anti-TNF-α agent such as adalimumab should be used. The recommended dosage of adalimumab, which should be administered through subcutaneous injection, for treating uveitis is 80 mg as the initial loading dose, 40 mg 1 week later, and then 40 mg every 2 weeks subsequently.

c. Anti-TNF-α agents such as adalimumab should be considered as first-line therapy or as early as possible in some exceptional situations. These include the presence of diffuse retinal vascular occlusions, chorioretinal lesions involving macula, disease progression despite treatment with high-dose systemic corticosteroids, blindness in the fellow eye due to the same disease, and having a history of severe intolerance or contraindication to systemic corticosteroids or IMTs.

d. After anti-TNF-α therapy is initiated, close monitoring of intraocular inflammation and the systemic condition should be conducted. According to clinical trials, disease activity and treatment efficacy should be re-evaluated and judged following 6 months of treatment. If uveitis is not under control, discontinuation of the current agent or shifting to another targeting biologic is recommended.

e. The time point to start tapering or discontinuing current anti-TNF-α agents in patients with inactive...
uveitis remains unclear and controversial on the basis of current evidence. A critical decisive factor is the course and severity of rheumatic disease associated with uveitis. In general, tapering current anti-TNF-α agents is suggested if uveitis activity remains quiescent for 2 years. However, reinstitution of anti-TNF-α therapy should be considered if uveitis recurs during or after the tapering process.

**Discussions and Summary**

Because high-level evidence for noninfectious uveitis treatment is lacking, and because uveitis is a disease with differing immunopathological etiologies, evidence-based treatment guidelines are not well established. Previous treatments with conventional drugs for NANIU usually maintain a balance between acceptable visual results and the systemic side effects of drugs. Adalimumab and other anti-TNF-α agents not only provide improved efficacy in controlling uveitis but also higher steroid-sparing rate. Although the Taiwan Food and Drug Administration approved the use of a5alimumab for treating NANIU, to date, no clear guidelines or suggestions exist for using anti-TNF-α therapy in Taiwan.
We believe that anti-TNF-α agents can be a vital step-up in the stepladder approach outlined in this paper. For some specific patients with NANIU, anti-TNF-α should be reinstituted as first-line therapy. In this proposed approach, the three major indications to initiate anti-TNF-α therapy with adalimumab are as follows: (1) when uveitis cannot be controlled by conventional therapy, (2) when quiescence of intraocular inflammation cannot be maintained under low-dose corticosteroid, and (3) when patients meet exceptional conditions that require emergent aggressive therapy. Tapering or discontinuing anti-TNF-α agents is suggested when uveitis is not fully controlled after 6 months of treatment or when inflammation is quiescent for more than 2 years. Based on experts’ recommendations, improved strategies for the use of anti-TNF-α agents were proposed in this paper. These strategies will hopefully help patients with NANIU to achieve better visual outcomes with a balance between cost-effectiveness and fewer drug-related side effects.

Financial support and sponsorship
This work was supported by Taipei Veterans General Hospital (106-107;V107B-019).

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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