Original Article

Adalimumab in Focus: Evaluating Effectiveness and Safety in Non-Infectious Uveitis at a Tertiary Referral Center in Türkiye

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Abstract

Objectives: To evaluate the indications, efficacy, and safety of adalimumab (ADA) in treating active non-infectious uveitis (NIU) in the Turkish population in a real-world setting.

Materials and Methods: This retrospective observational study included patients diagnosed with NIU treated with ADA on-label. The study assessed the impact of ADA treatment on best corrected visual acuity (BCVA), number of immunosuppressive therapies (IST), immunosuppressive drug load, and the frequency of required local treatment. BCVA was monitored at baseline and subsequent months to determine the onset of functional efficiency of ADA treatment.

Results: A total of 289 eyes of 146 patients (60 females, 86 males) diagnosed with NIU and treated according to the ADA protocol were included in the study. The mean age was 37.6±14.4 years (range, 4-73) and the median follow-up was 30 months (interquartile range, 18-57). The most common indication for ADA was panuveitis, with a diagnosis of Behçet's uveitis. The use of ADA reduced the number of IST, immunosuppressive drug load, and need for local treatment ($p<0.001$, 0.002, and <0.001, respectively). Corticosteroids could be discontinued in all but one patient. Following ADA, a significant improvement in BCVA was observed from the first month ($p<0.001$ for baseline vs. month 1) and stabilization occurred after the sixth month ($p=0.751$ for month 6 vs. 12). Side effects were reported by 55.2% of patients during IST, while only 8 patients (5.5%) experienced ADA-related side effects. At the end of the follow-up period, 8.9% of patients switched to a weekly dosing schedule. Patients who switched to a weekly regimen required more local treatment before and after ADA treatment ($p=0.02$ and 0.001, respectively), and the number of concomitant IST and drug load were higher during standard-dose ADA use ($p<0.001$ and $p=0.025$, respectively).

Conclusion: This study, the largest single-center investigation in Türkiye, reveals ADA to be a safe option with functional benefits across diverse indications and age ranges. Notably, ADA minimizes reliance on additional therapies.

Keywords: Adalimumab, Behçet uveitis, immunosuppressive drug load, non-infectious uveitis, TNF-α antagonist

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Introduction

Non-infectious uveitis (NIU) can be a significant cause of visual impairment. It accounts for approximately 70% of all uveitis and is the most common etiology of uveitis in the Turkish population.[1,2] This condition often affects individuals during their most productive years, leading to profound personal, social, and economic consequences.[3]

The current treatment algorithm for NIU is in the form of "step-ladder treatment".[4,5] Nevertheless, immunosuppressive therapies (ISTs) sometimes fail to control inflammation without increasing corticosteroids (CS) in resistant cases, or severe side effects limit the use of IST.[6] There is also a significant economic burden from the increasing number of drugs used.[7] Therefore, biologics may provide a targeted, relatively safe, and effective option for the management of NIU.[8,9]

Tumor necrosis factor-alpha (TNF-α) is a potent pro-inflammatory cytokine.[10] TNF-α antagonist monoclonal antibodies are effective in treating uveitis.[9,11,12] TNF-α inhibitors have become the first-line treatment for many inflammatory diseases, including NIU.[8,13,14] The efficacy of adalimumab (ADA) treatment has been demonstrated in the literature on NIU treatment.[15,16,17,18] Authorized for the treatment of NIU by the U.S. Food and Drug Administration in 2016, ADA is

the only TNF-α antagonist monoclonal antibody approved for this purpose (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf). ADA has been officially approved for NIU treatment in Türkiye since 2018. Positive outcomes of ADA treatment for different autoimmune diseases, including NIU, have been reported in Türkiye.[19,20,21]

The main objective of this study was to present our experience with ADA in patients with active NIU and to analyze the indications, long-term efficacy, and safety of ADA in the Turkish population.

Materials and Methods

Study Design and Patient Population

This retrospective observational study was conducted at a tertiary referral uveitis center. Consecutive patients diagnosed with NIU who received ADA (Humira®; AbbVie, Chicago, IL, USA) treatment for at least 6 months between October 2018 and March 2023 were included. The inclusion/exclusion criteria are presented in Supplementary Information S1.

The study was performed with ethics approval obtained from the Ethics Committee of the University of Health Sciences Türkiye, Hamidiye Scientific Research (decision number: 7/24, date: April 07, 2023) and complied with the tenets of the Declaration of Helsinki.

Outcome Measures

Medical records were systematically analyzed for demographic characteristics, anatomical classification of uveitis, etiology of uveitis, complete ocular examination findings, best corrected visual acuity (BCVA), tuberculin skin test (purified protein derivative [PPD]) and/or interferon-γ test (QuantiFERON) results, isoniazid (INH) prophylaxis status, duration of disease before ADA, number of medications used and immunosuppressive drug load at the time of ADA indication and concomitant with ADA, duration of standard-dose ADA usage, ADA-related adverse events, and reason for ADA discontinuation if applicable.

BCVA was assessed at baseline (at the time of first ADA injection) and at 1, 3, 6, and 12 months after the initiation of ADA therapy. The number of ISTs, immunosuppressive drug load, and number of required periocular steroid treatments before and after ADA therapy were recorded. BCVA was assessed using the Snellen chart and converted into logarithm of the minimum angle of resolution (logMAR) for analysis. Immunosuppressive drug load was evaluated with a weighted semiquantitative scale for each medication as described previously by Nussenblatt et al.[22]

Response to ADA therapy was evaluated in all patients within a period of 3 to 6 months following the initiation of treatment. The definitions of inactive disease/non-response/recurrence and the treatment modifications made accordingly are presented in Supplementary Information S2.

The effectiveness of ADA was assessed in terms of change in BCVA, number of ISTs, immunosuppressive drug load, and the frequency of required periocular steroid due to cystoid macular edema (CME) or uncontrolled inflammation. In patients switched to weekly ADA dosing due to non-response or recurrence, the time to transition from standard to weekly dosing was recorded and the same parameters were recorded after weekly dosing.

Treatment Protocol

All patients were in the active phase. The clinic adheres to international guidelines, although the preferred treatment regimen may vary depending on the disease. ADA is the preferred first-line therapy for Behçet uveitis (BU) with vision-threatening posterior segment involvement, as recommended by the European League Against Rheumatism.[13] This is also the preferred option when a patient has a condition that limits steroid usage or a systemic condition that limits IST usage.

ADA (Humira®; AbbVie, Chicago, IL, USA) is administered by subcutaneous injection. Adult patients received 80 mg ADA as an initial dose, followed by 40 mg 1 week later and continuing with 40 mg every 2 weeks thereafter. Children weighing less than 30 kilograms were started on 20 mg ADA once every 2 weeks. As recommended by the Turkish Ministry of Health, patients were screened by a pulmonologist/infectious disease specialist and internal medicine/rheumatology specialist for serious infections, especially tuberculosis (TB) and hepatitis B, and malignancies. In terms of intermediate uveitis, neurologist approval should also be sought due to the risk of demyelination with ADA. For patients with ankylosing spondylitis, ADA was initiated with approval from the rheumatology department. According to the results of PPD/QuantiFERON and pulmonologist's consultation, INH prophylaxis or anti-TB therapy (ATT) was started. INH was initiated at least 4 weeks prior to ADA and maintained for 9 months. Nevertheless, INH prophylaxis was initiated concurrently with ADA in a subset of patients with the authorization of the infectious diseases department, taking into account the patient's clinical status.

If ADA was initiated as first-line therapy, oral or intravenous steroid and at least one IST was also initiated concomitantly with ADA. If ADA was preferred as a second-line treatment, ADA was added to the existing IST regimen. Following the addition of ADA, other treatment agents are adjusted based on the patient's clinical condition.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Mac version 23.0 (IBM Crop., Armonk, NY, USA). The data distribution was evaluated using the Kolmogorov-Smirnov normality test. Categorical data are presented as frequency (n) and percentage (%), and numerical variables are presented as mean ± standard deviation or median and interquartile range (IQR). The chi-square test was used to compare categorical variables. Comparisons of subgroups based on diagnoses were conducted using either the independent-samples t-test or the Mann-Whitney U test. For comparison of more than two independent variables, the Kruskal-Wallis test (non-parametric ANOVA) was used. Changes in BCVA, immunosuppressive drug load, and periocular steroid injection requirement between baseline and final follow-up were examined by paired t-test or

Wilcoxon signed-rank test. The generalized estimating equation approach was used to adjust for the pool effect between the right and left eyes of the same patient for BCVA alterations. The statistical significance level was regarded as 0.05.

Results

The medical records of 146 patients (289 eyes) treated with ADA were evaluated. Table 1 presents the baseline demographic and clinical characteristics of the whole cohort.

ADA treatment was initiated as first-line therapy in 12 patients at a standard dose every 2 weeks. The patients were diagnosed with BU (6 patients), Vogt-Koyanagi-Harada disease (VKH; 2 patients), tubulointerstitial nephritis and uveitis syndrome (2 patients), ocular sarcoidosis (1 patient), and spondyloarthropathy (SpA)-associated uveitis (1 patient).

Seventy-four (55.2%) of 134 patients who received IST before ADA reported adverse events, with azathioprine (AZA) being the most frequently reported. Table 2 summarizes the side effects of ISTs used before ADA.

According to PPD/QuantiFERON results, latent TB was detected in 77 patients and INH prophylaxis was initiated as recommended in the Tuberculosis Diagnosis and Treatment Guideline of Türkiye. Additionally, 3 patients received quadruple ATT before ADA treatment. Two patients were diagnosed with TB-related uveitis and received ATT at presentation. One patient diagnosed with serpiginous choroiditis had a history of TB-meningitis, yet the standard duration of ATT was not clearly defined. Therefore, ATT was initiated before ADA.

Steroid treatment was discontinued in all patients except one patient who continued to use steroids at a dose of 16 mg/day for BU. Despite weekly ADA doses, inflammation persisted on angiography in this patient.

The preferred treatment option was ADA monotherapy in 18 patients. The majority of these patients were diagnosed with SpA-associated uveitis (55.5%), followed by BU (22.2%). Among the ISTs used concomitantly with ADA, AZA was the most frequently chosen (48.7%), followed by cyclosporine (27.4%), methotrexate (25.3%), and mycophenolate mofetil (1.4%). Furthermore, 21 patients received combined IST. The number of agents used, immunosuppressive drug load, and the frequency of local treatments were significantly reduced with ADA treatment ($p<0.005$, Wilcoxon signed-rank test, Table 3). A subsequent comparison of these parameters in terms of treatment line revealed no significant differences between first-line and second-line ADA use ($p=0.848$, 0.166, and 0.612, respectively, Mann-Whitney U test).

ADA-related adverse events occurred in 8 patients (5.5%). These included skin rash in 3 patients, cervical lymphadenopathy (LAP) in 2 patients, localized psoriasis in 2 patients, and pulmonary TB in 1 patient. Ultrasonography and tissue biopsy performed to investigate the cervical LAP revealed no malignancy. The symptoms of psoriasis regressed after discontinuing ADA and did not recur after resuming ADA. The patient diagnosed with pulmonary TB had bilateral progression of serpiginous

Table 1. Baseline demographic and clinical features

Number of patients/eyes, N/n	**146/289**
Age, mean ± SD (range), years	37.6 ± 14.4 (4-73)
<18 years, N (%)	8 (5.5)*
>60 years, N (%)	6 (4.1)**
Sex, N (%)	
Female	60 (41.1)
Male	86 (58.9)
Localization of uveitis, N (%)	
Anterior uveitis	17 (11.6)
Intermediate uveitis	8 (5.5)
Posterior uveitis	26 (17.8)
Panuveitis	95 (65.1)
Uveitis etiology, N (%)	
Behçet's uveitis	53 (36.3)
Sarcoidosis	28 (19.2)
Vogt-Koyanagi-Harada disease	18 (12.3)
Spondyloarthropathy-associated uveitis	12 (8.2)
Serpiginous choroiditis	7 (4.8)
Pars planitis	6 (4.1)
Juvenile idiopathic arthritis-associated uveitis	5 (3.4)
Ampiginous choroiditis	4 (2.7)
Idiopathic uveitis	4 (2.7)
Tubulointerstitial nephritis and uveitis syndrome	3 (2.1)
Sympathetic ophthalmia	3 (2.1)
Tuberculosis-related uveitis	2 (1.4)
Posterior scleritis***	1 (0.7)
Previous systemic steroid, N (%)	
None	109 (74.7)
<10 mg/day	12 (8.3)
16 mg/day	5 (3.4)
32 mg/day	9 (6.2)
48 mg/day	2 (1.4)
64 mg/day	9 (6.2)
Previous IST/immunomodulatory/biologics**, N (%)**	
None	12 (8.2)
Azathioprine	57 (39.1)
Methotrexate	37 (25.3)
Mycophenolate mofetil	1 (0.7)
Cyclosporine	51 (34.9)
Etanercept	6 (4.1)
Certolizumab	1 (0.7)
Interferon-α	18 (12.3)
Line of ADA, N (%)	
First-line therapy	12 (8.2)
Second-line therapy	134 (91.8)
Interval between diagnosis and initiation of ADA treatment, median (IQR), months	13.5 (7-36)
Duration of ADA treatment; median (IQR), months	12 (9-24)

N, Number of patients, n: Number of eyes, SD: Standard deviation, IST: Immunosuppressive treatment, ADA: Adalimumab, IQR: Interquartile range
*Patients started on ADA before the age of 18 years were diagnosed with juvenile idiopathic arthritis-associated uveitis (4 patients), tubulointerstitial nephritis and uveitis syndrome (2 patients), pars planitis (1 patient), and sympathetic ophthalmia (1 patient)
**Among patients over 60 years of age, ADA was initiated in one patient due to Vogt-Koyanagi-Harada and in the remaining five patients due to ocular sarcoidosis
***Posterior scleritis is included under posterior uveitis in the uveitis localization section.
****Some patients received combined ISTs

choroiditis despite treatment with AZA and ADA. This patient had a positive QuantiFERON test during the previous screening. However, the pulmonologist did not recommend ATT because a detailed assessment showed no evidence of active TB. They instead recommended only INH prophylaxis before ADA. Following re-evaluation by the pulmonologist due to progression under treatment, the patient was diagnosed with active pulmonary TB. ADA was stopped and quadruple ATT was started.

Table 2. Reported side effects associated with treatment agents used prior to adalimumab

Agents with side effect*, N (%)	Reported side effect*, N
Azathioprine, 22 (15.1)	Anemia, 2 Lymphopenia, 4 Fatigue, 6 Renal function test impairment, 2 Liver function test impairment, 9
Steroid, 20 (13.7)	Cushing syndrome, 5 Acne, 1 Osteoporosis, 4 Neuropathy/myopathy, 2 Steroid-responder glaucoma, 9 Central serous chorioretinopathy, 1
Cyclosporine, 17 (11.6)	Fatigue; 1 Renal function test impairment, 2 Neuropathy/myopathy, 8 Hirsutism, 3 Gingival hypertrophy, 3
Interferon-α, 13 (8.9)	Lymphopenia, 3 Fatigue, 4 Liver function test impairment, 2 Alopecia, 3 Weight loss, 3 Depression, 1
Methotrexate, 10 (6.8)	Anemia, 1 Nausea, 4 Liver function test impairment, 4 Shingles (herpes zoster), 1
Etanercept, 6 (4.1)	Paradoxical uveitis, 6

N: Number of patients
*Overlapping side effects in the same patient and/or different side effects to the same agent. The most common side effect against the agent is written in bold type

Table 3. Alternation of treatment with ADA (patients diagnosed with spondyloarthropathy-associated uveitis were excluded)

	Prior to ADA	Concomitant with ADA	p value
The number of agents, mean, median (IQR)	1.4 1 (1-2)	1.1 1 (1-1)	**<0.001**
Immunosuppressive drug load, mean, median (IQR)	6.7 6.5 (4-10)	5.6 5 (4-7)	**0.002**
The number of local treatments, mean, median (IQR)	1.1 0 (0-1)	0.3 0 (0-0)	**<0.001**

Wilcoxon signed-rank test. IQR: Interquartile range, ADA: Adalimumab. Significant p values written in bold

At the end of the median (IQR) follow-up period of 30 (18-57) months, 83.6% of patients (122 patients) continued to receive the standard bi-weekly treatment. Thirteen patients (8.9%) were escalated to weekly ADA treatment after a median (IQR) of 24 (12-36) months on standard bi-weekly ADA usage. Among the 13 patients (4 females/9 males) switched to weekly treatment, 4 received ADA for BU, 2 for VKH, 1 for sympathetic ophthalmia, 1 for TB-related uveitis, and 1 for idiopathic posterior uveitis.

Comparing the patients who had to be switched to weekly dosing with those who continued to receive ADA bi-weekly, the number of ISTs used and the immunosuppressive drug load during standard ADA usage were statistically significantly higher in the weekly dosing group ($p<0.001$ and $p=0.025$, respectively), although there was no difference before ADA indication. Patients who switched to weekly dosing had statistically significantly higher number of required local treatments before and after ADA indication ($p=0.02$ and 0.001, respectively).

A total of 11 patients (7.5%) discontinued ADA treatment. In one patient receiving ADA for sympathetic ophthalmia, syphilis infection was diagnosed during treatment despite a previous negative VDRL/TPHA (venereal disease research laboratory/reflex *Treponema pallidum* hemagglutination) test result. ADA was discontinued and the patient was referred to the infectious diseases department for 21-day intravenous penicillin therapy. Five patients achieved remission and ceased ADA treatment. Four patients experienced adverse events during the course of their treatment with ADA and discontinued the treatment. One other patient declined to continue ADA treatment for other reasons (Figure 1).

The BCVA (logMAR) results showed a statistically significant improvement at all time points compared to baseline ($p<0.001$ for all). Additionally, significant BCVA improvement was observed between all time points except months 6 and 12 (Figure 2). The change in BCVA did not differ statistically according to whether ADA was used as first- or second-line treatment ($p>0.05$).

The most prevalent indication was BU (36.3%). Consequently, the approach to BU was the dominant factor in the general approach. Specific analyses of the BU population are presented in Supplementary Information S3.

Discussion

The study analyzed large and heterogeneous patient data to investigate the efficacy and safety of ADA in the various subtypes of NIU. Previous studies have demonstrated the efficacy of ADA treatment in achieving better control of ocular inflammation, improving visual acuity and reducing the use of CS in patients with NIU.[16,17,18] The efficacy of ADA treatment was demonstrated in this single-center study involving a Turkish population. To the best of our knowledge, this is the largest single-center real-life experience of ADA use in NIU in the Turkish population.

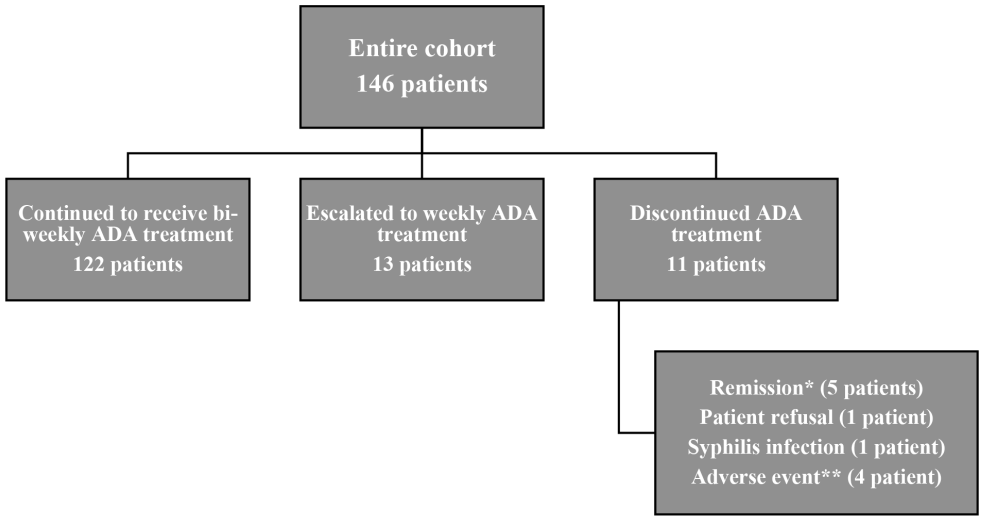

Figure 1. Adalimumab (ADA) use status of patients
**Remission was diagnosed in three patients with Behçet's uveitis, one with sarcoidosis and one with Vogt-Koyanagi-Harada (VKH) disease*
***ADA treatment was discontinued in 2 patients with serpiginous choroiditis due to skin rash, 1 patient with serpiginous choroiditis due to pulmonary tuberculosis and 1 patient with VKH due to lymph adenopathy. The symptoms of dermatological conditions that manifested during ADA administration abated with the cessation of ADA and did not recur upon the resumption of ADA*

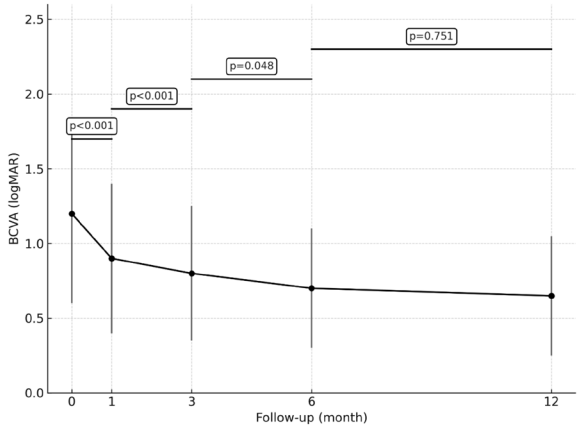

Figure 2. Changes in the mean best corrected visual acuity (BCVA). Patients diagnosed with spondyloarthropathy-associated uveitis were excluded (Wilcoxon signed-rank test)
logMAR: Logarithm of the minimum angle of resolution

The most common indications for ADA were panuveitis, in line with previous studies.[23,24,25] The most common diagnosis was BU. This observation is consistent with the unique epidemiological characteristics of our country. Similarly, BU was the most common NIU subtype in another study by Çam and Celiker[21] evaluating the efficacy of ADA in NIU in the Turkish population.

The most prevalent diagnosis in the pediatric cohort was juvenile idiopathic arthritis (JIA)-associated uveitis, also consistent with the existing literature, and no adverse events were observed. The effectiveness and safety of ADA in pediatric patients have been demonstrated in previous studies.[26,27] A study conducted in Türkiye has demonstrated the efficacy of ADA treatment in pediatric NIU.[28] However, the most common diagnosis in that series was pars planitis, while JIA-associated uveitis was the second most common diagnosis. This discrepancy may be attributed to the relatively low number of pediatric patients in the present clinical data (8 patients), which was a consequence of the absence of interdisciplinary clinical collaboration (e.g., with pediatric rheumatology or internal medicine).

An important outcome evaluated in our study was the efficacy of ADA in both first-line and second-line treatment settings. The impact of treatment line on prognosis remains controversial. The number of patients who received ADA as first-line treatment was limited, and no significant differences were observed between the first- and second-line treatment groups in terms of visual prognosis, number of immunosuppressive drugs used, immunosuppressive drug load, or need for local therapy. It is important to note that the statistical power of this comparison is limited due to the imbalance in sample sizes. However, these findings support the growing trend towards the use of ADA early in the disease course, especially when conventional therapies such as CS and IST are contraindicated or insufficient.

As demonstrated by previous studies, the potential of ADA as a first-line agent is evident, particularly in the context of BU and other forms of sight-threatening uveitis.[13,16,18]

Adverse effects were recorded for more than half of the patients using IST before ADA. However, only 5.5% of patients developed side effects with ADA. In this population with long-term drug use, adverse effects reduce patient compliance, increased visit numbers, and exacerbate the burden on the healthcare system. Considering these disadvantages of IST, early ADA treatment is a feasible option. Previous comparative studies have indicated that the use of ADA has the potential to facilitate a more prompt and efficacious treatment regimen with a comparable safety profile to conventional ISTs.[29,30,31] This is particularly important in the management of NIU subtypes resistant to conventional therapies or in patients who cannot tolerate these treatments.

Adverse events observed during ADA treatment included a skin rash, cervical LAP without evidence of malignancy, localized psoriasis, and pulmonary TB. As TB is endemic in our country, it is unclear whether the pulmonary TB in this patient was the result of the reactivation of latent TB or the development of primary TB. The estimated probability of developing TB during ADA use is 0.4-0.69%.[32,33] Similarly, the incidence of TB in this study was 0.68%. The relatively low adverse event rate in the present study suggests that ADA is generally well-tolerated. However, the risk of latent TB remains a concern, particularly in endemic countries like Türkiye, emphasizing the need for cautious pretreatment screening and monitoring.

In the presented cohort, one patient developed syphilis infection during ADA treatment, despite having a negative VDRL/TPHA test prior to ADA treatment. ADA was discontinued, and the patient was referred to the infectious diseases department, where intravenous penicillin therapy was prescribed. This underscores the broader risk of opportunistic infections in patients undergoing ADA therapy. Screening for syphilis and other infections is a standard approach in the diagnostic workup of NIU. Prior to the initiation of biologic drugs, it is imperative to undertake repeated general serologic tests. As described in several reports in the literature, cases of syphilis have emerged under IST, particularly in patients with dermatological and rheumatological conditions.[34,35,36] The overlapping symptoms of these conditions can delay diagnosis. Patel et al.[37] reported three cases of ocular syphilis under IST. However, baseline serological data were unavailable in these cases. The case in our study is noteworthy due to the documented seroconversion during ADA therapy, suggesting a likely new infection rather than a missed latent case. This finding is particularly important in the context of the global resurgence of syphilis.[38] Given these rising trends and potential diagnostic delays, especially in asymptomatic or latent stages, we believe syphilis serology may be considered as part of the routine infectious disease monitoring, similar to TB, in patients receiving ADA therapy.

A comparison of the pre-indication parameters of patients receiving bi-weekly and weekly ADA treatment demonstrated a statistically significant increase in the number of ISTs used and immunosuppressive drug burden due to insufficient response in patients switched to weekly dosing. The required number of local treatments was statistically significantly higher in patients who switched to weekly dosing, both before and after the indication of standard-dose ADA. The transition to a weekly dosing regimen was necessitated by the presence of uncontrolled inflammation and the increased need for local treatment (persistent CME and uncontrolled inflammation with systemic treatment). In view of the absence of prognostic distinction between first-line and second-line ADA patients, it is conceivable that ADA therapy could be initiated as a first-line therapy at an earlier stage in patients requiring a greater number of local treatments, and the transition could be made to a weekly regimen without insisting on a bi-weekly regimen. Although the clinical characteristics of patients transitioned to weekly dosing were analyzed in this study, follow-up data after the switch were not included in the scope of the analysis. Existing studies have demonstrated that the inflammation was effectively managed in patients transitioned to a weekly regimen with comparable indications.[21,28,39,40,41]

ADA was observed to significantly reduce the need for additional IST and local therapies, in line with previous studies.[23,42,43] Minimizing the use of CS and other IST is of crucial importance, as it reduces the long-term risk of side effects and complications associated with these therapies. This reduction in medication use not only reduces the potential for side effects but also improves patient compliance and overall quality of life. Diminished complications can also enhance patient productivity and healthcare costs. This is a pivotal consideration, given that a considerable proportion of NIU patients are in their most economically productive working years. In a study investigating cost-effectiveness, ADA was found to be a more cost-effective option than conventional treatment, particularly in cases of active uveitis threatening vision.[44] One of the most clinically noteworthy findings of this study was the rapid improvement observed in BCVA in patients treated with ADA. Visual improvement was observed during the first month of treatment, with continued gains until month 6, followed by stabilization through month 12. The rapid recovery of visual function is of vital importance in order to prevent long-term vision loss and to improve patients' quality of life. These findings are consistent with those obtained in previous studies that similarly reported early and sustained improvements in visual acuity with ADA, thereby further confirming its role in rapidly controlling ocular inflammation and restoring visual function.[25,28,45] In terms of the close follow-up of BCVA recovery, the initial weeks could not be evaluated in this study. Nevertheless, in studies conducted with shorter intervals, the rapid control of both anterior and posterior uveitis was observed in all eyes as early as the second week.[27,46]

The approach to BU was the dominant factor in the overall approach taken in the study, since BU was the most common NIU subtype in the present cohort. AZA was the most preferred IST agent in conjunction with ADA. This was mainly because AZA is the first choice of IST for the treatment of BU, in conjunction with CS. In a recently published study evaluating

the approaches of uvea specialists in Türkiye, CS+AZA was identified as the preferred initial treatment, with ADA added in cases of treatment failure. In instances of persistent inflammation unresponsive to standard doses of ADA, treatment was switched to weekly doses, as demonstrated in the presented study.[47] Upon analysis of the BU subgroup, it was observed that despite a notably higher number of IST drugs and need for local treatments, the immunosuppressive drug load did not differ. This is due to the preference for AZA from among the disease-modifying antirheumatic drugs as concomitant to ADA in the treatment regimen. In the chart presented by Nussenblatt et al.[22], which is employed in the calculation of the immunosuppressive drug load, the unit drug load of AZA is notably high. Notwithstanding its inclusion in the Nussenblatt chart, no patient in the study used AZA. It is possible that the AZA unit load may have been overestimated.

Study Limitations

The present study provides valuable insights into a large and heterogeneous group of NIU patients. However, the retrospective nature of the study represents a limitation in terms of evaluating the impact of ADA on inflammatory processes. The discrepancy between the recorded times of inflammation parameters and the times of ADA injections may result in a biased representation of the effect of ADA on inflammation. Therefore, intraocular inflammation parameters such as anterior chamber cell grading, vitreous haze, fluorescein angiography, or optical coherence tomography findings were not systematically evaluated, which may influence outcome interpretation. This limits the ability to quantify the direct impact of ADA on structural markers of inflammation. Furthermore, the broad range of uveitis etiologies and the inclusion of both pediatric and adult patients (aged 4-73 years) introduce heterogeneity that may affect direct comparisons between subgroups. However, this diversity reflects real-world clinical practice and highlights the broad applicability of ADA across different NIU subtypes and age groups. Moreover, clinical follow-up after switching to weekly ADA dosing was not evaluated in the current study, and TNF-α antibody levels could not be assessed in patients requiring escalation. Prospective studies with standardized inflammatory assessments and structured follow-up are needed to further clarify these findings.

Conclusion

The findings suggest that ADA is an effective and safe treatment option for various types of NIU in a wide age range in Turkish patients. Furthermore, it has been demonstrated to markedly decrease the encountered side effects and need for adjunctive IST and local therapeutic modalities. It also provides early and sustained visual improvement. These results suggest the potential for ADA to enhance patient outcomes by simplifying the treatment regimen and reducing the risk of complications.

Ethics

Ethics Committee Approval: The study was performed with ethics approval obtained from the Ethics Committee of the University of Health Sciences Türkiye, Hamidiye Scientific Research (decision number: 7/24, date: April 07, 2023) and complied with the tenets of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.Y.Ö., Ç.A., B.K.A., B.B., Concept: B.Y.Ö., Ç.A., Design: B.Y.Ö., Ç.A., Data Collection or Processing: B.Y.Ö., Analysis or Interpretation: B.Y.Ö., Literature Search: B.Y.Ö., Writing: B.Y.Ö.

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