# Long-Term Follow-up of Patients With Uveitis Treated With Adalimumab: Response Rates and Reasons for Discontinuation of Therapy

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• PURPOSE: To evaluate the effectiveness and reasons for discontinuation including the side effect profiles of adalimumab in a real-world setting.
• DESIGN: Retrospective clinical cohort study.
• METHODS: A medical chart review of clinical practice in 2 tertiary eye care services in Rotterdam, the Netherlands, was performed Data were collected from May 1, 2004, through September 1, 2020. Patients with noninfectious uveitis treated with adalimumab (n = 341; 633 affected eyes) were included. The primary outcome was the effectiveness of adalimumab, measured by the number of patients achieving inactive disease, remission, and relapse-free survival. The secondary outcomes were the reasons for discontinuation, including side effects, and the number of patients who developed antibodies.
• RESULTS: In total, 341 patients were treated with adalimumab between May 2004 and September 2020. The uveitis recurrence-free survival interval was 3.4 years (range, 0-13 years). Adalimumab had an acceptable side effect profile. A total of 178 patients achieved inactive disease while continuing adalimumab, and 51 patients maintained remission after discontinuing adalimumab. Reasons for discontinuation of adalimumab were no response, relapse, or reasons unrelated to the effectiveness of treatment. Adalimumab antibodies were present in 40 of 115 patients (35%). Antibodies were associated with lower adalimumab levels, and antibodies were observed more often in patients on adalimumab monotherapy ($P < .01$).
• CONCLUSIONS: Adalimumab is effective for patients with noninfectious uveitis, with an acceptable side effect profile. Although relapses can occur, the majority of the patients achieved inactive disease or remission after cessation of adalimumab, without other systemic immunosuppressive medication. (Am J Ophthalmol 2022;240: 194–204.


Systemic and topical glucocorticosteroids have been the first choice of treatment for noninfectious uveitis in the past 50 years.[1-5] Long-term use of systemic glucocorticosteroids is not advisable, because of severe side effects such as steroid-induced diabetes mellitus, osteoporosis, and cataracts.[6,7] To reduce glucocorticosteroid dosage and to prevent side effects, "second-line drugs" such as methotrexate, azathioprine, mycophenolate, and cyclosporine have been used.[1,5,8] Nowadays, treatment with biologics, such as anti–tumor necrosis factor (anti-TNF) is initiated as third-line therapy, if the inflammation cannot be controlled with second-line therapy or if unacceptable side effects occur.[2]

TNF-$\alpha$ is a pro-inflammatory cytokine that is synthesized by T-helper cells (Th cells), activated macrophages, and neutrophils. It activates the cytokine-driven inflammatory processes.[5] High TNF-$\alpha$ levels are present in the aqueous humor of patients with active uveitis.[9-11] From the early 2000s, TNF-$\alpha$ blocking therapy, using the chimeric TNF-$\alpha$ monoclonal antibody infliximab, has demonstrated efficacy in the treatment of refractory uveitis.[12,13]

Later on, several studies demonstrated the efficacy of adalimumab (Humira), a humanized recombinant monoclonal anti-TNF antibody, in infliximab-intolerant patients or patients with refractory uveitis.[14-17] An advantage of adalimumab over infliximab and other chimeric monoclonal antibodies is its lower immunogenicity, as shown in rheumatoid arthritis and Crohn disease because of the humanized recombinant compound.[18] Moreover, superiority of adalimumab over infliximab was reported in a study of chronic childhood uveitis by maintaining remission for more than 3 years.[19] In large case-control studies, adalimumab was well tolerated, decreased inflammatory activity, and enabled the reduction of steroid requirement.[20-23] Recently, studies with long-term follow-up, including 5 to

AJO.com Supplemental Material available at AJO.com.

AJO.com Meeting Presentation: An abstract with preliminary results of this study was presented at Science Days Internal Medicine in 2020.

Accepted for publication March 6, 2022.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2022.03.017

6 years of treatment duration, were published.[8,24,25] However, in these studies, concerning long-term follow-up, the reason for loss of effectiveness, how often antidrug antibodies were formed, and the relapse rate after adalimumab cessation were not addressed. Concerning the drug retention rate, there was a single observation study, showing a drug retention rate of 54% after 60 months.[8] Concerning adalimumab antibody formation, antibodies have been reported to develop in 2.7% to 35% of patients.[20,25] Data on relapse after cessation of adalimumab are scarce. In a small cohort study of 28 patients with juvenile idiopathic arthritis, 11 of 12 patients (92%) treated with adalimumab and methotrexate had a relapse within 1 to 2 years after discontinuation of treatment.[24]

The aim of the present study is to evaluate the long-term effectiveness of adalimumab in noninfectious uveitis and to determine the response rate, causes of lack of effectiveness, and treatment failure as well as long-term side effects.

## METHODS

• **DATA COLLECTION:** All patients with uveitis treated with adalimumab for noninfectious uveitis who visited the Rotterdam Eye Hospital (Rotterdam, the Netherlands), or the Department of Ophthalmology or Department of Immunology of the Erasmus University Medical Center (Rotterdam, the Netherlands) were eligible for inclusion in this observational clinical cohort study. Patients from the Erasmus University Medical Center were retrieved through a database search, including all patients visiting the Department of Ophthalmology and/or the Department of Immunology, who were prescribed adalimumab at any point in time. Manually, all patients with uveitis were selected from this search. Patients from the Rotterdam Eye Hospital were retrieved through a manual database search. All patients who were prescribed adalimumab were included. Data were collected through retrospective medical chart review. Approval from the Medical Ethic Committee for analysis of patient data was requested and obtained from the Rotterdam Eye Hospital and the Erasmus University Medical Center (MEC-2012-016). Additional informed consent was not deemed necessary, because of the retrospective observational character of this study.

• **PATIENTS AND DEFINITIONS:** Data included both adult patients and pediatric patients; "pediatric" was defined as uveitis onset before the age of 18 years. The anatomic classification of uveitis used in this study was defined by the Standardization of Uveitis Nomenclature Working Group criteria.[4]

In clinical practice, patients are screened for infectious diseases (eg, hepatitis B and C) before initiation of adalimumab therapy. Patients were screened for active tuberculosis by means of a Quantiferon test and/or Mantoux test. After initiation of adalimumab, patients were evaluated for treatment response within 3 months of treatment. Topical steroid therapy, disease-modifying anti-rheumatic drugs (methotrexate, azathioprine, mycofenolate/myfortic, cyclosporin, hydroxychloroquine) (DMARDs), and systemic therapy were continued, the dosage was adjusted, or the medication was discontinued according to the discretion of the treating physician.

Patients started with subcutaneous adalimumab with a dose of least 40 mg biweekly, although some patients started with a dose of 80 mg at baseline and 40 mg after 1 week in case of severe inflammation. If deemed necessary, the dosage and therapy interval were adjusted by the treating physician based on the response to therapy. Immunosuppressive drugs that were added or still used in addition to adalimumab 3 months after the start of adalimumab were included in the study analysis. Dosage of topical steroid drops was not taken into account in this study.

• **OUTCOME MEASUREMENT:** The primary outcome was effectiveness of adalimumab. Effectiveness was measured by the number of patients achieving inactive disease or remission and by the relapse-free survival.

The secondary outcomes were the percentage of patients with inactive disease at 6 months, 1 year, 3 years, 5 years and 10 years, and the number of patients developing antibodies, the number of patients experiencing side effects, and the reasons for discontinuation.

Remission was defined as no sign of inflammation for 3 months after cessation of systemic immunomodulating therapy. Inactive disease was defined as no sign of inflammation for 3 months during treatment with systemic immunomodulating therapy, including systemic corticosteroids. Because one of the treatment goals in clinical practice is tapering of systemic corticosteroids, the number of patients still using corticosteroids after inactive disease was reached was reported. A cut-off of 10 mg or less of prednisone per day was chosen as succesful tapering of systemic corticosteroid therapy, in accordance to the Standardization of Uveitis Nomenclature for Reporting Clinical Data.[4] Relapse of uveitis was defined as active inflammation after inactivity for at least 3 months. Cystoid macular edema was not included in this definition.

The worst eye analysis method was used. In the worst eye method, treatment is considered successful if improvement or quiescence is observed in both eyes of a single patient. A therapeutic switch is considered if 1 eye shows activity or does not improve despite therapy. Activity, inactivity while on therapy, and remission reflect the response of the worst eye, not of the individual eyes (eg, if both eyes respond to therapy, the remission or time to relapse will be calculated for the worst eye, or as a single response and not counted as 2 responses).

In case a patient discontinued therapy, defined as interruption of more than 4 weeks, the cause of discontinuation was reported. Reasons for discontinuation were classified as

remission, no primary response, relapse of disease, complications or adverse events, side effects, patient request, and pregnancy or plan for pregnancy. The primary response to therapy was defined as decrease of uveitis activity, as reported by an ophthalmologist. A diagnosis of no response was made in patients who did not exhibit a change in the severity of uveitis activity.

In case of a relapse, the treating physician decided whether adalimumab therapy was continued with additional immunosuppressive therapy or switched to other therapy.

• **STATISTICAL ANALYSIS:** Patient characteristics were summarized using descriptive statistics, including median, range, and percentage. The nonparametric test was used to test for significant differences. Differences in groups of unpaired categorical data (eg, antibody formation, prescribed therapy, or uveitis localization) were analyzed using the Fisher exact test. Survival analysis for uveitis relapse-free survival was performed by plotting a Kaplan—Meier curve. For the survival analysis, an event was defined as the first uveitis relapse during adalimumab treatment. Patients who stopped using adalimumab or patients who reached end of follow-up without a relapse were considered as censored at that time point. Differences in time to first relapse based on uveitis localization, uveitis etiology, and systemic vs solitary ocular involvement were tested using the log-rank (Mantel—Cox) test. Time to second relapse or time after restart of adalimumab was not included in this analysis.

All statistical analyses were performed using SPSS 25.0.0 for Windows (SPSS Inc). A *P* value of <.05 was considered statistically significant.

## RESULTS

• **PATIENT CHARACTERISTICS:** The database search revealed 342 patients, with uveitis in 1 or both eyes, resulting in 633 affected eyes treated with adalimumab. One patient was prescribed adalimumab, but did not start the treatment (due to noncompliance) and was excluded from the analysis (Table 1).

Uveitis was active in 244 of the 341 patients (72%) when starting adalimumab. Nearly half of the patients (160 of 341; 47%) had inflammation limited to the eye(s) (eg, birdshot retinopathy) or remained idiopathic after screening. The other patients (181 of 341; 53%) had a systemic noninfectious disease. The most prevalent systemic diseases were sarcoidosis (22%) and Behçet disease (8%) (Table 1). Most of these systemic diseases are associated with uveitis, with the exception of systemic sclerosis.

The median age at the start of adalimumab treatment was 44 years (range, 33-56 years). The cohort of 341 patients included 20 pediatric patients (5.9%). There were no differences in sex, bilateral involvement, localization of uveitis, number of relapses, and median time to relapse between pediatric and adult patients. Therefore, data from both adult and pediatric patients were combined.

All patients received immunosuppressive therapies before initiation of adalimumab (Table 1).

• **TREATMENT OUTCOME:** The median follow-up period after initiation of adalimumab was 4.9 years (range, 0.11-14.7 years). The median treatment duration of adalimumab was 3.3 years (range, 0.03-14.7 years). Of the patients, 18% started adalimumab monotherapy with or without topical steroids. All other patients had combination immunosuppressive therapy consisting of adalimumab with steroids and/or DMARDs. During the follow-up, 148 of the 341 patients (43%) continued treatment with adalimumab until end of follow-up (ie, time of data collection).

Inactive disease/remission was achieved in 298 of the 341 patients (87%). Inactive disease, which enabled the cessation of adalimumab, was achieved in 57 patients, with a median treatment duration until discontinuation of 3.2 years (range, 0.4-11 years). In all, 178 patients reached inactive disease and continued adalimumab treatment (Table 2). Adalimumab was effective in 235 patients ([57 + 178]/341 patients; 69%) of patients. In the remaining 63 of the 298 patients, inactive disease was achieved when patients switched to other medication. Of the 103 patients using adalimumab and systemic corticosteroids who reached inactive disease, systemic corticosteroids could be tapered to zero in 86 patients. None of the 103 patients had received intravitreal steroids in the prior 3 months. A minority of patients (33 of 86; 38%) still used systemic corticosteroids such as prednisolone. In total, 31 of 33 patients (94%) used prednisolone 10 mg or less. The remaining 2 patients used 12.5 and 15 mg, respectively. In those patients still using prednisone despite inactive disease, prednisone was not tapered further because of previous visual loss and because the risk of a relapse was considered too high.

At the end of follow-up, active disease was observed in 29 patients still on adalimumab treatment. Adalimumab was continued because the relapse was considered minor. However more than 92% of patients on adalimumab had inactive disease when evaluated at fixed time points, including 6 months, 3 years, 5 years, and 10 years (Supplemental Table 1).

Of the 341 patients, 32 (9%) were treated with adalimumab for more than 10 years. Among those patients, 18 (56%) used monotherapy with or without topical steroids. Patients had the following underlying diseases: birdshot chorioretinopathy (n = 8), Behçet disease (n = 4), sarcoidosis (n = 4), JIA (n = 3), sympathetic ophthalmia (n = 3), idiopathic uveitis (n = 2), spondyloarthropathy (n = 2), psoriasis (n = 2), inflammatory bowel disease (n = 2), postinfectious uveitis (n = 1), and retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, headache (ROSAH) syndrome (n = 1).

**TABLE 1.** Patient Characteristics at Baseline of 341 Uveitis Patients Starting Adalimumab Treatment

| Characteristic | N (%) |
|---|---|
| Total Number of Patients | 341 (100%) |
| Female Sex | 209 (61%) |
| Bilateral Eye Involvement | 292 (86%) |
| Median Age at Start of Adalimumab Treatment, years | 44 (IQR = 33-56) |
| Anatomical Localization of Uveitis | |
| Anterior | 66 (19%) |
| Intermediate | 22 (7%) |
| Posterior | 92 (27%) |
| Panuveitis | 160 (47%) |
| Not specified | 1 (0.3 %) |
| Diseases Limited to the Eye | |
| Idiopathic | 70 (21%) |
| Birdshot chorioretinopathy | 56 (16%) |
| Postinfectious | 13 (3.8%) |
| Sympathetic ophthalmia | 8 (2.3%) |
| Multifocal choroiditis with panuveitis | 5 (1.5%) |
| APMPPE | 3 (0.9%) |
| Serpiginous/ampiginous choroiditis | 2 (0.6%) |
| IRVAN syndrome | 1 (0.3%) |
| AZOOR | 1 (0.3%) |
| POHS | 1 (0.3%) |
| Systemic diseases | |
| Sarcoidosis, including ocular sarcoidosis (n = 7) | 75 (22%) |
| Behçet disease | 26 (7.6%) |
| Juvenile rheumatoid arthritis | 16 (4.7%) |
| Spondylarthropathy | 16 (4.7%) |
| Psoriasis | 15 (4.4%) |
| Inflammatory bowel disease | 8 (2.3%) |
| Rheumatoid arthritis | 7 (2.1%) |
| Vogt–Koyanagi–Harada disease | 7 (2.1%) |
| HLA-B27–associated uveitis | 6 (1.8%) |
| TINU | 2 (0.6%) |
| Systemic sclerosis | 1 (0.3%) |
| Morbus Sjögren | 1 (0.3%) |
| ROSAH syndrome (ALPK-1 mutation) | 1(0.3%) |
| Medication Before Starting Adalimumab[a] | |
| None | 22 (6.5%) |
| Topical steroids only | 39 (11%) |
| Steroids intravitreal and/or systemic[b] | 152 (45%) |
| Monotherapy/with DMARDS/with anti-TNF/with interferon | 44 /102/5 /1 |
| DMARDs[b] | 107 (31%) |
| Monotherapy/with anti-TNF/with interferon | 103/3/1 |
| Anti-TNF (etanercept, infliximab)[b] | 12 (3.5%) |
| Monotherapy | |
| Interferon[b] | 2 (0.6%) |
| Monotherapy | |

APMPPE = acute posterior multifocal placoid pigment epitheliopathy; AZOOR = acute zonal occult outer retinopathy; DMARDs = disease-modifying anti-rheumatic drugs (methotrexate, azathioprine, mycofenolate/myfortic, cyclosporin, hydroxychloroquine); HLA = human leukocyte antigen; IRVAN = idiopathic retinal vasculitis–aneurysm–neuroretinitis; POHS = presumed ocular histoplasmosis syndrome; ROSAH = retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, headache; TINU = tubulointerstitial nephritis and uveitis; TNF = tumor necrosis factor.

[a] In 7 patients, the exact medication prior to the start of adalimumab was unknown.

[b] With or without topical steroids.

**TABLE 2.** Medication and Uveitis Activity of 341 Patients at End of Follow-up

| Medication | Inactive Uveitis or Remission | Active Uveitis | Total (%) |
|---|---|---|---|
| None | 39 | 1 | 40/341 (12%) |
| Topical Steroids Only | 12 | 5 | 17/341 (5.0%) |
| Steroids, Intravitreal and/or Systemic | 10 | 3 | 13/341 (3.8%) |
| DMARDs, With/Without Steroids | 20 | 3 | 23/341 (6.7%) |
| Adalimumab, With/Without Topical Steroids | 94 | 12 | 106/341 (31%) |
| Adalimumab, With Intravitreal and/or Systemic Steroids | 23 | 3 | 26/341 (7.6%) |
| Adalimumab, with DMARDs | 61 | 14 | 75/341 (22%) |
| Other Anti-TNF Therapy[a], With/Without Steroids or DMARDs | 28 | 1 | 29/341 (8.5%) |
| Other Therapy[b], With/Without Steroids or DMARDs | 11 | 1 | 12/341 (3.5%) |
| | 298 | 43 | 341 |

DMARDS = DMARDs = disease-modifying anti-rheumatic drugs (methotrexate, azathioprine, mycofenolate/myfortic, cyclosporin, hydroxychloroquine); TNF = tumor necrosis factor.

[a]Infliximab (n = 23) and etanercept (n = 6).

[b]Tocilizumab (n = 9); interferon (n = 1); secukinumab (n = 1); anakinra (n = 1).

In summary, 298 of 341 patients (87%) achieved inactive disease or remission. The majority of patients (247 of 341; 72%) achieved inactive disease, whereas 51 patients (15%) achieved remission (ie, either no therapy or topical steroids only) (Table 2). The majority of patients treated with adalimumab (178 of 207; 86%) had inactive disease at the end of follow-up. In the remaining patients treated with adalimumab, some uveitis activity was observed. Adalimumab was continued because the relapse was considered minor.

Almost one-third (31%) of patients used adalimumab monotherapy (with or without topical steroids) at the end of data collection. Another one-third (30%) used steroids and/or DMARDs in addition to adalimumab. The remaining patients did not use adalimumab at the end of follow-up (Table 2).

In about half of the patients (177 of 341; 52%), other immunosuppressive agents were stopped between the start of adalimumab and the end of follow-up. A total of 78 patients stopped with a DMARD, 56 stopped with intravitreal and/or systemic steroids, and 43 patients stopped with both a DMARD and intravitreal and/or systemic steroids.

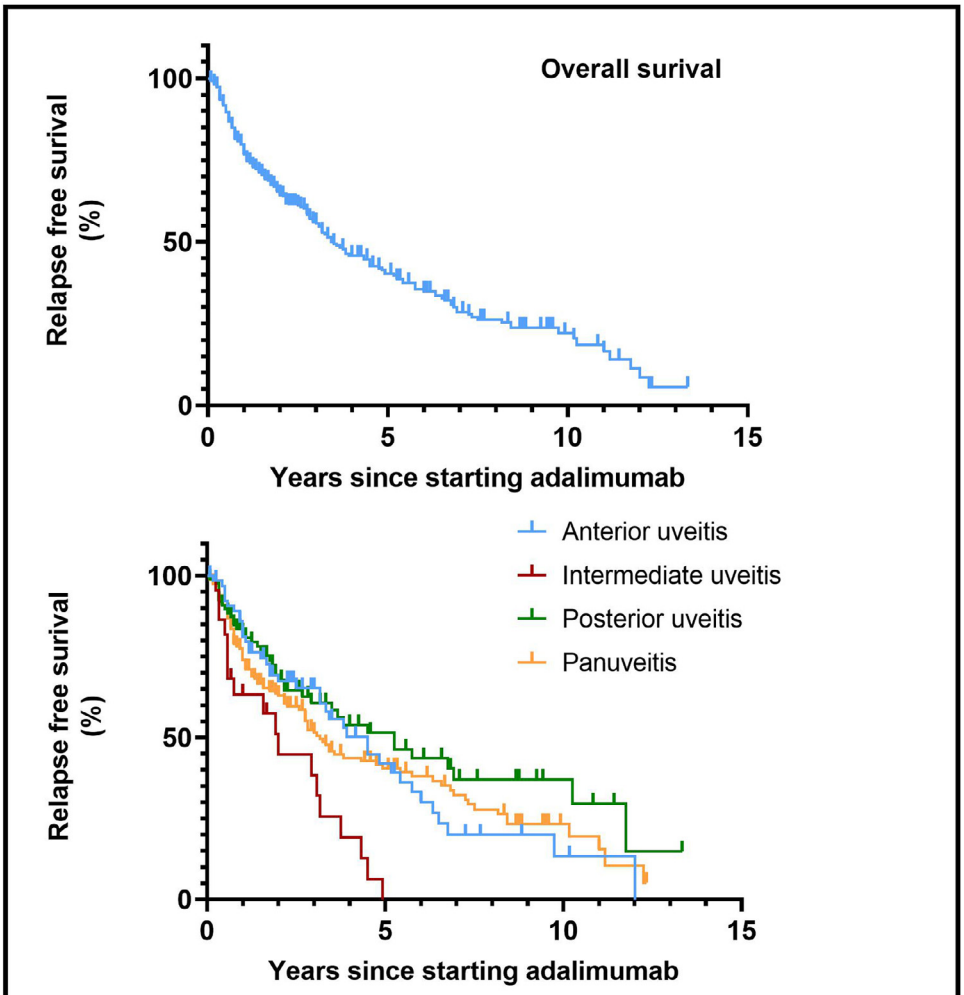
• **RELAPSE-FREE SURVIVAL AND RELAPSES:** Survival analysis showed that the median time to the first relapse was 3.4 years (95% CI = 2.7-4.2) (Figure 1). No differences in time to first relapse were seen between male and female patients or between patients with uveitis related to systemic disease and inflammation limited to the eye. No difference in time to first relapse was seen for the different uveitis etiologies. However, there was a difference in time to first relapse for uveitis localization (Figure 1). The time to first relapse in patients with intermediate uveitis was shorter compared to other localizations ($P = .001$). There was no difference in the dosage of adalimumab at the time of relapse or at end of follow-up between the different uveitis localizations. There were no differences in co-medication (eg, topical, systemic steroids, DMARDs, or anti-TNF) between the different uveitis localizations.

One or more relapses occurred in 193 of 341 patients (57%) during follow-up. Relapses were treated by intensifying the immunosuppressive therapy (n = 166), for example, increasing the dosage of adalimumab or adding immunosuppressive therapy, or switching from adalimumab (n = 27) to other immunosuppressive therapy such as other anti-TNF therapy or anti−interleukin-6 therapy. A relapse occurred in 37 patients after cessation of adalimumab. Adalimumab treatment was restarted in 31 of those patients, with the majority (23 of 31; 74%) achieving inactive disease. In some patients who experienced a relapse while still on adalimumab treatment, the adalimumab dosage was increased (32 of 156; 21%). The increase in adalimumab dosage led to inactive disease among approximately half of the patients (17 of 32; 53%).

Other reasons for relapse were a low dose of adalimumab without antibodies (n = 5), tapering of concomitant immunosuppressive medication (n = 8), noncompliance (n = 5), or eye surgery (n = 12). Another reason for relapse could be the formation of anti-adalimumab antibodies (n = 20). In the majority of patients (n = 106), no cause could be identified, although only in 40 of these 106 patients antibodies or adalimumab levels were measured.

• **ANTIDRUG ANTIBODIES AND SERUM LEVELS OF ADALIMUMAB:** In 115 of 341 patients (34%), additional evaluation was performed by measurement of adalimumab antibodies. Reasons for measuring antibody and /or drug levels were relapse, a change in adalimumab frequency, or suspicion of noncompliance.

Adalimumab antibodies were detected in 40 of 115 patients (35%), measured 21 months (interquartile range, 9-61 months) after the start of adalimumab.




| Years | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients at risk** | | | | | | | | | | | | | | | |
| Overall | 340 | 236 | 167 | 117 | 88 | 72 | 55 | 39 | 32 | 21 | 13 | 8 | 3 | 1 | 0 |
| | | | | | | | | | | | | | | | |
| Anterior | 66 | 53 | 37 | 27 | 19 | 15 | 10 | 6 | 4 | 3 | 2 | 1 | 0 | 0 | 0 |
| Intermediate | 22 | 12 | 7 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Posterior | 92 | 63 | 44 | 29 | 23 | 20 | 16 | 11 | 9 | 7 | 5 | 3 | 1 | 1 | 0 |
| Panuveitis | 160 | 108 | 79 | 55 | 43 | 37 | 29 | 22 | 19 | 11 | 6 | 4 | 2 | 0 | 0 |

**FIGURE 1. Kaplan–Meier curve of the time to relapse in years of patients started on adalimumab, overall and per uveitis localization. [a]All patients are represented in the Kaplan–Meier curves per localization, except for 1 patient whose uveitis localization was unknown. [b]The event was defined as the first uveitis relapse during adalimumab treatment. Patients who stopped using adalimumab or patients who reached the end of follow-up without a relapse were considered as censored at that time point.**

The majority of patients (31 of 40; 78%) with adalimumab antibodies were treated with adalimumab monotherapy. It was evaluated whether there was a difference in antibody formation between patients on adalimumab monotherapy compared to patients on additional steroids and/or DMARDs (including systemic steroids, methotrexate, azathioprine, mycophenolate, cyclosporine, or leflunomide). Indeed, monotherapy was correlated with anti-adalimumab antibodies ($P = .01$).

There was no difference in antibody formation in patients with a systemic disease compared to patients without a systemic disease. There were no differences in the

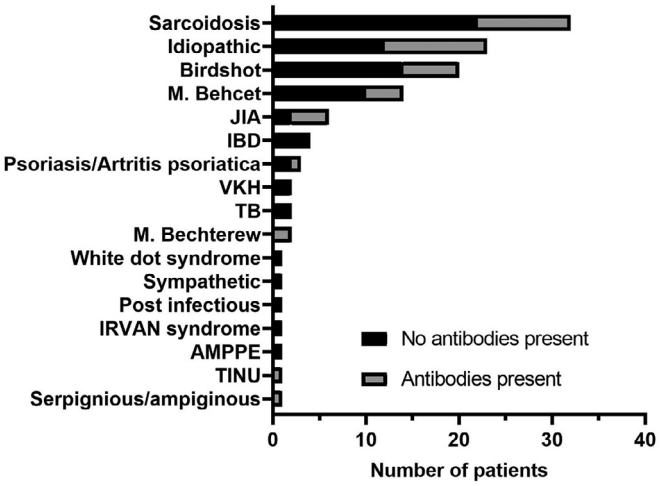



**FIGURE 2. Numbers of patients with and without adalimumab antibodies per disease etiology (percentage of patients with antibodies per disease etiology).**

frequency of antidrug antibodies between uveitis etiologies. However, in patients with idiopathic uveitis (11 of 23; 48%) and patients with JIA (4 of 6; 67%) (Figure 2), antibodies were detected relatively frequently, although the groups were small. Whether there is a difference in the risk of developing antibodies based on the underlying disease etiology deserves further study.

To assess whether the presence of antibodies was associated with low or nondetectable serum levels of adalimumab, the percentage of patients with low serum levels of adalimumab was compared between patients with antibodies and patients without antibodies. The majority of patients with adalimumab antibodies had low serum levels of adalimumab (28 of 33; 85%), whereas a minority of patients without adalimumab antibodies had low serum levels of adalimumab (18 of 65; 28%). Adalimumab antibodies were indeed correlated with low levels of adalimumab ($P = .001$).

There were 18 patients without detectable antibodies and with low serum levels of adalimumab. In 3 of these patients, adalimumab levels were measured multiple times and levels never reached the normal range. In 2 patients, the dosage of adalimumab was increased after the first measurement of low serum adalimumab levels, whereas the third patient admitted to being noncompliant. In this patient, the dosage was not increased, but motivational conversations were started to increase therapy adherence.

- **REASONS FOR DISCONTINUATION OF ADALIMUMAB:**

*Disease inactivity and remission*

The most common reason for discontinuation of adalimumab was disease inactivity. This was present in 57 of 341 patients (17%) (Table 3).

**TABLE 3.** Reasons for Adalimumab Discontinuation in 193 Uveitis Patients Started on Adalimumab

| Reason for Discontinuation | N (%) |
|---|---|
| Adalimumab Discontinuation | 193/341 |
| Related to Effectiveness of Therapy | 94/341 |
| Remission | 57/ 341 (17%) |
| No Response | 10/ 341 (2.9%) |
| Relapse of Inflammation | 27/341 (7.9%) |
| Not Related to Effectiveness of Therapy | 99/341 |
| Adverse Event or Complication[a] | 43/341 (13%) |
| Subjective Side Effects | 22/341 (6.5 %) |
| Patient Request | 23/341 (6.7%) |
| Pregnancy | 9/341 (2.6%) |
| Pre-emptive (in case of surgery) | 2/341 (0.6%) |

[a]Complications and comorbidities leading to discontinuation of treatment included infection (n = 20), malignancy (n = 8), central nervous system demyelinating disease (n = 2), cutaneous reaction/disease (n = 4), kidney disease (n = 2), other neurological disease (n = 2), relapse systemic disease (n = 2), suicide attempt (n = 1), other (n = 2).

*Nonresponse*

Ten of 341 patients (2.9%) did not respond to adalimumab treatment. However, 4 of them restarted adalimumab later, because of the occurrence of new or progressive ocular inflammation after discontinuation of adalimumab. This restart led to good results in 3 patients, whereas in 1 patient therapy was switched because of persistent cystoid macular edema. The remaining 6 patients (1.8%) who did not respond to the treatment were diagnosed with acute posterior multifocal placoid pigment epitheliopathy (APMPPE) n = 1), sarcoidosis (not confirmed by pathology) (n = 2), birdshot chorioretinopathy

(n = 1), idiopathic uveitis (n = 1), and acute zonal occult outer retinopathy (AZOOR) (n = 1). In a patient diagnosed with ocular sarcoidosis, the diagnosis was reconsidered when tractional retinal detachment was deemed more likely and adalimumab was discontinued.

*Relapse of inflammation*

Another reason for discontinuation of adalimumab was relapse. In 27 of 341 patients (7.9%), relapse was the reason for discontinuation of adalimumab. All patients were switched to other therapies.

*Adverse events and complications*

Adverse events and complications, leading to (temporary) discontinuation of adalimumab, were reported in 43 of 341 patients (13%). The majority of adverse events included infectious complications. In all, 19 of 341 patients (6%) had a temporary infection or temporary kidney dysfunction. Serious adverse events, such as malignancy (n = 8) and demyelinating disease (n = 2) were present in 10 of 341 patients (2.9%) (Table 3). Of the 8 patients (2.3%) with a malignancy, 2 patients developed acute myeloid leukemia (AML), one of them 45 months after the start of adalimumab treatment and the other patient after 19 months of treatment. The other 6 patients had melanoma (n = 3), breast cancer (n = 1), or lung cancer (n = 2) occurring between 5 and 100 months after the initiation of adalimumab. All of these patients were previously or concomitantly treated with DMARDs, corticosteroids, or other anti-TNF agents.

*Other reasons for discontinuation of adalimumab*

Other reasons for discontinuation of adalimumab included subjective side effects (eg, headache, muscle aches, pruritus), patient request, and pregnancy, as well as preemptively (in the case of surgery).

*Change in therapy: Restart of adalimumab after discontinuation*

Of the 193 patients who discontinued treatment, 86 (45%) restarted adalimumab at a later time point in the course of the disease. Of those 86 patients, 60 patients then continued adalimumab treatment until the end of follow-up. Nine patients discontinued adalimumab a second time because of inactive disease, whereas 11 patients stopped because of a relapse (11 of 86; 13%). Six patients stopped adalimumab treatment definitively because of side effects or at their own request. Of the 60 patients who continued adalimumab, 48 of 60 (80%) maintained inactive disease until the latest date of data collection.

To evaluate whether there was an increase in antibody formation when adalimumab was restarted after a period of discontinuation, antibodies were measured after a median of 12 months in 20 of 86 patients who restarted adalimumab. One-fourth of the patients (5 of 20; 25%) developed adalimumab antibodies and discontinued treatment because of a relapse.

*Change in therapy: Switch of therapy*

In total, 93 of 341 patients (27%) switched to other therapies, including topical therapy (n = 17), intravitreal or systemic steroids only (n = 13), DMARDs (n = 23), other anti-TNF (n = 29), interferon (n = 1), tocilizumab (n = 8), secukinumab in spondyloarthropathy (n = 1), and anakinra in JIA (n = 1). Inactive disease was achieved in 80 of 93 patients (86%) on this medication (Table 2), with the best responses observed with the use of other anti-TNF agents alone or combined with steroids or a DMARD (28 of 29 patients had inactive disease) and tocilizumab (7 of 8 patients had inactive disease).

• **DISCUSSION:** This large retrospective clinical cohort study showed a favorable long-term effectiveness of adalimumab in uveitis patients, with an estimated recurrence-free relapse time of the worst eye of more than 3 years and with an acceptable side effect profile.

The strength of this study is that real-world data are presented. An advantage over previous case-control studies is that all patients who started adalimumab were included, as there were no exclusion criteria. Furthermore the duration of follow-up exceeded by far previous published data.

In addition, studies on the practicalities of adalimumab treatment (eg, reasons for discontinuation, causes of loss of effectiveness, formation of antibodies) are scarce. One study, by Llorenc et al, showed that the drug retention rate declined during follow-up and was 54% after 60 months. Causes of loss of effectiveness were not further addressed. In addition, no information about temporary cessation and the effectiveness after restart of adalimumab was reported.[8]

In this study, the long-term and very long-term outcomes of patients using adalimumab were investigated. The majority of patients (61%) still used adalimumab at the end of follow-up, after a median follow-up of 4.9 years. Of the study population, 9% had a follow-up of more than 10 years. In our observational study, some patients stopped and restarted adalimumab, which gave novel insight into the causes of cessation and the effectiveness of restarting adalimumab. The major cause of cessation of adalimumab was remission, followed by adverse events or complications and relapse of inflammation. Restarting adalimumab was successful in the vast majority of patients and was not related to an increase in adalimumab antibody formation.

Previous studies showed that antibodies might develop during therapy and lead to treatment failure.[20,26,27] In the randomized controlled trial reported by Jaffe et al, antibodies were detected in 3 of 110 patient samples. Those patients had treatment failure.[20] In another cohort of 25 noninfectious uveitis patients, antibodies against adalimumab were measured during treatment, independent of treatment outcome; concomitant immunosuppression did not prevent the development of antibodies.[26] On the contrary, in another cohort of 31 JIA patients treated with adalimumab, 9 patients developed antibodies against adalimumab, more often in patients without concomitant methotrexate.[27] In

the current study, in 117 of 341 patients (34%), antibodies were measured at least once at any point in time. Interestingly, antibodies were detected more often in patients on adalimumab monotherapy compared to patients with additional steroids and/or DMARDS. It has been speculated that additional immunomodulating therapy could prevent antibody formation in uveitis patients treated with anti-TNF. This hypothesis has not yet been prospectively evaluated. The data in the current study suggest that steroids and/or DMARDS in addition to adalimumab treatment could prevent the formation of adalimumab antibodies. Preventing the formation of adalimumab antibodies is important for its effectiveness, as antibodies are related to treatment failure. In the vast majority of patients (85%) who had adalimumab antibodies, serum levels of adalimumab were low, whereas only one-third of the patients without antibodies had low serum adalimumab levels. This correlation indicates that antibodies could lead to lower serum adalimumab levels. Antibody formation was not related to a particular disease etiology. This could be due to the large number of different etiologies, with small subgroup sizes. The observation that JIA patients often develop adalimumab antibodies is in line with previous reports.[25] In the literature, the rate of adalimumab antibody formation varies between disease etiologies. For example, patients with rheumatoid arthritis have high rates of adalimumab antibodies (19%), whereas patients with Crohn disease have a much lower rate of antibody formation (2.6%).[28,29] The measurement of antibodies and adalimumab drug levels in patients presenting with a relapse can be of potential importance. So far, there has been no further evaluation of whether a dose increase could lead to a better response despite detectable antibodies. In this study, in 1 patient, a dose increase of adalimumab and starting methotrexate treatment led to inactive disease at the end of follow-up. More prospective studies are necessary to elucidate the formation of antibodies, to observe whether co-medication can prevent antibodies, and to determine whether continued treatment with adalimumab at an increased dosage can be successful.

Adalimumab is well tolerated in the majority of patients and was continued for as long as 14.7 years. Only 13% of patients had to stop because of a complication, with half of them quickly recovering and restarting medication. Serious adverse events were very rare (3%). Although the study population was too small to analyze the incidence divided in age subgroups, based on the average results the incidence of malignancy is not higher than in the general population.[30] This is in line with previous reports in literature, concerning solid malignancies after treatment with adalimumab.[31] There are some case reports of acute myeloid leukemia (AML) in adalimumab-treated patients; however, no correlation was found in multiple controlled trials between AML and adalimumab.[32,33]

Another complication with severe implications is demyelinating disease, which was reported in 2 of 341 patients (0.6%), both with panuveitis and spondyloarthropathy, after 10.9 years and 8 years of adalimumab treatment. Development of demyelination of the central nervous system has been reported during anti-TNF medication, as well oligoclonal bands in cerebro-spinal fluid.[34] The contribution of anti-TNF to the development of demyelinating disease has not been clarified. The occurrence of demyelination in patients using anti-TNF could be attributed to the unmasking of multiple sclerosis (MS) in patients with latent MS, the emergence of a new demyelinating disease or could be an incidental coexistence.[34,35] One of the study patients (with sarcoidosis) developed Guillain–Barré syndrome 1 year after the start of adalimumab. The patient was treated with high-dose immunoglobulins and almost fully recovered. The patient reported an upper respiratory tract infection 4 weeks prior to the development of Guillain–Barré syndrome. Previously, Guillain-Barré syndrome has been reported during anti-TNF therapy. However, in half of those cases, the patients had an infection preceding the development of Guillain–Barré syndrome, and adalimumab was introduced in 2 patients without recurrence of symptoms. This could indicate that Guillain–Barré syndrome was not the direct result of anti-TNF treatment.[36]

The relapse-free survival of patients with intermediate uveitis is shorter than that of patients with other uveitis locations. There is no clear explanation for this difference in relapse-free survival. To our knowledge, no study has reported the effectiveness of adalimumab based on the location of uveitis. The median age or disease etiologies or the use of co-medication in this group could explain the shorter relapse-free survival times. However, intermediate uveitis can be a first symptom of a demyelinating disease such as MS.[37-39] Anti-TNF therapy, such as adalimumab could worsen demyelinating diseases.[40] It may be that adalimumab is rarely prescribed in patients with intermediate uveitis, is only prescribed in very severe cases without any other treatment options, and these cases are therefore more refractory to therapy. This observation needs further exploration.

This retrospective observational study has some shortcomings inherent to retrospective studies. Levels of serum adalimumab and adalimumab antibodies were not measured in all patients. Although the cause of relapse was identified in a subgroup of patients, the reason of relapse was not identified in all patients. Detection of antibodies and low adalimumab levels in the remaining patients could probably identify more causes of treatment failure. However, some patients developed treatment failure despite the absence of antibodies and with normal adalimumab levels. It could be hypothesized that these patients respond better to other types of treatment, such as anti–interleukin-6. More studies are needed to investigate this further. Changes in topical therapy were not included in the analysis, as this was not always clear from medical chart review and as patients often change topical therapy doses of their own accord. This could have led to fewer reports of (minor) re-

lapses. A strength of this study is the long follow-up time. With a median follow-up time of 4.9 years and up to 14.7 years, both short and long-term outcomes, adverse events and complications have been studied.

In addition, this study shows real-world long-term data from daily clinical practice. Only 2 of the 341 patients in this study have participated in a clinical trial concerning adalimumab, the VISUAL II trial.[21] Treatment within the clinical trial took place for a maximum of 1.5 years. After that, these 2 patients were treated as part of clinical practice for over 5 years. Therefore, we believe that these data overwhelmingly represent clinical practice. Previous studies did not study the impact of cessation and restarting adalimumab, which is relatively common in clinical practice. As addressed before, the majority of the patients who restarted treatment showed a good response.

In conclusion, in this clinical cohort study consisting of uveitis patients treated with adalimumab, representing real-world data, it is demonstrated that the vast majority of patients treated with adalimumab have a good initial response and that the majority of patients have a favorable long term outcome, that is, inactive disease or remission. The main reasons for discontinuation are remission, adverse events or complications, or relapse of inflammation.

*Funding/Support*: Financial support was received from AbbVie, Lake Bluff, Illinois, USA, for this research. AbbVie had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. Financial Disclosures: P.M. van Hagen received consultancy fees from AbbVie in December 2019. All authors attest that they meet the current ICMJE criteria for authorship.
*Acknowledgments*: We would like to thank Manon M. Waling, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands, for assisting with the data collection.

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