Uveitis, which is a major cause of blindness worldwide, is defined as intraocular inflammation that affects the iris, ciliary body, vitreous, retina and choroid. Tumor necrosis factor-alpha (TNF-α) is a key cytokine involved in the pathogenesis of many inflammatory diseases including uveitis. Corticosteroids and immunosuppressive agents are the conventional therapy to treat non-infectious uveitis. In cases that are resistant to these therapies, anti-TNF agents are added. An anti-TNF-α agent, adalimumab, was recently approved for the treatment of refractory non-infectious uveitis. In this review, we provide an introduction to uveitis and summarize the effectiveness and safety of adalimumab in the treatment of non-infectious uveitis.

1. Introduction

Uveitis is a common cause of blindness worldwide [1,2]. Intraocular inflammation damages ocular tissue and causes various complications such as vitreous opacity, macular edema, retinal vasculitis, glaucoma and optic neuropathy, leading to a loss of vision. The etiology of uveitis is roughly divided into infectious and non-infectious causes. Non-infectious uveitis is usually associated with autoimmune-mediated ophthalmological diseases or systemic inflammatory diseases such as Behçet’s disease, Sarcoidosis and Vogt–Koyanagi–Harada (VKH) disease [3]. The treatment strategies for infectious and non-infectious uveitis differ depending on the etiology. Corticosteroid has been used as a first-line therapy for non-infectious uveitis, focusing on suppressing the severity of inflammation. The treatment includes topical, regional and systemic corticosteroid. Immunosuppressive agents such as methotrexate (MTX) and cyclosporine (CsA) are added based on the disease activity. However, some severe cases do not respond to these treatments and progress to permanent visual impairment due to persistent intraocular inflammation or a recurrence of the inflammation.

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that activates and recruits various immune cells and induces the production of inflammatory cytokines and chemokines. TNF-α is thought to be involved in the pathogenesis of non-infectious uveitis [4,5]. The serum level of TNF-α was shown to be elevated in uveitis patients, and this elevation was correlated with the patients’ disease activity [6,7]. Anti-TNF agents such as infliximab and etanercept have been used to treat patients with refractory uveitis for whom corticosteroids and immunosuppressive treatments were ineffective.

Adalimumab (ADA) is a recombinant human IgG1 monoclonal antibody against human TNF-α. ADA was approved in 2016 by the US Food and Drug Administration as the first anti-TNF-α agent for the treatment of non-infectious intermediate, posterior and pan uveitis. In Japan, ADA was also approved for the indication of the treatment of non-infectious uveitis in 2016. The standard ADA protocol for uveitis is 80 mg at the initial (subcutaneous, s.c.) administration followed by a 40 mg dose (s.c.) every 2 weeks. In this review, we highlight the clinical studies of ADA treatment in non-infectious immune-mediated uveitis, including Behçet’s disease, Sarcoidosis and Vogt–Koyanagi–Harada (VKH) disease.

2. Clinical studies of ADA in non-infectious uveitis

The most relevant clinical studies on ADA in non-infectious uveitis were recently published. The VISUAL studies are multicenter randomized controlled trials evaluating the efficacy of ADA for
non-infectious uveitis. The VISUAL I study included 217 patients with active uveitis despite systemic corticosteroid therapy; 110 patients received ADA treatment and the other 107 patients received a matched placebo with tapering of a corticosteroid over the course of 15 weeks [8]. The median time until treatment failure occurred was 24 weeks in the ADA group and 13 weeks in the placebo group. The VISUAL II study examined 229 patients with inactive uveitis treated with systemic corticosteroid therapy; 115 patients received ADA treatment and 114 patients received a matched placebo with tapering of a corticosteroid over the course of 19 weeks [9]. The median time to treatment failure was >18 months in the ADA group and 8.3 months in the placebo group. Both of the VISUAL studies thus demonstrated a lower risk of treatment failure in the ADA-treated groups.

The VISUAL III study, an extension of the VISUAL I and II studies, evaluated the efficacy of ADA for a ≤78 weeks’ follow-up in eyes with active or inactive uveitis [10]. At study entry, 242 of the 371 (65%) patients had active uveitis. At week 78, 60% (145/242) had achieved quiescence, and 66% (95/143) of those were corticosteroid-free. At study entry, 129 of the 371 (35%) patients had inactive uveitis. At week 78, 74% (96/129) had achieved quiescence, and 93% (89/96) of those were corticosteroid-free. The mean corticosteroid dose decreased from 13.6 mg/day (week 0) to 2.6 mg/day (week 78) in the patients with active uveitis and remained stable in those with inactive uveitis from 1.5 mg/day (week 0) to 1.2 mg/day (week 78). The VISUAL III results thus confirmed the efficacy of ADA in controlling intraocular inflammation and reducing the dose of corticosteroid, even over a longer term.

Another anti-TNF-α monoclonal antibody, infliximab (IFX), is currently the most frequently used antibody for non-infectious uveitis. Two studies have investigated the differences in the efficacy of ADA and IFX for non-infectious uveitis [11,12]. In a multicenter observational study of 160 patients with refractory non-infectious uveitis, 62 patients (39%) were treated with ADA and 98 patients (61%) were treated with IFX; equivalent complete or partial responses were attained by the ADA group (95%) and IFX group (97%) [11]. In a retrospective observational study of 107 patients, 66 patients (62%) were treated with ADA and 41 patients (38%) were treated with IFX; the study’s authors’ found that the frequency of uveitis relapses during the first 12 months of treatment was decreased in 84.2% of the ADA group and 66.7% of the IFX group (p = 0.09) [12]. ADA as well as IFX has thus shown efficacy in the treatment of non-infectious uveitis.

3. Effectiveness of ADA in each non-infectious uveitis diseases

3.1. Behçet’s disease

Behçet’s disease (BD) is a multisystem inflammatory disorder of unknown etiology. It is defined by a spectrum of systemic immune-mediated characteristics including recurrent oral and genital ulcers, skin symptoms, arthritis and ocular inflammation. Over two-thirds of BD patients will develop pan uveitis with retinal vasculitis [13]. Several clinical studies have shown that the concentration of TNF is increased in the serum and aqueous humor of BD patients, especially during periods of higher disease activity [14,15]. In recent years, ADA has increasingly proved to be useful for refractory BD with uveitis. Interlandi et al. reviewed the cases of 12 BD patients treated with ADA [16], and they reported that 11 of the patients achieved uveitis remission with visual acuity improvement at a 21-month follow-up. These patients also achieved reductions of both the number of uveitis attacks and the daily steroid dose. Fabiani et al. conducted a larger-scale multicenter retrospective study of ADA-treated BD patients with uveitis [17]. Sixty-six eyes of 40 BD patients treated with ADA (40 mg every 2 weeks) were examined. At the 3-month follow-up, 35/40 (87.5%) patients had responded to ADA. The number of ocular inflammatory flares and visual acuity were both significantly improved at 12 months compared to the time point of the treatment initiation.

3.2. Sarcoidosis

Sarcoidosis is a chronic granulomatous disease affecting systemic organs. The lung is the most often affected, but uveitis occurs in 20–30% of sarcoidosis patients [18]. Erckens et al. described good clinical effectiveness of ADA in sarcoidosis patients with refractory uveitis [19]. Twenty-six patients were treated with ADA (40 mg every 2 weeks) for 12 months. The intraocular inflammation was improved in 22/26 (85%) and stabilized in 4/26 (15%) of the patients. The patients also achieved a significant reduction of systemic corticosteroids and methotrexate. At 12 months after the initiation of ADA, no recurrences of uveitis had occurred among the patients.

In another study, 8/10 (80%) patients with sarcoidosis and uveitis treated with ADA achieved the control of intraocular inflammation at 24 months [20]. Two of the 10 patients discontinued ADA treatment because of their clinical improvement.

3.3. Vogt–Koyanagi–Harada (VKH) disease

VKH disease is a systemic disease. It is a mediated autoimmune response by T cells against melanocytes
## Table 1. Clinical studies of adalimumab treatment in patients with non-infectious uveitis.

| Behçet’s disease | Study design | Patient number | Follow-up duration | Dosage | Primary outcome | Results | Adverse events |
|------------------|--------------|----------------|--------------------|--------|-----------------|---------|----------------|
| Authors [Ref.]   | Retrospective | 12 (22 eyes)   | 21 ± 9.63 months   | 40 mg SC every 2 weeks | Ocular inflammatory activity | 11/12 (93%) remission | None |
| Fabiani et al. [17] | Multicenter retrospective | 40 (66 eyes) | 12 months | 40 mg SC every 2 weeks | Ocular inflammatory flares | 200 flares → 8.5 flares /100 patients/year | Pneumonia |
| Sarcoïdosis | Prospective | 26 (41 eyes) | 12 months | 40 mg SC 1x/week | Intraocular inflammatory signs: Macular edema, vitreous opacity, chorioretinal lesions etc. | 22/26 (88%) improved | Subcutaneous solid mass at injection site |
| Riancho-Zarrabeitia et al. [20] | Multicenter retrospective | 10 | 24 months | 40 mg SC every 2 weeks | Clinical scores: Macular thickness, visual acuity, sparing effect of corticosteroid, etc. | 8/10 (80%) improved | Psoriasis |
| Vogt-Koyanagi-Harada disease | Retrospective | 14 (28 eyes) | 6, 12 months | 40 mg SC every 2 weeks | Visual acuity | At 6 months: 8 → 3 eyes < 0.4 | None |
| Couto et al. [21] | Retrospective | 2 (28 eyes) | 12, 24 months | IFX 5 mg/kg | Anterior chamber inflammation | 2/2 (100%) Complete clinical remission | None |
| Flores-Robles et al. [22] | Retrospective | 2 | 12, 24 months | ADA 40 mg SC every 2 weeks | Anterior chamber inflammation | 2/2 (100%) Complete clinical remission | None |
in the eye, central nervous system, inner ear and skin, resulting in various clinical manifestations. In the eye, VKH disease is characterized by severe bilateral granulomatous intraocular inflammation associated with serous retinal detachments, optic disc edema and vitritis. ADA has been demonstrated to be effective in VKH disease. In their retrospective study of 14 patients with VKH treated with ADA, Couto et al. confirmed this effectiveness of ADA [21]; they assessed the following main outcomes: the patients' visual acuity, anterior segment inflammation, optic nerve inflammation, steroid sparing effect and number of immunosuppressive agents used. Of the patients' 28 eyes, eight eyes at initiation and three eyes at 6 months had ≤0.4 visual acuity. Active anterior segment inflammation was observed in 13 of the patients at initiation and five of the patients after 6 months of ADA treatment. The median corticosteroid dose was reduced from 20 mg at initiation to 4 mg at 6 months. Eleven of the patients were on immunosuppressive treatment at initiation, and this treatment was continued at 6 months in only four of the patients.

Flores-Robles et al. described the cases of two patients with severe VKH disease, and they reported the effectiveness of switching to ADA from IFX [22]. In both patients, IFX (5 mg/kg) was initiated as the first anti-TNF-α agent, administered every 2 weeks. Switching to ADA was required for both patients because of their inadequate clinical response to infliximab. After the initiation of ADA (40 mg every 2 weeks), complete clinical remission was observed in both cases.

5. Conclusion

Based on the results of several clinical studies (Table 1), ADA has been confirmed as a useful agent for reducing the ocular inflammation of non-infectious uveitis which is refractory to a corticosteroid or immunosuppressive drugs. ADA has also been demonstrated to be an effective corticosteroid-sparing therapy to reduce the various ocular and systemic side effects that are associated with the chronic use of corticosteroid.

In addition to its effectiveness, ADA has the advantage of being available for self-subcutaneous administration, unlike the other anti-TNF-α agents which require the patient’s hospitalization. However, like other anti-TNF-α agents, the possible adverse events such as infections, malignancies and demyelinating disorders must be monitored when ADA is used.

Disclosure statement

No potential conflict of interest was reported by the authors.

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