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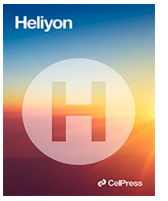

Research article

Risk factors for development of anti-adalimumab antibodies in non-infectious uveitis

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ABSTRACT

Purpose: To evaluate risk factors associated with development of anti-adalimumab antibodies (AAA) in patients with non-infectious uveitis treated with adalimumab.

Methods: A retrospective, cross-sectional, case-control study was done evaluating patients with non-infectious uveitis treated with adalimumab for at least 12 months and have undergone testing for AAA levels. Demographics, clinical characteristics, grading of ocular inflammation, and previous and concomitant immunomodulatory therapy were assessed. Univariate and multivariate analysis were done to estimate odds ratio (OR) with 95% confidence intervals for the various risk factors.

Results: A total of 31 patients were included in the analysis, in which 12 patients who tested positive (Group 1) were matched with 19 patients who tested negative for AAA (Group 2). The groups differed significantly in terms of sex (female) (91.7% vs 52.6%, $p = 0.046$), presence of systemic disease (91.7% vs 42.1%, $p = 0.008$), and presence of anterior chamber inflammation at baseline (100% vs 63.2%, $p = 0.026$). A history of interruption in anti-TNF therapy prior to starting or restarting adalimumab was found to have an increased odds for development of AAA (OR 16.89 [2.92, 107.11], $p = 0.008$), as well as flare-ups (reactivation of disease) during adalimumab therapy (OR 6.77 [1.80, 61.80], $p = 0.027$). Weekly dosing of adalimumab was shown to decrease odds of AAA development (OR 0.34 [0.02, 0.70], $p = 0.040$), while concomitant antimetabolite therapy was not shown to be a statistically significant protective factor (OR 2.22 [0.50, 9.96], $p = 0.148$).

Conclusions: History of interruption in anti-TNF therapy and flare during adalimumab were associated with development of AAA, while weekly dosing of adalimumab was protective against AAA. Identification of those with higher risk of developing AAA may guide in clinical decision making to optimize management for these patients.

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1. Introduction

Adalimumab is a humanized monoclonal antibody specific for tumor necrosis alpha (TNF-a) that has shown efficacy in the treatment of ocular inflammation leading to a lower risk of visual impairment in patients with uveitis [1,2]. It is currently the only non-corticosteroid therapy, local or systemic, approved by the United States Food and Drug Administration for the treatment of noninfectious uveitis. While outcomes reported in literature have generally been favorable, a good response may not occur in all patients and the drug may not be effective indefinitely. The formation of anti-adalimumab antibodies (AAA) is now recognized as a reason for the occurrence of flares (reactivation of disease) in these patients [3].

There is some degree of immunogenicity with all antibody-based biological therapy, eliciting an immune response with consequent

Table 1
Demographic data and baseline characteristics.

Parameter	Group 1 (n = 12), n (%)	Group 2 (n = 19), n (%)	p value
Age			
Mean ± SD (years)	36.4 ± 13.5	33.8 ± 20.7	
Range (years)	20–59	8–71	0.529
Sex			
Female	11 (91.7%)	10 (52.6%)	
Male	1 (8.3%)	9 (47.4%)	0.046
Race			
Caucasian	3 (25.0%)	10 (52.6%)	
Asian	7 (58.3%)	5 (26.3%)	
Hispanic	2 (16.7%)	4 (21.1%)	0.186
Anatomic Location of Uveitis			
Anterior	9 (75.0%)	11 (57.9%)	
Intermediate	0 (0%)	0 (0%)	
Posterior	1 (8.3%)	2 (10.5%)	
Panuveitis	2 (16.7%)	6 (31.6%)	0.605
Laterality of Involvement			
Bilateral	12 (100%)	15 (78.9%)	
Unilateral	0 (0%)	4 (21.1%)	0.139
Presence of Systemic Disease (Versus Idiopathic)			
Adamantiades-Behçet's Disease	2 (16.7%)	1 (5.3%)	
Ankylosing Spondylitis	2 (16.7%)	1 (5.3%)	
Juvenile Idiopathic Arthritis	2 (16.7%)	2 (10.5%)	
Rheumatoid Arthritis	2 (16.7%)	1 (5.3%)	
Crohn Disease	0 (0%)	2 (10.5%)	
Psoriasis	2 (16.7%)	0 (0%)	
Vogt-Koyanagi-Harada Disease	0 (0%)	0 (0%)	
IgA Nephropathy	0 (0%)	1 (5.3%)	
Sarcoidosis	1 (8.3%)	0 (0%)	
Idiopathic	1 (8.3%)	11 (57.9%)	0.008
Presence of Anti-Nuclear Antibody	3 (25.0%)	4 (21.1%)	1.000
Clinical Characteristics of Uveitis			
Anterior Chamber Inflammation	12 (100%)	12 (63.2%)	0.026
Vitritis	3 (25.0%)	9 (47.4%)	0.274
Retinal Vasculitis	4 (33.3%)	12 (63.2%)	0.149
Macular Edema	3 (25.0%)	6 (31.6%)	1.000
Optic Nerve Inflammation	3 (25.0%)	8 (42.1%)	0.452
Ocular Hypertension	3 (25.0%)	8 (42.1%)	0.452
Previous Immunosuppressive Therapy			
Topical Corticosteroids	11 (91.6%)	18 (94.7%)	1.000
Systemic Corticosteroids	12 (100%)	19 (100%)	1.000
Antimetabolite			
Methotrexate	6 (50.0%)	9 (47.4%)	
Mycophenolate Mofetil	5 (41.7%)	3 (15.8%)	
Azathioprine	1 (8.3%)	1 (5.3%)	0.588
Biologics			
Infliximab	2 (16.7%)	6 (31.6%)	
Etanercept	3 (25.0%)	2 (10.5%)	0.207
Characteristics of Adalimumab Therapy			
Dosing			
40 mg every 2 weeks	12 (100%)	12 (63.2%)	
40 mg every week	0 (0%)	7 (36.8%)	0.026
Duration of Therapy Prior to AAA Testing	33.60 ± 14.75	34.32 ± 14.55	0.168
Concomitant Antimetabolite Therapy			
Methotrexate	3 (25.0%)	5 (26.3%)	
Mycophenolate Mofetil	2 (16.7%)	4 (21.1%)	
Azathioprine	1 (8.3%)	0 (0%)	0.588
Flare During Adalimumab Therapy	3 (25.0%)	0 (0%)	0.049

host development of neutralizing anti-drug antibodies [4]. The presence of AAA are associated with lower circulating drug levels and decreased clinical efficacy, leading to disease flare-ups in the setting of previously well-controlled inflammatory disease [3,5]. While the role of AAA in the management of other autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease has been widely reported in literature, there is a scarcity of data regarding the risk factors, management, and prevention of AAA in patients with non-infectious uveitis [6–8]. The reported incidence of development of AAA in patients with noninfectious uveitis has been varied, ranging from 2.7 to 32% [1,5,9]. The development of permanent AAA has been shown to be associated with undetectable trough adalimumab levels and worse uveitis outcome [5].

The experience in other autoimmune diseases treated with adalimumab is that monitoring of serum adalimumab and AAA levels have a role in optimizing immunosuppressive therapy, leading to important clinical decisions that lead to improvement in disease status [8,10–12]. However, testing is not routinely done in clinical practice, not least because these tests are also not routinely available in most laboratories. Hence, identification of patients who are at higher risk for developing AAA has significance for clinicians.

The objective of our study is to determine the risk factors associated with an increased odds of development of AAA in patients with non-infectious uveitis treated with adalimumab.

2. Materials and methods

2.1. Study design

This was a retrospective, single-center, case-control study conducted at the Byers Eye Institute at Stanford University. The study followed the tenets of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. An electronic chart review of patients seen between 2012 and 2022 was done. Patients with a diagnosis of non-infectious uveitis treated with adalimumab for at least 12 months and with availability of serum AAA test results were included in the study. The patients who tested positive for AAA, who comprised the cases group, were matched with patients who tested negative for AAA, who comprised the control group.

Testing for AAA was ordered for all patients who have received at least 12 months of adalimumab therapy, or when indicated clinically. Adalimumab therapy was initiated in all patients for management of uveitis, and AAA testing was corollary to uveitis therapy. However, there was no standardized protocol for AAA testing. In addition, serial testing of AAA was not done for any patient.

Data were collection on age, sex, race, associated systemic disease, presence of anti-nuclear antibody (ANA), clinical characteristics of uveitis including anterior chamber inflammation, vitritis, retinal vasculitis, macular edema, and optic disc inflammation, history of previous immunomodulatory therapies including anti-metabolite and anti-TNF drugs, and characteristics of adalimumab therapy including flare-ups during therapy, frequency of administration of drug, and concomitant antimetabolite therapy. The presence or absence of these characteristics were compared between cases and controls.

2.2. Statistical analysis

Continuous variables were expressed in terms of mean, standard deviation, and range, while categorical variables were expressed in frequency and percentages. Mann-Whitney *U* test was used to compare continuous variables, while Fisher's exact test was used to compare categorial variables. Conditional logistic regression was applied to estimate the odds ratio (OR) with a 95% confidence interval for the various risk factors. The risk factors that proved to be significant in univariate analysis were then proceeded to be tested with multivariate analysis. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) (version 20, SPSS Inc., Chicago, IL, USA). A p value ≤ 0.05 was considered statistically significant.

3. Results

A total of 31 patients were included in the analysis. The study cohort consisted of 12 patients who tested positive for AAA (cases, group 1), and 19 patients who tested negative (controls, group 2). The demographic data and baseline characteristics are given in Table 1. While the age and race were comparable between groups, there was a higher proportion of females in group 1 (91.7% vs 52.6%, $p = 0.046$).

3.1. Clinical characteristics of uveitis

Based on anatomic location of uveitis, anterior uveitis comprised the majority in both groups with 75.0% patients in group 1 and 57.9% in group 2, with the distribution of location of uveitis being similar between groups ($p = 0.605$). Both groups 1 and 2 had more patients with bilateral involvement of uveitis (100% vs 78.9%, $p = 0.139$). The majority of patients (91.7%) in group 1 had systemic disease associated with their uveitis, a significantly higher proportion as compared to only 42.1% of patients in group 2 ($p = 0.008$). Table 1 lists the specific disease entities present in the study cohort. The proportion of patients who tested positive for anti-nuclear antibody (ANA) was similar between groups 1 and 2 (25.0% vs 21.1%, $p = 1.000$).

There was a significantly higher proportion of patients with anterior chamber inflammation in group 1 compared to group 2 (100% vs 63.2%, $p = 0.026$). The proportion of patients with vitritis was lower in group 1 (25.0%) compared to group 2 (47.4%) ($p = 0.274$), and similarly retinal vasculitis was less prevalent in group 1 (33.3%) compared to group 2 (63.2%) ($p = 0.149$). The prevalence of ocular hypertension, macular edema, and optic disc inflammation was statistically similar between groups 1 and 2 (25.0% vs 42.1%, p

= 0.452), 25.0% vs 31.6% (p = 1.000), and 25.0% vs 42.1% (p = 0.452), respectively).

3.2. Previous immunosuppressive therapy

Patients in groups 1 and 2 did not differ significantly in terms of use of topical corticosteroids (91.6% vs 94.7%, p = 1.000) and systemic corticosteroids (100% vs 100%, p = 1.000). There was a slightly higher proportion of patients with a history of antimetabolite therapy in group 1 compared to group 2 for methotrexate (50.0% vs 47.4%), mycophenolate mofetil (41.7% vs 15.8%), and azathioprine (8.3% vs 5.3%), but the overall difference was not statistically significant (p = 0.588). Furthermore, the overall proportion of patients with a history of previous anti-TNF therapy prior to starting adalimumab in groups 1 and 2, both for infliximab (16.7% vs 31.6%) and etanercept (25.0% vs 10.5%) (p = 0.207).

A history of any interruption in anti-TNF therapy (including adalimumab) followed by starting or restarting adalimumab was also examined in the study cohort. This was defined as any interval of time between starting adalimumab following discontinuation of previous anti-TNF therapy, or an interruption following starting adalimumab therapy. A history of interruption in anti-TNF therapy was found in a statistically greater proportion of patients in group 1 (83.3%) compared to group 2 (15.8%) (p < 0.001). The range of interruption in anti-TNF therapy (in months) was 6–180 in group 1 and 12 to 120 in group 2. However, the difference in the mean interval of interruption in anti-TNF therapy (in months) in groups 1 and 2 (48.22 ± 57.47 vs 60.00 ± 44.90) was not statistically significant (p = 0.774).

3.3. Adalimumab therapy

All patients in both group A and B started therapy with an induction dosing of adalimumab consisting of 80 mg at Day 1 followed by 40 mg at Day 8, then 40 mg in a once every two weeks dosing regimen. The mean duration of adalimumab therapy (in months) prior to AAA testing was similar in both groups (33.60 ± 14.75 vs 34.32 ± 14.55, p = 0.168). While on adalimumab therapy, a significantly lower proportion of patients group 2 experienced a flare in their uveitis in group 2 (0%) compared to group 1 (25.0%) (p = 0.049).

All patients (100%) in group 1 were maintained in a 40 mg once every two weeks dosing regimen. In group B, 7 (36.8%) of patients were switched to a 40 mg once every week regimen sometime during their therapy for better control of inflammation and maintained at that interval. The difference between groups was statistically significant (p = 0.026).

Concomitant antimetabolite therapy was instituted in 50.0% of patients in group 1 (25.0% on methotrexate, 20.0% on mycophenolate mofetil, and 8.3% on azathioprine) and 47.4% of patients in group 2 (16.7% on methotrexate and 21.1% on mycophenolate mofetil; the overall proportion of patients were similar between groups (p = 0.588).

3.4. Analysis of factors affecting development of AAA

The results of the univariate and multivariate analysis of risk factors are shown in Table 2, as well as Fig. 1. Univariate analysis showed that female sex, presence of systemic disease, anterior chamber inflammation, a history of interruption in anti-TNF therapy (including adalimumab), and flare during adalimumab therapy were significantly associated with increased odds for development of

Table 2
Univariate and multivariate analysis of risk factors for development of AAA with odds ratios with 95% confidence intervals.

	Univariate Analysis		Multivariate Analysis	
Risk Factor	OR [95% CI]	p Value	OR [95% CI]	p Value
Patient Characteristics				
Age Under 18 Years	0.13 [0.01, 1.15]	0.033	0.25 [0.05, 1.41]	0.789
Sex (Female)	9.90 [1.06, 92.66]	0.022	9.37 [3.22, 96.59]	0.052
Presence of Systemic Disease	15.12 [1.61, 142.15]	0.008	16.40 [1.58, 137.77]	0.404
Presence of ANA	1.25 [0.23, 6.91]	0.399	–	–
Baseline Clinical Characteristics of Uveitis				
Anterior Chamber Inflammation	8.00 [0.87, 73.40]	**0.033**	4.88 [0.18, 73.1]	0.157
Ocular Hypertension	0.45 [0.09, 2.25]	0.169	–	–
Vitritis	0.37 [0.07, 1.81]	0.110	–	–
Retinal Vasculitis	0.29 [0.06, 1.33]	0.056	–	–
Optic Disc Inflammation	0.45 [0.09, 2.25]	0.169	–	–
Macular Edema	0.72 [0.14, 3.67]	0.347	–	–
Previous Immunosuppressive Therapy				
History of Antimetabolite Therapy	2.70 [0.55, 13.20]	0.110	–	–
History of Anti-TNF Therapy	1.22 [0.28, 5.37]	0.394	–	–
History of Interruption in Anti-TNF Therapy (Including Adalimumab) Prior to Starting/ Restarting Adalimumab	16.00 [2.65, 96.47]	**0.001**	16.89 [2.92, 107.11]	0.008
Adalimumab Therapy				
Flares During Adalimumab Therapy	8.00 [1.79, 81.33]	**0.039**	6.77 [1.80, 61.80]	0.027
Weekly Maintenance Dosing of Adalimumab	0.13 [0.01, 0.91]	**0.033**	0.34 [0.02, 0.70]	0.045
Concomitant Anti-Metabolite Therapy	2.22 [0.50, 9.96]	0.148	–	–

AAA. On the other hand, age under 18 years and weekly maintenance dosing of adalimumab were significantly associated with decreased odds for development of AAA.

When the significant risk factors on univariate analysis were tested in multivariate analysis, only history of interruption in anti-TNF therapy (including adalimumab) (OR 16.89 [2.92, 107.11], p = 0.008) and flare during adalimumab therapy (OR 6.77 [1.80, 61.8], p = 0.027) remained as significant risk factors, while only weekly maintenance dosing of adalimumab (OR 0.34 [0.02, 0.70], p = 0.045) remained as the sole protective factor.

4. Discussion

In this case-control study, we determined the risk factors for development of AAA in patients with non-infectious uveitis. The use of adalimumab in the treatment of non-infectious uveitis has been increasing over the past few years as it has been well established that adalimumab has safety and efficacy in controlling intraocular inflammation [13]. However, good clinical response to adalimumab in these patients is not universal and some patients eventually develop flares despite an favorable initial outcome. It is now known that one reason for this loss of therapeutic efficacy is the development of neutralizing AAA [5]. The presence of AAA has been shown to be associated with undetectable trough adalimumab levels and worse uveitis outcomes. Thus, determining which patients are at a higher risk for development of AAA can provide clinical significance in the management of patients who require therapy with anti-TNF pharmacologic agents such as adalimumab.

A history of interruption of anti-TNF therapy prior to starting or restarting adalimumab was associated with the highest odds for development of AAA, a finding consistent with previous studies. In patients with Crohn's disease, episodic dosing as compared to continuous maintenance dosing of anti-TNF therapy was associated with increased rates of immunogenicity [14–16]. Interruption of therapy is theorized to allow time for unwanted immunogenicity, allowing the immune system to develop neutralizing antibodies upon subsequent reintroduction of drug [17,18]. The risk of AAA development is increased with the use of other anti-TNF drugs such as infliximab, possibly owing to the similarities in the structures of adalimumab and infliximab. The formation of AAA in patients previously treated with infliximab has also been documented in a previous study involving patients with psoriasis, where AAA formation was observed in 33% of patients previously treated with infliximab (even higher compared to 18.4% of patients previously treated with adalimumab itself) [17].

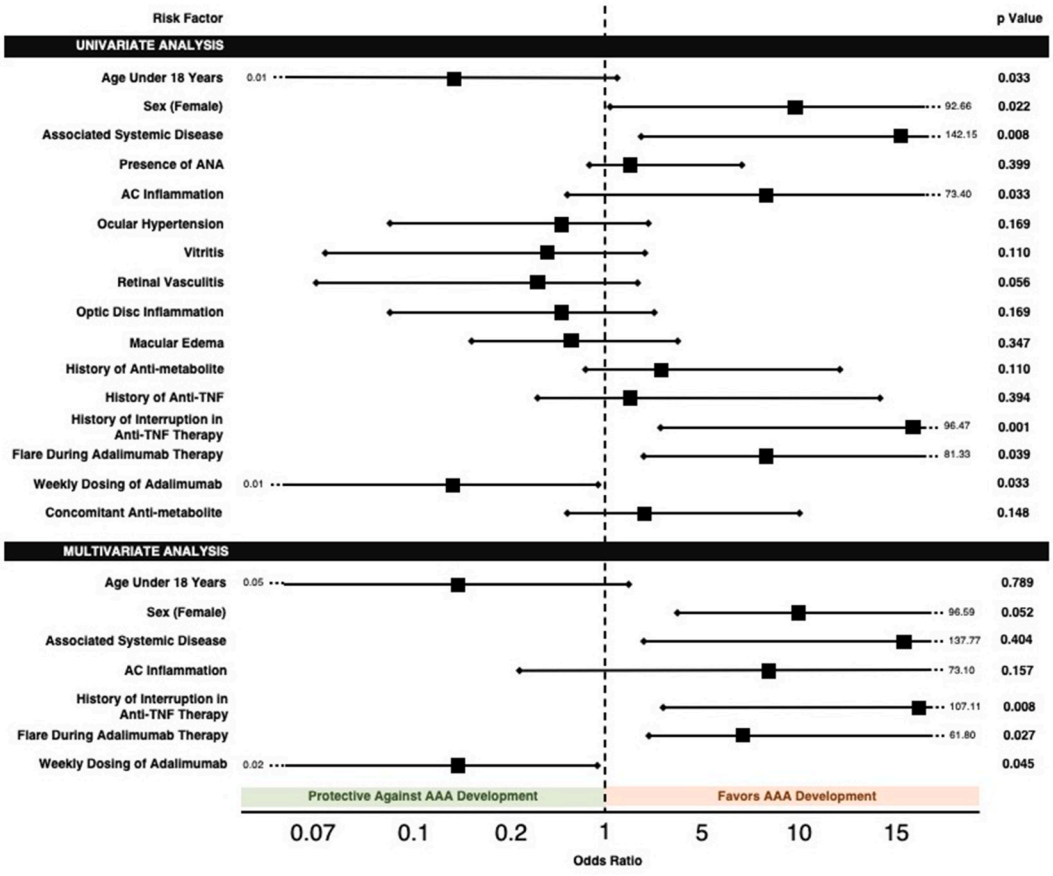

Fig. 1. Forest plot showing odds ratio (squares) along with 95% confidence intervals (lines) for each analyzed risk factor.

Flare during adalimumab therapy was also identified in our study to be associated with increased odds of AAA development, although it is more logical to think that uveitis flares occur as a result of already developed AAA. The development of AAA causes decreased serum drug trough levels, which causes decreased anti-inflammatory efficacy of the drug that then leads to disease flares [7]. There is an association between AAA and worse uveitis outcomes, particularly in patients who develop permanent AAA which lead to undetectable adalimumab trough levels [5]. In a case series of 8 patients with non-infectious uveitis who developed anti-adalimumab antibodies, McKay et al. reported that all 8 patients developed flares some time while ongoing adalimumab therapy and was the primary reason for AAA testing [3]. Thus, the occurrence of flares in the setting of well-controlled uveitis should prompt the clinician to consider AAA testing so that subsequent proper management can be initiated.

Our study showed an association with development of AAA in patients with an associated systemic disease, as compared to an idiopathic cause of uveitis. Cordero-Coma et al. similarly found a significantly higher proportion of patients having uveitis associated with systemic disease in those who showed AAA positivity [5]. While the development of anti-drug antibodies is a complex multifactorial process that can evolve over time, our results highlight the increased immunogenicity in patients with autoimmune disease [19]. However, it is interesting to note that this association did not remain following multivariate analysis. We also investigated the potential relationship between ANA and AAA in patients with uveitis. Mori et al. found that the presence of ANA before anti-TNF therapy with either infliximab, adalimumab, or etanercept was a risk factor for anti-drug antibody appearance as well as for treatment inefficiency. The proposed mechanism was interaction between immunogenicity and autoimmunity that is brought about during anti-TNF therapy [20]. However, our results not only found no significantly increased odds with ANA positivity, but also a lower proportion of patients with ANA positivity among those who were AAA positive.

There are currently no studies in literature that have investigated the effect of the various clinical characteristics of uveitis in anti-drug antibody development. Adalimumab first proved its safety and efficacy in the treatment of intermediate, posterior, and panuveitis [1,2]. While there are certainly more studies regarding the use of adalimumab in posterior segment inflammation, its efficacy in the treatment of anterior segment inflammation has also been well demonstrated, particularly in anterior uveitis associated with juvenile idiopathic arthritis and ankylosing spondylitis [21]. While anterior chamber inflammation seemed to be a risk factor in univariate analysis, the finding was not confirmed in multivariate analysis. The presence of ocular hypertension, vitritis, retinal vasculitis, optic disc inflammation, and macular edema all proved to be non-significant risk factors. Therefore, it would seem that the clinical characteristics of uveitis *per se* may not be helpful in identifying patients at increased risk for AAA development.

Our study showed that weekly maintenance dosing of adalimumab is associated with decreased odds of AAA development. It was the only *protective* factor identified to be statistically significant in multivariate analysis. Escalation to weekly dosing has been shown to be a useful strategy for treating recalcitrant ocular inflammation in patients on standard, every other week dosing, although the relationship to serum AAA levels was not studied [22]. Escalation to weekly dosing has also been an effective strategy for patients with rheumatoid arthritis and ulcerative colitis who have lost response to adalimumab owing to the development of AAA [6,23,24]. Thus, it is reasonable to hypothesize that if weekly dosing can be effective for treating AAA, it may also be a useful albeit an impractical strategy for prevention.

Lastly, our study determined concomitant antimetabolite therapy was not protective against AAA development. The effect of concomitant antimetabolite therapy on the development of AAA is unclear based on current literature. While previous studies showed a protective effect of methotrexate in patients with rheumatoid arthritis treated with adalimumab, outcomes have been mixed in patients with uveitis [6]. Leinonen et al. found in their study of 31 patients with JIA-associated uveitis that AAA was more prevalent in patients not taking concurrent methotrexate [25]. McKay et al. also found a low proportion of patients taking concurrent antimetabolite therapy in their case series of 8 patients with uveitis who tested positive for AAA, comprising only 25% of cases, though their results were limited by the lack of a comparison group [3]. However, Cordero-Coma et al. found in their study of 25 patients with uveitis that there was no decreased risk of adalimumab immunogenicity associated with methotrexate use [5]. Our results similarly show no protective effect of concurrent anti-metabolite use in our analysis for both methotrexate alone and grouped together with other anti-metabolites (i.e. mycophenolate mofetil and azathioprine). However, it is important to note that reports that have studied the effect of antimetabolites on AAA development in patients with uveitis are limited by small patient numbers, thus generalizations are difficult to make.

There is currently no consensus among uveitis specialists regarding when to test for serum adalimumab and AAA levels. Personalized and rationalized clinical guidelines are developing across specialties, particularly in the fields of rheumatology and gastroenterology, on the implications of testing in clinical decision making [11,12]. Some clinicians would support routine testing as a cost-effective strategy to make optimal treatment decisions [26,27]. However, other clinicians would advocate reactive testing as means to determine cause for inadequate response to therapy or occurrence of flare [3,26,28]. Our approach recommends routine testing at around 12 months of therapy to monitor for adequate therapeutic levels of adalimumab, as well as anticipate possible changes in therapy in response to subclinical levels of AAA. The cost of testing for serum adalimumab and AAA levels is certainly non-trivial; hence, routine testing may not be accessible to all patients [27]. Our results add crucial information in determining which patients might require a lower threshold for testing while on adalimumab therapy.

Our study has some evident limitations. The small sample size precludes extrapolating the conclusions, as demonstrated statistically by the very wide range of the confidence intervals. The study cohort also predominantly comprised of female patients, although multivariate analysis showed that it was not a significant risk factor. Non-infectious uveitis has been shown to have a greater preponderance in women than men [29], which is consistent with the greater number of females in our study cohort. The heterogeneity of included types of uveitis also limits generalizations. Further randomized controlled trials which include a larger number of patients are warranted. In addition, since there is no standardized protocol for AAA testing, bias in the selection of patients being tested for AAA cannot be completely ruled out (e.g. patients with flare-ups of uveitis may have been tested more frequently). Despite the limitations,

we believe the data generated from our study to be relevant and useful for clinicians in their use of adalimumab in patients with uveitis.

Ethics declaration

Review and/or approval by an ethics committee was not needed for this study because of its design as a retrospective chart review.

Data availability statement

Data will be made available on request to the corresponding author.

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CRediT authorship contribution statement

Albert John Bromeo: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Irmak Karaca:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hashem H. Ghoraba:** Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation. **Xun Lyu:** Writing – review & editing, Formal analysis, Data curation. **Ngoc Trong Tuong Than:** Writing – review & editing, Validation, Data curation, Conceptualization. **Prapatsorn Ongpalakorn:** Writing – review & editing, Project administration, Methodology. **Yong Un Shin:** Writing – review & editing, Resources, Investigation. **Gunay Uludag:** Writing – review & editing, Validation. **Anh Ngoc Tram Tran:** Writing – review & editing. **Zheng Xian Thng:** Writing – review & editing. **Diana V. Do:** Writing – review & editing. **Chi Mong Christopher Or:** Writing – review & editing, Project administration, Methodology, Formal analysis. **Quan Dong Nguyen:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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none.

Appendices.

None.

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