



Anti-infliximab antibodies and clinical response in noninfectious uveitis and scleritis patients treated with infliximab: A retrospective review

Lianna Valdes¹, Jacob T. Cox¹, Janine Yang¹, Gayatri Susarla, Samuel Han, George N. Papaliadis, Lucia Sobrin^{*}

Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:

Infliximab
Anti-drug antibodies
Uveitis
Scleritis

ABSTRACT

Purpose: To investigate the clinical response to infliximab in ocular inflammation patients who develop anti-infliximab antibodies (AIA) vs. those patients who do not develop AIA.

Observations: A retrospective review was performed of patients treated with infliximab for noninfectious uveitis (NIU) or scleritis. Clinical response was determined as a composite clinical endpoint and classified as complete, partial, or absent. Nine of 32 infliximab-treated patients (28%) were found to develop AIA. Among the AIA-positive patients, clinical response was complete in 7 patients (78%) and partial in 2 patients (22%). Among the AIA-negative patients, clinical response was complete in 15 patients (65%), partial in 6 patients (26%) and absent in 2 patients (9%). Serum infliximab levels tended to decrease with appearance of AIA but rarely became undetectable.

Conclusions and Importance: In this pilot study, AIA-positive patients did not have diminished clinical response to infliximab when compared with AIA-negative patients. There was a high rate of complete clinical response to infliximab in this group of NIU and scleritis patients. Approximately a quarter of patients developed AIA. AIA-positive patients did not have diminished rates of clinical response when compared with AIA-negative patients. This suggests that routine AIA monitoring may not be clinically useful, although validation of this finding in larger cohorts is necessary.

1. Introduction

Infliximab is a chimeric murine-human monoclonal antibody that reduces inflammation by binding both free-circulating tumor necrosis factor- α (TNF- α) and TNF- α receptors. It is used for a wide variety of immune-mediated diseases including inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis.¹

Some infliximab patients develop antibodies against the medication. In one study, the presence of anti-infliximab antibodies (AIA) in patients receiving infliximab for rheumatoid arthritis was associated with lower serum infliximab levels and a reduced treatment response.¹ This suggests that AIA may accelerate clearance of infliximab and limit its therapeutic effect. A randomized controlled trial found that some patients receiving infliximab monotherapy became nonresponsive after repeated infusions, whereas those receiving the infliximab with concomitant methotrexate had prolonged therapeutic response,

suggesting that concomitant methotrexate may decrease the immunogenicity of infliximab.² However, there are also studies that have not found that concomitant antimetabolite therapy limits the development of anti-TNF- α inhibitor antibodies.^{3,4}

The reported prevalence of AIA varies widely and may differ by disease. For instance, the prevalences of AIA were reported as 17.4%, 29.4%, and 50% in separate studies on three different rheumatologic diseases.⁵⁻⁷ There are currently no unifying guidelines among rheumatologists regarding when to assess for AIA. The American Gastroenterological Association guidelines recommend reactive monitoring (i.e., in response to suboptimal disease control) of trough drug levels to guide treatment changes in patients receiving biologics for management of active inflammatory bowel disease. For noninfectious uveitis (NIU), there are no guidelines regarding when to evaluate serum infliximab levels or for the presence of AIA.

Cordero-Coma et al. sought to clarify interpretation of serum

^{*} Corresponding author. Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA, 02114, USA.

E-mail addresses: lianna.valdes@umassmemorial.org (L. Valdes), jacob_cox@meei.harvard.edu (J.T. Cox), jyyang@meei.harvard.edu (J. Yang), gayatri_susarla@meei.harvard.edu (G. Susarla), samhan@bu.edu (S. Han), George_papaliadis@meei.harvard.edu (G.N. Papaliadis), lucia_sobrin@meei.harvard.edu (L. Sobrin).

¹ indicates first co-author.

adalimumab levels and anti-drug antibodies in patients with NIU. They tracked trough serum adalimumab levels and anti-adalimumab antibodies in 25 NIU patients on biweekly adalimumab and found trough levels were significantly higher in adalimumab responders than non-responders. Permanent anti-adalimumab antibodies were observed in 4 patients, all of whom subsequently developed undetectable adalimumab trough levels. Concomitant immunomodulatory therapy did not seem to protect against the development of anti-adalimumab antibodies.⁵

The purpose of this study was to investigate the clinical response to infliximab in ocular inflammation patients who develop AIA vs. those patients who do not develop AIA.

2. Methods

This study was approved by the Mass General Brigham Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

The retrospective observational study included patients seen at the Massachusetts Eye and Ear Infirmary between 2012 and 2020 who were treated with infliximab for NIU and/or scleritis and who had AIA and infliximab levels documented. Patients received infliximab at a starting dose of 5 mg/kg; after two loading doses two weeks apart, maintenance doses were given every 4 weeks initially. The dose was increased as needed to achieve complete inflammation control. Infliximab and AIA levels were drawn at infusion visits, immediately prior to starting the infliximab infusion. AIA levels were always associated with a paired infliximab level performed on the same day. The frequency of obtaining the infliximab and AIA levels was at the discretion of the prescribing physician. Both tests were ELISA assays submitted to Quest Diagnostics (San Juan Capistrano, CA, USA). The Quest Diagnostics results report states the following about infliximab levels: "Data from clinical studies suggest a target infliximab trough concentration of 2.0–8.0 mcg/mL or 2.0–10.0 mcg/mL in rheumatoid arthritis." No data for target concentrations for other diseases are provided.

Demographic and applicable clinical parameters were recorded from infusion and office visits over the course of infliximab treatment. Clinical parameters included Snellen visual acuity, anterior chamber cell grade (based on the SUN grading criteria⁹), vitreous haze grade,¹⁰ conjunctival injection and edema, the presence of macular edema, leakage on fluorescein angiography, concomitant immunomodulatory therapy (IMT), blood infliximab levels in mcg/mL, and AIA titers (measured in arbitrary units [AU]). Patients were considered to be AIA-positive if AIA were detected at more than one visit (permanent AIA).⁸ Any AIA level reported by Quest Diagnostics as greater than 50 AU was recorded as 50 AU for analyses.

Clinical response was judged as a composite evaluation of various clinical parameters by the treating fellowship-trained uveitis specialist (LS or GNP) and was classified as complete, partial, or no response. Complete response was defined as achieving inactivity (no injection, grade 0 anterior chamber cells, no vitreous haze, no macular edema, no leakage on fluorescein angiogram, as applicable to the anatomic location of uveitis).¹¹ Partial response was defined as a two-step improvement in inflammation (anterior chamber cell or vitreous haze)¹¹ but not complete resolution of these; partial response could also occur if injection, macular edema or fluorescein angiographic leakage improved but did not resolve. No response was defined as worsening or a change less than or equal to one-step improvement in inflammation of the relevant inflammatory parameters. The assessment of clinical response was an assessment of the patient as a whole rather than by eye; therefore, a patient with ocular inflammation in both eyes would require both eyes to be clinically quiescent to be considered a complete responder. Clinical response was determined at the visit when the patient was receiving the maximal tolerated dose of infliximab. Patients who developed AIA were compared with patients who did not develop AIA with regards to clinical response.

3. Results

3.1. Demographics and clinical characteristics

43 patients were treated with infliximab over the study period, but eleven of these patients were excluded because AIA or infliximab levels were never checked in these patients. Of the 32 included patients, 29 had multiple, longitudinal AIA and infliximab levels drawn, while three only had one AIA and infliximab level drawn. Of the 32 included patients, 28% were male ($n = 9$) and 72% were female ($n = 23$). The mean age at diagnosis was 32.8 years. Anatomic locations of inflammation included scleritis ($n = 4$), anterior uveitis ($n = 4$), intermediate uveitis ($n = 3$), posterior uveitis ($n = 14$), and panuveitis ($n = 7$). The underlying causes of inflammation by order of frequency were birdshot chorioretinopathy ($n = 4$), sarcoidosis ($n = 2$), Vogt-Koyanagi-Harada syndrome ($n = 1$), Behcet's disease ($n = 1$), and idiopathic retinal vasculitis-aneurysms-neuroretinitis syndrome ($n = 1$). The ocular inflammation was idiopathic in the remaining 23 patients.

The mean maximal infliximab dose was 7 mg/kg (range: 5–12.5 mg/kg). Patients treated with infliximab were either treated with biosimilar infliximab-dyyb (Inflectra) or brand name infliximab (Remicade). Two patients who were initially started on Remicade were subsequently switched to Inflectra due to insurance coverage reasons, and eventually restarted Remicade due to intolerance of medication side effects from Inflectra. Four patients initially started treatment on Remicade and later switched to Inflectra due to insurance coverage reasons and remained on Inflectra without any issues. One patient initially started treatment on Inflectra and later switched to Remicade due to lack of clinical improvement on Inflectra. One patient remained exclusively on Inflectra for the entire duration of treatment. The remaining 24 patients received Remicade exclusively. Overall mean length of treatment of infliximab was 29 months. Mean infliximab serum level at 6 months post infliximab initiation was 29 mcg/mL. For more details on patient demographics, infliximab levels and anti-infliximab antibodies, please refer to [Table 1](#).

Patients commonly had been treated with other steroid-sparing immunomodulatory therapies (IMT) and/or steroids prior to being treated with infliximab. In the thirteen patients previously treated with mycophenolate, the mean time on mycophenolate prior to infliximab initiation was 7.8 months and the mean time for concurrent mycophenolate and infliximab treatment was 19 months. In the eight patients previously treated with methotrexate, the mean time on methotrexate prior to infliximab initiation was 14.1 months and the mean time for concurrent methotrexate and infliximab treatment was 24.1 months. For patients treated with oral prednisone immediately prior to infliximab initiation, mean overall time on oral prednisone prior to infliximab initiation was 6.5 months and the mean time for concurrent prednisone and infliximab treatment was 10.9 months. Full details on infliximab dosage, infliximab trough levels, AIA levels, and concomitant IMT or systemic steroid use are available in [Supplemental Table 1](#).

3.2. AIA development and clinical response

Twenty-three patients never developed AIA while nine patients did develop AIA during the course of treatment, for an AIA positive prevalence of 28%. Overall, clinical response at 6 months after infliximab initiation was complete in 75% of patients ($n = 24$), partial in 19% of patients ($n = 6$), and absent in 6% of patients ($n = 2$). Clinical response in the 23 patients who did not develop AIA was complete in 65% ($n = 15$), partial in 26% ($n = 6$), and absent in 9% ($n = 2$). Clinical response in the nine patients who did develop AIA was complete in 78% ($n = 7$), partial in 22% ($n = 2$) and absent in no patients. There were no changes in assessment of clinical response in the most recent six months of treatment compared with the initial six months of treatment for any of the patients. It is also noted that there was no instance where adjustment of concurrent medication was the clinical change that led to a complete response.

Table 1
Demographic and clinical characteristics of patients treated with infliximab.

ID	Age/ Sex	Diagnosis	Months on infliximab	AIA at 6 m ($\mu\text{g}/\text{mL}$)	AIA final ($\mu\text{g}/\text{mL}$)	AIA month ($\mu\text{g}/\text{mL}$)	AIA at 6 m level ($\mu\text{g}/\text{mL}$)	Min AIA level ($\mu\text{g}/\text{mL}$)	Max AIA level ($\mu\text{g}/\text{mL}$)	Clinical response final at max tolerate dose†	Serum Infliximab level at clinical response ($\mu\text{g}/\text{mL}$)
^a 1	70/F	Posterior /idiopathic	63	-	-	-	-	-	-	Complete (7.5 mg/kg)	>50
2	48/F	Panuveitis /idiopathic	61	-	Y	29	-	10	23	Complete (5 mg/ kg)	21
3	54/F	Posterior /birdshot chorioretinopathy	4	-	-	-	-	-	-	Failed (7.5 mg/ kg)	64
4	22/M	Panuveitis /VKH	27	-	-	-	-	-	-	Complete (7.5 mg/kg)	>50
5	53/M	Posterior /birdshot chorioretinopathy	42	-	-	-	-	-	-	Complete (5 mg/ kg)	13
6	42/M	Posterior /idiopathic	40	-	Y	31	-	10	74	Partial (5 mg/kg)	33
^a 7	40/M	Panuveitis /Behçet's	81	-	-	-	-	-	-	Partial (7.5 mg/ kg)	4.8
8	29/F	Posterior /IRVAN	38	-	Y	31	-	27	98	Complete (5 mg/ kg)	9
9	57/F	Panuveitis /idiopathic	82	-	Y	63	-	11	26	Partial (5 mg/kg)	15
10	36/M	Posterior /idiopathic	43	-	-	-	-	-	-	Partial (7 mg/kg)	19.7
^a 11	15/M	Intermediate /idiopathic	80	-	-	-	-	-	-	Partial (10.5 mg/ kg)	23
12	63/F	Scleritis /idiopathic	11	Y	Y	6	11	11	99	Failed (5 mg/kg)	8.1
^a 13	55/F	Posterior /idiopathic	12	-	-	-	-	-	-	Complete (8.5 mg/kg)	33
^a 14	39/F	Posterior /idiopathic	33	-	-	-	-	-	-	Failed (7.5 mg/ kg)	44
15	20/F	Posterior /idiopathic	19	-	-	-	-	-	-	Partial (10 mg/ kg)	>50
16	22/F	Scleritis /idiopathic	4	-	-	-	-	-	-	Partial (6.5 mg/ kg)	55
^a 17	48/M	Panuveitis /idiopathic	29	-	-	-	-	-	-	Partial (9 mg/kg)	14.1
18	56/F	Posterior /birdshot chorioretinopathy	47	-	-	-	-	-	-	Complete (5 mg/ kg)	29.4
^a 19	66/F	Scleritis /idiopathic	34	-	-	-	-	-	-	Complete (5 mg/ kg)	10.1
20	58/F	Anterior /idiopathic	47	-	-	-	-	-	-	Complete (7.5 mg/kg)	26
21	35/M	Panuveitis /VKH	36	-	Y	21	-	11	51	Complete (7 mg/ kg)	7.7
22	28/F	Intermediate /idiopathic	41	-	Y	38	-	19	39	Complete (5 mg/ kg)	10.9
23	53/F	Posterior /sarcoidosis	33	-	-	-	-	-	-	Complete (9.5 mg/kg)	13.1
24	26/F	Anterior /idiopathic	11	Y	Y	4	26	11	68	Complete (5 mg/ kg)	9.2
25	38/M	Panuveitis /idiopathic	15	-	-	-	-	-	-	Complete (7.5 mg/kg)	48.1
26	77/F	Posterior cyclitis /idiopathic	12	-	Y	11	-	37	59	Complete (7.5 mg/kg)	17
±27	54/F	Anterior /idiopathic	5	-	-	-	-	-	-	Complete (5 mg/ kg)	47.6
28	82/F	Panuveitis /idiopathic	11	-	-	-	-	-	-	Complete (7.5 mg/kg)	9.7
29	32/F	Anterior /idiopathic	18	-	-	-	-	-	-	Complete (5 mg/ kg)	2
30	63/F	Posterior /sarcoidosis	26	-	-	-	-	-	-	Complete (5 mg/ kg)	5.2
31	31/F	Intermediate /idiopathic	8	-	-	-	-	-	-	Complete (5 mg/ kg)	24.2
32	38/F	Scleritis /idiopathic	38	-	-	-	-	-	-	Complete (9 mg/ kg)	>50

AIA = anti-infliximab antibodies, F = female, M = male, VKH = Vogt-Koyanagi-Harada, IRVAN = idiopathic retinal vasculitis aneurysms neuroretinitis.

† Response was determined at the time patient was receiving maximally tolerated dose of infliximab, denoted in parenthetical values in mg/kg.

± Only received brand name Inflectra during treatment course.

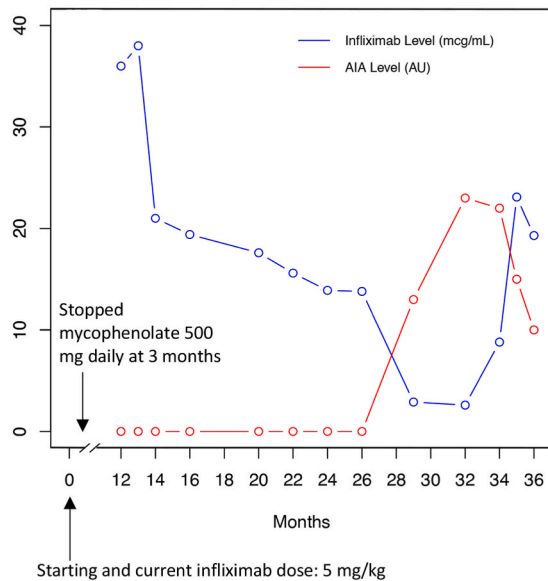
^a Received brand name Inflectra in addition to brand name Remicade.

Among the nine patients who developed AIA, none received the biosimilar Inflectra at any time during their treatment course. Seven of the nine patients were on concomitant antimetabolite therapy at some point during infliximab therapy [mycophenolate (n = 5), methotrexate (n = 2)], but only four were taking an antimetabolite at the time of AIA detection. Mean time to AIA development relative to infliximab initiation was 25 months. Mean initial AIA level was 5.7 AU and mean infliximab level at the time of initial AIA development was 16.3 mcg/mL.

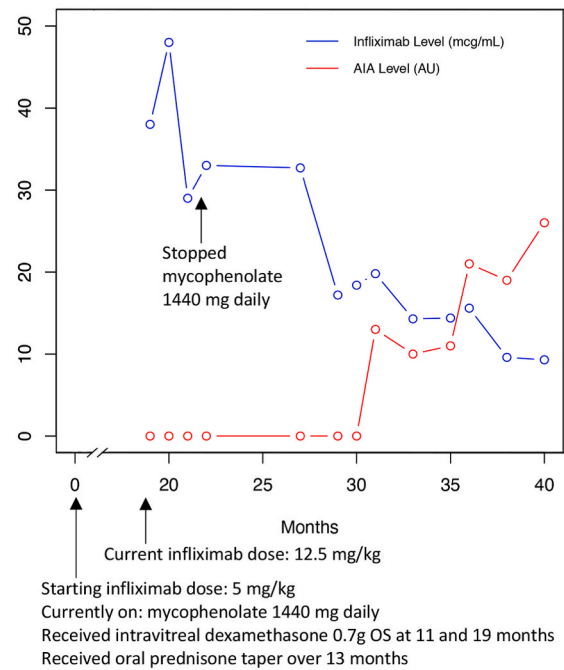
Overall, there was a decrease in infliximab levels with the initial

appearance of the AIA (Fig. 1). For Patient 2 (Fig. 1A) and Patient 9 (Fig. 1D), infliximab levels rebounded after a nadir, while in the remaining patients the infliximab levels plateaued (Patient 8, Fig. 1C; Patient 12, Fig. 1E; Patient 24, Fig. 1H) or declined moderately (Patient 6, Fig. 1B; Patient 22, Fig. 1G; Patient 26, Fig. 1I) after the initial drop. One patient displayed a steep rise in AIA coupled with a moderate fall of infliximab levels with AIA levels becoming undetectable for a period of three months before peaking and falling until undetectable again (Patient 21, Fig. 1F).

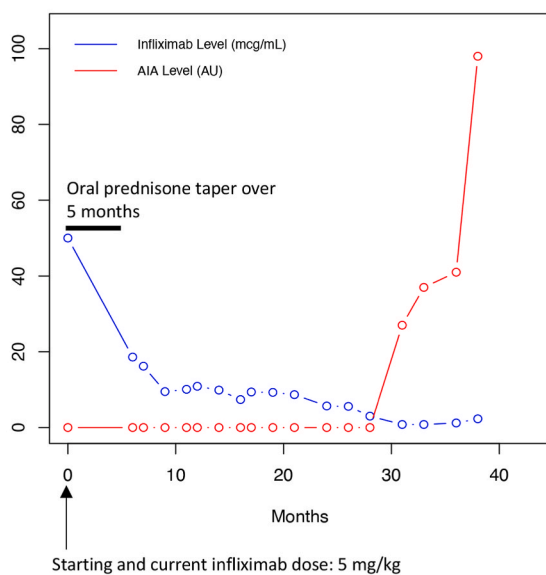
A. Patient 2. Complete response



B. Patient 6. Partial response



C. Patient 8. Complete response



D. Patient 9. Partial response

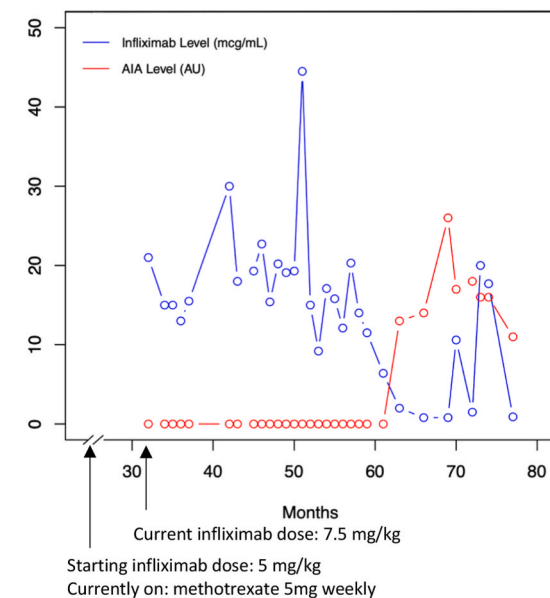
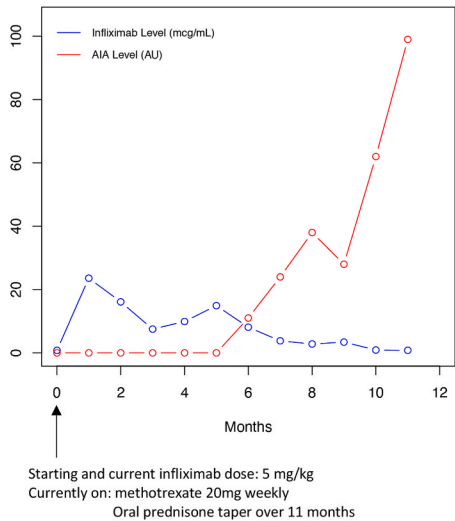
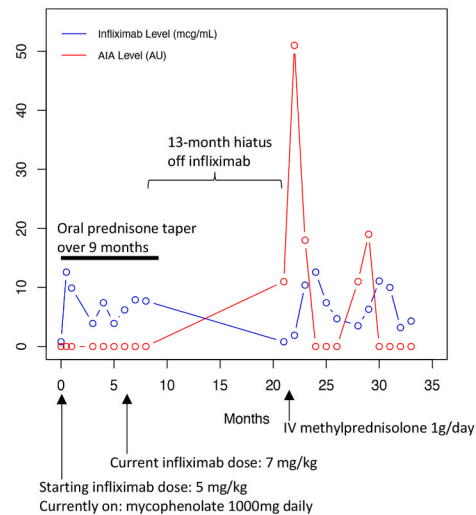


Fig. 1. Infliximab, anti-infliximab antibodies (AIA) serum levels, clinical response and concomitant IMT or steroid treatment over time in patients with positive AIA: (A) Patient 2. (B) Patient 6. (C) Patient 8. (D) Patient 9. (E) Patient 12. (F) Patient 21. (G) Patient 22. (H) Patient 24. (I) Patient 26.

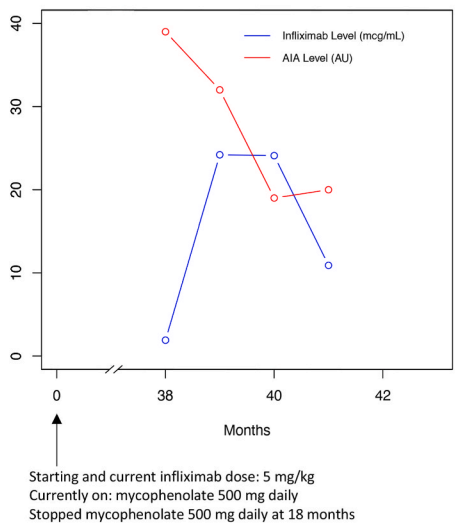
E. Patient 12. Complete response



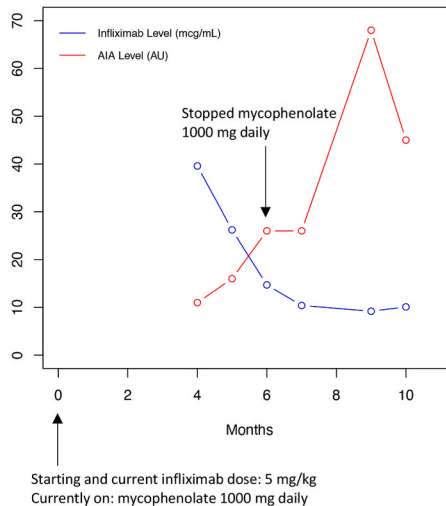
F. Patient 21. Complete response



G. Patient 22. Complete response



H. Patient 24. Complete response



I. Patient 26. Complete response

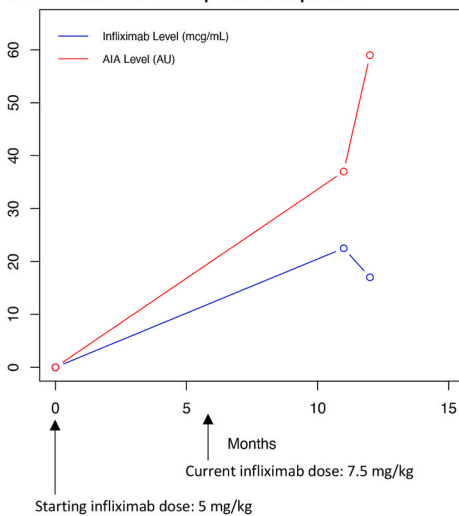


Fig. 1. (continued).

3.3. Detailed clinical course of AIA-positive patients

Patient 2 (Fig. 1A) was on mycophenolate mofetil 500 mg daily overlapping for the first 3 months of infliximab treatment; mycophenolate was stopped because of persistent leukopenia and neutropenia. She developed AIA 29 months after initiation of infliximab and 26 months after discontinuation of mycophenolate. She is currently still on infliximab without complications with a complete clinical response.

Patient 6 (Fig. 1B) was on mycophenolate sodium 1440 mg daily for the first 21 months of infliximab; mycophenolate was stopped because of leukopenia and an upper respiratory infection. He developed AIA 31 months after initiation of infliximab and 9 months after discontinuation of mycophenolate. He was on an oral prednisone taper over 13 months during the initiation of infliximab. During the course of his infliximab treatment, he also received two intravitreal dexamethasone 0.7 mg implant injections in his left eye for cystoid macular edema secondary to uveitis. This patient had a partial clinical response both prior to and after development of AIA. Infliximab was not changed to a different agent despite only a partial response because the patient tolerated the medication well, visual function was stable and the patient did not want to escalate to another therapy. Infliximab was discontinued after 40 months due to patient's wish to not be on immunosuppression during the COVID-19 pandemic.

Patient 9 (Fig. 1D) was on methotrexate 5 mg weekly initiated at the same time as infliximab. She developed antibodies 63 months after initiation of infliximab and methotrexate while still receiving both treatments. She is currently still on infliximab without complications with a partial clinical response. Some of her infliximab levels are undetectable because the patient often fails to show up for her infusions due to social issues and thus the interval between infusions is extended longer than anticipated, so that the serum infliximab levels become undetectable. It is also possible that this lack of consistent follow-up is responsible for the partial clinical response. She has not been changed to another therapy because of her complex social situation and other medical issues. The partial clinical response has been deemed acceptable in the larger context of the patient's care and her visual function has remained stable thus far.

Patient 12 (Fig. 1E) was on methotrexate 20 mg weekly 5 months prior to initiation of infliximab and then overlapping the entirety of infliximab treatment course for 11 months. She developed AIA six months after initiation of infliximab and 11 months after the initiation of methotrexate while still receiving both treatments. The patient was also on an oral prednisone taper over 11 months during the initiation of infliximab. Infliximab was discontinued at 11 months due to rising AIA and undetectable serum infliximab levels despite a complete clinical response because of the potential increased risk of infusion reactions with rising AIA and unclear benefit given undetectable drug levels. Infliximab was replaced with adalimumab.

Patient 21 (Fig. 1F) was on mycophenolate mofetil 1000 mg daily for 19 months prior to infliximab initiation, overlapping the entirety of infliximab treatment course of 23 months. In addition, the patient received a 3-day course of intravenous methylprednisolone 1g per day at month 21 of infliximab treatment for acute relapse of symptoms after 13 months without receiving infliximab due to the COVID-19 pandemic. He developed antibodies 22 months after initiation of infliximab and 41 months after the initiation of mycophenolate while still receiving both treatments. The patient was on an oral prednisone over 9 months during the initiation of infliximab. He is currently still on infliximab without complications with a complete clinical response.

Patient 22 (Fig. 1G) was on mycophenolate mofetil 500 mg daily overlapping for the first 18 months of infliximab; mycophenolate was stopped for spine surgery and never restarted again because the patient noted significant decrease in side effects while off mycophenolate and did not want to take it again. AIA were first detected 38 months after initiation of therapy and 20 months after discontinuation of mycophenolate. The patient eventually switched to adalimumab for the

convenience of home injections during the COVID-19 pandemic after 41 months on infliximab despite a complete clinical response.

Patient 24 (Fig. 1H) was on mycophenolate mofetil 1000 mg daily overlapping for the first 6 months and AIA were first detected 4 months after initiation of therapy while she was still on both treatments. Infliximab was eventually discontinued at 11 months due to the potential risk of infusion reactions from the high AIA levels and despite a complete clinical response, and replaced with adalimumab.

There were two patients treated with infliximab without a steroid-sparing IMT at any point during their infliximab therapy who developed AIA: Patient 8 (Fig. 1C) and Patient 26 (Fig. 1I). Patient 8 developed AIA at 31 months after infliximab initiation and infliximab was discontinued after 38 months due to rising AIA levels and low serum infliximab levels despite a complete clinical response. Of note, Patient 8 was on an oral prednisone taper over 5 months during the initiation of infliximab. Patient 26 developed AIA at 11 months and was discontinued from infliximab after 12 months due to a lupus-like reaction with rising ANA titers despite a complete clinical response.

4. Discussion

Overall, there was a high rate of favorable clinical response to infliximab and a 28% rate of AIA positivity in our cohort of NIU and scleritis patients. AIA-positive patients did not have diminished rates of clinical response when compared with AIA-negative patients. This suggests that routine monitoring of AIA may not be clinically useful, although validation of this finding in larger cohorts is necessary.

The prevalence of AIA in our cohort is similar to that seen in some studies of non-ocular disease,⁷ but lower than that reported in others.^{5,7,12} Several studies indicate that concomitant use of an antimetabolite with infliximab is associated with lower AIA prevalence. In our study, seven out of nine patients who developed AIA were on concomitant antimetabolite therapy at some point during their infliximab therapy, although three had stopped the antimetabolite before AIA were detected. In the three patients who stopped antimetabolite therapy before AIA were detected, the mean time from discontinuation to first detection of AIA was 18 months. Due to the limited sample size and relatively wide range of follow up time (4–82 months of total follow up time), further investigation on the chronologic association between antimetabolite cessation and AIA development is warranted. Overall, because of the modest size of the study sample, conclusions about the effectiveness of antimetabolites in preventing AIA development in this population cannot be drawn. We also note that the five of the patients with AIA were on mycophenolate as their antimetabolite; this particular antimetabolite has not been investigated in prior studies concerning the effect of antimetabolites on the prevention of AIA.^{2,13,14} It is primarily methotrexate that has been investigated in this context. There may be a difference between antimetabolite agents regarding their effect on AIA development. Cordero-Coma et al. also noted that concomitant antimetabolite therapy, which 3 of their 8 patients with anti-adalimumab antibodies were taking, did not seem to prevent immunogenicity.

There was no association between AIA-positivity and treatment response to infliximab. In fact, the majority of partial/non-responders did not have AIA so it is likely that their deficient response to infliximab was because their disease did not respond to the mechanism of action of this drug. Unlike in the adalimumab study by Cordero-Coma et al., none of the patients with anti-drug antibodies in our cohort failed treatment. Two AIA-positive patients were classified as partial responders, but both patients were also partial responders before the development of AIA. One caveat to note is that infliximab was discontinued in three patients (Patients 8, 12, and 24) pre-emptively because of the risk of infusion reactions from rising AIA levels.¹⁵ These patients had a complete clinical response in the presence of AIA for ten, six and six months, respectively. It is possible if infliximab had been continued for longer that they might have eventually lost their clinical response, however they did each maintain a complete clinical

response for at least six months in the presence of AIA. A clinical response to infliximab despite presence of AIA may occur because the antibodies formed did not inhibit a sufficient amount of infliximab molecules to impact drug efficacy or because the antibodies did not interfere with the drug's therapeutic effect even when bound to infliximab.

The use of anti TNF- α biologics with resulting development of AIA has been investigated in the context of general rheumatic and gastrointestinal diseases in multiple case series and case reports.^{16–22} The presence of anti-drug antibodies with TNF- α inhibitors, in particular infliximab, has been heavily studied in the context of inflammatory bowel disease (IBD). In these IBD studies, similarly to the findings in the current study, the presence of AIA also does not necessarily correlate with clinical response.²¹ Of note, a large portion of IBD patients can exhibit a decrease in AIA with eventual disappearance²¹; we did observe this phenomenon in one of our patients (Patient 21). It is notable that many anti-drug antibodies have been found to be non-neutralizing when investigated in other immune-mediated diseases and therefore not expected to affect treatment efficacy.²³ As alluded to above, this is one potential explanation for the lack of a strong correlation between AIA and clinical response.

The limitations of this study include its modest sample size with concomitant limited power, heterogeneity in both infliximab dosing and concomitant antimetabolite use, and heterogeneity in the etiologies and anatomic locations of inflammation. The small sample size is due to the fact that infliximab is often a third- or fourth-line systemic immunomodulatory agent used in the treatment of uveitis and scleritis; only a small subset of patients who need systemic treatment (who are already a fraction of patients with these ocular inflammatory diseases) are treated with infliximab. In real world clinical practice, patients with a variety of ocular inflammatory problems may be escalated to infliximab therapy and in this sense, the results in this heterogeneous group are more applicable and generalizable to clinical practice. To our best knowledge, this is the first study to examine the impact of AIA on clinical response to infliximab in NIU and scleritis. While it is a preliminary and small study, it suggests that the presence of AIA may generally have no significant negative clinical effect on infliximab efficacy. Future studies involving larger cohorts are needed to confirm these results.

Ethics approval and consent to participate

This study was approved by the Mass General Brigham Institutional Review Board with waiver of consent given the de-identified and retrospective nature of the data. It adhered to the tenets of the Declaration of Helsinki.

Consent for publication

Waiver of patient's consent was granted by the Institutional Review Board.

Data availability statement

The data that support the findings of this study are available from the corresponding author, LS, upon reasonable request.

Financial Support

This work was not supported by grants received from any funding agency.

Authors' contributions

Conception and design – LV, LS, JTC.
Acquisition of data – LV, JTC, GS, SH, JY, LS.
Analysis and interpretation of data – LV, JTC, GNP, LS.

Drafting or revising the article – LV, JTC, GS, SH, JY, GNP, LS.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2022.101634>.

References

1. *Infliximab [package Insert]*. Horsham, PA: Janssen Biotech; 2013.
2. Wolbink GJ, Vis M, Lems W, et al. Development of anti-infliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum.* 2006;54(3):711–715. <https://doi.org/10.1002/art.21671>.
3. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998; 41(9):1552–1563. [https://doi.org/10.1002/1529-0131\(199809\)41:9<1552::aid-art5>3.0.co;2-w](https://doi.org/10.1002/1529-0131(199809)41:9<1552::aid-art5>3.0.co;2-w).
4. Pascual-Salcedo D, Plasencia C, Ramiro S, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology.* 2011;50(8):1445–1452. <https://doi.org/10.1093/rheumatology/ker124>.
5. Mease PJ, Collier DH, Saunders KC, Li G, Kremer JM, Greenberg JD. Comparative effectiveness of biologic monotherapy versus combination therapy for patients with psoriatic arthritis: results from the CORRONA registry. *RMD Open.* 2015;1(1). <https://doi.org/10.1136/rmdopen-2015-000181>.
6. Pixley J. Immunogenicity, the elephant in the room. comment on “drug levels, anti-drug antibodies and clinical efficacy of the anti-tnf α biologics in rheumatic diseases. *Clin Rheumatol.* 2013;32(10). <https://doi.org/10.1007/s10067-013-2364-6>, 1413–1413.
7. Moots RJ, Xavier RM, Mok CC, et al. Correction: the impact of anti-drug antibodies on drug concentrations and clinical outcomes in rheumatoid arthritis patients treated with adalimumab, etanercept, or infliximab: results from a multinational, real-world clinical practice, non-interventional study. *PLoS One.* 2017;12(6). <https://doi.org/10.1371/journal.pone.0179308>.
8. Quistrebert J, Hässler S, Bachelet D, et al. Incidence and risk factors for adalimumab and infliximab anti-drug antibodies in rheumatoid arthritis: a European retrospective multicohort analysis. *Semin Arthritis Rheum.* 2019;48(6):967–975. <https://doi.org/10.1016/j.semarthrit.2018.10.006>.
9. Trusko B, Thorne J, Jabs D, et al. The Standardization of Uveitis Nomenclature (SUN) Project. Development of a clinical evidence base utilizing informatics tools and techniques. *Methods Inf Med.* 2013;52(3). <https://doi.org/10.3414/ME12-01-0063>, 259–S6.
10. Cordero-Coma M, Calleja-Antolín S, Garzo-García I, et al. Adalimumab for treatment of noninfectious uveitis: immunogenicity and clinical relevance of measuring serum drug levels and antidrug antibodies. *Ophthalmol Times.* 2016;123(12):2618–2625. <https://doi.org/10.1016/j.ophtha.2016.08.025>.
11. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol.* 2005;140(3): 509–516. <https://doi.org/10.1016/j.ajo.2005.03.057>.
12. Nussenblatt RB, Palestine AG, Chan C-C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmol Times.* 1985; 92(4):467–471. [https://doi.org/10.1016/s0161-6420\(85\)34001-0](https://doi.org/10.1016/s0161-6420(85)34001-0).
13. Zitomersky NL, Atkinson BJ, Fournier K, et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. *Inflamm Bowel Dis.* 2015;21(2):307–314. <https://doi.org/10.1097/mib.0000000000000284>.
14. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med.* 2003;348(7):601–608. <https://doi.org/10.1056/nejmoa020888>.
15. Jani M, Dixon WG, Chinoy H. Drug safety and immunogenicity of tumour necrosis factor inhibitors: the story so far. *Rheumatology (Oxford).* 2018;57(11):1896–1907. <https://doi.org/10.1093/rheumatology/keu434>.
16. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of dmards in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology.* 2013;53(2):213–222. <https://doi.org/10.1093/rheumatology/ker260>.
17. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. *Inflamm Bowel Dis.* 2009; 15(8):1264–1275. <https://doi.org/10.1002/ibd.20899>.
18. Freeman K, Taylor-Phillips S, Connock M, et al. Test accuracy of drug and antibody assays for predicting response to antitumour necrosis factor treatment in Crohn's disease: a systematic review and meta-analysis. *BMJ Open.* 2017;7(6), e014581. <https://doi.org/10.1136/bmjopen-2016-014581>. Published 2017 Jul 2.
19. Aeschlimann FA, Angst F, Hofer KD, et al. Prevalence of anti-infliximab antibodies and their associated Co-factors in children with refractory arthritis and/or uveitis: a

- retrospective longitudinal cohort study. *J Rheumatol*. 2017;44(3):334–341. <https://doi.org/10.3899/jrheum.160072>.
20. Bar-Yoseph H, Levhar N, Selinger L, et al. Early drug and anti-infliximab antibody levels for prediction of primary nonresponse to infliximab therapy. *Aliment Pharmacol Ther*. 2018;47(2):212–218. <https://doi.org/10.1111/apt.14410>.
 21. Steenholdt C, Al-khalaf M, Brynskov J, Bendtzen K, Thomsen OØ, Ainsworth MA. Clinical implications of variations in anti-infliximab antibody levels in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(12):2209–2217. <https://doi.org/10.1002/ibd.22910>.
 22. Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. *Clin Therapeut*. 2002;24(11). [https://doi.org/10.1016/s0149-2918\(02\)80075-3](https://doi.org/10.1016/s0149-2918(02)80075-3), 1720-1719.
 23. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: a systematic review. *Br J Dermatol*. 2014;170(2):261–273. <https://doi.org/10.1111/bjd.12654>.