J Rheum Dis 2025;32(2):136-144
https://doi.org/10.4078/jrd.2024.0114
pISSN: 2093-940X, eISSN: 2233-4718

Original Article

Factors associated with anti-drug antibody production in ankylosing spondylitis patients treated with the infliximab biosimilar CT-P13

Yongbum Kim, M.D.[1,2], Nayeon Choi, M.S.[3], Ji-Hui Shin, M.S.[1], Sungsin Jo, Ph.D.[4], Bora Nam, M.D., Ph.D.[1,2], Tae-Hwan Kim, M.D., Ph.D.[1,2]

[1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, [2]Hanyang University Institute for Rheumatology Research, [3]Biostatistical Consulting and Research Lab, Medical Research Collaborating Center, Hanyang University, Seoul, [4]Department of Biology, College of Natural Sciences, Soonchunhyang University, Asan, Korea

Objective: CT-P13, a biosimilar of infliximab, is widely used for treating ankylosing spondylitis (AS). However, the formation of anti-drug antibodies (ADAs) can reduce its efficacy. This study aimed to identify risk factors associated with high ADA levels in AS patients treated with CT-P13.

Methods: A prospective observational study enrolled patients with intravenous CT-P13. Clinical data and disease activity was assessed at baseline, 24 weeks, and 54 weeks after CT-P13 treatment. Blood concentrations of CT-P13 and ADAs were measured at 24 and 54 weeks, and their correlation was investigated. Patients were grouped by ADA levels at 54 weeks. Univariable and multivariable logistic regression identified factors associated with high ADA concentrations.

Results: A total of 34 patients was enrolled. Significant decreases in Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index scores were observed relative to baseline after 24 weeks of CT-P13 therapy. Serum concentrations of CT-P13 and ADA levels increased following treatment. The median serum CT-P13 concentration was 17.6 [12.8, 22.7] μg/mL at 24 weeks and 23.5 [11.7, 34.2] μg/mL at 54 weeks. ADA levels were 6.7 [6.5, 9.1] AU/mL at 24 weeks and 11.4 [9.0, 28.4] AU/mL at 54 weeks. The serum concentrations of CT-P13 and ADA exhibited a negative correlation. In multivariable analysis, current smoking was associated with high ADA production at 54 weeks.

Conclusion: Smoking is identified as a significant risk factor for elevated ADAs in AS patients treated with CT-P13. The findings underscore the importance of smoking-cessation strategies in the management of AS patients.

Keywords: Ankylosing spondylitis, Anti-drug antibody, CT-P13, Infliximab biosimilar, Smoking

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the spine and sacroiliac joints, leading to pain and stiffness. Initial treatment for AS often involves nonsteroidal anti-inflammatory drugs (NSAIDs), which are used to manage symptoms and reduce inflammation. When NSAIDs are not sufficient to control the disease, biologic agents, particu-

Received October 11, 2024; **Revised** November 25, 2024; **Accepted** December 9, 2024, **Published online** January 16, 2025

Corresponding author: Bora Nam, https://orcid.org/0000-0003-0215-3855
Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. **E-mail:** 2210205@hyumc.com
Tae-Hwan Kim, https://orcid.org/0000-0002-3542-2276
Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. **E-mail:** thkim@hanyang.ac.kr

larly tumor necrosis factor (TNF) inhibitors, are recommended. These biologics have shown significant efficacy in controlling disease activity and preventing structural damage in AS patients [1-4].

Despite their effectiveness, the high cost of biologics has been a major limitation preventing their widespread use. The introduction of biosimilars has resulted in availability of more cost-effective alternatives without compromising efficacy or safety. Biosimilars are biologic medical products highly similar to already approved reference products, with no significant differences in terms of safety, purity, and potency [5-7]. CT-P13, a biosimilar of infliximab, has been approved for the treatment of AS and other inflammatory conditions, offering a more affordable treatment option while maintaining similar therapeutic effects [3,5].

As the use of biologics has increased and the introduction of biosimilars has broadened the range of available biologic agents, the importance of monitoring anti-drug antibodies (ADAs) has increased. ADAs are antibodies that the body produces against biologic agents, potentially neutralizing their effects and reducing their clinical efficacy. The presence of ADAs is associated with a decreased therapeutic response, increased drug clearance, and a greater incidence of adverse reactions [5,8]. Understanding the factors influencing ADA formation is crucial for optimizing treatment outcomes [3,8,9].

Several studies have investigated ADA levels in AS patients treated with CT-P13, revealing various risk factors associated with increased ADA production, such as previous use of biologics, dosage, and patient-specific factors like genetics and concurrent medications. However, specific data on Korean patients with AS are lacking [5,8,9]. Therefore, this study aims to identify the risk factors associated with high ADA levels in Korean AS patients treated with CT-P13, addressing a significant gap in the current understanding of ADA formation in this population.

MATERIALS AND METHODS

Study population

This was a single-center, prospective observational study conducted at the Department of Rheumatology, Hanyang University Hospital, Seoul, Korea. All patients met the diagnostic criteria for AS defined by the 1984 modified New York criteria [10]. AS patients >18 years of age who received intravenous CT-P13 therapy were included in this study. Patients with a history of prior anti-TNF use were excluded. This study was approved by Institutional Review Board of Hanyang University Seoul Hospital (IRB no. HYUH 2018-04-036). Written informed consent was obtained from each participant prior to their inclusion in the study.

As mentioned, all eligible patients met the diagnostic criteria for AS according to the 1984 modified New York criteria; these include the presence of low back pain for ≥3 months that improves with exercise but is not relieved by rest, limitations in lumbar spine motion in both the sagittal and frontal planes, and the limitation of chest expansion relative to normal values corrected for age and sex. Radiographic criterion requires the presence of sacroiliitis grade ≥2 bilaterally or grade 3~4 unilaterally [10].

Measurement of CT-P13 concentration and anti-drug antibody levels

All blood samples were collected in ethylenediaminetetraacetic acid tubes and allowed to clot for 2~4 hours at 4°C. Then, each tube was centrifuged for 15 minutes at approximately 3,000 rpm. All serum samples were immediately aliquoted into a 1-mL tube and maintained at −80°C before the assay was performed. Serum levels of CT-P13 and ADAs were evaluated using an enzyme-linked immunosorbent assay kit (ADA Quantitative ELISA Kit [HUMB00007; Assay Genie, Dublin, Ireland]), following the manufacturer's instructions (cut off of detection for ADA=10 AU/mL) [11,12]. The detailed protocol was previously described [8,13].

Data collection

Clinical data of enrolled patients was assessed, including age, sex, height, weight, body mass index (BMI), smoking, CT-P13 treatment dose, CT-P13 dose per weight, extra-articular symptoms, and uveitis. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, Bath Ankylosing Spondylitis Functional Index (BASFI) score, and C-reactive protein (CRP) level at baseline and 24 and 54 weeks after CT-P13 treatment. Assessments of the blood concentrations of CT-P13 and ADAs were conducted at 24 and 54 weeks with each concentration measured twice at each time point. The median value of these two measurements was used for analysis.

Statistical analysis

Clinical variables are presented as median with interquartile values for continuous variables and as frequencies with percentages for categorical variables. Patients were categorized at 54 weeks based on the ADA levels in high and low ADA groups. Differences in clinical characteristics between groups were compared using the Wilcoxon rank-sum test or Fisher's exact test. To identify factors associated with high ADA concentrations at 54 weeks, univariable and multivariable logistic regression analyses were conducted. In the multivariable logistic regression model, a stepwise variable selection method was employed to determine significant predictors of elevated ADA levels at 54 weeks. To assess the monotonic relationship between variables, Spearman's correlation coefficient was calculated. Data analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was achieved at $p<0.05$.

Table 1. Baseline characteristics of total patients (n=34)

Variable	Value
Age (yr)	32.0 [28.0, 44.0]
Sex (male)	26 (76.5)
Height (cm) (n=32)	172.2 [164.2, 175.9]
Weight (kg) (n=32)	70.1 [61.8, 85.3]
BMI (kg/m^2) (n=32)	23.8 [21.8, 27.6]
Smoking (n=33)	
Never smoker/ex-smoker	19 (57.6)
Current smoker	14 (42.4)
BASDAI (n=33)	6.7 [6.2, 7.9]
BASFI (n=33)	3.6 [1.9, 6.1]
CRP (mg/dL) (n=25)	1.6 [0.9, 3.9]
CT-P13 dose (mg)	
200, 300	25 (73.5)
400	9 (26.5)
CT-P13 dose/weight (n=32)	4.3 [4.0, 4.7]
Extra-articular symptoms	11 (32.4)

Values are presented as median [interquartile range; Q1, Q3] or number (%). BMI: body mass index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-reactive protein.

RESULTS

Demographics and clinical characteristics of enrolled patients

A total of 34 patients was enrolled, and their baseline characteristics are described in Table 1. Among them, eight participants were lost to follow-up at 24 weeks and an additional four participants were lost to follow-up at 54 weeks. Consequently, 22 patients were evaluated at 54 weeks. A summary of the study design is given in Figure 1.

Enrolled patients showed a male predominance (76.5%) with a median age of 32.0 [28.0, 44.0] years, and 42.4% were current smokers. At baseline, the median BASDAI and BASFI scores were 6.7 [6.2, 7.9] and 3.6 [1.9, 6.1] points, respectively, and the median CRP level at baseline was 1.6 [0.9, 3.9] mg/dL.

Effects of CT-P13 therapy on disease activity and ADA level

Disease activity as assessed by BASDAI and BASFI was significantly decreased after 24 weeks of CT-P13 therapy, with BASDAI scores dropping from 6.7 [6.2, 7.9] points at baseline to 2.1 [1.4, 3.3] points at 24 weeks and BASFI scores dropping from 3.6 [1.9, 6.1] points at baseline to 1.1 [0.1, 2.3] points at 24 weeks. Serum concentrations of CT-P13 and ADA levels increased following treatment; the median serum CT-P13 concentration was 17.6 [12.8, 22.7] μg/mL at 24 weeks and 23.5 [11.7, 34.2] μg/mL at 54 weeks, while the ADA level was 6.7 [6.5, 9.1] AU/mL at 24

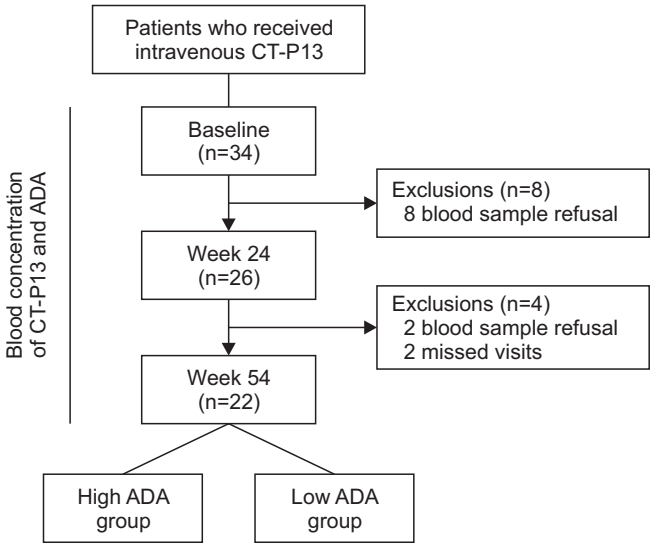

Figure 1. Flow diagram of study design. ADA: anti-drug antibody.

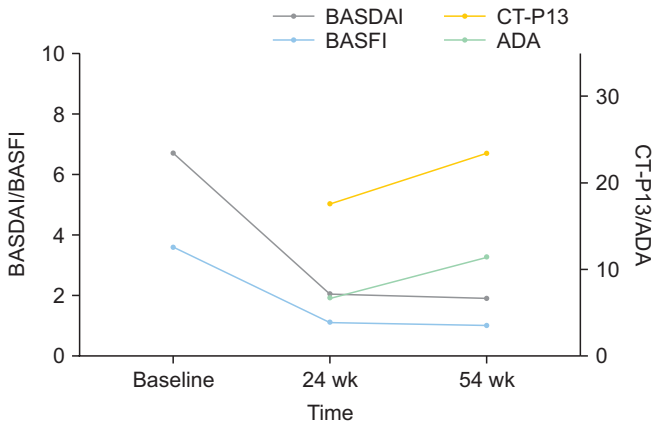

Figure 2. Changes in disease activity, blood concentration of CT-P13, and ADA level. Disease activity was evaluated using BASDAI and BASFI. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ADA: anti-drug antibody.

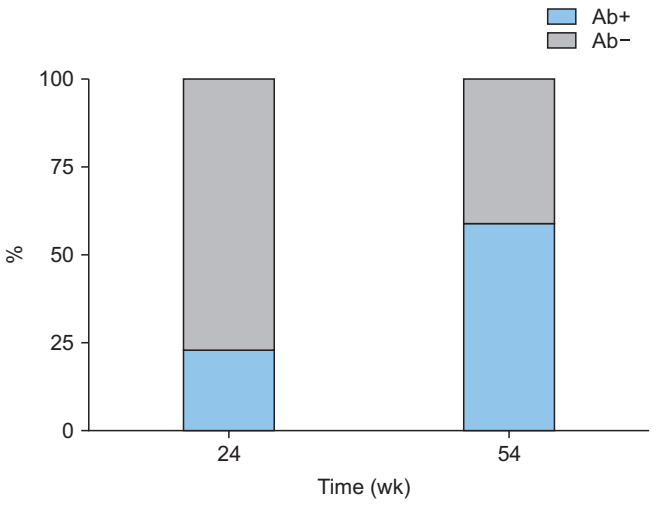

Figure 3. Percentages of patients with ADA concentrations >10 AU/mL at 24 and 54 weeks. An antibody concentration >10 AU/mL signaled Ab+ status, while that <10 AU/mL signaled Ab− status. Ab+: antibody positive, Ab−: antibody negative.

weeks and 11.4 [9.0, 28.4] AU/mL at 54 weeks (Figure 2). Over time, the proportion of patients who were Ab+ (antibody positive, ADA level >10 AU/mL) increased from 23.1% (6/26 patients) at 24 weeks to 59.1% (13/22 patients) at 54 weeks (Figure 3).

Factors associated with high ADA concentration

The high and low ADA groups at 54 weeks were compared (Table 2). The median ADA serum concentration was significantly greater in the high ADA group compared to that in the low ADA group (28.4 [17.3, 44.6] AU/mL vs. 9.0 [8.7, 9.9] AU/mL, p<0.001). No other differences were found between the two groups except for smoking status and CT-P13 serum concentration: smoking was significantly different between the groups (p=0.024), while there was a non-significant trend in CT-P13 serum concentrations between the groups (p=0.053).

To identify risk factors for a high ADA concentration after 54 weeks of CT-P13 treatment, we performed univariable and multivariable logistic regression analyses. In the univariable analysis, current smoking at baseline was related to high ADA group inclusion at 54 weeks (odds ratio, 17.500; 95% confidence interval [CI], 1.596~191.892; p=0.019). Using stepwise methods, current smoking was only associated with the high ADA group at 54 weeks in the multivariable analysis (odds ratio, 13.500; 95% CI, 1.197~152.211; p=0.035). Other variables, such as age, sex, BMI, disease activity score, CT-P13 serum concentration, CT-P13 dose, CT-P13 dose per weight, and extra-articular symptoms, did not show a significant association with increased ADA concentration at 54 weeks (Table 3).

Correlations between disease activity and blood concentrations of CT-P13 and ADAs

Correlations between disease activity and the blood concentrations of CT-P13 and ADA at 54 weeks are shown in Table 4. There was a significant negative correlation between the CT-P13 serum concentration and the ADA serum concentration (ρ=−0.621, p=0.003). Additionally, BMI showed a positive correlation with both BASDAI (ρ=0.424, p=0.028) and BASFI (ρ=0.426, p=0.027). CRP also positively correlated with ADA serum concentration (ρ=0.539, p=0.017), while inversely correlating with CT-P13 serum concentration (ρ=−0.494, p=0.031).

However, no significant correlation was found between CT-P13 serum concentration and disease activity scores (BASDAI and BASFI). Meanwhile, BASFI scores showed a significant positive correlation with BASDAI scores (ρ=0.609, p=0.001), indicating a potential association between functional impairment and disease activity.

DISCUSSION

In this prospective observational study, we examined the prevalence and risk factors of ADAs in Korean patients with AS treated with the infliximab biosimilar CT-P13. Our results dem-

Table 2. Comparison between high and low 54-week ADA concentration groups

Variable	Total (n=22)	High ADA (n=11)	Low ADA (n=11)	p-value
Age (yr)	31.5 [27.0, 40.0]	30.0 [27.0, 32.0]	37.0 [27.0, 46.0]	0.278
Sex (male)	16 (72.7)	8 (72.7)	8 (72.7)	>0.999
BMI (kg/m^2)	23.7 [22.2, 27.6]	26.0 [22.7, 27.6]	22.9 [21.4, 28.6]	0.470
Smoking				0.024
Never smoker/ex-smoker	14 (63.6)	4 (36.4)	10 (90.9)	
Current smoker	8 (36.4)	7 (63.6)	1 (9.1)	
BASDAI (n=21)	6.2 [6.0, 7.6]	6.3 [6.0, 7.7]	6.2 [5.7, 7.6]	0.831
BASFI (n=21)	3.3 [1.6, 5.1]	3.1 [1.1, 4.5]	3.6 [1.6, 6.3]	0.324
CT-P13 serum concentration at 54 wks (μg/mL) (n=21)	23.5 [11.7, 34.2]	11.8 [5.5, 31.4]	30.0 [15.2, 40.7]	0.053
ADA serum concentration at 54 wks (AU/mL)	11.4 [9.0, 28.4]	28.4 [17.3, 44.6]	9.0 [8.7, 9.9]	<0.001
CRP (mg/dL) (n=17)	1.5 [0.8, 3.8]	1.1 [0.8, 3.9]	2.0 [0.7, 3.6]	0.962
CT-P13 dose (mg)				0.635
200, 300	16 (72.7)	7 (63.6)	9 (81.8)	
400	6 (27.3)	4 (36.4)	2 (18.2)	
CT-P13 dose/weight	4.2 [3.9, 4.7]	4.2 [3.9, 4.7]	4.3 [3.8, 4.7]	>0.999
Extra-articular symptoms	6 (27.3)	2 (18.2)	4 (36.4)	0.635

Values are presented as median [interquartile range; Q1, Q3] or number (%).ADA: anti-drug antibody, BMI: body mass index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-reactive protein.

Table 3. Risk factors for increased ADA concentration at 54 weeks

Variable	Univariable analysis	p-value	Multivariable analysis	p-value
Age (yr)	0.933 (0.837~1.041)	0.217	NA	NA
Sex (male)	1.000 (0.153~6.531)	>0.999	NA	NA
BMI (kg/m^2)	1.045 (0.863~1.267)	0.650	NA	NA
Current smoker	17.500 (1.596~191.892)	0.019	13.500 (1.197~152.211)	0.035
BASDAI	1.086 (0.481~2.452)	0.842	NA	NA
BASFI	0.795 (0.540~1.172)	0.247	NA	NA
CT-P13 serum concentration at 54 weeks (μg/mL)	0.936 (0.871~1.006)	0.071	NA	NA
CRP (mg/dL)	1.095 (0.776~1.547)	0.604	NA	NA
CT-P13 dose 400 mg	2.571 (0.361~18.323)	0.346	NA	NA
CT-P13 dose/weight	1.151 (0.186~7.122)	0.880	NA	NA
Extra-articular symptoms	0.389 (0.055~2.772)	0.346	NA	NA

Values are presented as OR (95% CI). OR: odd ratio, CI: confidence interval, ADA: anti-drug antibody, BMI: body mass index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-reactive protein, NA: not available.

onstrated that a significant proportion of patients developed ADAs. Additionally, we identified smoking as a risk factor for high ADA level.

In this study, ADA positivity among AS patients treated with the infliximab biosimilar CT-P13 increased significantly from 18.8% at 24 weeks to 59.3% at 54 weeks. Previous studies have reported ADA rates between 20%~30% within the first 6 months for similar patient populations treated with infliximab or its biosimilars [14,15], aligning with our results at 24 weeks but lower than our rate at 54 weeks. This trend suggests a potential increase in ADA formation over time, underscoring the need for long-term monitoring to mitigate potential effects on treatment efficacy.

The simultaneous increase in ADA and CT-P13 concentra-

Table 4. Correlation between disease activity and blood concentration of CT-P13 and ADA at 54 weeks

	CT-P13 serum concentration	ADA serum concentration	BASDAI	BASFI	Age	BMI	CRP
CT-P13 serum concentration	1	NA	NA	NA	NA	NA	NA
ADA serum concentration	−0.621 (0.003)	1	NA	NA	NA	NA	NA
BASDAI	0.102 (0.661)	0.079 (0.726)	1	NA	NA	NA	NA
BASFI	0.291 (0.201)	−0.222 (0.320)	0.609 (0.001)	1	NA	NA	NA
Age	0.120 (0.603)	−0.328 (0.136)	0.103 (0.594)	0.337 (0.074)	1	NA	NA
BMI	−0.112 (0.630)	0.113 (0.617)	0.424 (0.028)	0.426 (0.027)	−0.107 (0.559)	1	NA
CRP	−0.494 (0.031)	0.539 (0.017)	−0.184 (0.389)	−0.042 (0.845)	0.093 (0.665)	0.207 (0.355)	1

Values are presented as ρ (p-value). ADA: anti-drug antibody, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BMI: body mass index, CRP: C-reactive protein, NA: not available.

tions observed at 24 and 54 weeks may result from transient ADA formation or immune complex formation, which delays drug clearance early in treatment [4,16]. Some ADAs may initially be low-affinity or non-neutralizing, minimally affecting CT-P13 clearance and allowing drug levels to remain elevated [17]. Additionally, variability in individual immunogenic responses and the timing of measurements could contribute to this pattern, as ADAs often have delayed effects on serum drug levels [18].

Previous studies have established the efficacy of CT-P13 in treating AS, reporting comparable clinical outcomes to those of the reference infliximab in terms of efficacy and safety [6,8,19,20]. Our study supports these findings, demonstrating that CT-P13 effectively reduces disease activity and improves functional outcomes in AS patients. Specifically, we observed significant reductions in BASDAI and BASFI scores over the treatment period.

The rationale for investigating ADA levels lies in their potential to impact the therapeutic efficacy of biologic agents [18,21]. Elevated ADA levels have been associated with reduced drug efficacy, increased drug clearance, and a greater likelihood of treatment discontinuation due to inadequate response [6,8,19]. Importantly, there was no significant difference in the administered CT-P13 dose or the CT-P13 dose per weight between the high ADA and low ADA groups, indicating that the observed differences in CT-P13 serum concentrations were not due to variations in dosing. However, we did not observe a significant difference in clinical outcomes between the high ADA and low ADA groups, which could be due to the relatively short follow-up period or the variability in individual patient responses.

In our study, smoking emerged as a significant risk factor for the development of high ADA levels, consistent with previous research that identified smoking as a contributor to ADA formation in patients treated with TNF inhibitors [9,22,23]. Beyond smoking, other studies have reported additional risk factors for ADA development, including genetic predispositions, concomitant medications, and disease duration [6,19]. These findings may suggest a multifactorial basis for ADA formation, with smoking serving as a prominent modifiable factor.

The detrimental impact of smoking on AS and ADA formation is supported by both clinical and mechanistic evidence. Smoking is a well-established poor prognostic factor in AS, associated with higher disease activity, greater functional impairment, and accelerated radiographic progression even in patients receiving anti-TNF treatment [4,6,23-27]. This may be partly due to the exacerbation of systemic inflammation, which smoking is known to induce [28]. Smokers with AS often exhibit worse clinical outcomes compared to non-smokers, further underscoring the importance of addressing smoking in the management of AS patients. Moreover, the association between smoking and ADA formation may reflect its broader impact on immune dysregulation.

Previous studies have indicated that smoking introduces reactive oxygen species and pro-inflammatory agents, creating an environment of chronic inflammation and oxidative stress [22,28]. This inflammatory milieu activates antigen-presenting cells, which facilitates the presentation of drug-derived antigens to T cells. In turn, this promotes B cell activation and differentiation into plasma cells producing ADAs. Additionally, cigarette smoke components have been shown to activate nuclear factor-

κB and mitogen-activated protein kinase signaling pathways in B cells, enhancing cytokine production (e.g., interleukin-6) and supporting B cell survival and proliferation [29]. Smoking may also impair regulatory B cell function, further amplifying ADA formation [30]. These mechanistic insights provide a plausible explanation for the observed association between smoking and increased ADA levels, emphasizing the critical need for smoking cessation strategies in patients receiving biologic therapies.

Our study identified significant correlations that may provide insights into the clinical implications of ADA formation in AS patients treated with CT-P13 [16]. The negative correlation between CT-P13 serum concentration and ADA levels aligns with previous findings suggesting that ADA formation may reduce drug efficacy by increasing drug efficacy by increasing drug clearance, the positive correlations between BMI and disease activity indices, BASDAI and BASFI, support existing literature that links higher BMI with worse disease outcomes in AS [31]. Furthermore, association between elevated ADA levels and CRP suggests that ADA formation could be related to increased inflammatory burden [17]. Monitoring ADA, CRP clinical practice may thus enhance treatment personalization and predict treatment responses [32].

Our study has the advantage of being one of the few to investigate ADA levels associated with CT-P13 therapy in Korean AS patients. Additionally, our findings highlight smoking as a significant risk factor for ADA development, which could have important implications for patient management and therapeutic strategies in clinical practice. However, there are several limitations that need to be acknowledged. The sample size of our study is relatively small, which may limit the statistical power; however, few studies have specifically investigated ADA production in AS patients treated with the biosimilar CT-P13. Although the association between ADA and smoking in inflammatory diseases is documented [33], our study uniquely reaffirms this association within the context of CT-P13 treatment, adding another layer of evidence to the detrimental impact of smoking on ADA formation. As smoking is a modifiable risk factor, these findings have practical implications for patient management and treatment optimization in AS. Additionally, the observational nature of this study precludes definitive conclusions about causality.

CONCLUSION

Our study highlights smoking as a significant risk factor for ADA formation in AS patients treated with CT-P13. Given the modifiable nature of smoking, we strongly advocate for smoking cessation as a critical component of AS management to optimize treatment outcomes and reduce the risk of adverse immune responses. Further studies with larger cohorts and longer follow-up periods are needed to confirm these findings and to explore additional strategies to mitigate ADA formation.

FUNDING

The study was funded by Celltrion Pharm Inc. (Chungcheongbuk-do, Korea).

ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in this study, as well as the staff at Hanyang University Hospital for Rheumatic Diseases for their assistance in data collection and management.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

BN and THK conceived and designed the study. JHS and SJ were responsible for data acquisition. NC performed statistical analysis. YK drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

ORCID

Yongbum Kim, https://orcid.org/0009-0006-6333-0535
Nayeon Choi, https://orcid.org/0000-0001-8925-3714
Ji-Hui Shin, https://orcid.org/0000-0003-2482-1586
Sungsin Jo, https://orcid.org/0000-0003-3034-5029
Bora Nam, https://orcid.org/0000-0003-0215-3855
Tae-Hwan Kim, https://orcid.org/0000-0002-3542-2276

REFERENCES

1. Chang J, Wang G. The efficacy of tofacitinib combined with bDMARDs in the treatment of ankylosing spondylitis patients with inadequate response to bDMARDs: a retrospective study. BMC Rheumatol 2024;8:3.
2. Noureldin B, Barkham N. The current standard of care and the unmet needs for axial spondyloarthritis. Rheumatology (Oxford) 2018;57(suppl_6):vi10-7.
3. Haroon N, Kim TH, Inman RD. NSAIDs and radiographic progression in ankylosing spondylitis Bagging big game with small arms? Ann Rheum Dis 2012;71:1593-5.
4. Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, Lanzon A, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2017;76:355-63.
5. Cheon JH, Nah S, Kang HW, Lim YJ, Lee SH, Lee SJ, et al. Infliximab biosimilar CT-P13 observational studies for rheumatoid arthritis, inflammatory bowel diseases, and ankylosing spondylitis: pooled analysis of long-term safety and effectiveness. Adv Ther 2021;38:4366-87.
6. Sakane H, Okamura K, Inoue M, Inoue H, Yonemoto Y, Mitomi H, et al. Anti-drug antibodies and rheumatoid factor level in patients with rheumatoid arthritis using the infliximab biosimilar CT-P13. BMC Rheumatol 2022;6:74.
7. Chang S, Hanauer S. Extrapolation and interchangeability of infliximab and adalimumab in inflammatory bowel disease. Curr Treat Options Gastroenterol 2017;15:53-70.
8. Park W, Yoo DH, Jaworski J, Brzezicki J, Gnylorybov A, Kadinov V, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther 2016;18:25.
9. Blair HA, Deeks ED. Infliximab biosimilar (CT-P13; infliximab-dyyb): a review in autoimmune inflammatory diseases. BioDrugs 2016;30:469-80.
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
11. Lee SJ, Baek K, Lee S, Lee YJ, Park JE, Lee SG. Post-marketing pooled safety analysis for CT-P13 treatment of patients with immune-mediated inflammatory diseases in observational cohort studies. BioDrugs 2020;34:513-28.
12. Husman J, Černá K, Matthes K, Gilger M, Arsova M, Schmidt A, et al. Subcutaneous infliximab in Crohn's disease patients with previous immunogenic failure of intravenous infliximab. Int J Colorectal Dis 2024;39:151.
13. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013;72:1605-12.
14. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. BioDrugs 2017;31:299-316.
15. Thomas SS, Borazan N, Barroso N, Duan L, Taroumian S, Kretzmann B, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. A systematic review and meta-analysis. BioDrugs 2015;29:241-58.
16. Edlund H, Steenholdt C, Ainsworth MA, Goebgen E, Brynskov J, Thomsen OØ, et al. Magnitude of increased infliximab clearance imposed by anti-infliximab antibodies in Crohn's disease is determined by their concentration. AAPS J 2017;19:223-33.
17. Krishna M, Nadler SG. Immunogenicity to biotherapeutics - the role of anti-drug immune complexes. Front Immunol 2016;7:21.
18. Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: a prospective, multicentre, nationwide cohort. J Crohns Colitis 2016;10:133-40.
19. Bronswijk M, Moens A, Lenfant M, Tops S, Compernolle G, Van Assche G, et al. Evaluating efficacy, safety, and pharmacokinetics after switching from infliximab originator to biosimilar CT-P13: experience from a large tertiary referral center. Inflamm Bowel Dis 2020;26:628-34.
20. Yoo DH, Oh C, Hong S, Park W. Analysis of clinical trials of biosimilar infliximab (CT-P13) and comparison against historical clinical studies with the infliximab reference medicinal product. Expert Rev Clin Immunol 2015;11 Suppl 1:S15-24.
21. McKeage K. A review of CT-P13: an infliximab biosimilar. BioDrugs 2014;28:313-21.
22. Smits LJ, Derikx LA, de Jong DJ, Boshuizen RS, van Esch AA, Drenth JP, et al. Clinical outcomes following a switch from Remicade to the biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. J Crohns Colitis 2016;10:1287-93.
23. Mattey DL, Dawson SR, Healey EL, Packham JC. Relationship between smoking and patient-reported measures of disease outcome in ankylosing spondylitis. J Rheumatol 2011;38:2608-15.
24. Farouk HM, Abdel-Rahman MA, Hassan RM. Relationship between smoking, clinical, inflammatory, and radiographic parameters in patients with ankylosing spondylitis. Egypt Rheumatol Rehabil 2021;48:26.
25. Nam B, Koo BS, Choi N, Shin JH, Lee S, Joo KB, et al. The impact of smoking status on radiographic progression in patients with ankylosing spondylitis on anti-tumor necrosis factor treatment. Front Med (Lausanne) 2022;9:994797.
26. Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. Rheumatol Int 2005;25:357-60.
27. Zhao SS, Goodson NJ, Robertson S, Gaffney K. Smoking in spondyloarthritis: unravelling the complexities. Rheumatology (Oxford) 2020;59:1472-81.
28. Addissouky TA, El Sayed IET, Ali MMA, Wang Y, El Baz A, Elarabany N, et al. Oxidative stress and inflammation: elucidating mechanisms of smoking-attributable pathology for therapeutic targeting. Bull Natl Res Cent 2024;48:16.
29. Khan D, Zhou H, You J, Kaiser VA, Khajuria RK, Muhammad S.

Tobacco smoke condensate-induced senescence in endothelial cells was ameliorated by colchicine treatment via suppression of NF-κB and MAPKs P38 and ERK pathways activation. Cell Commun Signal 2024;22:214.
30. Jacobs M, Verschraegen S, Salhi B, Anckaert J, Mestdagh P, Brusselle GG, et al. IL-10 producing regulatory B cells are decreased in blood from smokers and COPD patients. Respir Res 2022;23:287.
31. Rubio Vargas R, van den Berg R, van Lunteren M, Ez-Zaitouni Z, Bakker PA, Dagfinrud H, et al. Does body mass index (BMI) influence the Ankylosing Spondylitis Disease Activity Score in axial spondyloarthritis?: data from the SPACE cohort. RMD Open 2016;2:e000283.
32. Mc Gettigan N, Afridi AS, Harkin G, Lardner C, Patchett S, Cheriyan D, et al. The optimal management of anti-drug antibodies to infliximab and identification of anti-drug antibody values for clinical outcomes in patients with inflammatory bowel disease. Int J Colorectal Dis 2021;36:1231-41.
33. Michelsen B, Berget KT, Kavanaugh A, Haugeberg G. Association between TNFi anti-drug antibodies, smoking, and disease activity in patients with inflammatory arthritis: results from a Norwegian cross-sectional observational study. Rheumatol Ther 2022;9:1171-9.