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Original article

Higher body mass index and anti-drug antibodies predict the discontinuation of anti-TNF agents in Korean patients with axial spondyloarthritis

Jiwon Hwang[a], *Hye-Mi Kim*[b], *Hyemin Jeong*[c], *Jaejoon Lee*[c], *Joong Kyong Ahn*[d], *Eun-Mi Koh*[c], *Eun-Suk Kang*[e,*], *Hoon-Suk Cha*[c,*]

[a] *National Police Hospital, Department of Internal Medicine, Seoul, South Korea*
[b] *Samsung Biomedical Research Institute, Seoul, South Korea*
[c] *Sungkyunkwan University School of Medicine, Samsung Medical Center, Department of Medicine, Seoul, South Korea*
[d] *Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Department of Internal Medicine, Seoul, South Korea*
[e] *Sungkyunkwan University School of Medicine, Samsung Medical Center, Department of Laboratory Medicine and Genetics, Seoul, South Korea*

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ABSTRACT

Objective: The development of anti-drug antibodies against tumor necrosis factor inhibitors is a likely explanation for the failure of TNF-inhibitors in patients with spondyloarthritis. Our study determined the existence and clinical implications of ADAbs in axial spondyloarthritis patients.

Methods: According to the Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis, patients treated with adalimumab or infliximab were recruited consecutively. Serum samples were collected at enrollment to measure anti-drug antibodies and drug levels.

Results: Of 100 patients, the mean duration of current TNF inhibitor use was 22.3 ± 17.9 months. Anti-drug antibodies were detected in 5 of 72 adalimumab users compared to 5 of 28 infliximab users (6.9% vs. 17.9%). Anti-drug antibodies-positive patients had a significantly higher body mass index than anti-drug antibodies-negative patients among both adalimumab (28.4 ± 5.9 kg/m^2 vs. 24.3 ± 2.9 kg/m^2, respectively, $p = 0.01$) and infliximab users (25.9 ± 2.8 kg/m^2 vs. 22.6 ± 2.8 kg/m^2, respectively, $p = 0.02$). During the median 15-month follow-up period, drug discontinuation occurred more frequently in the anti-drug antibodies-positive group than the anti-drug antibodies-negative group (30.0% vs. 6.5%, respectively, $p = 0.04$). In logistic regression, anti-drug antibodies positivity (OR = 5.85, 95% CI 1.19–28.61, $p = 0.029$) and body mass index (OR = 4.35, 95% CI 1.01–18.69, $p = 0.048$) were associated with a greater risk of stopping TNF inhibitor treatment.

Conclusions: Our result suggests that the presence of anti-drug antibodies against adalimumab and infliximab as well as a higher body mass index can predict subsequent drug discontinuation in axial spondyloarthritis patients.

* *Corresponding authors.*
E-mails: esk.kang@samsung.com (E. Kang), hoonsuk.cha@samsung.com (H. Cha).

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O maior índice de massa corporal e a presença de anticorpos antifármacos predizem a interrupção no uso de agentes anti-TNF em pacientes sul-coreanos com espondiloartrite axial

Palavras-chave:
Adalimumabe
Anticorpos antifármacos
Espondiloartrite axial
Infliximabe
Inibidores da necrose tumoral

RESUMO

Objetivo: O desenvolvimento de anticorpos antifármacos (ADAb) contra o fator de necrose tumoral (TNF) é uma explicação provável para a falha dos anti-TNF em pacientes com espondiloartrites (EspA). O presente estudo determinou a presença e as implicações clínicas dos ADAb em pacientes com EspA axiais.

Métodos: De acordo com os critérios de classificação para EspA axial da *Assessment of SpondyloArthritis International Society*, recrutaram-se consecutivamente pacientes tratados com adalimumabe ou infliximabe. Coletaram-se amostras de soro no momento da entrada no estudo para medir os níveis de ADAb e de fármaco.

Resultados: Dos 100 pacientes, a duração média de uso dos anti-TNF atuais foi de 22,3 ± 17,9 meses. Os ADAb foram detectados em cinco de 72 pacientes em uso de adalimumabe, em comparação com cinco de 28 usuários de infliximabe (6,9% *vs.* 17,9%). Os pacientes ADAb-positivos tinham um índice de massa corporal maior do que aqueles ADAb-negativos, tanto entre indivíduos em uso de adalimumabe (28,4 ± 5,9 kg/m^2 *vs.* 24,3 ± 2,9 kg/m^2, respectivamente, p = 0,01) quanto de infliximabe (25,9 ± 2,8 kg/m^2 *vs.* 22,6 ± 2,8 kg/m^2 respectivamente, p = 0,02). Durante o período médio de seguimento de 15 meses, a suspensão do fármaco ocorreu com maior frequência no grupo ADAb-positivo do que no grupo ADAb-negativo (30,0% *vs.* 6,5%, respectivamente, p = 0,04). Na regressão logística, a positividade no ADAb (OR = 5,85, IC 95% 1,19 a 28,61, p = 0,029) e o IMC (OR = 4,35, IC 95% 1,01 a 18,69, p = 0,048) esteve associada a um maior risco de interromper o tratamento com anti-TNF.

Conclusões: Os resultados do presente estudo sugerem que a presença de ADAb contra o adalimumabe e o infliximabe, bem como um IMC mais alto, pode predizer a subsequente interrupção do fármaco em pacientes com EspA axial.

Introduction

The advent of tumor necrosis factor (TNF) inhibitors represented a breakthrough in the management of chronic inflammatory diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriasis, and inflammatory bowel disease (IBD). Not only ankylosing spondylitis (AS), but also the non-radiographic form of axial SpA have benefitted from these drugs with response rates of 60–70%.[1–3] Regardless, a considerable proportion of SpA patients fail to respond ab initio (primary failure), or the inhibitors lose their efficacy over time despite an initial good response (secondary failure).[4,5] Some patients may also need to discontinue TNF inhibitor treatment due to significant adverse events.[6]

Recently, immunogenicity has been implicated as a primary cause of response failure, because all biologics, including TNF inhibitors, have immunogenic potential. The development of anti-drug antibodies (ADAbs) leads to low or undetectable drug levels, resulting in the failure or loss of efficacy of the drug and adverse events; this phenomenon has been well documented in patients with RA and Crohn's disease (CD).[7,8] To date, ADAbs have been detected against infliximab (IFX), adalimumab (ADL), and golimumab (GLM) in SpA patients and there are several reports about the associations of these ADAbs with clinical response.[9] In addition to ADAbs, there are other factors that affect the pharmacokinetics of TNF inhibitors, such as concomitant use of disease-modifying antirheumatic drugs (DMARDs), especially methotrexate, the degree of systemic inflammation (e.g., serum albumin, C-reactive protein, and TNF burden), body weight, and gender.[10] Historically, in the meantime, ADAbs against IFX were more often observed in RA patients compared to AS patients. It was thought to be higher doses of IFX used in axial SpA patients.[11] Established combination therapy with biologic agent and immunomodulators has also been described to prevent the development of ADAbs in patients with RA and CD as well.[12,13] With respect to DMARDs, there is no solid evidence to support their use in axial SpA.

Previous studies of ADAbs in SpA patients have focused mostly on the incidence of ADAbs and their effects in western populations. We undertook the present study to investigate whether ADAbs exist in Korean patients with axial SpA and the clinical significance of this. Additionally, we investigated whether factors such as body weight and smoking affected ADAb levels in Korean SpA patients.

Methods

Study design and patients

This study was performed in an ambispective observational manner. From May 2012 to April 2013, a total of 100 axial

SpA patients were recruited consecutively from a single tertiary hospital. Both ADAb and drug levels were measured in 89 AS patients, nine SpA-associated-with-IBD patients, one psoriatic SpA patient, and one undifferentiated axial SpA case. All patients fulfilled the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial SpA.[14] AS patients also satisfied the 1984 modified New York Criteria.[15] At enrollment, they were treated with either ADL or IFX after failing to respond to at least two non-steroid anti-inflammatory drugs (NSAIDs) or other kinds of TNF inhibitors. ADL was administered subcutaneously at 40 mg biweekly. IFX was given intravenously at 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. Dosing intervals for each drug were adjusted according to disease activity and the treating physician's decision. Disease activity was scored by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the difference in score between baseline and the time of sampling or last observation was calculated. Data were reviewed retrospectively via medical records or obtained prospectively to assess the following variables: demographics, laboratory findings including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, BASDAI score, concomitant use of NSAIDs or DMARDs, presence of infections, including latent or reactivated tuberculosis infection, side-effects including infusion reaction or injected site reaction, and the cause for switching or discontinuation of TNF inhibitors. Smoking status was not available in all participants and the accessible numbers were shown in brackets for each item in tables. Latent tuberculosis infection was diagnosed by experienced pulmonologists based on a positive QuantiFERON-TB Gold In-tube test result (Cellestis Limited, Carnegie, Victoria, Australia) and chest radiograph findings. Body mass index (BMI) at enrollment was calculated and patients were divided into three classes according to BMI based on the National Institute of Health classification[16]: BMI < 25 kg/m^2, normal; BMI 25–30 kg/m^2, overweight; BMI > 30 kg/m^2, obese. Patients with a follow-up period of 6 months or greater after sampling were included in post-sampling statistical analyses. Study protocol was approved by the institutional review board of Samsung Medical Center and all participants gave written informed consent.

Measurement of drug and ADAb concentrations

Blood samples were collected at the time of enrollment before the next ADL injection or IFX infusion. Trough serum level of drugs (ADL or IFX) and the amount of ADAbs (anti-ADA or anti-IFX) were measured by enzyme-linked immunosorbent assay (TNFα-Blocker-Monitoring and TNFα-Blocker ADA, Immundiagnostik AG, Bensheim, Germany). We performed ELISA according to the manufacturer's instructions. To determine the quantity of free therapeutic TNF inhibitors, six calibrators were used to generate a standard curve, and positive and negative controls were included on all plates. The lower limit of detection was 0.4 μg/mL. The presence or absence of ADAb was determined using the cut-off control included in the kit, which had a concentration of 10 AU/mL.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 18.0 (SPSS, Chicago, IL, USA). Descriptive data are reported as means, standard deviations (SD), or percentages. Differences between groups were tested with Student's *t*-test, Pearson's chi-square test, or the Mann–Whitney *U* test as appropriate. Odds ratios (OR) were calculated by logistic regression to determine factors predictive of drug discontinuation. Last observational carried forward (LOCF) analysis was performed during the follow-up. When patients were categorized into four groups according to their drug levels and presence of ADAbs, the cut-off of adequate drug levels was set to 5 μg/mL for ADL and 0.8 μg/mL for IFX based on the suggested levels of adequacy in IBD patients.[17,18] Threshold for significance was set to $p < 0.05$.

Results

Patient characteristics

Mean age of the patients was 34.8 ± 10.1 years and mean disease duration from symptom onset was 11.1 ± 7.8 years. Demographic data and baseline characteristics of ADL users and IFX users are compared in Table 1. ADL was prescribed mostly in patients with AS (95.8%), while IFX was prescribed to 25% of patients with SpA-associated IBD. Concomitant DMARD use was more frequent with IFX than ADL ($p = 0.015$). History of ever-smoking was more frequently observed in ADL users than non-ADL users ($p = 0.02$, $n = 75$). Other clinical characteristics were comparable between ADL users and IFX users. Eighty-two patients were first-time users of TNF-inhibitors (anti-TNF naïve). Among 18 switchers previously treated with other kinds of TNF-inhibitors, the most commonly used agent was ETN ($n = 12$), followed by IFX ($n = 3$) and ADL ($n = 1$). Other two switchers had been prescribed two agents previously. Secondary failure was the major reason for switching (83.3%). Compared with switchers, first-time users had dosing intervals significantly extended relative to the scheduling suggested by the manufacturer (1.27 times vs. 1.64 times; equivalent to 2.54 weeks vs. 3.28 weeks, respectively, $p = 0.02$).

Anti-drug antibodies against current TNF-inhibitors

At the time of sampling, mean duration of use of current TNF inhibitors was 22.3 ± 17.9 months. Five of 74 ADL users (6.9%) had detectable ADAbs, while five of 28 IFX users (17.9%) had detectable ADAbs; this difference was not statistically significant ($p = 0.13$). Immunogenicity and clinical variables are shown in Tables 2 and 3. Baseline ESR, CRP level, and BASDAI were significantly different between ADAb-negative and ADAb-positive groups, as was the improvement in BASDAI from baseline in ADL and IFX users. Mean BMI of patients with ADAbs was significantly higher than that of ADAb-negative patients; among ADL users, 28.4 ± 5.9 kg/m^2 vs. 24.3 ± 2.9 kg/m^2, respectively, $p = 0.01$; among IFX users, 25.9 ± 2.8 kg/m^2 vs. 22.6 ± 2.8 kg/m^2,

Table 1 – Patient demographics and baseline clinical characteristics (N = 100).

Variables	Adalimumab (*n* = 72)	Infliximab (*n* = 28)	*p*-Value
Age at sampling, yrs (mean ± SD)	34.9 ± 9.6	34.8 ± 11.7	0.97
Male (%)	91.7	23 (82.1)	0.28
BMI, kg/m² (mean ± SD)	24.5 ± 3.33	23.2 ± 3.10	0.07
Normal (%)	63.9	67.9	
Overweight (%)	30.6	32.1	
Obese (%)	5.6	0	
Ever smoker[a] (%)	68.5 (*n* = 54)	38.1 (*n* = 21)	0.02
Disease duration, yrs (mean ± SD)	11.8 ± 7.7	9.5 ± 8.0	0.17
HLA-B27 positive (%)	87.5 (*n* = 56)	84.2 (*n* = 19)	0.71
History of peripheral arthritis (%)	70.8	22 (78.6)	0.43
History of enthesitis (%)	29.2	6 (21.4)	0.43
History of uveitis (%)	29.2	5 (17.9)	0.25
Radiographic SI joint involvement (%)	88.9	27 (96.4)	0.44
Diagnosis of axial SpA			0.001
AS (%)	95.8	71.4	
SpA-associated IBD (%)	2.8	25.0	
Psoriatic SpA (%)	1.4	0	
Undifferentiated axial SpA (%)	0	3.6	
Concomitant DMARDs[b]			0.015
Sulfasalazine (%)	1.4	10.7	
Methotrexate (%)	2.8	3.6	
Other immunosuppressant (%)	0	10.7	
Concomitant NSAIDs[c] *(%)*	52.8	42.9	0.37
Baseline ESR,[d] *mm/h (mean ± SD)*	42.8 ± 32.6	54.4 ± 38.3	0.14
Baseline CRP,[d] *mg/dL (mean ± SD)*	2.17 ± 2.30	3.08 ± 3.20	0.13
Baseline BASDAI[d] *(mean ± SD)*	9.34 ± 1.36	8.92 ± 2.11	0.25
Switcher from other kinds of TNF-inhibitors (%)	20.8	10.7	0.24
LTBI positive (%)	23.6	17.9	0.53

BMI, body mass index; SI, sacroiliac; SpA, spondyloarthritis; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroid anti-inflammatory drugs; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; LTBI, latent tuberculosis infection.

[a] Ever-smoker percentage was calculated on the basis of the number in brackets, of which patients were available for smoking status.

[b] Concomitant DMARDs meant the use at initiation of current TNF-inhibitors for at least 3 months.

[c] Concomitant NSAIDs were used on demand, not on a regular basis.

[d] Values are baseline values of current TNF inhibitors.

Table 2 – Adalimumab immunogenicity and clinical variables at the time of sampling (N = 72).

Variables	ADAb(−) (*n* = 67)	ADAb(+) (*n* = 5)	*p*-Value
Male (%)	61 (91.0)	5 (100)	1.00
Disease duration, yrs (mean ± SD)	12.0 ± 7.7	10.2 ± 8.0	0.62
Baseline ESR, mm/h (mean ± SD)	41.5 ± 30.5	60.0 ± 55.0	0.21
Baseline CRP, mg/dL (mean ± SD)	2.07 ± 2.18	3.40 ± 3.72	0.22
Baseline BASDAI (mean ± SD)	9.29 ± 1.40	9.96 ± 0.06	0.29
ΔBASDAI[a] *(mean ± SD)*	7.26 ± 2.24	7.12 ± 3.96	0.89
BMI, kg/m² (mean ± SD)	24.3 ± 2.9	28.4 ± 5.9	0.01
Ever smoker[b] *(%)*	68.0 (*n* = 50)	75.0 (*n* = 4)	1.00
Serum albumin, g/dL (mean ± SD)	4.50 ± 0.33	4.38 ± 0.27	0.45
Concomitant DMARDs (%)	10.5	20.0	0.45
Switcher from other kinds of TNF-inhibitors (%)	22.4	0	0.57
Duration of current TNF inhibitor use, months (mean ± SD)	23.6 ± 19.1	16.4 ± 12.0	0.26
Dosing interval[c] *(mean ± SD)*			0.19
n × times	1.7 ± 0.9	3.1 ± 2.0	
Corresponding period (weeks)	3.4 ± 1.8	6.2 ± 4.0	
Drug level, μg/mL (mean ± SD)	5.64 ± 4.12	0.45 ± 0.68	<0.001

ADAb, anti-drug antibodies; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs.

Cut-off for ADAb positivity was 10 AU/mL.

[a] Difference in BASDAI between baseline and time of sampling.

[b] Ever-smoker percentage was calculated on the basis of the number in brackets, of which patients were available for smoking status.

[c] Concomitant.

Table 3 – Infliximab immunogenicity and clinical variables at the time of sampling (N = 28).

Variables	ADAb(−) (*n* = 23)	ADAb(+) (*n* = 5)	*p*-Value
Male (%)	78.3	100	0.55
Disease duration, yrs (mean ± SD)	8.3 ± 7.1	14.4 ± 10.5	0.13
Baseline ESR, mm/h (mean ± SD)	57.4 ± 39.9	41.8 ± 30.9	0.42
Baseline CRP, mg/dL (mean ± SD)	2.96 ± 3.02	3.56 ± 4.23	0.71
Baseline BASDAI (mean ± SD)	8.78 ± 2.27	9.62 ± 0.29	0.47
ΔBASDAI[a] (mean ± SD)	7.68 ± 2.20	6.64 ± 4.67	0.68
BMI, kg/m^2 (mean ± SD)	22.6 ± 2.8	25.9 ± 2.8	0.02
Ever smoker[b] (%)	23.5 (*n* = 17)	100.0 (*n* = 4)	0.01
Serum albumin, g/dL (mean ± SD)	4.58 ± 0.34	4.58 ± 0.24	0.99
Concomitant DMARDs (%)	34.7	20.0	1.00
Switcher from other kinds of TNF-inhibitors (%)	13.0	0	1.00
Duration of current TNF inhibitor use, months (mean ± SD)	18.7 ± 16.2	27.8 ± 9.9	0.24
Dosing interval,[c] *n* × times (mean ± SD)	1.0	1.0	u.a.
Drug level, μg/mL (mean ± SD)	4.25 ± 3.29	1.65 ± 1.57	0.10

ADAb, anti-drug antibodies; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs; u.a., unavailable.
Cut-off for ADAb positivity was 10 AU/mL.
[a] Difference in BASDAI between baseline and time of sampling.
[b] Ever-smoker percentage was calculated on the basis of the number in brackets, of which patients were available for smoking status.
[c] Concomitant.

respectively, $p = 0.02$. Among IFX users, current and ex-smokers were overrepresented in the ADAb-positive group relative to the ADAb-negative group (100.0% vs. 23.5%, respectively, $p = 0.01$), whereas there was no difference in the proportions of current and ex-smokers between ADAb-positive and ADAb-negative ADL users (75.0% vs. 68.0%, respectively, $p = 1.00$). No switchers had ADAbs against their current TNF-inhibitors. In ADL users, the dosing intervals tended to be prolonged in the ADAb-positive group (3.1 ± 2.0 times vs. 1.7 ± 0.9 times; equivalent to 6.2 ± 4.0 weeks vs. 3.4 ± 1.8 weeks, $p = 0.19$), whereas it was not adjusted in IFX users. Drug level of ADL was significantly lower in ADAb-positive patients than ADAb-negative patients (0.45 ± 0.68 μg/mL vs. 5.64 ± 4.12 μg/mL, respectively, $p < 0.001$). In IFX users, the ADAb-positive group tended to have a lower drug level than the ADAb-negative group but without statistical significance (1.65 ± 1.57 μg/mL vs. 4.25 ± 3.29 μg/mL, respectively, $p = 0.10$). Concomitant use of DMARDs was not different between ADAb-negative and ADAb-positive ADL or IFX users. BMI ≥ 25 kg/m^2 was the only risk factor associated with ADAb presence [OR = 9.33 (95% confidence interval (CI) 1.85–46.86), $p = 0.007$]; inversely, normal weight protected from the presence of ADAbs [OR = 0.10 (95% CI 0.02–0.52), $p = 0.006$]. No other variables showed a correlation with ADAb positivity, including concomitant DMARDs.

Associations among discontinuation of treatment, adverse events, and ADAb status

Follow-up data for 98 patients who had been observed for at least 6 months or more (71 ADL patients and 27 IFX patients) were analyzed. One patient was lost to follow-up at 1 month (one IFX user) and another at 4 months (one ADL user) and were therefore excluded from the post-sampling analysis. Two female patients stopped taking TNF inhibitors because of pregnancy (one IFX user at 7 months and one ADL user at 14 months and) and their missing values were replaced by the LOCF method.

Median follow-up duration was similar between the two groups (15.0 months in the ADAb-negative group vs. 13.5 months in the ADAb-positive group, $p = 0.15$). Regardless of the type of current TNF inhibitor, discontinuation of treatment occurred more frequently in the ADAb-positive group than the ADAb-negative group (30.0% vs. 6.5% respectively, $p = 0.04$). Of the patients who discontinued ADL during follow-up, drug levels was significantly lower at the time of sampling compared to baseline than that of patients who maintained ADL during follow-up (2.18 ± 1.49 μg/mL vs. 5.55 ± 4.26 μg/mL, respectively, $p = 0.04$). For IFX users, there was no significant difference in drug level at baseline and follow-up between those patients who discontinued treatment and those who did not (1.79 ± 2.06 μg/mL vs. 3.95 ± 3.22 μg/mL, respectively, $p = 0.21$). Reasons for discontinuing TNF inhibitor use between groups were so variable that statistical analysis was not possible. There were several adverse events during follow-up, but none of these required discontinuation of treatment (Table 4).

Irrespective of the type of TNF inhibitor, patients could be divided into four categories based on drug level and the presence of ADAbs: 53 (54.1%) patients had an adequate drug level and no ADAbs (group 1); 35 (35.7%) patients had a low drug level and no ADAbs (group 2); three (3.1%) patients had an adequate drug level and detectable ADAbs (group 3); seven (7.1%) patients had an undetectable drug level and were ADAb positive (group 4). In the 71 ADL patients who were followed-up, four patients in group 2 and one patient in group 4 discontinued taking drugs, while among the 27 IFX patients who were followed-up, two patients in group 1 and two patients in group 4 discontinued drug use.

In univariate logistic regression analysis, predictors of subsequent drug discontinuation were the presence of ADAbs [OR = 5.85 (95% CI 1.19–28.61), $p = 0.029$] and a BMI ≥ 25 kg/m^2 [OR = 4.35 (95% CI 1.01–18.69), $p = 0.048$]. Multivariate logistic regression analysis was not performed due to the lack of

Table 4 – Clinical response during the follow-up period of patients with ADAbs and those without ADAbs (N = 98).

	ADAb(−) (*n* = 88)	ADAb(+) (*n* = 10)	*p*-Value
Follow-up duration, months median (range)	15.0 (6–17)	13.5 (6–17)	0.15[a]
Discontinuation of current TNF-inhibitors (%)	6.8	30.0	0.04
Adverse events			
Abnormal LFT (%)	1.1	0	1.00
Injection/infusion site reaction (%)	3.4	10.0	0.35
New-onset psoriasis or dermatitis (%)	10.2	0	0.59
TB reactivation (%)	0	0	u.a.

Table shows the results of 98 patients whose data were available during follow-up.
ADAbs, anti-drug antibodies; LFT, liver function tests; TB, tuberculosis; u.a., unavailable.
[a] Mann–Whitney.

significant variables from univariate analysis. ADAb positivity had no impact on adverse events.

Discussion

Our goals in this study were assess the presence of ADAbs against ADL and IFX in Korean axial SpA patients, to determine the clinical importance of this, and to investigate factors associated with the development of ADAbs. We detected ADAbs in patients receiving either ADL or IFX treatment, and these ADAb-positive patients were at risk of subsequent drug discontinuation. A higher BMI was also related to a higher risk of ADAb positivity, and predicted subsequent drug discontinuation.

Detectable ADAbs to ADL and IFX have previously been reported to decrease treatment response.[19] These ADAbs may reduce drug levels in several ways. First, ADAbs may neutralize therapeutic drugs by blocking binding sites for TNFs. Another possibility is that ADAbs may form immune complexes with therapeutic drugs, enhancing drug clearance.[10] IFX as a chimeric monoclonal antibody is considered to have more immunogenic potential than ADL, and ADAbs against IFX were investigated as human anti-chimeric antibodies (HACAs). HACAs reduce or shorten IFX efficacy in patients with RA and CD.[7,8] Recently, the epitope of IFX immunogenic to the paratope of HACA was localized to $F(ab')_2$.[20] In contrast, ADL is a humanized monoclonal antibody that was engineered to have good in vivo tolerability and weakened immunogenicity. Unfortunately, however, ADAbs have also been found in ADL-treated patients, and these ADAbs have been shown to hamper the clinical response to ADL, as was observed in IFX-treated patients.[21] Immune response against ADL has been suggested to be highly restricted to the idiotype, resulting in anti-idiotypic antibodies that functionally neutralize ADL, despite the existence of small immune complexes.[10] In our study, among nine patients who discontinued drugs during follow-up, seven had low drug levels, including four patients without detectable ADAbs. The other two patients belonged to group 1 of IFX, indicating adequate drug levels and no ADAbs at sampling. Of these two patients, one had a slightly lower drug level (2.49 μg/mL) than the mean in ADAb negative patients (4.25 μg/mL), but this level was somewhat higher than the mean of ADAb-positive patients (1.65 μg/mL). The second patient had sufficient drug levels (4.40 μg/mL) but developed pleural effusion resembling serositis at the 13 month of follow-up. This patient received a thorough work-up for etiology, including thoracentesis, and based on this, we concluded that pleural effusion was a lupus-like manifestation based on the high titer of positive anti-nuclear antibodies and anti-double strand DNA antibodies. Autoimmune-like diseases such as psoriasis and systemic lupus erythematosus (SLE) are documented adverse events of TNF-inhibitors, and ADAbs may underlie these adverse events. Despite undetectable ADAbs at certain time points, long-lasting small immune complexes may induce type III hypersensitivity reactions such as serum sickness and SLE.[10]

Detection rate of ADAb was 6.9% in ADL-receiving axial SpA patients and 17.9% in IFX-receiving axial SpA patients. ADAb incidence in the literature ranges from 18 to 31% in response to ADL treatment and 15.4 to 29% in response to IFX treatment of patients with AS and psoriatic arthritis.[9] Incidence of ADAb was therefore relatively low in our study. Several factors may have contributed to this discrepancy. One factor is diverse detection methods. ELISA and radioimmunoassay (RIA) are the two major methods used to detect ADAbs, but although ELISA is more broadly used, it is less specific than RIA, which might contribute to our relatively low detection rate. Furthermore, different ELISA kits have variations in the amount of serum or plasma used, incubation conditions, and type of molecule conjugated to the detection antibody. Recommended cut-off and measurement strategies (e.g., qualitative vs. quantitative) also vary widely among kits. Disparate measurement time-points, such as the timing between the assay and last injection of TNF inhibitor, and the timing of sampling of longitudinal use of TNF-inhibitors, could also affect the results. Drug concentration of the sample between injections may also vary, which would affect the sensitivity of the assay.[9] Considering that some patients with transient ADAbs develop tolerance to the drugs and ADAbs detected at later time points are related to a decrease in drug level,[22] detection rates of 6.9% and 17.9% for ADL and IFX ADAbs are reasonable for a mean sampling time of 22.3 ± 17.9 months of using TNF inhibitors. Dissimilar study populations could also have contributed to the lower incidence of ADAbs detected in our study. There are striking variations in the distribution of immunoglobulin GM and KM allotypes among different ethnic groups. Associations between certain types of allotypes and antibody responses can

yield differential immunity to infectious diseases.[23] For example, individuals with the G1m3 phenotype were shown to have ADL ADAbs less often than those with the G1m1, 17-allotype.[24] The types of immunoglobulin GM and KM allotypes present in the Korean population could have affected our results, but this was beyond the scope of our study.

Among 100 axial SpA patients, concomitant DMARDs were used in only 10 patients. Because our practice complies with the recommendations for the management of axial disease, most patients were treated with TNF inhibitors and/or NSAIDs unless they had other requirements.[25] DMARDs were more often prescribed together with IFX than ADL. This is likely because more patients with SpA-associated IBD were treated with IFX than ADL and these patients required mesalazine, sulfasalazine, or azathioprine. During the post-sampling period, concomitant DMARDs were stopped in half of the patients while they were maintained in the other 50% of patients because of IBD and peripheral arthritis. Nevertheless, logistic regression revealed that the use of DMARDs was not associated with ADAb positivity, although larger sample sizes are required to test this hypothesis in a rigorous statistical manner.

Unlike IFX users who had fixed, regular dosing intervals, ADL users had variable dosing intervals. Compared to patients without ADAbs to ADL, ADAb-positive patients had significantly prolonged dosing intervals. Scheduled IFX treatment strategies are known to be less immunogenic than variable IFX treatment strategies,[26] but this has not been investigated for ADL. It is also not clear whether a scheduled regimen helps diminish immunogenicity or whether labile dosing intervals are directly related to eventual treatment failure.

Intriguingly, ADAb-positive patients were significantly overweight or obese compared to ADAb-negative patients in both ADL and IFX groups. BMI was the only variable that increased the risk of ADAb development or protected against it in logistic regression analysis. Obesity is a strong determinant of inflammation in the general population.[27] In recent studies, BMI has been shown to strongly influence the response to TNF inhibitors in RA and SpA patients; a higher BMI is associated with a decreased chance of achieving remission.[28,29] In particular, response to IFX was reduced to a greater extent than that to ADL or ETN in obese axial SpA patients, but the reason for this has not been elucidated.[29] Adipose tissue can modulate the inflammatory response by producing several inflammatory cytokines, including TNF-α, and expressing Fc receptors.[30] Decreased efficacy of TNF inhibitors in obese patients could be caused by interactions between Fc receptors expressed on adipocytes and the Fc portion of drugs as ligands. While TNF inhibitors could potentially interact with Fc receptors on adipocytes, variable regions of the drugs, such as the Fab′ or $F(ab')_2$ fragments, may be exposed, thereby serving an immunogenic function. In our study, BMI was not significantly related to ADAb positivity when patients were stratified based on the type of TNF inhibitor they used. This may be due to the small numbers of patients evaluated in this study; these results need to be confirmed in a larger cohort of patients.

Another notable finding was that among ADL users, a history of smoking was more frequent in ADAb-positive patients than ADAb-negative patients. This indicates that smoking may be a risk factor for ADAb development in patients treated with TNF inhibitors. Smoking has also been shown to be associated with RA pathogenesis and disease activity.[31] Recent studies showed that smoking was a negative prognostic factor for response to both MTX and TNF inhibitors in RA.[32,33] A possible mechanism linking smoking to a poor TNF inhibitor response may be significantly higher serum soluble IL-2 receptor (sIL-2R) levels in smokers.[34] Meanwhile, human leptin has been reported to enhance proliferation and activation of circulating T lymphocytes in a dose-dependent manner by stimulating the synthesis of IL-2. In light of this, increased leptin levels in obese patients could activate circulating T cells via IL-2, resulting in a decreased response to TNF inhibitors.[35] Smoking and obesity might have a synergistic effect on a poor response to TNF inhibitors; however, the underlying mechanisms still have to be determined.

This study had several limitations. First, the sample size was small and missing data were present. Second, ADAb and drug levels were assayed only once in a cross-sectional manner, not in a serial manner, preventing more comprehensive deductions about the relationship between drug responses, side effects, and ADAb status. There are still arguments about the utility of ADAb and drug level measurement in clinical practice for decision-making purposes. Lastly, it requires a more cautious approach to generalizing our data to other populations or races due to the genetic differences. Nevertheless, we concluded that the development of ADAbs to ADL and IFX could be associated with a reduction in serum levels of ADL and IFX, leading to subsequent discontinuation of treatment, and that overweight and obese patients may be more prone than their counterparts to develop immunogenicity to TNF inhibitors. These data need to be confirmed in a larger cohort of axial SpA patients in a long-term prospective study. The underlying mechanisms by which obesity and smoking contribute to the immunogenicity of TNF inhibitors in axial SpA patients also require elucidation.

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Conflicts of interest

The authors declare no conflicts of interest.

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