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RESEARCH

Adalimumab treatment in adult patients with refractory non-infectious uveitis

Dirençli non-enfeksiyöz üveitli erişkin hastalarda adalimumab tedavisinin etkinliği

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Abstract

Purpose: To assess the efficacy of adalimumab treatment in patients with refractory non-infectious uveitis.
Materials and Methods: A retrospective analysis was carried out on patients with chronic non-infectious uveitis treated with adalimumab for longer than 12 months. All patients had active intraocular inflammation and were nonresponsive to other immunosuppressive agents before initiating adalimumab treatment.
Results: Twenty-one patients (39 eyes) were treated with adalimumab for a mean duration of 26.2 ± 13.2 months. Eleven patients (52.4%) remained relapse-free during the treatment. In only one patient (4.8%) adalimumab was switched to another drug due to insufficient response. Adalimumab treatment was discontinued in five patients (23.8%) after an attack-free period of at least 18 months.
Conclusion: Adalimumab is an effective and well-tolerated therapeutic option for patients with refractory non-infectious uveitis, to achieve and maintain disease quiescence.
Keywords:. Adalimumab; non-infectious uveitis; refractory uveitis

Öz

Amaç: Enfeksiyöz olmayan dirençli üveit hastalarında adalimumab tedavisinin etkinliğini değerlendirmek.
Gereç ve Yöntem: Kronik non-enfeksiyöz üveit tanısıyla 12 aydan uzun süre adalimumab tedavisi alan hastalar retrospektif olarak değerlendirildi. Tüm hastalar adalimumab tedavisine başlamadan önce diğer immünosüpresif ajanlara dirençli olup aktif intraoküler inflamasyon bulgularına sahipti.
Bulgular: Yirmi bir hasta (39 göz), ortalama 26.2 ± 13.2 ay süreyle adalimumab tedavisi aldı. Tedavi süresince 11 hastada (%52.4) nüks izlenmedi. Sadece bir hastada (%4,8) yetersiz yanıt nedeniyle adalimumab tedavisi başka bir ilaç ile değiştirildi. Beş hastada (%23.8) en az 18 aylık ataksız dönem sonunda adalimumab tedavisi sonlandırıldı.
Sonuç: Adalimumab, dirençli enfeksiyöz olmayan üveit hastalarında remisyonu sağlamak ve sürdürmek için etkili ve iyi tolere edilen bir terapötik seçenektir.

Anahtar kelimeler: Adalimumab; enfeksiyöz olmayan üveit; dirençli üveit.

INTRODUCTION

Uveitis is a challenging eye disease that might cause serious eye damage and visual disability. Depending on the etiology of the intraocular inflammation, uveitis is classified as infectious or non-infectious, and the management is planned accordingly. In developed countries, non-infectious cases constitute the majority, either associated with a systemic inflammatory disorder or specific syndrome confined to the eye, or without an identifiable specific etiology, which is termed idiopathic[1]. Non-infectious uveitis is an immune-mediated disease, and corticosteroids are still the mainstay of the treatment used to provide rapid control of the inflammation[2]. However, their long-term use is limited due to potential well-recognized local and systemic complications[3]. Corticosteroid-related side effects constitute an important problem in the management of this disease, especially in cases with prolonged inflammation and frequent relapses. Hence, to achieve durable remission and avoid recurrences, steroid-sparing immunomodulatory agents are required in the treatment of these patients, to reduce the need for corticosteroids. Conventional immunosuppressive drugs such as methotrexate,

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azathioprine, cyclosporine A, and mycophenolate mofetil have been used for many years in the treatment of uveitis with their well-established efficacy and safety profile, and are commonly considered as initial treatment option. However, some severe cases do not respond to these treatments[4].

Tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, has become one of the target molecules in the treatment, as its key role in the pathophysiology of uveitis has been demonstrated in both animal and human studies[5,6]. TNF-α antibodies have been reported to be effective in reducing the need for corticosteroids in patients with uveitis[7]. In the expert panel recommendations, anti-TNF-α agents have been considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation[8]. Adalimumab, a fully human monoclonal TNF-α antibody, has been approved for use in adults for the treatment of non-infectious intermediate, posterior, and panuveitis, based on the results of double-masked, randomized, and placebo-controlled clinical trials[9,10]. Specifically, the drug had received orphan status for the treatment of non-infectious uveitis. This retrospective study aimed to evaluate the efficacy and safety of adalimumab treatment in adult patients with refractory non-infectious uveitis, in the real-life practice of a tertiary referral center. Its contribution to the literature would be to highlight Adalimumab as an effective and well-tolerated therapeutic option to achieve and maintain disease quiescence, for patients with refractory non-infectious uveitis, as well as non-responsive patients to previous other biological drugs.

MATERIALS AND METHODS

Subjects

We retrospectively analyzed the clinical records of adult patients with non-infectious uveitis who were treated with adalimumab and followed up regularly for longer than 12 months at Cukurova University School of Medicine, between March 2016 and January 2022. The data included gender, age at the onset of uveitis, specific diagnosis or associated systemic disease, affected eye/laterality, anatomic classification of inflammation, prior immunosuppressive therapies, age at the initiation of adalimumab treatment, treatment duration, follow-up time, best-corrected visual acuity (BCVA) and intraocular pressure at baseline and final follow-up visits, and the number of recorded recurrences during adalimumab treatment. The patients who received adalimumab as a first-line agent and were treated for less than 12 months were excluded from the study.

Ophthalmologic examination

A complete ophthalmologic examination including BCVA and intraocular pressure measurement, slit-lamp biomicroscopy, and dilated fundus examination was performed for all patients. Optical coherence tomography, fundus fluorescein angiography, and ocular ultrasonography were performed if necessary. Snellen chart was used for the measurement of BCVA and subsequently converted into the logarithm of the minimum angle of resolution (LogMAR) units for the calculation of average values. The anatomical categorization of uveitis was made considering the primary site of inflammation (as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis), according to the Standardization of Uveitis Nomenclature Working Group guidance[11].

Treatment

All patients had been previously given immunomodulatory treatment including conventional immunosuppressive agents (methotrexate, azathioprine, cyclosporine A, mycophenolate mofetil) and biological drugs (infliximab, interferon), either as monotherapy or in combination, and they all showed insufficient response. Adalimumab treatment was initiated as an attempt to achieve remission and reduce corticosteroid need.

Laboratory tests were performed for all patients before the initiation of adalimumab treatment, including complete blood cell count, blood biochemistry, serological tests, PPD skin test and chest x-ray; and other tests based on clinical necessity. All patients were evaluated by rheumatologists and chest diseases or infectious diseases specialists for systemic examination and assessment of laboratory test results to evaluate the patient's eligibility for TNF-α blocker therapy, and these evaluations were repeated every three months. All patients with intermediate uveitis underwent neuroimaging and neurology consultation to rule out demyelinating disease.

Complete uveitis remission was defined as the complete absence of inflammatory signs across all visits spanning at least 3 months. Uveitis attack was defined as any active inflammation after inactivity for at least 3 months.

The study was carried out in accordance with the tenets of the Declaration of Helsinki, and approved by the Cukurova University Ethics Committee (KN: 19/119-2022)

Statistical analysis

Descriptive statsitice are used in this study to evaluate frequency, mean and standard deviation.

RESULTS

This study involved 21 patients with refractory chronic non-infectious uveitis who have received adalimumab treatment for at least 12 months. There were 8 (38.1%) females and 13 (61.9%) males. The mean age of the patients at the onset of uveitis was 29.7 ± 9.3 (range 18-57, median 29) years. The mean age of the patients at the initiation of adalimumab was 32.9 ± 10.4 (range 19-63, median 33) years. The mean duration of adalimumab treatment was 26.2 ± 13.2 (range 12-48, median 24) months. The mean duration of follow-up after the initiation of adalimumab was 28.3 ± 15.7 (range 12-62, median 24) months.

Adalimumab treatment was administered 40 mg by subcutaneous injection every other week to all patients. Ocular involvement was unilateral in 3 patients (14.3%) and bilateral in 18 patients (85.7%). All patients had previously been treated with an immunomodulatory drug other than adalimumab, either as monotherapy or combination therapy. The most commonly used immunosuppressive drug was azathioprine, prescribed in 16 of 21 patients with a proportion of 76.2%. Eight patients continued other immunosuppressive drugs with adalimumab therapy, including azathioprine in six and methotrexate in two patients. The demographic characteristics and previous immunomodulatory treatments are shown in Table 1.

The most common diagnosis was idiopathic uveitis (n=7, 33.3%), followed by Behçet's disease (n=6, 28.6%), and pars planitis (n=3, 14.3%). Regarding the anatomical location, the predominant type was panuveitis, accounting for 57.1% (n=12) of the patients. Distributions of the uveitis etiology and anatomical location of inflammation are given in Table 2.

Table 1. Demographic characteristics and previous immunomodulatory treatments of the study group.

Patients, n	**21**
Gender, n (%)	
Female	8 (38.1%)
Male	13 (61.9%)
Age at onset of uveitis (years, mean ± SD)	29.7 ± 9.3
Age at initiation of ADA (years, mean ± SD)	32.9 ± 10.4
Duration of ADA treatment (months, mean ± SD)	26.2 ± 13.2
Follow-up time after initiation of ADA (months, mean ± SD)	28.3 ± 15.7
Ocular involvement, n (%)	
Bilateral	18 (85.7%)
Unilateral	3 (14.3%)
Drugs used before ADA treatment*, n (%)	
Conventional	
Methotrexate	3 (14.3%)
Azathioprine	16 (76.2%)
Cyclosporine A	12 (57.1%)
Mycophenolate mofetil	1 (4.8%)
Biological	
Infliximab	1 (4.8%)
Interferon	3 (14.3%)

SD=Standard deviation; ADA=Adalimumab
*Patients might have been treated with more than one agent as monotherapy or in combination

Table 2. Distribution of patients according to etiology and anatomical location of inflammation.

Classification	**Patients (n= 21)**	
	n	%
Etiology		
Idiopathic	7	33.3
Behçet's disease	6	28.6
Pars planitis	3	14.3
Vogt-Koyanagi-Harada	2	9.5
Sarcoidosis	1	4.8
Ankylosing spondylitis	1	4.8
Reiter syndrome	1	4.8
Anatomical location		
Anterior uveitis	2	9.5
Intermediate uveitis	3	14.3
Posterior uveitis	4	19.1
Panuveitis	12	57.1

At the beginning of adalimumab treatment, all patients had active intraocular inflammation and were receiving corticosteroids. After the initiation of adalimumab, all patients showed complete remission,

and prednisolone could be discontinued in a tapering regimen. During the adalimumab treatment period, 11 patients (52.4%) were relapse-free, while 10 patients (47.6%) experienced at least one active uveitis attack (range 1-3, mean 1.6 ± 0.96 relapses).

In all cases but one, recurrent inflammation was controlled with short-term corticosteroid treatment and complete quiescence could be managed for longer than 3 months after cessation of corticosteroid. Eight patients (38.1%), remained on their conventional immunosuppressive agent (azathioprine in 6, methotrexate in 2) and received adalimumab concomitantly. In only one patient (4.8%) who was not able to discontinue corticosteroid treatment after recurrent inflammation, adalimumab was switched to another TNF-α blocker because of insufficient response. Adalimumab was ceased after a mean treatment duration of 32.2 ± 9.5 months (range 18-40 months) in five patients (23.8%), after demonstrating a relapse-free period of at least 18 months (range 18-24, mean 22.8 ± 2.7 months). Among these patients, only one showed active inflammation one year after discontinuation of treatment, and adalimumab injections were restarted. At the last follow-up, 16 patients (76.2%) were still on adalimumab medication. In a total of 39 affected eyes, the mean BCVA at the initiation of adalimumab treatment was 0.54 ± 0.58 LogMAR and improved to 0.35 ± 0.47 LogMAR at the last recorded visit. No adverse events were reported related to adalimumab injections.

DISCUSSION

Adalimumab has been approved for the treatment of non-infectious uveitis, following the pivotal clinical phase 3 clinical trials in which adalimumab was shown to significantly lower the risk for uveitic flare or vision loss, with low safety concerns[9,10]. In the post hoc analysis of these clinical trials, adalimumab treatment has also been found to be associated with significant improvements in patient-reported visual functioning for patients with non-infectious uveitis[12]. With increasing recognition and clinical experiences, adalimumab has become one the most commonly used biological agents in the treatment of uveitis, with its advantage of administration at home, established efficacy, and favorable safety profile. Although traditional stepladder approach is recommended, adalimumab has also been regarded as a first-line immunomodulatory therapy based on some conditions or factors, such as age, the severity of ocular inflammation, and the range of complications[13-15].

In this study, we reported clinical real-world data revealing the efficacy and safety of adalimumab treatment for refractory non-infectious uveitis in adult patients. In all patients, the indication for adalimumab treatment was uncontrolled inflammation, and prolonged use of corticosteroids to control inflammation. At study entry, all patients had active uveitis despite immunomodulatory treatment. After the initiation of adalimumab injections, they were all able to achieve quiescence and stop corticosteroid treatment. Ocular inflammation was controlled with adalimumab injections alone in 52.4% of the patients, without re-administration of corticosteroids and other immunosuppressive treatment. Although the remaining patients showed active inflammatory findings at least once during the adalimumab treatment, all except one required only a short-term corticosteroid treatment and were able to cease prednisolone treatment, and experienced relapse-free periods of longer than 3 months after cessation of steroid. Moreover, visual acuity improvement was achieved. The findings of this study, consistent with the results of previous reports, suggest adalimumab as a valuable option for patients with frequent and prolonged uveitis attacks who fail to respond to conventional immunosuppressive agents or other biological drugs[16-22]. In the current study only one patient with ankylosing spondylitis, who was non-responsive to infliximab infusions, daily topical corticosteroid dose couldn't decrease under five to control anterior chamber inflammation despite adalimumab treatment and concurrent methotrexate injections. In this patient, adalimumab was switched to certolizumab.

There have been several studies reporting clinical data about adalimumab therapy for the treatment of patients with vision-threatening uveitis, in real-world settings. Say et al[18] reported 46 uveitis patients who received adalimumab with different indications, both as a first-line agent and for refractory cases. In their study, the most common diagnosis was undifferentiated, the most common anatomical classification was panuveitis, and prednisolone was ceased or reduced in all but one patient (97.8%). The authors highlighted the efficacy of adalimumab in non-infectious uveitis for preserving vision and allowing the reduction of corticosteroid dose,

considering their real-world clinical experience. Another report assessed a three-center experience with adalimumab in 60 patients with non-infectious uveitis[19]. The study group included both pediatric and adult patients; besides, the indication for adalimumab treatment was not only the activity of uveitis but also systemic disease in the majority of patients. Nevertheless, in this large and heterogeneous retrospective case series, adalimumab was found effective in up to 80% of patients with uveitis. Our findings were consistent with the results of these studies indicating that adalimumab is effective to reduce uveitis-related corticosteroid use, confirming the results of clinical trials in real-life settings.

There have also been studies investigating the efficacy of adalimumab for the treatment of a particular subgroup of uveitis patients, including only cases that did not have satisfactory inflammatory control with other immunosuppressive therapies. Diaz-Llopis et al[20] evaluated a total of 131 patients in a prospective, multicenter study that enrolled both pediatric and adult patients. The authors reported that continued treatment allowed all patients to discontinue topical steroids and taper systemic corticosteroids without having high rates of relapses. Suhler et al[21] conducted a multicenter, prospective clinical trial to assess the effectiveness of adalimumab for the treatment of adult patients with non-infectious uveitis, refractory to corticosteroids, and at least one other immunosuppressive medication. Idiopathic panuveitis was the most common diagnosis. Adalimumab was found effective in 68% of refractory uveitis patients, and 39% exhibited durable response for one year. Park et al[22] investigated 23 eyes of 14 adult patients who received adalimumab injections for refractory non-infectious uveitis in a real-world setting. The authors reported that visual acuity was maintained, and clinically relevant outcomes with uveitic inflammation were significantly improved after adalimumab treatment. Our results were in accordance with the findings of these previous reports, confirming the efficacy of adalimumab treatment for refractory non-infectious uveitis.

In conclusion, adalimumab is a safe and effective therapeutic option for patients with severe, vision-threatening uveitis. This study highlights that adalimumab is an efficacious and well-tolerated therapeutic option to achieve and maintain disease quiescence, for patients with refractory non-infectious uveitis. In recent years, by increasing experience and easier access to the drug, our traditional treatment approach is changing towards earlier introduction of adalimumab, for patients who fail to respond to conventional immunosuppressive therapy, to avoid complications due to severe or prolonged inflammation, as well as corticosteroid therapy. Adalimumab might also be a reasonable choice of treatment for patients who are non-responsive to previous other biological drugs. The main strength of the present study is to be conducted in real-life settings. The retrospective design and relatively small sample size are the limitations. Besides, the study is conducted in a tertiary referral center dealing primarily with challenging cases that might limit the outcomes of adalimumab treatment. Further experiences with larger case series and longer follow-up would provide more comprehensive data about the efficacy and safety of adalimumab treatment.

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