The Evaluation of The Efficacy of Adalimumab in Refractory Non-Infectious Uveitis With Ultra-Widefield Fundus Fluorescein Angiography

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Abstract

Aim: To investigate the efficacy of adalimumab in the cases with refractory non-infectious uveitis and evaluate retinal vascular leakage changes on ultra-widefield fundus fluorescein angiography.

Methods: Twenty-three patients with refractory uveitis were included in study.

Results: Forty-four eyes of 23 patients with non-infectious uveitis were evaluated. Clinically active inflammation was present in 19 eyes (43.18%), while 25 (56.8%) were inactive. The mean drug burden was a 9.91 ± 3.78 (5-21) in baseline, 7.3 ± 4.25 at third and 8.0 ± 4.71 at sixth month ($p=0.022$). The mean choroidal thickness was 256.65 ± 43.63 μm in baseline, 240.49 ± 36.73 μm at third and 224.81 ± 34.91 μm at sixth month ($p \leq 0.05$). In terms of leakage extend, leakage was initially present in a mean of 2.95 ± 4.55 clock hour quadrants, 2.41 ± 3.91 at third and 1.76 ± 3.44 at sixth month ($p < 0.001$).

Conclusion: Adalimumab was found to be effective in establishing inflammation control by reducing drug burden, controlling retinal vascular leakage and choroidal inflammation in refractory uveitis.

Introduction

Uveitis is a sight-threatening intraocular inflammation and our understanding of the pathogenesis of the disease, other than infectious causes, is still limited. It is responsible 5–20% of legal blindness in developed countries.^[1, 2] Systemic autoimmune diseases such as Behçet disease, sarcoidosis, spondyloarthropathies, and Vogt-Koyanagi-Harada syndrome or unclassifiable idiopathic uveitis constitute non-infectious uveitis.^[3, 4] The main objective in the treatment of uveitis is to keep the intraocular inflammation under control, to prevent recurrences, to establish full remission, and to protect the vision.^[5] Steroids are used as the first therapeutic choice in active inflammations. However, severe ocular and systemic side-effects may develop with long-term steroid use. Since recurrences are common under steroid monotherapy, conventional immunosuppressive agents are employed in long-term treatment. Conventional immunosuppressive agents such as azathioprine, cyclosporine, and methotrexate can be used alone or in combination in treatment. However, some patients are resistant to treatment, and the disease cannot be brought under control, despite the use of combination therapies.^[5]

TNF- α is a cytokine produced from macrophages and neutrophils that contributes to inflammation in immune diseases, including non-infectious uveitis. Increased TNF- α levels have been reported in both serum and aqueous humor in uveitis patients, and this elevation being correlated with disease activity.^[6] Due to the pivotal role of TNF- α in inflammation, inhibiting its activity may be an effective strategy in the treatment of uveitis. Anti-TNF agents are of proven efficacy in non-infectious uveitis, and are today widely employed.^[7–10] These agents are the most important choice in posterior/intermediate uveitis and panuveitis refractory to conventional treatment, and reduce exposure to and dependence on steroids. They make a positive contribution to treatment in severe cases, and prevent permanent loss of vision. Adalimumab (Humira, AbbVie, Chicago, IL, USA) is a completely human monoclonal IgG1 TNF- α antibody and the first drug approved for the treatment of rheumatoid arthritis by the US Food and Drug Administration (FDA) in 2002. Following two randomized placebo-controlled trials, VISUAL-I and VISUAL-II, adalimumab has now been approved for use in non-infectious intermediate, posterior and panuveitis in adults by the European Medicines Agency and the FDA.^[9, 10]

The efficacy of adalimumab in non-infectious uveitis has frequently been investigated in terms of degree of clinically detectable ocular inflammation (anterior chamber and vitreous inflammation) and attack frequency. The efficacy of adalimumab in uveitis and inflammation control has been proved in several studies, although especially evaluating retinal vascular and optic disc leakages in posterior segment have been investigated in a few studies. The purpose of the present study was to investigate retrospectively the efficacy of adalimumab in retinal vascular leakage, and controlling vascular and choroidal inflammation in patients with non-infectious uveitis, which is refractory to conventional immune suppressive therapy, by evaluating the posterior segment and peripheral retina with ultra-widefield fundus fluorescein angiography.

Materials And Methods

The patients who were resistant to conventional immunosuppressive therapy and started on adalimumab therapy at the Ophthalmology Department Uvea Unit, Medical Faculty, Karadeniz Technical University, Turkey, between April 2017 and March 2020 were included in the study. All patients were receiving prednisolone and immunomodulator (azathioprine, cyclosporine, methotrexate and/or interferon) drug combination. Patients who still had signs of active uveitis despite receiving single or combined therapy were considered as resistant and were included in the study. The study protocol was approved by the ethical committee of medical faculty, and written informed consent was obtained from all patients. The study was conducted in accordance with the Helsinki declaration.

Patients receiving adalimumab therapy for at least six months and attending regular follow-ups were enrolled. All patients underwent full protein derivative (PPD) tests, complete blood count, and kidney and liver function tests at baseline. Patients diagnosed with latent tuberculosis, defined as a protein-purified derivative skin conversion involving an induration of 5 mm in the absence of radiographic or clinical disseminated or pulmonary disease findings, received anti-tuberculosis prophylaxis at least three weeks before the first dose of adalimumab. Magnetic resonance imaging of the brain was performed in all cases with pars planitis in order to exclude demyelinating disease.

Adalimumab was administered via the subcutaneous route at a dose of 40 mg at two-week intervals. The inflammatory status of each eye at baseline was classified as either 'active' (based on clinical findings of at least one active inflammatory chorioretinal or retinal vascular lesion, an anterior chamber

cell grade of 1 + or higher or vitreous haze grade of 1 + or higher, according to the Standardization of Uveitis Nomenclature (SUN) Working Group and adapted National Eye Institute criteria) or as 'inactive' (corresponding to eyes without active inflammatory chorioretinal or retinal vascular lesions in addition to an anterior chamber cell grade and vitreous haze grade of 0.5 + or less).^[11, 12] For the analysis of systemic outcomes, patients who have one or two active eyes at baseline were classified as 'active', while individuals in whom both eyes were quiet at baseline were classified as 'inactive'.

Patients were evaluated at baseline and at third month and sixth month. Best corrected visual acuity (BCVA), slit-lamp anterior segment and vitreous examination, intraocular pressure measurement, and comprehensive funduscopy examination including posterior vitreous assessment were performed at each examination. Visual acuity was assessed using a Snellen chart and was converted into a logarithm of minimum angle of resolution (logMAR) for analysis. Ultra-widefield fundus fluorescein angiography (FFA) images were taken using an Optos device (OptosCalifornia, PLC, Dunfermline, UK). FFA was performed on all visits, and the staining on the head of the optic disk, retinal vascular leakage, and ischemia were evaluated. Optic nerve hyperfluorescence was investigated on late-phase images. The peripheral retina was defined as the region from the equator to the ora serrata. Retinal vascular leakage was classified as peripheral leakage, diffuse leakage (involving both the peripheral retina and posterior pole) or no leakage. The extent of leakage was classified under four grades for clock hour quadrant (Grade 0 = no leakage, grade 1 = mild, grade 2 = moderate, or grade 3 = severe). Both retinal vascular structures and the optic disk were evaluated by two specialists who were blinded to one another. Optical coherence tomography was performed using Optovue RTVue (RT 100, software version 6.3, Optovue, Fremont, CA, USA). Choroidal imaging was conducted in cross-line scanning mode, with the scan protocol being set to a retina cross-line involving two orthogonal 6-mm lines consisting of 1024 A scans. For the purpose of better visualization of the choroidal layer, the scan number was later adjusted to 80 by selecting chorioretinal scanning mode on 'Manual Tab' and the 'Auto All' function on 'Auto Tab.' Choroidal thickness was defined as the vertical distance between the retinal pigment epithelium and the choriocleral interface. Subfoveal choroidal thickness (SFCT) and central retinal thickness (CRT) were calculated manually in subfoveal section by two separate researchers based on OCT images showing visible and measurable choroid.

Patients' immunosuppressive drug burdens were calculated according to the immunosuppressive agents as described by Nuseenblatt et al.^[13]

Patients were asked about side-effects occurring during treatment, and complete blood count and serum sample tests were repeated at two-month intervals.

STATISTICAL ANALYSIS

Statistical analyses were performed on SPSS 21.0 (Statistical Package for Social Science) for Windows. Normality tests were performed for all variables. Compatibility with normal distribution was assessed using the Shapiro-Wilk test. The matched t test was applied for normally distributed dependent groups, and the Mann-Whitney U test for non-normally distributed dependent groups. Time-dependent changes in the same parameters at repeated measurements were analyzed using analysis of variance (ANOVA). Descriptive statistics for continuous variables exhibiting normal distribution were expressed as mean $\pm$ standard deviation, while those not exhibiting normal distribution were expressed as median, maximum, and minimum values and were reported together. p values < 0.05 were regarded as significant.

Results

Forty-four eyes of 23 patients with non-infectious uveitis, 13 (56.5%) women and 10 (43.5%) men, were included in the study. One eye of one patient was excluded from the study because of neovascular glaucoma and another patient because of phthisis bulbi. Behçet uveitis was diagnosed in 14 (60.9%) patients, sarcoidosis in two (8.7%), and idiopathic uveitis in seven (30.4%) patients. All patients were classified anatomically based on International Uveitis Study Group criteria. Panuveitis was present in 10 (43.5%) cases, posterior uveitis in four (17.4%), intermediate uveitis in five (21.7%), and anterior and uveitis in four (17.4%). The mean duration of uveitis was 5.26 ± 5.16 years. Etiologies and locations of uveitis, and drug therapies prior to adalimumab are shown in Table 1.

Table 1
Distribution of diagnoses, involvements, durations of disease, and medications used

Patient/Gender/Age	Diagnosis	Site of involvement	Duration of disease	Medications used
1/M/51	BEHÇET	PANUVEITIS	20 YEARS	Prednol, azathioprine, interferon
2/M/26	BEHÇET	PANUVEITIS	2 YEARS	Prednol, azathioprine, interferon
3/F/34	BEHÇET	POSTERIOR	2 YEARS	Prednol, azathioprine, interferon
4/M/45	BEHÇET	POSTERIOR	2 YEARS	Prednol, azathioprine, cyclosporine, interferon
5/M/46	BEHÇET	PANUVEITIS	5 YEARS	Prednol, cyclosporine, infliximab
6/M/39	BEHÇET	PANUVEITIS	1 YEAR	Prednol, azathioprine, interferon
7/M/42	BEHÇET	POSTERIOR	16 YEARS	Prednol, azathioprine, interferon
8/F/19	BEHÇET	POSTERIOR + INTERMEDIATE	2 YEARS	Prednol, methotrexate, infliximab
9/F/62	IDIOPATHIC	POSTERIOR + INTERMEDIATE	2 YEARS	Prednol, azathioprine
10/F/48	IDIOPATHIC	PANUVEITIS	2 YEARS	Prednol, azathioprine
11/M/70	IDIOPATHIC	INTERMEDIATE	11 YEARS	Prednol, azathioprine
12/F/36	SARCOIDOSIS	INTERMEDIATE	6 YEARS	Prednol, azathioprine
13/M/28	BEHÇET	PANUVEITIS	2 YEARS	Prednol, azathioprine, interferon
14/57/M	IDIOPATHIC	INTERMEDIATE	2 YEARS	Prednol, azathioprine
15/F/20	BEHÇET	PANUVEITIS	2 YEARS	Prednol, azathioprine, interferon
16/F/23	BEHÇET	POSTERIOR	2 YEARS	Prednol, azathioprine
17/F/44	BEHÇET	PANUVEITIS	17 YEARS	Prednol, azathioprine, cyclosporine
18/F/23	IDIOPATHIC	INTERMEDIATE	4 YEARS	Prednol, methotrexate
19/M/47	IDIOPATHIC	INTERMEDIATE	4 YEARS	Prednol, azathioprine
20/F/28	BEHÇET	PANUVEITIS	3 YEARS	Prednol, azathioprine, sulfasalazine
21/F/49	SARCOIDOSIS	INTERMEDIATE	1 YEAR	Prednol, azathioprine
22/M/38	BEHÇET	PANUVEITIS	8 YEARS	Prednol, azathioprine, cyclosporine, interferon
23/F/56	IDIOPATHIC	PANUVEITIS	8 YEARS	Prednol, azathioprine
M: Male F: Female				

All patients had bilateral involvement. Active inflammation was observed in 19 (43.18%) eyes, while 25 (56.8%) eyes were clinically inactive. Active inflammation was present in both eyes in seven patients, and in one eye of five patients, while 11 patients were clinically inactive. The mean anterior chamber cell grade was 0.72 ± 1.29 at baseline, 0.22 ± 0.41 at thirdmonth, and 0.15 ± 0.41 at sixth month ($p < 0.001$). Vitreous cell grade was a mean of 1.13 ± 1.46 at baseline, 0.26 ± 0.44 at thirdmonth, and 0.17 ± 0.43 at sixth month ($p < 0.001$). Both anterior chamber reaction and vitreous reaction compared to initial values decreased significantly ($p < 0.001$).

While the mean initial drug burden was 9.91 ± 3.78 , it was 7.3 ± 4.25 at third month, and 8.0 ± 4.71 at sixth month after adalimumab therapy. The drug burden decreased significantly compared to baseline ($p = 0.022$). No significant relationship was determined between drug burden and uveitis etiologies ($p = 0.23$). Twenty of the 23 patients were receiving oral Prednisolone prior to adalimumab therapy. The mean baseline prednisolone dose was 17.5 mg/day (4–64 mg), which decreased to 5.56 mg/day by the third month. The mean oral prednisolone dose at six months was 8.34 mg. Prednisolone doses were lowered significantly in each consecutive visit compared to baseline ($p < 0.001$). Recurrence developed in only one patient receiving adalimumab therapy during six months and prednisolone at 1 mg/kg was again started on. With this exception, no patients developed attacks during receiving adalimumab therapy.

The mean visual acuity was 0.58 ± 0.96 logMAR at baseline, 0.47 ± 0.96 logMAR at thirdmonth, and 0.54 ± 1.05 logMAR at sixth month. There was no significant difference in visual acuity between the visits ($p = 0.07$). The mean central retinal thickness was 182.38 ± 43.89 μ m, compared to 177.24 ± 49.37 μ m at third month and 180.73 ± 50.17 μ m at sixth month. There was no significant difference in retinal thickness between the visits ($p > 0.05$). The mean choroidal thickness was 256.65 ± 43.63 μ m at baseline, 240.49 ± 36.73 μ m at third month, and 224.81 ± 34.91 μ m at sixth month. The changes in choroidal thickness values between the examinations were significant ($p = 0.005$).

Retinal vascular leakage was observed in 16 eyes at fundus fluorescein angiography performed before adalimumab therapy (in two eyes of six patients, and in one eye of four patients). Leakages in peripheral were in 11 (68.75%) eyes and diffuse in five eyes (31.25%). Leakage was present in a mean of 2.95 ± 4.55 clock hour quadrants at baseline, in 2.41 ± 3.91 at third month, and in 1.76 ± 3.44 at sixth month. Statistically significant difference was

observed in leakage extend between the visits ($p < 0.001$). However, the grade of leakage decreased significantly during the study ($p < 0.001$). The changes in leakage extent and grades are shown in Table 2.

Table 2
Changes in extents and grades of leakage before and after treatment in patients with leakage observed at fundus fluorescein angiography

Changes in extent and grade of leakage before and after treatment in patients with leakage observed at Peradex nuclear scintigraphy												
Before adalimumab treatment					Third month after treatment				Sixth month after treatment			
	Clock hour quadrant right	Clock hour quadrant left	Leakage grade right	Leakage grade left	Clock hour quadrant right	Clock hour quadrant left	Leakage grade right	Leakage grade left	Clock hour quadrant right	Clock hour quadrant left	Leakage grade right	Leakage grade left
1	0	12	0	Grade2	0	10h	0	Grade1	0	6h	0	Grade1
2	8	6	Grade2	Grade1	8h	3h	Grade2	Grade1	8h	3h	Grade1	Grade1
3	5	5	Grade 1	Grade1	2h	5h	Grade1	Grade1	0	0	0	0
4	3	5	Grade2	Grade2	4h	5h	Grade2	Grade2	4h	3h	Grade2	Grade2
5	12	4	Grade2	Grade1	12h	2h	Grade1	Grade1	0	0	0	0
6	12	12	Grade3	Grade3	12h	12h	Grade2	Grade3	12h	12h	Grade2	Grade3
7	8	0	Grade2	0	8h	0	Grade1	0	4h	0	Grade1	0
8	12	8	Grade3	Grade2	6h	4h	Grade1	Grade1	9h	3h	Grade2	Grade1
9	12	0	Grade3	0	8h	0	Grade1	0	7h	0	Grade 2	0
10	0	12	0	Grade2	0	10h	0	Grade1	0	10h	0	Grade1

Statistically significant correlation was observed between extent and grade of leakage at baseline ($r = 0.98$, $p < 0.001$). The choroidal thickness exhibited significant correlation with extent and grade of leakage ($r = 0.31$, $p = 0.04$, and $r = 0.37$, $p = 0.016$, respectively). At the beginning of treatment, optic disk staining was observed in eight eyes, compared to four eyes at third month and five eyes at the sixth month. No significant difference was determined in terms of optic disc staining between the visits (Chi square, $p = 0.074$). However, significant correlation was observed between optic disc staining and extent and grade of leakage ($r = 0.73$, $p < 0.001$, and $r = 0.68$, $p < 0.001$, respectively). Significant correlation was also determined at the third month of treatment between extent of leakage and optic disc staining, and between extent of leakage and leakage grade ($r = 0.537$, $p < 0.001$, and $r = 0.952$, $p < 0.001$, respectively).

No statistically significant correlation was observed at the third month of treatment between choroidal thickness and extent or grade of leakage ($r = 0.18$, $p = 0.24$ and $r = 0.23$, $p = 0.14$, respectively). Significant correlation was observed between extent of leakage and optic disc staining at the sixth month of treatment ($r = 0.661$, $p < 0.001$). Similarly, significant correlation was observed between extent and grade of leakage at the sixth month of treatment ($r = 0.984$, $p < 0.001$). No significant correlation was observed at the sixth month of treatment between choroidal thickness and extent or grade of leakage ($r = 0.21$, $p = 0.19$ and $r = 0.24$, $p = 0.12$, respectively). Macular leakage was observed at fluorescein angiography in five eyes (one eye in three patients and two eyes in one patient). No edema at OCT was observed in none of these patients. Macular leakage resolved entirely at angiography in two eyes with adalimumab therapy, while decreasing from grade 2 to grade 1 in the other three eyes.

Adalimumab therapy was well-tolerated by patients, although local side-effects such as pain in the injection site, rash and itching were frequently seen. Pulmonary thromboembolism was observed in one patient. We think that this embolism is secondary to the vasculitis seen in Behçet's disease. These were regarded as the mild risk group and were started on anticoagulant therapy, while adalimumab therapy was maintained.

Figure 1. A, B, C image from a patient with grade 3, 12 clock hour quadrant peripheral leakage and optic disk staining in the right eye. D, At the third month of adalimumab therapy, the leakage decreased to grade 1, the extent of leakage improved to six quadrants, and the optic disk staining also decreased

Figure 2. A, B. Images from a patient with initial optic disk staining and grade 2, 12 clock hour quadrant ,peripheral leakage in the left eye, improving to grade 1 and 10 clock hour quadrants at the third month of treatment (C, D), and to grade 1 and six clock hour quadrant at the six month (E, F).

Discussion

TNF- α is a cell signaling protein (cytokine) playing an important role in systemic inflammation and makes up the acute phase reaction. It is produced chiefly by activated macrophages as well as T helper cells, neutrophils, mast cells and eosinophils. Increased expression and production of TNF- α are of critical importance in the induction phase of experimental autoimmune uveitis, while suppression of TNF- α in experimental uveitis models has been shown to lower both the incidence and severity of intraocular inflammation.^[14] Several studies have shown the efficacy of the TNF- α inhibitors such as infliximab and adalimumab in non-infectious uveitis.^[15-17] The VISUAL I and VISUAL II studies showed the effectiveness of adalimumab in active and inactive refractory non-infectious uveitis and reported that it reduced the frequency of inflammation relapses in uveitis patients with a broad range of uveitic conditions.^[9, 10]

The effects of TNF- α antagonist on visual acuity, attack frequency, and anterior chamber and vitreous inflammation have frequently been researched in the literature, but their efficacy against retinal vascular and choroidal inflammation has not been evaluated in detail. Studies have shown the efficacy of infliximab against retinal vasculitis, but information concerning the vascular effect of adalimumab is limited. Retinal and optic disc pathology developing in association with retinal and choroidal inflammation, particularly in panuveitis and posterior uveitis, lead to vision loss in uveitis. Keino et al.^[18] reported that retinal and optic disk damage occurring in patients with Behçet's disease was not solely associated with acute inflammation attacks, but also potentially with chronic inflammation capable of causing background vascular leakage.

With the introduction of the ultra-widefield angiographies, it has become possible to identify retinal peripheral leakages in clinically active or inactive patients. In this way, evaluating the presence and extent of retinal pathologies, diagnosis, treatment planning and follow-up can be done more accurately in the patients with uveitis. Several studies have reported that active vasculitis findings can be determined in the early period with wide-angle angiographies, and that treatment can thus be arranged early, with better potential outcomes.^[19, 20] In the present study, we investigated the effect of adalimumab therapy, not only in clinically identifiable uveitis attacks, but also particularly on retinal vascular structures and choroidal involvement.

Keino et al.^[18] evaluated the effectiveness of infliximab on retinal vascular leakage and optic disc leakage in the patients with Behçet disease, and reported 79% improvement in retinal vascular and optic disc leakage at 12-month follow-up. Pirani et al.^[21] reported a statistically significant decrease in vasculitis in the four retinal quadrants at 12-month follow-up with adalimumab therapy ($p = 0.01$). Fabiani et al.^[22] investigated the efficacy of adalimumab in patients with Behçet uveitis and reported that vasculitis was initially present in 22 (55%) patients, and decreased to eight (20%) patients at three months and to one (2.5%) at 12 months. Again, in another study of Fabiani et al.^[23] evaluated the efficacy of adalimumab and infliximab in treatment of recalcitrant retinal vasculitis, it was found that there was no difference between adalimumab and infliximab therapy, and both provided a significant reduction in retinal vasculitis findings at 12-month follow-up ($p < 0.001$). Sharma et al.^[24] reported that remission was achieved in 88.23% of patients with infliximab therapy on recalcitrant retinal vasculitis at six-month follow-up. In another study, Keino et al.^[25] reported that background vascular leakage and optic disc leakage in inactive eyes decreased with infliximab treatment in Behçet patients over four-year follow-up. Since we could not find detailed studies in the literature similar to our study evaluating the severity and extent of vasculitis, retinal vascular leakage, we could not make a comparison in this respect. In our study, the presence of the retinal leakage was evaluated in clock hour quadrants, and we found a significant decrease in the extent and grade of leakage at 3 and 6 months ($p < 0.001$) with treatment. Our results are compatible with the American Academy of Ophthalmology's recommendation for the use of anti-TNF- α as a first-line therapy in severe uveitis attacks in patients with Behçet disease.^[26]

Pirani et al.^[21] reported that choroidal thickness decreased from $236 \mu\text{m}$ to $208.75 \mu\text{m}$ following adalimumab therapy. In the present study, choroidal thickness significantly decreased from $256.65 \pm 43 \mu\text{m}$ to $224.81 \pm 34.91 \mu\text{m}$ at six-month treatment. In our study, we found a statistically significant decrease in choroidal thickness at the 3rd and 6th months with treatment ($p = 0.005$).

Lee et al.^[7] reported no marked improvement in vision levels following adalimumab therapy. In a study of 131 patients, Diaz Llopis et al.^[4] reported that vision levels remained unchanged over six months in 75.4% of patients, while improving from $0.39 \pm 0.244 \log\text{MAR}$ to $0.26 \pm 0.39 \log\text{MAR}$ in 21.3% at the end of six-month follow-up. Durrani et al.^[27] reported no improvement in vision levels at three- and six-month follow-ups after adalimumab therapy. In contrast to these studies, Bawazeer et al.^[8] reported improved visual acuity of three lines or more in 17 out of 21 patients at an average follow-up of 10.8-month. In our study, we did not find any statistically significant change in visual acuity during follow-up ($p = 0.07$).

Another important issue in patients with uveitis is use of steroids. Because they need to be used for a long time and serious side effects may occur. The ability to control inflammation with other agents will reduce both the drug load and dose and duration of steroids. The great majority of patients in the present study had Behçet uveitis and were frequently in receipt of prednisolone and azathioprine therapy. While, the mean initial dosage of Prednisolone in this study was 17.5 mg/day ($4\text{--}64 \text{ mg}$), it was 7.11 mg at the sixth month. Prednisolone therapy was discontinued entirely in four patients at three months and in eight patients at six months. In one patient having recurrence, orally Prednisolone at 1 mg/kg was restarted at the sixth month. Since severe ocular and systemic side-effects may develop with long-term steroid use, prednisolone therapy is used for as short a time as possible, and steroid sparing agents that suppress inflammation are then used. In addition, the drug load decreased from 9.91 ± 3.78 initially to 8.0 ± 4.71 at the end of 6 months ($p = 0.022$). This is important in terms of reducing possible complications of the drugs.

Kempen et al.^[28] reported uncorrelation agreement between central macular thickness measured using OCT and macular leakage in fundus angiography, and stated that these two methods are not a substitute but complementary methods in evaluating macular pathology. They particularly recommended the use of OCT due to its non-invasive and inexpensive nature.^[28] Similarly, Ossewaarde-van Norel et al.^[29] reported that macular leakage was detected in 34 (30%) out of 112 eyes with uveitic macular edema using FFA, while no edema was detected using OCT. In the present study, macular leakage was detected at FFA in five eyes, while no edema was detected at OCT.

Although serious side effects of the drugs used in the treatment of uveitis are an important problem, adalimumab therapy was well-tolerated by patients, with side-effects consisting of local erythema, pain, hemorrhage, and rash in the injection site in the present study. Systemic side-effects developed were leukopenia in two patients and pulmonary thromboembolism in one. One patient with suspected embolism secondary to Behçet disease-related vasculitis was started on anticoagulant therapy. Additionally, adalimumab therapy was maintained, rather than being stopped, in these patients. None of our patients developed severe side-effects such as viral or bacterial infection, demyelinating neurological disease, tuberculosis activation, or tumor development.

The limitations of this study are that it is retrospective and includes a small number of patients. The efficacy of adalimumab therapy was evaluated during only six-month follow-up, and its effectiveness or failure of treatment were not evaluated in terms of long-term outcomes.

In conclusion, this study shows that adalimumab therapy is effective in the cases with persistent active and inactive uveitis in terms of controlling inflammation, reducing the drug burden, and controlling retinal vascular leakage and choroidal inflammation. Controlling of these pathologies in uveitis will provide a better visual prognosis in patients. Adalimumab therapy appears to be particularly effective in cases of refractory retinal vasculitis due to uveitis, although further longer-term studies with larger case numbers are needed to evaluate treatment failure and resistance development over long-term follow-up.

Declarations

The Authors declares that there is no conflict of interest. There is no funding support for this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figures

Figure 1

A,B,C image from a patient with grade 3, 12 clock hour quadrant peripheral leakage and optic disk staining in the right eye. D, At the third month of adalimumab therapy, the leakage decreased to grade 1, the extent of leakage improved to six quadrants, and the optic disk staining also decreased

Figure 2

A and B, Images from a patient with initial optic disk staining and Grade 2 peripheral 12 quadrant leakage in the left eye, improving to grade 1 and 10 quadrants at the third month of treatment (C, D), and to grade 1 and six quadrants at the six month (E, F).