Current standardized therapeutic approach for uveitis in Japan

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ABSTRACT
Uveitis is an ocular disease associated with systemic immune-mediated diseases such as rheumatoid arthritis, inflammatory bowel disease and ankylosing spondylitis; and infectious diseases. Infectious uveitis occasionally shows symptoms similar to those of non-infectious uveitis. Therefore, distinguishing between non-infectious and infectious uveitis is critical for definitive diagnosis and appropriate choice of treatment. Once the cause of infection is known, treatment can be promptly initiated. However, in contrast to infectious uveitis, non-infectious uveitis is more difficult to diagnose clinically. Eliminating the possibility of infectious uveitis is important because unlike the infectious type, non-infectious uveitis is treated with immunosuppressive drugs such as corticosteroids and biological agents. Compared to other countries, the drugs available in Japan are limited. Cyclosporin A is the only immunosuppressive drug available for treating uveitis in Japan, and infliximab and adalimumab are the only biological drugs that have been approved for use in the treatment of uveitis in Japan. In this review, I describe the characteristics of typical non-infectious uveitis in Japan and its treatment methods.

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1. Introduction
Uveitis is an ocular disease and one of the major causes of blindness. In 2009, the Japanese Ocular Inflammation Society (JOIS) established a multi-center retrospective study to investigate the frequency of uveitis in the Japanese population [1]. A similar retrospective study was previously conducted by JOIS in 2002 [2]. However, the studies did not yield similar results. Although both found sarcoidosis was the most frequent cause of uveitis, followed by Vogt-Koyanagi-Harada disease (VKH), in 2009, the number of patients with Behcet’s disease decreased from the third to sixth rank, whereas those with acute anterior uveitis, scleritis, and herpetic iritis increased. Nevertheless, patients with Behcet’s disease are often encountered in the outpatient clinic (Table 1).

Uveitis cases are frequently encountered in medical practice. In Japan, as in the United States, a step wise approach to its treatment is commonly employed [3]. Most cases of uveitis are treated with topical steroid treatment, more particularly with eye drops. However, some patients do not respond to topical treatment, in which case they are referred to hospitals for further investigation and treatment. Especially in severe Behcet disease, Japanese ophthalmologists move directly to biological drugs such as infliximab [3]. In the hospital, these patients undergo clinical tests such as blood tests and chest X-rays in order to investigate the cause of uveitis. One of the most important factors to consider when treating uveitis is to determine whether the underlying cause is an infection, as this will determine the course of treatment. For example, in endophthalmitis or other infectious uveitis, steroid monotherapy or other immunosuppressive treatments can promote disease progression. Moreover, excluding malignant lymphoma and optic neuritis is also important to decide the course of uveitis treatment. In summary, an accurate diagnosis is required for effective treatment. Furthermore, treatment must also be decided in consideration of the etiological, anatomical and chronological aspects of each patient.

Corticosteroid treatment has been the most commonly used course of treatment for non-infectious uveitis for several decades. In most cases of non-infectious uveitis, oral corticosteroid is able to effectively control the inflammatory condition. However, long-term use of corticosteroids can often lead to adverse events such as diabetes, infection (e.g., tuberculosis) and osteoporosis. Moreover, in severe cases in which corticosteroid treatment fails to reduce inflammation, immunosuppressive drugs such as Cyclosporin A (CSA) are used for treatment. In Japan, the only immunosuppressive drug...
approved for uveitis treatment is CSA. Methotrexate (MTX) and other immunosuppressive drugs are not approved for the treatment of uveitis in Japan [3]. Using immunosuppressive drug to treat uveitis is also not approved by the Food and Drug Administration in the USA. However, it is worth noting that the insurance system in Japan is different from US. If an insured patient requires expensive immunosuppressive medication, the insurer will often need to approve its use [3]. Therefore, in comparison with the USA, there are few options available in Japan for controlling inflammation in patients with uveitis. Immunosuppressive drugs are used as a second choice for controlling uveitis. Until recently, there were no treatment options available for patients in whom corticosteroid and immunosuppressive drug therapy was ineffective, specifically in those with Behc¸et’s disease. However, in 2007, the use of the biological drug ‘infliximab’ was approved for the first time in Japan for the treatment of patients with Behc¸et’s disease. Following this, adalimumab was also approved for the treatment of intractable uveitis in Japan in 2016. Biological drugs are defined as bioengineered receptor complexes, antibodies, and Fab fragments that affect the expression of inflammatory agents. Biological agents, especially antibody drugs against tumor necrosis factor alpha (TNF-α) protein, led to a revolution in the treatment methods for severe uveitis in patients who are at a risk of losing visual function. However, similar to immunosuppressive drugs, biological drugs are also considered as ‘second choice’ to treat patients suffering from severe (recurrent) uveitis in Japan.

This review article describes the nature of uveitis and currently available treatment modalities such as corticosteroids, immunosuppressive agents, and biological drugs in Japan including characteristics and usage methods, with a particular emphasis on infliximab and adalimumab.

2. Uveitis – Types, epidemiology, pathogenesis and management approaches

Uveal tissue consists of the iris, ciliary body and choroid. When inflammation occurs in the uveal tissue, it extends to the surrounding ocular tissues, such as the cornea, retina and optic nerve. This phenomenon is known as uveitis. Uveitis can be caused by infectious agents such as viruses, bacteria and fungi, or can be induced by an autoimmune mechanism. To investigate the etiopathogenesis of infection, multiplex PCR analysis is useful. Previously, it had been reported that several pathogenic DNA from aqueous humor or vitreous body were detected by multiplex PCR analysis [4]. Diagnosis of uveitis becomes relatively easier on the detection of the pathogen, thereby enabling precise and effective management of the condition. In contrast to infectious uveitis, autoimmune uveitis (non-infectious uveitis) is sometimes difficult to treat, even after diagnosing the cause of uveitis. Animal models of uveitis or samples from uveitis patients have helped to investigate the mechanism of pathogenesis in autoimmune uveitis [5–8].

One of the most affected tissues in uveitis is the retina. When retinal tissue is affected by inflammation, it can lead to retinal vasculitis. This may also lead to macular dysfunction. The vascular retinal layer has a specific function, similar to that of the blood-brain barrier in the brain. In the presence of inflammation, such as that seen in cases of uveitis, the blood-retina barrier (BRB) is disrupted by inflammatory agents such as cytokines including interleukin-1 (IL-1), IL-6 and TNF-α. These cytokines are secreted by several inflammatory cells that infiltrate the ocular tissue. In autoimmune uveitis, especially in VKH, active CD4+ T cells that respond to tyrosinase450-462 peptide contribute to the immunopathogenic mechanism [6,9,10]. Tyrosinase regulates melanin production, and it is expressed in both melanoma cells and melanocytes. Therefore, infiltrating CD4+ T cells easily recognize tyrosinase on melanocytes, thus triggering the inflammatory processes in a VKH patient. Moreover, the vitreous samples from sarcoidosis patients have revealed that a high amount of CD4+ T cells existed in the vitreous cavity [11]. Therefore, in sarcoidosis patients, local CD4+ T cells may be of concern in the pathogenesis of uveitis. In Behc¸et’s disease, it has been previously reported that neutrophils in peripheral blood and T cell clones from the regional site of inflammation at the retina secreted high amounts of TNF-α and other inflammatory cytokines. Therefore, to treat non-infectious uveitis, it is important to control the immune cell function or suppress the inflammatory cytokines.

3. Non-infectious uveitis

3.1. Behc¸et’s disease

Behc¸et’s disease causes a range of symptoms by systemically affecting organs such as skin, ocular tissue, or oral tissue, among others [12,13]. Clinical examination revealed that HLA-B51 allele is the genetic
factor most strongly correlated with Behçet’s disease in Japanese patients (50–70%) [14]. Moreover, many patients with Behçet’s disease elicited a positive reaction for skin prick test induced by streptococcus vaccine [15]. Specifically, in the ocular tissue, uveitis, particularly the non-infectious and non-granulomatous type, is the most common presentation. The inflammation area typically covers the entire ocular tissue (panuveitis). The typical ocular signs are iritis with hypopyon, chorioretinitis, retinal vasculitis (Figure 1), retinal vein occlusion, optic neuritis, vitreous hemorrhage and retinal neovascularization. When severe inflammation occurs at the posterior pole of the retina, retinal vessel occlusion can damage the sensory retina. Unfortunately, a majority of the patients with severe Behçet’s disease are affected by pan-uveitis. Therefore, it is important to avoid ocular inflammation in Behçet’s disease patients. Colchicine and immunosuppressive drugs, such as CSA, are usually able to manage the inflammation in the majority of patients with Behçet disease. However, these drugs are sometimes inadequate. In acute phase Behçet disease, sub-tenon injection of triamcinolone is the first choice to suppress the acute severe inflammation at the posterior segment, which is important to avoid ocular immune attack. Moreover, intravenous corticosteroid injections (betamethasone: 8 mg) are usually administered for a number of days in response to posterior attacks. Additionally, 30–40 mg of prednisolone is used to suppress ocular attack around 7 days. To avoid ocular immune attacks, Behçet’s disease ocular attack score 24 (BOS24) has been used to identify potential Behçet’s disease patients as candidates for intensive treatment [16]. Recent reports have shown that anti-TNF-α antibody (infliximab) dramatically suppresses ocular inflammation [17–19]. Infliximab administration dramatically controls inflammation and reduces inflammatory attacks in Behçet’s disease patients [16].

3.2. VKH

The uveitis in VKH presents initially as a non-infectious and granulomatous posterior uveitis and can be associated with retinal detachment (serous) (Figure 2(a,b)), disc edema (sometimes induces neuritis) and vitritis. VKH is known to manifest as 2 types – a retinal detachment type or a disc edema type. The disc edema type frequently occurs at middle to old age. Moreover, some VKH patients have systemic disorders such as hearing loss, tinnitus, vertigo and meningitis. Therefore, VKH is known as a systemic disorder and is not limited to only being an ocular disease. In Japan, high dose systemic corticosteroid therapy is the standard initial treatment for VKH. This typically starts with either 1 gram/day intravenous corticosteroid treatment (corticosteroid pulse) for 3 days, or high amount of oral corticosteroid treatment, after which the corticosteroid amount is gradually decreased (to 60 mg/day or 1 mg/kg/day). It is the second most frequently encountered ocular inflammatory disease in outpatient clinics in Japan [1]. The incidence of VKH varies among races; it is particularly common in Asia, Latin America and the Middle East, but rare in the United States [20,21]. It was reported that HLA-DR4, -DRw53, -Dw15 and -Bw54 are genetic factors associated with VKH [22]. VKH is an autoimmune inflammatory disorder mediated by CD4+ T cells. Activated CD4+ T cells attack melanocytes, which are localized to the ocular tissue, skin and hair roots. VKH diagnosis is accomplished using the following techniques, and characterized by the following observational criteria, as previously published by the American Journal of Ophthalmology [23]: several ocular examinations such as optical coherence tomography (OCT), fluorescence angiography and indocyanine green (ICG) angiography. In OCT, especially swept-source OCT (S-S OCT), a thicker choroid is detected at the initial or recurrent phases of VKH (Figure 2(b)) [24,25]. In ICG angiography, multiple dark spots appear, especially during the
acute phase (Figure 2(c)), which may be used as a marker for the active phase of the disease [26,27]. If a thicker choroidal layer or dark spots are seen on ICG, treatment intensity should be increased to prevent recurrent inflammation [28]. Moreover, previous studies have shown that dynamic blood flow at the choroid during treatment or a flare in the aqueous humor at the initial phase of treatment are predictors of VKH severity [29–31]. Recurrent VKH involves severe forms of ocular inflammation such as anterior uveitis or pan-uveitis, and cannot be controlled with corticosteroid treatment alone. Recurrent inflammation is associated with a worse prognosis for visual acuity due to the development of complications such as cataract, and secondary glaucoma. Therefore, it is important to avoid recurrent inflammation in VKH, and if it does occur, it is of paramount importance to control the inflammation.

The CD4+ T cells that mediate VKH secrete IL-2, interferon-γ (IFN-γ) and TNF-α. Therefore, as well as corticosteroids, immunosuppressive agents or biological drugs such as adalimumab can be used to control CD4+ T cells and improve VKH prognosis. In conclusion, when corticosteroid and immunosuppressive drugs cannot control VKH, the use of biological drugs is the preferred choice of treatment for inflammation.

3.3. Sarcoidosis

Sarcoidosis is an inflammatory disease of unknown cause, characterized by the formation of noncaseating epithelioid cell granulomas. One of the tissues affected in this condition is the ocular tissue. In sarcoidosis patients, mutton-fat type of corneal posterior keratoprecipitate (Figure 3(a)), iris nodule, and typical peripheral anterior synechia (Figure 3(b)) are formed at the anterior segment. In the posterior segment, strings-of-pearl type of vitreous opacity, typical posterior segmented vasculitis (Figure 3(c,d)), and areas of retinal atrophy resembling photocoagulation scars are frequently seen. In contrast, conjunctival, choroidal, or optic disc granulomas are not frequently seen. Ophthalmoplegia is a rare clinical feature in sarcoidosis patients. Usually, most clinical symptoms are not very aggressive.

Although the exact cause of sarcoidosis is unknown, previous reports have shown that bacterial infection, especially Propionibacterium acnes infection, could be one of the causes of uveitis in sarcoidosis patients.
However, the relationship between bacterial infection and induction of sarcoidosis uveitis remains unknown. In Japan, diagnosis of sarcoidosis requires evidence of multiple organs being affected, supported by multiple results from different examinations including clinical, radiological, and pathological (for definitive histopathological diagnosis of sarcoidosis) examinations. Diagnosis of ocular sarcoidosis also requires several ocular features to be present. In Japan, the diagnosis of ocular sarcoidosis follows the criteria of the International Workshop on Ocular Sarcoidosis (IWOS) [34,35].

In some cases, ocular sarcoidosis can be controlled with topical treatments such as corticosteroid eye drops or sub-Tenon injection of corticosteroids in the active phase. However, in aggressive cases, systemic corticosteroid (starting at 0.5–1.0 mg/kg), immunosuppressive drugs, or combination therapy (corticosteroids and immunosuppressive drugs) are used for controlling uveitis in sarcoidosis patients. However, chronic uveitis is sometimes inadequately managed with corticosteroids or immunosuppressive drugs. Chronic uveitis causes dense vitreous opacity, cystoid macular edema and epiretinal membrane complications that may not resolve with medical treatment alone. In such cases, patients receive surgical intervention. Previous data suggest that a high amount of CD4+ T cells exist in the vitreous cavity of patients with uveitis and sarcoidosis [8,11]. Activated CD4+ T cells mainly secrete IL-2 and IFN-γ in the initial acute phase, leading to vitreous opacity. In the chronic stage, cystoid macular edema or epiretinal membrane are formed under inflammatory conditions, with the secretion of high
amounts of IL-12 and granulocyte macrophage-colony stimulating factor (GM-CSF) [36]. Moreover, some reports have presented evidence that TNF-α is increased in the vitreous of sarcoidosis patients. Based on this evidence, cases of sarcoidosis uveitis also require anti-inflammatory treatment to prevent loss of visual function caused by retinal damage such as cystoid macular edema and retinal vasculitis. Biological drugs, such as anti-TNF-α, are used to control inflammation in sarcoidosis patients in cases refractory to corticosteroid and immunosuppressive treatment.

### 3.4. Acute anterior uveitis

Acute anterior uveitis (AAU) cases are more frequently encountered in the outpatient clinic compared to other types of uveitis. AAU is a phenotype typically associated with HLA-B27 linked diseases such as spondyloarthritis (SpA), but other genetic associations are not well known. Other autoimmune systemic diseases such as inflammatory bowel disease (IBD) or psoriatic arthritis also induce AAU. AAU has a sudden onset and sometimes manifests as severe inflammation (Figure 4) characterized by hypopyon and hyphemia in the anterior chamber. The symptoms are unilateral, including severe pain and blurred vision due to inflammation. When inflammation becomes chronic, general inflammatory conditions such as hyphemia, hypopyon, diffuse retinal vasculitis, vitreous opacity and papillitis may occur. AAU treatment usually involves topical corticosteroid eye drops administered several times a day. Periocular steroid injection (sub-conjunctival injection) or systemic corticosteroid treatment (tapering) are used for preventing severe visual impairment in AAU. HLA-B27-associated AAU has high recurrence and complication rates. MTX and other immunosuppressive drugs such as azathioprine do not reduce disease activity [23]. In contrast, sulfasalazine is able to reduce the recurrence of inflammation in SpA-related uveitis [37].

A high concentration of TNF-α is seen in the aqueous humor and serum of AAU patients [38], and therefore, TNF-α concentration is considered as an activity biomarker in uveitis [39]. In line with this, anti-TNF-α is a candidate drug for suppressing inflammation in patients with severe AAU who have experienced recurrent inflammation. However, anti-TNF-α drugs have not currently been approved for use in AAU in Japan, and Ophthalmologists in Japan look forward to using them to treat severe AAU in the future.

### 3.5. Juvenile idiopathic arthritis-associated uveitis

Juvenile idiopathic arthritis (JIA) exhibits symptoms of chronic uveitis in patients under 16 years of age. Uveitis occurs in approximately 12–38% of cases within 7 years after the onset of JIA [40–42]. Most patients are female, have oligoarthritis, are positive for anti-nuclear antibodies, and are negative for rheumatoid factor [43]. Clinical practice guideline for JIA 2018 in Japan [44] reported that the activity of uveitis does not run parallel with the activity of arthritis, and sometimes occurs before the onset of arthritis symptoms. Thus it can indicate early phase JIA [44]. Therefore, uveitis, particularly anterior uveitis, is the most common extra-articular feature in JIA. In contrast, pan-, intermediate-, or posterior-type uveitis are uncommon [45,46]. The guidelines for uveitis in JIA were proposed by the British Society for Pediatric and Adolescent Rheumatology (BSPAR) and the Royal College of Ophthalmologists (RCOphth) (https://www.bspar.org.uk/DocStore/FileLibrary/PDFS/BSPAR%20Guidelines%20for%20Eye%20Screening%202006.pdf). The onset of JIA-associated uveitis often follows the onset of arthritis, although it may occasionally precede the onset of arthritis. JIA-associated uveitis sometimes has an uncontrollable inflammation and is one of the causes of blindness at a young age. A typical anterior segment feature is band keratopathy at a young age (Figure 5(a)). In posterior segment uveitis, severe macular edema is observed when inflammation becomes uncontrollable during treatment (Figure 5(b)). However, the pathogenesis of JIA uveitis is complex. Previous studies have reported that immunohistochemical examinations revealed non-granulomatous or granulomatous inflammation in JIA-associated uveitis [47]. Moreover, the affected uveal tissue contains a focal collection of CD20+ B cells and numerous T cells [48]. Especially, T cells secrete high amounts of TNF-α. To control JIA-associated uveitis, corticosteroids and immunosuppressive drugs are used in Japan.

![Figure 4. Acute anterior uveitis. Severe ciliary injection is seen at initial examination.](image)
previous study revealed that combined therapy using the anti-TNF-α drugs adalimumab and MTX prolonged the suppression of recurrent uveitis in JIA [49]. Therefore, anti-TNF-α drugs are candidate agents to suppress uveitis in JIA.

### 3.6. TNF-α in uveitis

Inflammatory cytokines, such as TNF-α are known to be important factors in the induction of uveitis symptoms. In fact, TNF-α concentration in the aqueous humor of uveitis patients is high [38]. TNF-α is the most important target to control inflammation in non-infectious uveitis [50–52]. TNF-α has several functions that promote both hem-angiogenesis and lymphangiogenesis [53,54] and breakdown of the BRB due to retinal vasculitis [55]. These phenomena induce retinal dysfunction associated with vision problems. The breakdown of BRB is the major cause of macular edema. Corticosteroids are generally the first choice of treatment to suppress inflammation in uveitis patients. Immunosuppressive drugs such as CSA are frequently used as drugs that facilitate the tapering of corticosteroid doses. These drugs are efficient at reducing inflammation in uveitis, but they also have associated side effects such as high blood glucose level, osteoporosis and opportunistic infections during or after treatment. Therefore, there is a need for other immune modulating drugs that may control inflammation, and have fewer side effects. It has been previously reported that systemic anti-TNF-α treatment may help reduce inflammation in several types of non-infectious uveitis such as Behçet’s disease [17], VKH [56], spondyloarthritis, sarcoidosis [57] and JIA [49,58]. In addition to an improvement in systemic symptoms, ocular symptoms have also been reported to be relieved with anti-TNF-α therapy. It may resolve vasculitis and TNF-α-induced inflammation in the eye. Indeed, in Behçet’s disease patients, several ocular inflammation attacks (vasculitis, inflammatory cell infiltration) were dramatically suppressed by anti-TNF-α treatment such as intravenous infliximab administration [16]. It is well known that in Behçet’s disease patients, peripheral blood monocytes secrete high amounts of TNF-α [52]. Moreover, T cell clones from the original site of inflammation also secrete TNF-α [59]. Clinically, anti-TNF-α treatment is more effective for suppressing inflammation in Behçet’s disease than corticosteroids or immunosuppressive drugs (MTX, CSA). Long-term infliximab administration could significantly control inflammatory attacks. Recurrent ocular attacks sometimes occur during treatment, however, the number of these attacks has been shown to be significantly reduced in long-term trials of infliximab administration. These studies confirm the efficacy of infliximab, even in long term administration.

### 3.7. Biological drugs for uveitis in Japan

In Japan, only two biological drugs are used for uveitis treatment: infliximab and adalimumab. Both these drugs are anti-TNF-α monoclonal antibodies. Infliximab is only used for Behçet’s disease treatment, while adalimumab can be used for Behçet’s disease and other non-infectious uveitis, including sarcoidosis, VKH, ankylosing spondylitis (not available in Japan if the patient only exhibits anterior uveitis), and JIA uveitis. The administration routes of infliximab and adalimumab differ. Infliximab is administered intravenously every 2 months at hospital. In contrast, adalimumab is administered by self-injection into subcutaneous tissue every 2 weeks. In our clinical experience, an intravenous route has a greater efficacy than a subcutaneous route in suppressing severe ongoing inflammation. Therefore, for the severe inflammation that occurs in Behçet’s disease, ophthalmologist choose to use infliximab. After suppressing severe inflammation or reducing the attack frequency, subcutaneous injection of
drugs such as adalimumab may be clinically useful due to their ease-of-use for the patient.

3.8. **Infliximab**

Infliximab is a chimeric monoclonal antibody against human TNF-α. It may be used for the treatment of Crohn’s disease, rheumatoid arthritis and Behçet’s disease, and is approved and clinically used in Japan. Infliximab acts by specifically binding to human TNF-α and inhibiting its activity. Moreover, it has also been reported that infliximab is able to bind to membrane-bound TNF-α receptors expressed on TNF-α producing cells, such as macrophages and activated T cells [60]. Infliximab is the most effective biological drug for suppressing inflammation in Behçet’s disease because unlike other drugs that fail to control inflammation, such as CSA, infliximab is able to effectively suppress Behçet’s disease. However, before considering treatment with infliximab, clinical examination for tuberculosis or other infections should be performed. Unfortunately, patients suspected of suffering from tuberculosis infection should also receive anti-tuberculosis drugs during infliximab treatment. Indeed, previous work reported that clinical examination of rheumatoid arthritis patients often revealed that they were infected with tuberculosis and *Pneumocystis carinii* [61]. Infliximab is a chimeric protein and therefore contains both human and mouse protein fragments. Since humans react to foreign mouse proteins, infusion reactions are also an important adverse event to be considered during infliximab treatment. Secondary non response to infliximab (NIR) has been detected during treatment with infliximab. NIR is an initial response to infliximab therapy, which is later lost and leads to relapse of disease. However, NIR has not been extensively investigated. A previous report showed that the reticuloendothelial system degrades and eliminates the monoclonal antibodies. If this system is saturated in chronic inflammatory conditions, the half-life of monoclonal antibodies such as infliximab may be shortened [62]. Moreover, anti TNF-x-antibody levels increase during treatment without any immune suppressive agents such as MTX or CSA [62].

3.9. **Adalimumab**

Adalimumab is a human monoclonal antibody against human TNF-α. It is approved for use in several types of non-infectious uveitis with inflammation that cannot be controlled by other means. In the ophthalmological field, a retrospective study of JIA indicated that adalimumab is able to control the inflammation of JIA-related uveitis [58]. However, the patient in question, who experienced significant improvement of inflammation, was young and had endured the illness only for a short period of time and had less severe joint symptoms. Nevertheless, most reports showed that adalimumab treatment was only able to weakly suppress inflammation [58]; only 35% of patients had improved visual function after using adalimumab. MTX combined therapy is effective in suppressing the recurrence of inflammation and prolonging the survival rate [49]. The VISUAL-I (active disease) study indicated improvements in 11 of the 12 domains of the National Eye Institute Visual Function Questionnaire-25 compared with the control group [63]. In the VISUAL-II study, the effect of adalimumab treatment was best correlated with the visual acuity component of the primary efficacy endpoint. Moreover, adalimumab could facilitate the reduction, or tapering off, of patient’s corticosteroid dose [64]. The VISUAL-III open label extension study investigating the use of adalimumab also found it could significantly reduce daily systemic corticosteroid use in patients with active uveitis, and stabilize corticosteroid dose in patients with inactive uveitis [65].

It is important to create awareness about the side-effects and treatment-related adverse events that can occur with adalimumab [66]. In Japan, the most important adverse event that can occur is infection [49], especially tuberculosis or fungal infection. Therefore, before using adalimumab, a clinical examination for tuberculosis or fungal infection should be performed. Moreover, currently, paradoxical adverse effects from using anti-TNF-α agents such as infliximab, etanercept and adalimumab have been reported [67–69]. Previously, a report showed that noncaseating granulomas were developed in the skin during adalimumab treatment [69]. Moreover, in psoriatic arthritis, treatment with adalimumab (after switching from infliximab to adalimumab) induced pulmonary sarcoid reaction [67]. To resolve these adverse events, discontinuing adalimumab is important, which should be followed by the initiation of corticosteroid treatment. During adalimumab treatment, anti-adalimumab antibodies affected to adalimumab serum level. Non responder for adalimumab treatment had high level of anti-adalimumab antibodies in their serum [70]. To avoid anti-adalimumab antibodies, immunomodulatory drugs such as steroids or immune suppressive agents should be used during adalimumab treatment [62].

4. **Conclusion**

Recently, several types of drugs have been developed for the treatment of uveitis. Particularly important are biological drugs, which target specific cytokines such as TNF-α and inflammatory cells including,
macrophages. In ophthalmology, until biological drugs were developed, prolonged corticosteroid or immunosuppressive therapy were the only choices for management of uveitis, causing a range of side-effects and treatment-related complications. Therefore, the use biological drugs for the treatment of uveitis, more particularly, the use of infliximab for the treatment of Behcet’s disease or adalimumab for treatment of intractable uveitis, has been a key advancement. However, biological drugs may also have many side effects. When using those biological drugs, ophthalmologists in Japan should understand and be aware of complications, and pay attention to consult with immunologists.

**Disclosure statement**

The authors report no conflict of interest.

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