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Adalimumab for Treatment of Noninfectious Uveitis

Immunogenicity and Clinical Relevance of Measuring Serum Drug Levels and Antidrug Antibodies

Miguel Cordero-Coma, MD, PhD,[1,2] *Sara Calleja-Antolín, MD,*[3] *Irene Garzo-García, MD,*[1] *Ana M. Nuñez-Garnés, MD,*[3] *Carolina Álvarez-Castro, MD,*[4] *Manuel Franco-Benito, MD,*[1] *Jose G. Ruiz de Morales, MD, PhD*[2,3]

Purpose: To evaluate the rate of immunogenicity induced by adalimumab and its relationship with drug serum levels and clinical responses in patients with noninfectious uveitis.

Design: Prospective observational study.

Participants: Consecutive patients from 1 referral center who initiated treatment with adalimumab for active noninfectious uveitis resistant to conventional therapy.

Methods: All patients received 40 mg adalimumab every other week. Patients were evaluated clinically and immunologically before and after 4, 8, and 24 weeks of treatment.

Main Outcome Measures: Clinical evaluation included assessment of changes in visual acuity, degree of inflammation in the anterior chamber and vitreous cavity, central macular thickness, and retinal angiographic leakage. Immunologic evaluation included assessment of serum trough adalimumab and antibodies against adalimumab (AAA) levels and class II HLA typing.

Results: Twenty-five patients were enrolled. Overall, 18 of 25 patients (72%) showed a favorable clinical response to adalimumab therapy. Eleven patients (44%) achieved a complete response and 7 (28%) achieved a partial response. However, 7 of 25 patients (28%) were considered nonresponders. Median trough adalimumab serum levels were higher in responders than in nonresponders ($P < 0.001$). We observed AAA positivity (AAA+) at least 1 time point in 8 of 25 patients (32%), including 4 with transitory AAA and 4 with permanent AAA. In all patients with permanent AAA+, trough adalimumab levels became undetectable ($P < 0.001$). However, in patients who demonstrated transitory AAA+, no correlation was observed between AAA titers and adalimumab trough levels ($P = 0.2$).Concomitant immunosuppression did not show any protective effect on adalimumab immunogenicity in our cohort. An association between the presence of AAA+ and a worse uveitis outcome was observed only in patients with permanent AAA+, which correlated with undetectable adalimumab trough levels ($P = 0.014$).

Conclusions: Treatment of noninfectious uveitis with adalimumab is associated with high rates of favorable clinical response. Overall, adalimumab trough levels were higher in responder patients. Development of permanent AAA was associated with undetectable trough adalimumab levels and worse uveitis outcome. Immunogenicity was more common in patients in whom uveitis was associated with a systemic disease and was not influenced by concomitant immunosuppressors. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology*

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Adalimumab is a widely used monoclonal antibody that targets tumor necrosis factor (TNF) α, a cytokine involved in the pathogenesis of several immune-mediated diseases. Although adalimumab has not yet been approved specifically for uveitis, it is currently used in refractory noninfectious immune-mediated uveitides with encouraging results in some, but not all, cases. There is good-quality evidence for the use of adalimumab in spondyloarthropathy-associated uveitis, HLA-B27–associated uveitis, and juvenile idiopathic arthritis-associated uveitis. There is moderate-quality evidence for adalimumab in the treatment of pars planitis, idiopathic posterior uveitis, and Behçet's disease-associated uveitis.[1,2] In these disorders, adalimumab is quite efficacious in suppressing inflammation, allowing for a significant reduction in the mean immunosuppression load and the mean corticosteroid dose.[3]

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However, even in these potentially adalimumab-responsive uveitis entities, some patients do not respond initially to adalimumab (primary failure) or have a diminished response over time (secondary failure). Several known and unknown factors may be responsible for such failures. Among the former, non TNF-dependent pathogenic mechanisms, different factors related to drug pharmacokinetics and local drug bioavailability, and development of antibodies against adalimumab (AAA) have been well documented in diseases other than uveitis.[4]

Although adalimumab is a fully human immunoglobulin G1 monoclonal antibody, it has been demonstrated clearly to be immunogenic. Thus, AAA has been reported in 5% to 54% of adalimumab-treated patients, regardless of the underlying disease, and consistently have been associated with decreased clinical efficacy[5–9] and adverse effects.[10,11] Both neutralizing (directed to the region of adalimumab that binds to TNF) and nonneutralizing (directed to the Fc region of adalimumab) AAA have been described. Adalimumab–AAA immunocomplexes, formed either with neutralizing or with nonneutralizing AAA, increase adalimumab clearance, resulting in reduced adalimumab levels.[12]

Accumulated experience in patients with rheumathoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, and inflammatory bowel disease treated with adalimumab suggests that monitoring adalimumab and AAA serum levels is a helpful and cost-effective tool for optimizing treatment, allowing for appropriate clinical decisions and cost savings.[13,14] Moreover, disease-specific algorithms already have been proposed.[15,16] However in most centers, drug and AAA monitoring are not performed routinely. Literature regarding serum adalimumab monitoring and AAA formation in uveitis patients is scarce. As far as we are aware, appropriate therapeutic trough adalimumab levels associated with clinical benefits and rate of AAA formation in uveitis patients treated with adalimumab have not yet been described. In the present study, we prospectively evaluated serum adalimumab levels and AAA production and its potential relationship with trough adalimumab levels and clinical responses in a cohort of patients from a single center who initiated treatment with adalimumab for noninfectious uveitis resistant to conventional therapy.

Methods

Design

This was a nonrandomized, prospective observational study evaluating adalimumab and AAA trough serum levels in a cohort of patients with active noninfectious uveitis refractory to conventional treatment who initiated adalimumab therapy. All included patients were treated and evaluated at the same health center (University Hospital of León). Patients were evaluated clinically and immunologically before and after 4, 8, and 24 weeks of treatment.

Patients

A total of 25 patients with active refractory uveitis were recruited between January 2012 and April 2015 and followed up prospectively for up to 6 months. None had received adalimumab or any other biological therapy previously. An extensive work-up was performed to rule out infectious or masquerade uveitis before adalimumab initiation. Twelve patients had uveitis associated with a recognized systemic disease and 13 patients had endogenous uveitis. Table 1 summarizes demographic information, type of uveitis, and anatomic location according to the Standardization of Uveitis Nomenclature criteria,[17] laterality of disease, associated systemic disease, previous or concomitant systemic treatments, and presence of retinal vasculitis and macular edema before the study period. (Individualized information on every patient is shown online; see Supplemental Material and Supplemental Table S1, available at www.aaojournal.org).

Off-label adalimumab treatment was initiated in all 25 patients with active uveitis because of failure of systemic steroids and at least 1 systemic immunosuppressor. Patients previously had been screened thoroughly for chronic infectious diseases including human immunodeficiency virus, hepatitis B virus (HBV), hepatitis C virus (HCV), and latent tuberculosis. All participants signed an informed consent form after approval by the hospital's ethics committee. All proceedings followed the tenets of the Declaration of Helsinki.

Table 1. Summary of Demographic Data, Clinical Features, and Therapeutic Information of All Included Patients

	No. (%)
Parameter	
Mean age (range), yrs	40.88 (3–73)
Gender	
Male	17 (68)
Female	8 (32)
Uveitis type by location	
Anterior	5 (20)
Intermediate	2 (8)
Posterior	3 (20)
Panuveitis	13 (52)
Laterality	
Unilateral	5 (20)
Bilateral	20 (80)
Associated disease	
No	13 (52)
Yes	12 (48)
SpA	5 (42)
JIA	2 (17)
Behçet's disease	1 (8)
Sarcoidosis	4 (33)
CME before adalimumab	
Yes	11 (44)
No	14 (56)
Vasculitis before adalimumab	
Yes	5 (20)
No	20 (80)
Treatment	
Previous immunosuppressive treatment	
MTX	13 (52)
CsA	7 (28)
MFM	5 (20)
Concomitant treatment (at baseline)	
MTX	10 (40)
CsA	5 (20)
MFM	3 (12)
No treatment	7 (32)

CME = cystoid macular edema; CsA = cyclosporine A; JIA = juvenile idiopathic arthritis; MFM = mycophenolate mofetil; MTX = methotrexate; SpA = spondyloarthritis.

Included patients received 40 mg subcutaneous adalimumab every other week without modifications throughout the 24-week study period. Adalimumab was the only immunomodulatory agent used in 7 patients, and in 18 patients, adalimumab was used alongside previous immunosuppressors without any dosage modification throughout the study period (10 patients were treated concomitantly with methotrexate, 3 with mycophenolate mofetil, and 5 with cyclosporine). In all patients, systemic steroids were withdrawn progressively within the first month after adalimumab introduction.

Clinical Evaluation

Uveitis clinical evaluation during the study period included visual acuity (Snellen best-corrected visual acuity) and ophthalmic examination. A slit-lamp examination was used to evaluate the anterior chamber. Anterior chamber cells were graded according to the Standardization of Uveitis Nomenclature classification.[18] Indirect ophthalmoscopy also was performed in all patients to evaluate the vitreous and posterior segments. Vitreous haze was considered following the system for the evaluation of vitreal inflammatory activity reported previously.[15] Spectral-domain optical coherence tomography (OCT; Cirrus HD-4000; Carl Zeiss Meditec, Dublin, CA) was used in all patients to determine the presence of cystoid macular edema. Cystoid macular edema was defined as 1-mm central retinal thickness of more than 315 μm with presence of intraretinal or subretinal fluid in OCT examination.[19] Fluorescein angiography (FA) was performed in all patients to determine the presence or absence of vasculitis or any abnormal retinal angiographic leakage. Fluorescein angiography was repeated at the end of the study (after 24 weeks of treatment) in all patients showing signs of inflammation on baseline FA images.

All included patients were active before initiation of therapy with adalimumab. We classified inactive uveitis as grade 0 cells in the anterior or posterior segment, or both, in addition to absence of other signs of intraocular inflammation (cystoid macular edema, vasculitis, or both).

All but 2 patients completed 24 weeks of treatment. After 24 weeks of adalimumab, the patient's response to treatment was categorized as no response, partial response, or complete response to treatment defined as follows: No response was defined as persistent intraocular inflammation without any finding consistent with the criteria of partial response or improvement. Partial response or improvement was defined as new onset from either baseline visit or when compared with previous clinical examination of any of the following: (1) a 2-step decrease in the Standardization of Uveitis Nomenclature grading scheme (e.g., anterior chamber cells, vitreous haze) or decrease to grade 0; (2) resolution of cystoid macular edema (1-mm central retinal thickness <300 μm and absence of intraretinal or subretinal fluid in OCT examination); or (3) absence of any retinal angiographic leakage in FA examination. Complete response was defined as grade 0 cells in both anterior and posterior segment in addition to absence of any other sign of intraocular inflammation on ophthalmologic, OCT, and FA examination.

Measurement of Adalimumab Concentration and Antibodies against Adalimumab

Trough serum adalimumab and AAA levels were measured by commercial capture enzyme-linked immunosorbent assay (detection range, 20−14 000 ng/ml) and bridging enzyme-linked immunosorbent assay (detection range, 2−2000 units/ml), respectively (Progenika Biopharma, Bizkaia, Spain). To avoid interferences in the assay because of high levels of adalimumab, we made sure to perform blood venipuncture just before drug administration. At least 4 adalimumab and AAA measurements—including baseline and after 4, 8, and 24 weeks—were performed in 23 of 25 patients and at baseline and after 4, 8, and 12 weeks in the remaining 2 patients.

HLA Typing

Molecular medium-high resolution HLA class II typing of DQ and DR loci was performed in peripheral lymphocytes by using Sequence Specific Primers (Micro-SSP; One Lambda, Canoga Park, CA) in all patients.

Statistical Analysis

Statistical analysis was performed with Prism 5 software (GraphPad, San Diego, CA). Categorical variables are depicted as numbers and percentages, and quantitative variables as median and standard error of the mean (SME). Because of the small number of participants, we used nonparametric tests. Comparisons among categorical variables were performed by contingency tables with the Fisher exact test. The continuous data were compared between groups using the Mann−Whitney U test. Correlation among quantitative variables was performed by means of Spearman regression curves. Two-tailed P values of less than 0.05 were considered statistically significant.

Results

Clinical Responses to Adalimumab and Its Relationship with Adalimumab Trough Levels

Twenty-five patients with refractory uveitis were included: 8 women and 17 men with a mean age of 41.1 years (range, 3−73 years). Five had anterior uveitis, 2 had intermediate uveitis, 5 had posterior uveitis, and 13 had panuveitis. The disease was unilateral in 5 patients and bilateral in 20, was associated with a systemic disease in 12 patients (5 had spondyloarthropathy, 4 had sarcoidosis, 2 had juvenile idiopathic arthritis, and 1 had Behçet's disease), and was idiopathic in 13 patients. Table 1 summarizes relevant clinical data from all included patients.

Twenty-three of 25 patients completed 6 months of treatment with adalimumab without relevant incidences. Overall, 18 of 25 patients (72%) showed a favorable clinical response. Eleven patients (44%) achieved a complete response and 7 patients (28%) achieved a partial response. All of them were maintained on adalimumab for at least 6 additional months.

However, 7 of 25 patients (28%) were considered nonresponders. One patient with a diagnosis of Behçet's disease-associated uveitis dropped out of the study after the third dose (week 6) because of an adverse event (acute myocardial infarct). Adalimumab also was withdrawn in another patient with bilateral panuveitis after 12 weeks because of treatment failure and clinical worsening. The remaining 5 patients showing no response to treatment (2 patients with idiopathic panuveitis, 1 patient with spondyloarthropathy-associated panuveitis, 1 patient with idiopathic posterior uveitis, and 1 patient with spondyloarthropathy-associated anterior uveitis) discontinued adalimumab after 24 weeks.

Adalimumab trough levels were measured at least 3 times (4, 8, and 24 weeks after adalimumab treatment) in 23 of 25 patients who completed 6 months of adalimumab and at weeks 4, 8, and 12 and weeks 4, 6, and 8 in the remaining 2 patients who interrupted adalimumab treatment. As shown in Figure 1, after 6 months of treatment, responders had significantly higher trough serum adalimumab levels than patients who did not respond (median, 9550 ng/ml vs. 600 ng/ml, respectively; $P < 0.001$). However, no significant differences in adalimumab trough levels were observed at that point between complete and partial responders

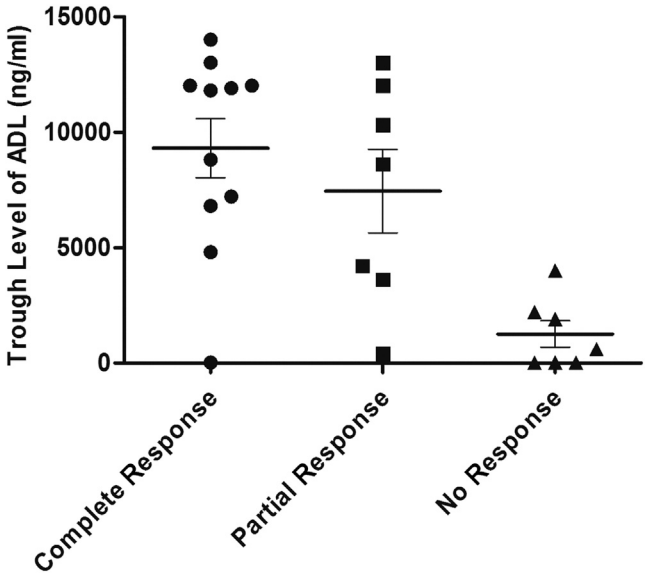

Figure 1. Graph showing a comparison of adalimumab (ADL) trough levels among uveitis patients showing a complete response, partial response, and no response to adalimumab after 6 months of treatment (or at the moment of adalimumab discontinuation in 2 patients). Responders (n = 18) versus nonresponders (n = 7): $P < 0.001$. Complete response (n = 11) versus partial response (n = 7): $P = 0.440$.

(median, 11 800 ng/ml vs. 8600 ng/ml, respectively; $P = 0.440$; Fig 1).

Antibodies against Adalimumab and Their Relationship with Trough Adalimumab Levels

Antibodies against adalimumab were measured before adalimumab treatment to rule out interferences with heterophile antibodies and rheumatoid factor and after 4, 8, and 24 weeks of treatment in all but 2 patients. Antibodies against adalimumab were measured before and after 4, 8, and 12 weeks and at 4, 6, and 8 weeks in the remaining 2 patients who did not complete 24 weeks of adalimumab treatment. Patients were considered to have positive AAA results if titers were more than 10 U/ml on 1 single measurement (transitory AAA) or on 2 or more occasions (permanent AAA). We observed AAA positivity in at least 1 time point in 8 of 25 patients (32%). From these patients showing AAA, 4 patients (16%) had transitory AAA and 4 patients (16%) had permanent AAA. A summary of patients who demonstrated AAA is shown in Table 2. Among patients who showed positive AAA results, antibody titers were much higher in patients with permanent antibodies (Fig 2). Interestingly, all 4 patients showing permanent antibodies were detected early after adalimumab administration (within the first 8 weeks).

Antibodies against adalimumab form immunocomplexes with adalimumab. It has been described that adalimumab−AAA immunocomplexes increase adalimumab clearance.[10] To investigate the effect of AAA on adalimumab clearance, we simultaneously measured adalimumab drug levels and AAA in all included patients at every time point. Six representative patients are depicted in Figure 2 (patients 6, 16, 20, 23, 24, and 25). In all patients with permanent AAA (patients 3, 4, 20, and 25), trough adalimumab levels became undetectable (<20 ng/ml). Of note, in these 4 patients, an inverse correlation between adalimumab trough levels and AAA titers was observed ($P < 0.001$). However, in patients who demonstrated transitory AAA (patients 2, 10, 15, and 24), detectable trough adalimumab levels of 3800 ng/ml, 980 ng/ml, 650 ng/ml, and 3600 ng/ml, respectively, were measured when AAA results were positive, and no correlation was observed between AAA titers and adalimumab trough levels ($P = 0.2$).

Effect of Concomitant Immunosuppression, Type of Uveitis, and Adalimumab Immunogenicity

Because most patients (18/25) were treated concomitantly with systemic immunosuppressors, which may reduce adalimumab immunogenicity, we also investigated the effect of concomitant treatment on AAA development (Table 2). In 8 of 25 patients who demonstrated AAA at any time point, 5 patients (including 3 with permanent AAA) were receiving concomitant treatment with other immunosuppressors (2 patients were receiving methotrexate, 2 were receiving cyclosporine A, and 1 was receiving mycophenolate), suggesting lack of protective effect because of concomitant immunosuppression on adalimumab immunogenicity in our cohort (AAA formation in patients with vs. without concomitant immunosuppressors; $P = 0.3592$, not significant). In addition, among patients who did not demonstrate AAA, no differences in mean trough adalimumab levels after 8 weeks were found between those who were receiving concomitant immunosuppressors (13 patients) and those who were not (4 patients; data not shown).

Trying to gain some insight into the mechanisms underlying AAA immunogenicity, we also investigated whether there were any associations with the type of the uveitis that may anticipate an

Table 2. Summary of Relevant Features of Patients in Whom Antibodies against Adalimumab Developed

Patient No.	Diagnosis	Transitory Antibodies against Adalimumab	Permanent Antibodies against Adalimumab	Concomitant Immunosuppressor	HLA DR Alleles	Response to Adalimumab
2	Serpiginous	+	−	No	11, 15	Complete
3	SpA	−	+	No	15, −	No
4	Behçet	−	+	Yes (CsA)	4, 7	No
10	JIA	+	−	Yes (MTX)	10, 13	Complete
15	Sarcoidosis	+	−	No	7, 13	Partial
20	SpA	−	+	Yes (MTX)	8, 11	Complete
24	Idiopathic panuveitis	+	−	Yes (CsA)	4,13	Partial
25	Idiopathic panuveitis	−	+	Yes (MFM)	7, −	No

CsA = cyclosporine A; HLA = human leukocyte antigen; JIA = juvenile idiopathic arthritis; MFM = mycophenolate mofetil; MTX = methotrexate; SpA = spondyloarthropathy; + = positive; − = negative.

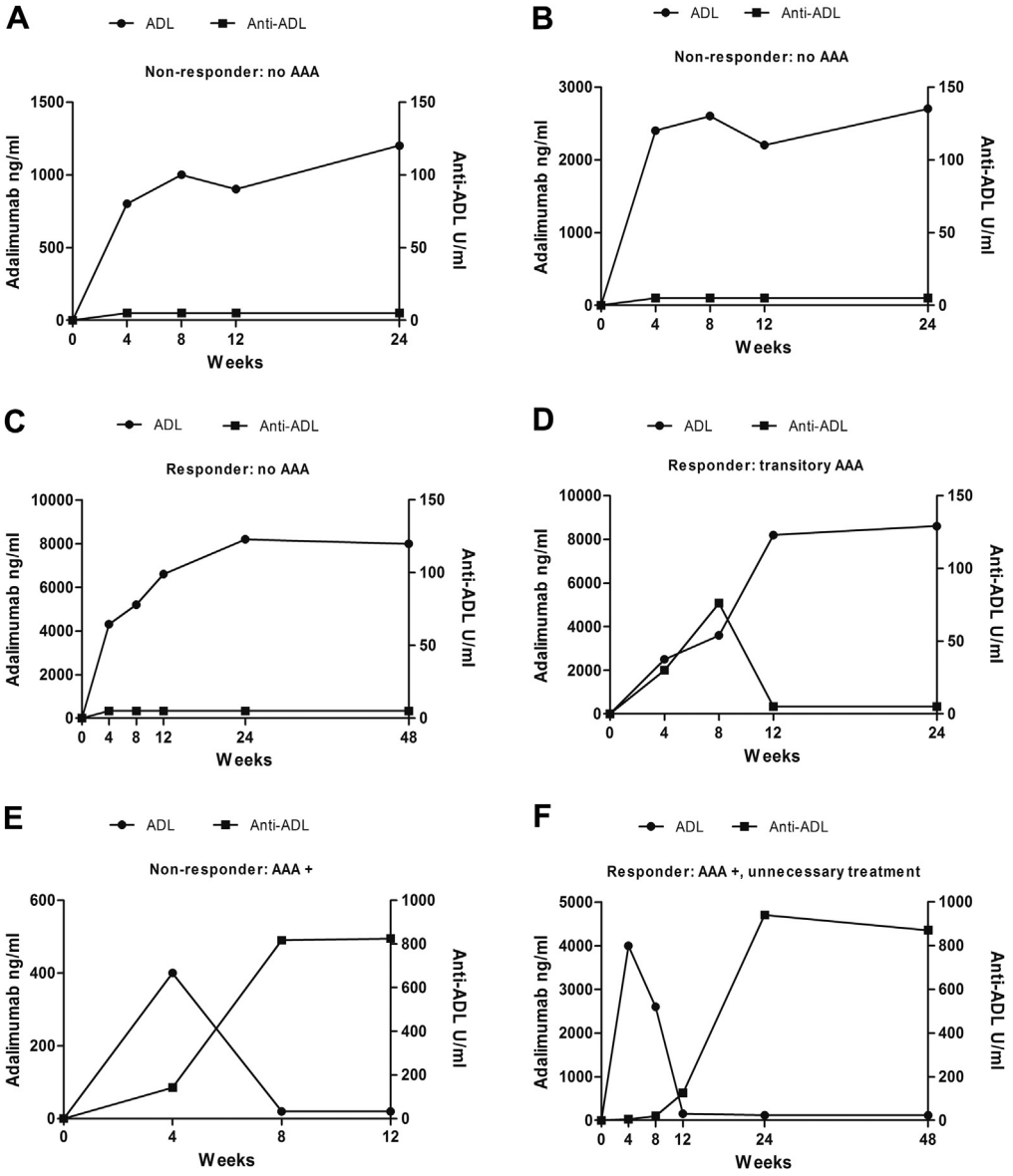

Figure 2. Graphs showing representative figure of adalimumab (ADL) and antibody against adalimumab (AAA) trough levels in 6 different patients: (**A**) and (**B**) nonresponder patients with low adalimumab levels not resulting from AAA; (**C**) responder, high adalimumab levels, no AAA; (**D**) responder, high adalimumab levels despite transitory AAA; (**E**) nonresponder because of permanent high AAA with undetectable adalimumab levels; (**F**) undetectable adalimumab because of permanent high AAA, but sustained control of inflammation. AAA+ = antibody against adalimumab positivity.

increased risk for AAA formation. We therefore compared the individual characteristics of all included patients (demographics, uveitis diagnoses, and association with a systemic disease). Interestingly, in 5 of 8 patients showing AAA positivity (2 patients with spondyloarthropathy-associated uveitis, 1 with juvenile idiopathic arthritis, 1 with sarcoidosis, and 1 with Behçet's disease), the uveitis was associated with a systemic disease ($P = 0.02$).

HLA-II Genotype and Adalimumab Immunogenicity

Antibody against adalimumab generation by B lymphocytes requires restricted HLA II antigen presentation to CD4 T lymphocytes. To address whether adalimumab-induced immunogenicity was related to specific HLA class II alleles, we performed molecular HLA DQ and DR typing in all patients. We did not find any association between specific HLA DQ or DR alleles and AAA generation. We found no AAA+ patients within DR1 patients, which was the more prevalent allele in our uveitis cohort (Table 2).

Clinical Relevance of Antidrug Antibodies

We finally evaluated whether the presence of AAA had any potential association with observed clinical responses, adverse effects to adalimumab therapy, or both (Table 2). Seven of 25 patients were considered nonresponders to adalimumab therapy, and 8 of 25 patients demonstrated AAA. An association between the presence of AAA and a worse uveitis outcome was observed only in patients with permanent AAA, which correlated with undetectable adalimumab trough levels ($P = 0.014$). Two of 4 patients with

permanent AAA were considered nonresponders, including a patient with a bilateral panuveitis who discontinued adalimumab after 12 weeks because inefficiency and a patient with spondyloarthropathy-associated anterior uveitis who stopped adalimumab after completing 24 weeks of treatment. One additional patient with a diagnosis of Behçet's disease had permanent AAA and dropped out from the study because of acute myocardial infarction at week 6. The remaining patient with permanent AAA was considered a full responder, suggesting that clinical outcome was not related to adalimumab therapy. Among the 4 patients who had transient AAA but detectable adalimumab trough levels, 2 were considered full responders and 2 were considered partial responders, and they all continued adalimumab therapy for at least 1 year.

Discussion

Anti-TNF drugs increasingly are being used as an off-label and often effective treatment option, although they are not yet specifically approved for the management of noninfectious uveitis, with the exception of Behçet's disease-associated uveitis in Japan. Because of their off-label use, there are no clear recommendations regarding the specific uveitis entities that may benefit from this therapy and, as soon as the appropriate patient selected, how these drugs should be used.

We herein present further evidence of the usefulness of adalimumab in refractory uveitis: 72% of our treated patients showed a positive response to therapy, thus adding more data to the literature advocating for its approval in selected uveitis cases.[20] However, it must be stressed that only 44% of all included patients achieved a complete inflammatory control after 6 months of treatment. All uveitis patients included in our study had severe and resistant conditions. Patient responses to adalimumab were associated with neither a systemic disease nor with a specific uveitis location. Among patients included in this study, it is worth mentioning that 4 of 4 sarcoidosis-associated uveitis patients responded to adalimumab, including 2 complete and 2 partial responders. These results are concordant with those from a Dutch prospective study of 26 patients[21] and with a recently published retrospective multicenter study of 10 sarcoidosis-associated refractory uveitis patients treated with adalimumab.[22]

After almost 15 years of clinical use, personalized and rational therapeutic guidelines based on adalimumab trough levels and the presence of AAA are emerging across different diseases.[13,23,24] In concordance with those studies, we herein show that responsiveness to adalimumab in refractory uveitis is associated with higher trough adalimumab levels. Moreover, by taking advantage of the experience accumulated in pathologic features other than selected uveitis that share TNF as an inflammatory pathogenic effector cytokine, we describe the relevance of AAA in patients who initiated adalimumab treatment because of refractory uveitis. In addition, we evaluated some potential mechanisms of immunogenicity and how AAA may affect the outcome of adalimumab-treated uveitis patients.

Eight uveitis patients (32%) from our series developed objective and measurable immunogenicity, which was equally transient or permanent in 4 cases. A prevalence of permanent antibodies to adalimumab of 14% in our cohort is similar to the results published in a recent meta-analysis computing indications other than uveitis.[25] Surprisingly, development of AAA in our cohort of uveitis patients was independent of concomitant use of immunosuppressors, contrary to previous reports on the effect of methotrexate in rheumatoid arthritis patients treated with adalimumab.[26] Perhaps the small number of patients, the diversity of the immunosuppressors used, and the different uveitides included in the present study may explain such discrepancy. Moreover, it should be considered that results obtained in one immune-mediated disease cannot be extrapolated directly to other immune-mediated diseases, as recently reported when analyzing adalimumab survival in different diseases.[27]

It has been demonstrated that most antibodies to adalimumab (as with infliximab, another anti-TNF) are directed toward the idiotype (Fab region of the antibody that binds to TNFα),[28] suggesting a restricted HLA-dependent immune response to anti-TNF drugs. A recent study evaluating a cohort of infliximab-treated inflammatory bowel disease patients showed that the presence of *DRB1*03* was an independent risk factor for anti-infliximab neutralizing antibodies developing.[29] In our cohort, we found no associations between AAA and specific HLA DQ and DR alleles, but larger populations of patients and controls need to be studied to rule out a genetic linkage definitively.

By blocking adalimumab idiotype (neutralizing antibodies) and forming immunocomplexes (neutralizing and nonneutralizing antibodies), AAA interfere with adalimumab clinical efficacy[12]; have been related with adverse effects, that is, thromboembolic events[10]; and also may be related to immunoglobulin G-mediated anaphylactoid reactions and cutaneous vasculitis, as described with infliximab.[30] In our series of cases, 4 of 4 patients with permanent AAA had nondetectable adalimumab trough levels, confirming that AAAs were related to diminished drug bioavailability, and therefore to decreased clinical efficacy. Three patients were considered nonresponders, but 1 of 4 AAA+ patients was considered a responder because uveitis in this patient was not active after 1 year of follow-up. This patient may well represent uveitis natural history,[31] suggesting that some patients may not need further treatment. In addition, another permanent AAA+ nonresponder patient demonstrated an adverse effect—an acute myocardial infarction—that may be related to the presence of adalimumab−AAA immunocomplexes. However, transitory AAA titers usually were low and did not correlate with decreased adalimumab levels, stressing that its formation is a dynamic process. They were associated neither with therapeutic failure nor with adverse effects, suggesting both an insufficient amount to block all the available drugs, and/or presence of antibodies directed toward nonrelevant epitopes.

This study was intended to illustrate the potential clinical relevance of drug and antidrug monitoring in patients with noninfectious uveitis receiving treatment with adalimumab. It has some evident limitations. The small size of the population studied precludes extrapolating the conclusions. In addition, the heterogeneity of the included uveitis further limits generalizations. However, we believe the data are relevant and constitute a step forward in the difficult daily management of refractory uveitis patients. These determinations may add crucial

information in certain cases, facilitating treatment decision making and contributing to a personalized, sustainable, and more rational therapy with adalimumab in such patients. Two main immediate practical questions related to adalimumab use in refractory uveitis emerge from our study. First, should adalimumab be initiated with a loading dose to achieve higher adalimumab initial levels? Second, should adalimumab always be associated with another immunosuppressor to maximize drug efficacy and minimize antiadalimumab formation? Further randomized controlled studies including larger numbers of patients with endogenous and systemic disease—associated refractory uveitis are warranted.

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[1] Uveitis Unit, Department of Ophthalmology, University Hospital of León, León, Spain.

[2] Instituto de Biomedicina (IBIOMED), University of León, León, Spain.

[3] Immunology Service and Uveitis Unit, University Hospital of León, León, Spain.

[4] Rheumatology Service, University Hospital of León, León, Spain.

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Conception and design: Cordero-Coma, Calleja-Antolin, Ruiz de Morales

Analysis and interpretation: Cordero-Coma, Calleja-Antolin, Garzo-García, Nuñez-Garnés, Ruiz de Morales

Data collection: Cordero-Coma, Calleja-Antolin, Garzo-García, Nuñez-Garnés, Alvarez-Castro, Franco-Benito, Ruiz de Morales

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Abbreviations and Acronyms:
AAA = antibody against adalimumab; **AAA+** = antibody against adalimumab positivity; **FA** = fluorescein angiography; **HLA** = human leukocyte antigen; **OCT** = optical coherence tomography; **TNF** = tumor necrosis factor.

Correspondence:
Jose G. Ruiz de Morales, MD, PhD, Immunology Service, University Hospital of León, Altos de Nava S/N, 24080 León, Spain. E-mail: jgarcir@gmail.com.