Original Article

The Effect of Biological Agents on Antinuclear Antibody Status in Patients with Psoriasis: A Single-Center Study

Abstract

Background and Aims: Biological agents are being used as treatment of psoriasis for years. However, autoimmunity can develop after the using of these agents. Antinuclear antibody (ANA) status changes during biological therapy can be affected by certain factors including the presence of immunosuppression. We aimed to evaluate the effect of antitumor necrosis factor agents and ustekinumab on ANA status, as well as other factors leading to change in ANA status such as history of phototherapy and methotrexate combination therapy. **Methods:** In this study, the laboratory findings of thirty-one patients with psoriasis who received biological agents including infliximab, etanercept, adalimumab, and ustekinumab from 2016 to 2018 managed at the department of dermatology were reviewed. The ANA status of the patients was evaluated every 2–3 months. **Results:** Twelve (38.7%) out of the thirty-one patients developed ANA positivity during treatment. Nine patients receiving infliximab, two patients receiving etanercept, and one patient receiving adalimumab developed ANA positivity. The nuclear homogeneous, nuclear fine speckled, and nuclear large/coarse speckled were the most common patterns of ANA. A patient receiving infliximab also developed anti-dsDNA positivity. None of the patients developed drug-induced lupus erythematosus or any autoimmune diseases. Concomitant methotrexate use and phototherapy history had no effect on ANA status statistically (P = 0.240 and 0.717, respectively). **Conclusion:** The emergence of ANA positivity during infliximab therapy among all biological agents was more common. ANA positivity during biologic agents does not cause any signs and symptoms of autoimmune diseases in patients with psoriasis; thus, it can be suggested that biological agents are not major risk factors for autoimmunity.

Keywords: *Antinuclear antibody, autoimmunity, biologic agents, methotrexate, phototherapy, psoriasis*

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Background

Biological agents are proteins that target specific sites of the inflammatory cascade, including antibodies against cell surface markers, cytokines, and adhesion molecules.[1] Biological agents have been used for numerous diseases in dermatology. The use of biological agents has introduced a novel, effective, and relatively target-specific approach to the treatment of psoriasis and has a great impact on the quality of life of patients, especially in cases resistant to conventional therapies.[2,3] However, autoimmunity can develop after the use of these agents. Antinuclear antibody (ANA) changes during biological therapy can be affected by certain factors such as type of the disease and the presence of immunosuppression. Biological agents, especially anti-TNF agents, inhibit Th1 response while they can increase Th2 mediated autoimmunity.[4,5]

Methotrexate (MTX) is a recommended and widely prescribed evidence-based therapy for psoriasis.[6] Many studies of coadministration of immunosuppressives such as MTX with TNF alpha inhibitors have found no effect on induction of formation of autoantibodies or change in levels of ANA/Anti-dsDNA.[7] There is no study investigating the effect of narrowband UVB therapy on autoimmunity. In this study, we evaluated the effect of biological agents, concomitant MTX use, and history of phototherapy on ANA status.

Methods

Study design

In this retrospective study, the records of patients with psoriasis in the Department

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of Dermatology, a tertiary referral center in Turkey, from 2016 to 2018 were reviewed. There were thirty-one patients with plaque-type psoriasis who were also ANA-negative before the initiation of therapy. Therapy with biological agents was initiated if the patients had resistance to conventional treatments due to inefficacy, conventional treatments were not appropriate due to safety issues, and the disease lasted at least 6 months with Psoriasis Area and Severity Index score (PASI) >12. These patients had use of biological agents for at least 4 months, including ustekinumab (UST) and anti-TNF alpha drugs such as infliximab (IFX), etanercept (ETC), and adalimumab (ADA). The total duration of therapy was between 4 and 117 months. Routine laboratory tests including complete blood count, urinalysis, liver function tests, kidney function tests, and posteroanterior chest X-ray were performed every 2–3 months during the follow-up of these patients. Since these agents are known to induce the formation of antinuclear antibodies, ANA status was also checked in addition to routine investigations including complete blood count and biochemical parameters every 2–3 months.

All biological agents were administered as per standard recommended dosage protocols for psoriasis. Infliximab was administrated intravenously at 5 mg/kg at baseline, after 2 and 6 weeks, and every 8 weeks thereafter. The dose of UST for an adult patient with psoriasis weighing up to 100 kg was 45 mg (one injection) at week 0, one injection at week 4, and then an injection once every 12 weeks from then on. For patients weighing more than 100 kg, the dose was 90 mg (two injections) and was given at the same time intervals as the lower dose schedule (i.e., week 0, week 4, and then every 12 weeks from then on). Etanercept dose for induction was 50 mg once a week. The initial loading dose of ADA was 80 mg, followed by 40 mg every other week starting one week after the initial dose.

Indirect immune-fluorescence assay (IIFA), which uses a combination of HEp-20-10 cells and monkey liver tissue as substrates (Euroimmune Medizinische Labordiagnostica AG, Germany), was used for screening ANA status. The test was performed with a 1/100 dilution of the serum samples. The results were reported as negative or positive with the fluorescence score and "anti-cell" (AC) patterns such as nuclear homogeneous, nuclear large/coarse speckled, punctate nucleolar, etc., are determined according to at the international consensus on antinuclear antibody pattern (ICAP).[8] Enzyme-linked immunosorbent assay (ELISA) (Organtec Diagnostika GmbH, Germany) was performed for testing anti-ds DNA. Levels above 20 IU/mL were considered positive according to the test protocol.

Patients were also evaluated for concomitant MTX use along with biological agents and history of phototherapy. The MTX doses were 7.5 mg per weekly. The history of phototherapy was including both narrow-band UVB and psoralen-UVA (PUVA).

Institutional ethics committee approval was obtained for the study (Approval number: 0040/405 Approval date: 28.03.2018). All participants were informed about the study and an informed consent form was obtained.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 statistical package (IBM Corp, Armonk, NY, USA) and a P value less than 0.05 was considered statistically significant. Normality of the data was tested. Continuous variables were expressed by mean ± standard deviation or as median and minimum-maximum. Categorical variables were expressed by number (percentage). Dichotomous variables were analyzed by Chi-square test or by Fisher's exact test, which was performed if ≥1 expected cell count(s) was <5.

Results

Of the thirty-one patients, there were fourteen (45.2%) males and seventeen (54.8%) females. The mean age was 46.9 ± 16.48 years. The median disease duration was 20 (minimum 1, maximum 65) months. Twelve patients (38.7%) had plaque-type psoriasis with psoriatic arthritis (PsA), while nineteen patients (61.3%) had plaque-type psoriasis without psoriatic arthritis. Twenty patients (64.5%) had been treated with IFX, five patients (16.13%) had been treated with ETC, two patients (6.45%) had been treated with ADA, and four patients (12.90%) had been treated with UST. Ten patients (32.3%) have concomitant use of MTX along with biological agents. Twelve patients (38.7%) had a history of phototherapy at least 6 months before receiving biological treatment.

Twelve patients (38.7%) developed ANA positivity during the treatment. The nuclear homogeneous, nuclear fine speckled, and nuclear large/coarse speckled were the most common patterns of ANA [Figures 1-3]. A patient receiving IFX also developed anti-dsDNA positivity. Nevertheless, none of the patients developed any symptoms of drug-induced lupus erythematosus nor any autoimmune disease. The mean duration treatment until the emergence of ANA positivity was 22 ± 11.72 (median: 22, min: 4, max: 39) months. The mean follow-up of the patients was 33.77 ± 28.67 (median: 28, min: 4, max: 117) months. The demographic and clinical characteristics of the patients with ANA-positive and negative test results are shown in Table 1. Nine (45%) out of twenty patients receiving IFX, two (40%) out of five patients receiving ETC, and one (50%) out of two patients receiving ADA developed ANA positivity [Table 2]. Laboratory characteristics of ANA-positive patients are shown in Table 3. ANA conversion was not detected in patients receiving UST.

Table 1: Demographic and clinical characteristics of the patients

	ANA-positive patients	ANA-negative patients
Female [*n* (%)]	8 (47.1%)	9 (52.9%)
Male [*n* (%)]	4 (28.6%)	10 (71.4%)
Mean age	44.08±19.39	48.68±14.64
Psoriatic arthritis [*n* (%)]	5 (41.7%)	7 (58.8%)
Mean duration of disease [month]	22.33±17.70	23.26±14.7
Median duration of ANA positivity [month]	22 (min:4, max:39)	None
Phototheapy history [*n* (%)]	4 (33.3%)	8 (66.7%)
Methotrexate history [*n* (%)]	6 (33.3%)	12 (66.7%)
Concomitant methotrexate use [*n* (%)]	2 (20%)	8 (80%)

Table 2: Duration of treatment and ANA positivity

Duration of treatment (months)	ANA positive patients (*n*=12)			ANA negative patients (*n*=19)
	Infliximab (*n*=9)	Etanercept (*n*=2)	Adalimumab (*n*=1)	
Mean	23.11±10.86	26.0±14.14	4	31.16±29.45
Median [minimum, maximum]	24 [5, 39]	26 [16, 36]	4 [4]	16 [8, 117]

n=number of patients

Table 3: Laboratory characteristics of ANA-positive patients

Drug	Age	Gender	Presence of PsA	Concomitant methotrexate use	Time of emergence of ANA positivity [month]	ANA titre	Features of ANA	Anti-dsDNA positivity
IFX	72	Female	None	-	5	1/100	1 (+) nuclear homogeneous (AC-1) 1 (+) cytoplasmic/dense fine speckled (AC-19)	None
IFX	49	Male	Yes	-	39	1/100	2 (+) nuclear fine speckled (AC-4)	Positive
IFX	34	Female	Yes	-	19	1/100	1 (+) nuclear fine speckled (AC-4) 1 (+) nuclear homogeneous (AC-1)	None
IFX	46	Male	None	-	20	1/100	3 (+) nuclear homogeneous (AC-1)	None
IFX	32	Female	None	+	32	1/100	1 (+) nuclear homogeneous (AC-1) 1 (+) nuclear fine speckled (AC-4)	None
IFX	51	Female	Yes	-	31	1/100	2 (+) nuclear fine speckled (AC-4) 1 (+) nuclear large/coarse speckled (AC-5)	None
IFX	70	Male	No	-	28	1/100	1 (+) nuclear fine speckled (AC-4)	None
IFX	17	Female	None	+	10	1/100	2 (+) nuclear large/coarse speckled (AC-5)	None
IFX	26	Female	None	-	24	1/100	1 (+) nuclear homogenous (AC-1)	None
ETC	34	Female	Yes	-	16	1/100	3 (+) nuclear fine speckled (AC-4) 1 (+) nuclear large/coarse speckled (AC-5)	None
ETC	73	Male	None	-	36	1/100	1 (+) nuclear fine speckled (AC-4)	None
ADA	25	Female	Yes	-	4	1/100	1 (+) nuclear fine speckled (AC-4)	None

IFX: Infliximab, ETC: Etanercept, PsA: Psoriatic arthritis, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA

The duration of ustekinumab use was ranged from 10 to 38 months.

Two (20%) out of ten patients who had concomitant use of MTX with biological agents developed ANA positivity, while ten (47.6%) out of twenty-one psoriatic patients who had use of biological agents alone developed ANA positivity. No statistically significant difference was found between single biological agent use and concomitant MTX use with biological agents in terms of ANA positivity (P = 0.240). Four (33.3%) out of twelve patients who had phototherapy history, and eight (42.1%) out of nineteen patients who had no history of phototherapy developed ANA positivity. No statistically significant difference was found between groups with positive and negative phototherapy history in terms of ANA positivity (P = 0.717).

Discussion

Biological therapy has dramatically changed treatments in dermatology, specifically psoriasis. Ustekinumab and anti-TNF agents including IFX, ETC, and ADA are the most commonly used agents in psoriasis.[9] Ustekinumab is a human IgG1 monoclonal antibody that particularly binds to the p40 protein subunit of interleukin (IL)-12 and IL-23.[10] On the other hand, TNF-α is a 17-kDa protein consisting of 157 amino acids. Its gene is mapped to chromosome 6.[11] Anti-TNF agents have been shown to

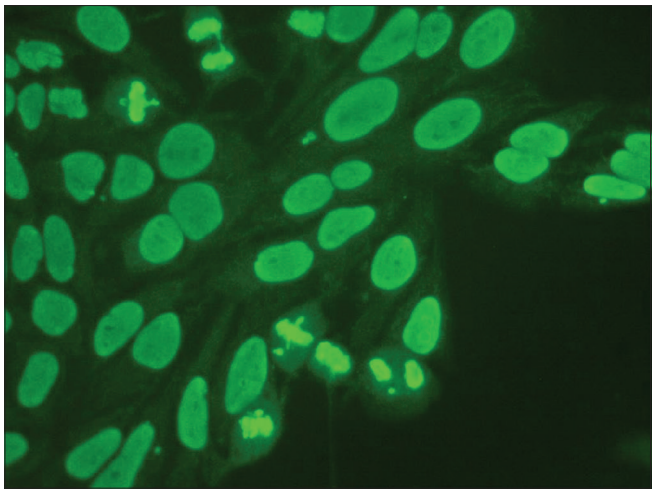

Figure 1: The nuclear homogeneous pattern in ANA positivity

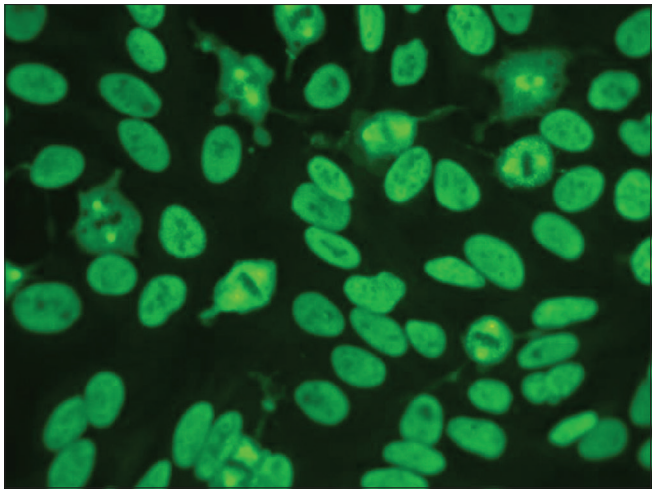

Figure 2: The nuclear large/coarse speckled pattern in ANA positivity

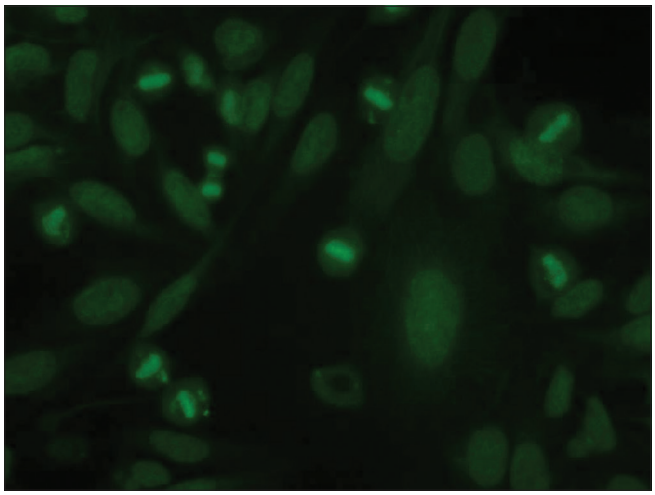

Figure 3: The nuclear fine speckled pattern in ANA positivity

increase humoral autoimmunity by inhibiting cytotoxic T-lymphocyte response that would normally suppress autoreactive B cells.[12,13]

It is considered that systemic inhibition of TNF-α activity may affect apoptosis by decreasing the expression of CD44. It causes decreased removal of cellular waste by phagocytes, including nuclear material accumulating after apoptosis, and therefore leads to the production of autoantibodies against DNA and other nuclear antigens.[5] Although the prevalence of autoantibodies is high with biologics, clinical development of lupus erythematosus is rare.[14,15] An increase in the IgG isotype of anti-dsDNA antibodies has been implicated in the pathogenesis of lupus erythematosus. However, anti-TNF-α induced lupus erythematosus is usually observed reversibly due to IgM type of anti-dsDNA antibodies which have a short half-life.[16] ANA is used as a screening test for the diagnosis of autoimmune diseases.[17] Approximately, 25% of the population has ANA positivity but the prevalence of significantly high levels is roughly 2.5%, which indicates an autoimmune disease.[18,19] In this study, 45% (9/20) of patients receiving IFX and 40% (2/5) of patients receiving ETC developed ANA positivity. The mean duration of treatment until the emergence of ANA positivity was 23.11 ± 10.86 months for patients receiving IFX, and 26.0 ± 14.14 months for patients receiving ETC [Table 2]. A patient with IFX also developed anti-dsDNA positivity. Nevertheless, none of patients developed clinical signs and laboratory findings including ANA, anti-dsDNA for an autoimmune disease or drug-induced lupus with a follow-up period of 2 years after ANA positivity. Although biological agents, specifically TNF-α blockers, are drugs that have recently been reported in the induction of drug-induced lupus, with the findings of this study it can be speculated that biological agents may be reliable in patients with psoriasis in terms of autoimmunity.[14,20,21] However, according to the data compiled by BIOGEAS registry, there were 357 cases of lupus induced by anti-TNF-α therapies (2017 data). Many psoriatic patients were among them but their number was less compared to other autoimmune conditions.[22]

Viana *et al*. performed a prospective study with twenty-three patients with PsA on anti-TNF-α treatment (19 of 23 patients used IFX), detecting autoantibody titers before and at least 5 months after treatment. Four of the ANA-negative patients (33.3%) developed ANA positivity. Ten out of eleven (90.9%) ANA-positive patients remained positive while none of the patients developed anti-dsDNA.[23] Lora *et al*. performed a study with twenty-seven patients with IFX and showed that ANA positivity increased from 22% to 63% over 12 months while anti-dsDNA increased from 7% to 48%.[24] Chimenti *et al*. scanned ANA tests in patients with psoriasis at baseline, week 6, and week 22. They found ANA positivity increased from 21.6% (8) to 32.4% (12) at week 22 compared with baseline. The status of ANA did not change at week 6.[25] Pirowska *et al*. reported that ANA positivity increased in patients with psoriasis and psoriatic arthritis who received biological agents. An increase in the titer or appearance of antibodies was reported in 66.7% in

the IFX group, 18.2% in the ETC group, and 54.7% in the ADA group. In that study, no subjects developed symptoms of drug-induced lupus, as in our study. Only one report of UST-induced subacute cutaneous lupus erythematosus in the literature till now.[13,26] In our study, none of the patients receiving UST developed ANA positivity, although the inadequacy of the number of patients for this group restricted evaluation of autoimmunity. However, four patients receiving UST were followed up for between 10 and 24 months and this follow-up period is sufficient to detect ANA conversion. In addition, it was found that the mean duration of treatment until the emergence of ANA positivity was 23.11 ± 10.86 months in patients receiving IFX, and 26.0 ± 14.14 months in patients receiving ETC.

The nuclear homogeneous (AC-1), nuclear fine speckled (AC-4), and nuclear large/coarse speckled (AC-5) were the most common patterns of ANA in this study. In systemic lupus erythematosus, there is usually a nuclear homogeneous (AC-1) pattern on ANA or less commonly smooth nuclear envelope (AC-11), punctate nucleolar (AC-10) pattern when the disease is active.[27] On the other hand, autoimmune diseases including Sjögren syndrome, scleroderma, mixed connective tissue disease, and rheumatoid arthritis most commonly have a punctate nucleolar (AC-10) ANA pattern.[28] It can be speculated that the presence of a nuclear homogeneous (AC-1) ANA pattern with biological agents suggests that these patients have an increased risk of systemic lupus erythematosus rather than other autoimmune diseases. Although the nuclear homogeneous (AC-1) pattern is more commonly seen in SLE and drug-induced LE, occasionally it can also be seen in association with other conditions such as rheumatoid arthritis and scleroderma.

In the literature, most of the studies evaluating the relationship between autoimmunity and the use of biological agents were carried out with patients with rheumatoid arthritis, ankylosing spondylitis, or Crohn disease.[22] Therefore, the aim of this study was to raise awareness specifically for dermatologists about the risk of autoimmunity in psoriasis patients receiving biological agents. Concomitant immunosuppression may reduce autoantibody formation in patients receiving biological agents, and the withdrawal of anti-TNF-α therapy usually leads to resolution of autoimmunity symptoms.[29] In this study, 83.3% of the patients without concomitant use of MTX developed ANA positivity. On the other hand, 16.7% of the patients with concomitant use of MTX developed ANA positivity. Although it was not statistically significant, the group receiving MTX and biological agents together seemed to have developed less ANA positivity. This result may become significant as the number of patients increases. This finding was compatible with other studies.[30]

There is some controversy about whether all patients should undergo an ANA test before the initiation of ultraviolet radiation treatment.[31] It is suggested that ANA should be repeated at regular intervals. This is probably to follow conversion from negative to positive results and also vice versa, the significance of either change being still unknown.[32] To date, there is no study assessing the relationship between a history of phototherapy and ANA positivity in patients with psoriasis receiving biological agents. In this study, phototherapy history did not have an effect on ANA formation in our study population. However, a small number of cases was the limitation of this study. A large sample is required to evaluate the relationship between phototherapy history and ANA positivity more precisely. In case of a possible positive relationship between phototherapy history and ANA positivity, phototherapy history might become a determinant in the selection of biological agents.

Conclusion

According to this study, among all biological agents, the emergence of ANA positivity during IFX therapy is more common while ANA positivity was not detected with UST. ANA positivity did not cause any signs, symptoms, or laboratory findings of SLE or any other autoimmune disorders in patients who did not have anti-dsDNA positivity; thus, it can be suggested that biological agents are not major risk factors for autoimmunity. Concomitant MTX use and phototherapy history have been shown to have no significant effect on ANA status. Further studies in large groups are needed to evaluate autoimmunity and ANA status in patients receiving biological agents and also to show the effect of concomitant MTX use and phototherapy history on ANA status.

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Conflicts of interest

There are no conflicts of interest.

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