—Original—

Change in Antinuclear Antibody Titers during Biologic Treatment for Psoriasis

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Background: We previously evaluated blood screening data, including antinuclear antibodies (ANA), before initiating biologic treatment for patients with psoriasis in a real-world setting. However, we did not analyze change in ANA titers after the start of biologics. No previous study has comprehensively investigated change in ANA titers over time in individual patients or the effectiveness of certolizumab pegol or tildrakizumab.

Objectives: This study evaluated change in ANA titers in individual patients during treatment with biologics, including certolizumab pegol and tildrakizumab.

Methods: 111 patients were included in this study. Change in ANA was regarded as significant when the ANA titer was ×80 or more in patients with a previously undetectable ANA titer or when it increased by fourfold or more in those with a detectable ANA titer before treatment.

Results: The ratios of patients with a significant change in ANA titer who were treated with a tumor necrosis factor (TNF) inhibitor, interleukin (IL)-17 inhibitor, or IL-23 inhibitor were 34.9% (15/43), 0.0% (0/32), and 0.0% (0/36), respectively. There were 4 patterns of significant change in ANA titer: (i) an increase (n=8), (ii) a decrease after an increase (n=4), (iii) a decrease after an increase with a drug change (n=2), and (iv) an increase after a decrease after an increase (n=1). No symptom suggesting lupus syndrome was noted.

Conclusions: ANA titers must be carefully monitored throughout treatment with biologics, especially TNF inhibitors, and the possibility of lupus-like syndrome should be excluded.

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Key words: antinuclear antibodies, biologics, changes, psoriasis, tumor necrosis factor inhibitor

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes[1,2]. Biologics have been marketed in Japan for treatment of refractory psoriasis since 2010; as of July 2022, eleven biologics were available[3]: 3 tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, and certolizumab pegol), 4 interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab), and 4 IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab).

The Biologics Review Committee of the Japanese Dermatological Association for Psoriasis recommends blood testing for antinuclear antibodies (ANA) before and after starting biologics at screening and monitoring[3]. TNF inhibitors may cause positive conversion of ANA and anti-double strand DNA (ds-DNA), as well as symptoms suggestive of lupus-like syndrome[3–5]. We previously evaluated blood screening data, including ANA, before starting biologics for 127 psoriasis patients in a real-world setting[6]. The number of ANA-positive patients was 27 (21.3%), and the ANA titers were ×40, ×80, ×160, and ×640 in 18 (14.2%), 7 (5.5%), 1 (0.8%), and 1 (0.8%) patient, respectively[6]. However, we did not follow change in ANA titers after the start of biologics in that study.

There have been several follow-up studies on the in-

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duction of ANA titers after the start of TNF inhibitors[7–14], and some studies of ustekinumab +/− TNF inhibitors[15–18]. Recently, Sugiura et al. conducted a follow-up study of biologics, including TNF inhibitors (infliximab and adalimumab), IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), and IL-23 inhibitors (ustekinumab, guselkumab, and risankizumab)[19]. However, few studies have investigated change in ANA titers over time during biologic therapy[14,16]. Furthermore, no study has comprehensively examined change in ANA titers over time in individual patients, or the use of certolizumab pegol or tildrakizumab. In this study, we evaluated change in ANA titers in individual patients during treatment with several biologics, including certolizumab pegol and tildrakizumab.

Methods

Data Collection

In this retrospective study we collected data from all patients from June 2014 to November 2021 who were aged 15 years or older, had received a diagnosis of intractable psoriasis, were prescribed biologics at Nippon Medical School for the first time (bio-naïve patients), and were observed for at least 6 months. None of the included patients had a history of autoimmune disease. The psoriasis cases consisted of plaque-type psoriasis (psoriasis vulgaris: PsV), psoriatic arthritis (PsA), and generalized pustular psoriasis (GPP). Three types of psoriasis were diagnosed, as described elsewhere[6]. As a rule, patients visited our department at time 0, at 1 month after the start of biologics, and at least once every 3 months thereafter.

Peripheral blood was obtained from each patient at each visit and ANA titers were measured. When the ANA titer exceeded ×160, anti-ds-DNA-IgG and anti-Smith (Sm) antibodies were also measured. ANA were identified by indirect immunofluorescence with serial dilutions and anti-ds-DNA-IgG and anti-Sm antibodies by fluorescence enzyme immunoassay (BML, Tokyo, Japan). The study was approved by the ethics committee of the Nippon Medical School (No. 2022-217). Consent was obtained by the opt-out method from all patients.

One of 10 biologics—infliximab, adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, ustekinumab, guselkumab, risankizumab, or tildrakizumab—was administered to each psoriasis patient, according to a protocol described elsewhere[6]. Disease activity was defined as the psoriasis area and severity index (PASI) score at each visit, when such assessment was possible[20].

Table 1 Biologics prescribed for the first time and duration of use

Biologics	n	%	Duration of use (months)*
TNF inhibitors	43	38.7	37.2 ± 27.8
Infliximab	10	9.0	48.6 ± 33.5
Adalimumab	28	25.2	37.4 ± 16.0
Certolizumab pegol	5	4.5	13.4 ± 1.5
IL-17 inhibitors	32	28.8	34.7 ± 25.1
Secukinumab	17	15.3	40.9 ± 29.1
Ixekizumab	6	5.4	43.4 ± 7.4
Brodalumab	9	8.1	17.1 ± 15.4
IL-23 inhibitors	36	32.4	25.5 ± 19.1
Ustekinumab	17	15.3	29.8 ± 24.1
Guselkumab	4	3.6	36.5 ± 9.0
Risankizumab	10	9.0	23.1 ± 8.5
Tildrakizumab	5	4.5	6.8 ± 0.4

TNF, tumor necrosis factor; IL, interleukin
*mean ± standard deviation

Statistical Analysis

Change in ANA was regarded as significant when the ANA titer was ×80 or higher in patients with previously undetectable ANA (positive conversion) or when it increased by a factor of four or more in those with detectable ANA before treatment (increased titer)[7,17]. The rate of patients with a 75% reduction in PASI score (PASI-75) was compared between psoriasis patients with a significant ANA change and those with a nonsignificant ANA change during treatment with biologics. The Yates 3×2 chi square test was used to compare frequencies of ANA change among drugs. The Yates 2×2 chi square test was used to compare frequencies of PASI-75 response rates, ANA-positive ratios before treatment between male and female patients, and ANA changes between male and female patients. A P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Data from 111 patients (77 males) were analyzed in this study. Mean (± SD) patient age was 56.7 ± 16.8 years. The numbers of patients with PsV, PsA, and GPP were 81 (73.0%), 24 (21.6%), and 6 (5.4%), respectively. Biologics prescribed for the first time and duration of use are shown in **Table 1**. TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were initiated for 43 (38.7%), 32 (28.8%), and 36 (32.4%) patients, respectively. The duration of use for TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors was 37.2 ± 27.8 months, 34.7 ± 25.1 months, and 25.5 ±

Table 2 Change in ANA titer during treatment with biologics

Biologics	Positive conversion	Increased titer	Significant change
TNF inhibitors	35.3% (12/34)	33.3% (3/9)	34.9% (15/43)
Infliximab	50.0% (5/10)	0.0% (0/0)	50.0% (5/10)
Adalimumab	30.0% (6/20)	37.5% (3/8)	32.1% (9/28)
Certolizumab pegol	25.0% (1/4)	0.0% (0/1)	20% (1/5)
IL-17 inhibitors	0.0% (0/28)	0.0% (0/4)	0.0% (0/32)
Secukinumab	0.0% (0/16)	0.0% (0/1)	0.0% (0/17)
Ixekizumab	0.0% (0/6)	0.0% (0/0)	0.0% (0/6)
Brodalumab	0.0% (0/6)	0.0% (0/3)	0.0% (0/9)
IL-23 inhibitors	0.0% (0/28)	0.0% (0/8)	0.0% (0/36)
Ustekinumab	0.0% (0/14)	0.0% (0/3)	0.0% (0/17)
Guselkumab	0.0% (0/3)	0.0% (0/1)	0.0% (0/4)
Risankizumab	0.0% (0/7)	0.0% (0/3)	0.0% (0/10)
Tildrakizumab	0.0% (0/4)	0.0% (0/1)	0.0% (0/5)
Total	13.3% (12/90)	14.3% (3/21)	13.5% (15/111)

TNF, tumor necrosis factor; IL, interleukin

19.1 months, respectively.

The number of ANA-positive patients was 21 (18.9%), and ANA titers were ×40, ×80 in 14 (12.6%) and 7 (6.3%), respectively. The numbers of patients with homogeneous, speckled, nucleolar, and granular patterns were 14, 10, 2, and 1, respectively. No patient had symptoms suggesting lupus syndrome. The ANA-positive ratio tended to be higher in female patients than in male patients (29.4% vs. 14.3%, P=0.06).

Change in ANA Titers during Treatment with Biologics

Change in ANA titers during treatment with biologics is shown in **Table 2**. Among all patients, the ratios of positive conversion, increased titers, and significant changes were 13.3% (12/90), 14.3% (3/21), and 13.5% (15/111), respectively. In patients treated with TNF inhibitors, the ratios of positive conversion, increased titers, and significant changes were 35.3% (12/34), 33.3% (3/9), and 34.9% (15/43), respectively. No patient treated with IL-17 inhibitors or IL-23 inhibitors had a significant change in ANA titer. There were significant differences in the ratios of significant change in ANA titers among TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors ($P = 8.0 \times 10^{-6}$). However, there was no significant difference in the ratios of significant change in ANA titers between female and male patients (17.6% vs. 11.7%, P=0.59).

The ratios of significant change in ANA titers in patients treated with infliximab, adalimumab, and certolizumab pegol were 50.0% (5/10), 32.1% (9/28), and 20.0% (1/5), respectively. There were no significant differences in the ratios of significant changes in ANA titers among patients treated with infliximab, adalimumab, and certolizumab pegol ($P = 0.77$).

Table 3 shows change in ANA titer during treatment in 15 patients with a significant change in ANA titer. Patients 12-14 had increased titers and the other patients had positive conversion. Homogeneous, speckled, and nucleolar patterns were observed in 14, two, and three patients, respectively. In all patients with ANA titers exceeding ×160, both anti-ds-DNA-IgG and anti-Sm antibodies were negative. No symptom suggesting lupus syndrome was noted. There were 4 patterns of change in ANA titers: (i) an increase (n=8: Nos. 6, 7, 9-12, 14, and 15), (ii) a decrease after an increase (n=4: Nos. 2, 4, 5, and 8), (iii) a decrease after an increase with a drug change (n =2: Nos. 1 and 3), and (iv) an increase after a decrease after an increase (n=1: No. 13).

Table 4 shows PASI-75 response rates in patients with significant (n=12) and nonsignificant (n=21) changes in ANA titers when treated with TNF inhibitors. In an analysis of all patients, the PASI-75 response rate did not differ between those whose ANA titers did and did not significantly change (83.3% vs. 61.9%, P=0.37), and there was no significant difference between groups in relation to the drug received (infliximab, adalimumab, or certolizumab pegol).

Discussion

We comprehensively evaluated change in ANA titers during treatment with 10 biologics, including certolizumab pegol and tildrakizumab. In patients treated with infliximab or adalimumab, 36.8% (14/38) showed significant changes, which is consistent with previous reports[7–18]. This is the first study of certolizumab pegol, and

Table 3 Change in ANA titer during treatment in the 15 patients with a significant change in ANA titer

No.	Age	Sex	Duration* (months)	Disease type	Drug used	ANA titer	Homo titer	Speck titer	Nucle titer
1	34	M	0	PsV	IFX	<40			
			38			×160	×160		
			39		IXE				
			44			×80	×80		
			53			×40	×40		
2	68	M	0	PsV	IFX	<40			
			24			×40	×40		
			47			×80	×80		
			88			×40	×40		
3	41	M	0	PsA	IFX	<40			
			13			×160	×160		
			15			×320	×320		
			17		ADA				
			23			×160	×160		
			35			×80	×80		
			47			×40	×40		
4	51	M	0	PsA	IFX	<40			
			13			×40	×40		
			16			×160	×160		
			24			×320	×320		
			48			×160	×160		
			86			×80	×80		
5	56	F	0	GPP	IFX	<40			
			13			×40	×40		×40
			22			×80	×80		×80
			38			×160	×160		×160
			50			×640	×640		×640
			57			×1,280	×1,280		×1,280
			62			×640	×640		×640
6	45	M	0	PsV	ADA	<40			
			35			×40			×40
			40			×80	×40		×80
7	51	M	0	PsA	ADA	<40			
			17			×80	×80		
			28			×160	×160		
8	61	M	0	PsV	ADA	<40			
			7			×40	×40		
			14			×80	×80		
			33			×160	×160		
			59			×80	×80		
9	45	M	0	PsA	ADA	<40			
			3			×40	×40		
			6			×80	×80		
			13			×160	×160		
10	60	F	0	PsA	ADA	<40			
			11			×40	×40		
			40			×80	×80		
11	53	F	0	PsV	ADA	<40			
			5			×40	×40		
			11			×80	×80		
			22			×160	×160		
			28			×320	×320		
			40			×640	×640		
			56			×1,280	×1,280		
12	36	M	0	PsA	ADA	×40	×40	×40	
			3			×80	×80	×80	
			27			×160	×160	×160	
13	45	F	0	PsA	ADA	×80			×80
			1			×160			×160
			4			×80			×80
			25			×40			×40
			37			×80	×80		×80
			49			×160	×160		×160
			94			×320	×320		×320
14	73	F	0	PsA	ADA	×80	×40	×80	
			22			×160	×160	×160	
			57			×320	×320	×320	
15	52	F	0	PsV	CER	<40			
			4			×80	×80		
			7			×160	×160		

No., Number; PsV, psoriasis vulgaris; PsA, psoriatic arthritis; GPP, generalized pustular psoriasis; IFX, infliximab; ADA, adalimumab; CER, certolizumab pegol; IXE, ixekizumab; Homo, homogeneous; Speck, speckled; Nucle, nucleolar;
*Duration, Months after the initiation of the first biologic

Table 4 PASI-75 response rate in relation to TNF inhibitor administration

Biologics	Patients	PASI-75 response rate	*P* value
Infliximab	Changed*	50.0% (2/4)	
	Unchanged**	100.0% (1/1)	0.08
Adalimumab	Changed*	100.0% (7/7)	
	Unchanged**	52.9% (9/17)	0.82
Certolizumab pegol	Changed*	100.0% (1/1)	
	Unchanged**	100.0% (3/3)	0.56
Total	Changed*	83.3% (10/12)	
	Unchanged**	61.9% (13/21)	0.37

*Patients whose ANA titers were significantly changed.
** Patients whose ANA titers were not significantly changed.

20.0% (1/5) of patients had a significant change, suggesting that any TNF inhibitor may induce a significant change in ANA titer, including etanercept[8,11–14], which is not available in Japan for psoriasis. A previous study of ustekinumab reported that no or very few patients developed ANA during treatment[15–18], which is consistent with the present results. A study of other IL-23 inhibitors (guselkumab and risankizumab) and IL-17 inhibitors (secukinumab, ixekizumab, and brodalmab)[19] found no increase in ANA, which is also consistent with our findings. The present study is the first to investigate tildrakizumab; no patient developed ANA, confirming that no or very few patients develop ANA during treatment with IL-23 inhibitors. Among the 15 patients with a significant change in ANA titer, most (14) had a homogeneous staining pattern, a finding that is consistent with the anti-ds-DNA frequently observed in patients with systemic lupus erythematosus. However, no patient had a positive result for anti-ds-DNA or developed symptoms suggesting lupus syndrome.

TNF inhibitors may affect apoptosis, thus reducing expression of CD44[13]. This leads to reduced phagocyte removal of cellular waste (nuclear material) left after apoptosis and therefore promotes production of autoantibodies against nuclear antigens[21]. Furthermore, TNF inhibitors reduce levels of C-reactive protein (CRP), which helps clear nuclear material after apoptosis[8]. Low CRP levels result in prolonged exposure to nuclear material and further increase the chance of antibody formation[22]. Although we observed no significant difference in the ratio of significant change in ANA titer between infliximab, adalimumab, and certolizumab pegol, the ratio was higher for infliximab than for adalimumab and certolizumab pegol, which is consistent with previous findings[11,12,18]. Infliximab seems to be the drug most closely related to development of autoantibodies, probably because it is a chimeric antibody, obtained from the combination of mouse and human amino acid sequences, and therefore induces a greater immune response[11]. Although the ANA-positive ratio before biologic therapy was higher in female patients than in male patients, there was no significant difference between sexes in the ratio of those with a significant change in ANA titer after biologic therapy, which suggests that there is no apparent sex difference in the effect of TNF inhibitors on ANA titers.

Some studies reported that development of ANA was associated with a loss of response[8,12], whereas several other studies reported that it was not associated with a loss of efficacy[7,9,11,14,15]. In the present study, the PASI-75 response rate did not differ between patients with a significant and nonsignificant change in ANA titer (83.3% vs. 61.9%, P=0.37), suggesting that development of ANA was not associated with a loss of efficacy.

Positive conversion was observed in 80% (12/15) of patients with a significant change in ANA titer. There were 4 patterns of change in ANA titers: (i) an increase, (ii) a decrease after an increase, (iii) a decrease after an increase with a drug change, and (iv) an increase after a decrease after an increase. The drug was changed for 2 patients (Nos. 1 and 3). In both cases the starting drug was infliximab and ANA titers decreased after the drug change. ANA titers increased in 62% (8/13) of patients with no drug change (Nos. 6, 7, 9-12, 14, and 15), which was the most common pattern in previous reports[14,16]. Thirty-one percent (4/13) of patients with no drug change exhibited the decrease after an increase pattern (Nos. 2, 4, 5, and 8), which was also reported in a previous study[14]. In patient No. 4, methotrexate (MTX) 2 mg/week was concomitantly administered with infliximab for 11 months (from the 11th to the 21st month after the

start of infliximab); thus, we cannot exclude the possibility that MTX affected change in ANA titer over time in this patient. The only other patient in this study who received MTX 2 mg/week concomitant with a biologic (infliximab) (for 2 months) exhibited no significant change in ANA titer. Poulalhon et al. reported no significant difference in the prevalence of ANA between MTX+ and MTX− groups treated with infliximab[7]. Considering the low dose of concomitant MTX for patient No. 4, MTX likely had little effect on change in ANA titer in this patient. In patient No. 13, the pattern of ANA titer change was complex (an increase after a decrease after an increase). Although we were unable to find the same pattern of change in previous studies or determine the reason for this pattern, the long interval after the start of the drug (94 months) in this patient may explain, at least in part, this complicated pattern of change.

This study had limitations. The number of patients examined was small. The duration of biologic use varied: it was short for newly applied drugs, such as certolizumab pegol and tildrakizumab, which might have affected the results. In addition, the study design was retrospective. Therefore, future prospective studies with a larger number of patients and the same duration of biologic use are necessary.

In summary, we evaluated change over time in ANA titer in 111 psoriasis patients treated with several biologics, including certolizumab pegol and tildrakizumab. The ratios of patients with a significant change in ANA titer during treatment with a TNF inhibitor, IL-17 inhibitor, or IL-23 inhibitor were 34.9% (15/43), 0.0% (0/32), and 0.0% (0/36), respectively. There were 4 patterns of significant change in ANA titers: (i) an increase, (ii) a decrease after an increase, (iii) a decrease after an increase with a drug change, and (iv) an increase after a decrease after an increase. ANA titers must be carefully monitored during treatment with biologics, especially TNF inhibitors, and the occurrence of lupus-like syndrome must be excluded.

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