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ORIGINAL ARTICLE

Treatment pattern, satisfaction, and productivity loss of patients with ankylosing spondylitis treated with tumor necrosis factor inhibitors in Korea: A multicenter cross-sectional observational study

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Abstract

Aim: To provide in-depth understanding of real-world tumor necrosis factor inhibitor (TNFi) treatment patterns in patients with ankylosing spondylitis (AS) and treatment satisfaction, productivity loss, and associated factors.

Methods: This was a multicenter observational hybrid retrospective chart review and cross-sectional survey study. Disease activity and physical functioning were measured using the Bath AS Disease Activity Index and Bath AS Functional Index, respectively. Treatment satisfaction was determined with the Treatment Satisfaction Questionnaire for Medication (TSQM). Productivity loss was evaluated using the Korean version of the World Health Organization–Health and Work Performance Questionnaire.

Results: A total of 497 patients were enrolled (mean age 40.3 years, 85.3% male, mean AS duration 10 years). The mean duration of TNFi treatment was 6.2 years. Among the four TNFi considered, adalimumab (39.6%) and etanercept (23.5%) were most commonly used at study enrollment. The TSQM convenience domain score was lower than scores in the effectiveness, adverse effects, and global satisfaction domains. Subcutaneous syringe-type injection and intravenous injection were associated with lower patient convenience satisfaction than subcutaneous pen-type injection. Increased costs of lost productivity time were associated with female sex, unemployed status, and higher disease activity.

Conclusions: The most frequently prescribed TNFi was adalimumab, followed by etanercept. Etanercept was used for the longest duration. More convenient treatment options may enhance overall treatment satisfaction. Considerable loss in productivity due to AS was observed in this study. To reflect patients' perspectives, further attention should be paid to factors associated with treatment satisfaction and productivity loss when selecting treatment options.

KEYWORDS
ankylosing spondylitis, patient satisfaction, productivity loss, treatment pattern, tumor necrosis factor inhibitor

1 | INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, which leads to structural and functional impairments and decreased quality of life.[1] Men are more often affected than women, with a mean ratio of 3.4:1.[2] Approximately 80% of patients develop the first AS symptoms at an age younger than 30 years, and fewer than 5% of patients present symptoms at more than 45 years.[3] In South Korea, the prevalence of AS has been reported to be 52.30 per 100 000 persons (95% confidence interval [CI] 51.68-52.92 per 100 000 persons) and, from 2010 to 2015, this figure increased linearly at a rate of 7.7% per year.[4]

Because patients with AS have impaired body functioning, the disease has a significant influence on working conditions. Patients with AS experience limitations in working without breaks, standing, walking, concentrating, client friendliness, and work outputs in terms of quantity, quality, and timelines. These limitations result in a 6.3% decrease in productivity compared with healthy people or a 7.1% increase in working time.[5]

In an attempt to reduce the burden attributable to AS, it is critical to select an appropriate treatment. According to the 2016 European Alliance of Associations for Rheumatology (EULAR) guidelines for the management of AS, tumor necrosis factor inhibitors (TNFi) are recommended for patients who, despite continued conventional treatment, continue to experience discomfort in daily life because of persistently high disease activity.[6] In an analysis using claims data from the Health Insurance Review and Assessment Service in South Korea, 32.4% of patients with AS were prescribed TNFi; 14.5% of patients used a TNFi concomitantly with nonsteroidal anti-inflammatory drugs, and 1.4% used a TNFi with conventional disease-modifying antirheumatic drugs (cDMARD). In addition, 79.3% of South Korean patients with AS using TNFi were prescribed adalimumab or etanercept.[7]

When selecting a treatment based on patient preference, patients' perspectives regarding their treatments, including treatment satisfaction, can play an important role, particularly with regard to efforts to enhance treatment adherence. In this regard, the convenience of drug administration has resulted in an evolution of TNFi. For example, the delivery of TNFi via an autoinjection pen has been reported to be more satisfactory and acceptable to patients with AS.[8]

In this study conducted in patients with AS in Korea, we aimed to provide an in-depth understanding of TNFi treatment patterns in real practice and to evaluate patients' treatment satisfaction, productivity loss, and associated factors.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicenter observational hybrid study consisting of a retrospective chart-review and cross-sectional survey. The study was conducted between July 2018 and November 2018 at four university hospitals that are representative for treatment of patients with AS in Korea.

2.2 | Patients and methods

Patients aged 19 years or older, diagnosed with AS, who had been treated with a current TNFi for at least 3 months were eligible for this study. The definition of AS was based on the Modified New York Criteria 1984 with following conditions: (I) Clinical criteria—(a) low-back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest, (b) limitation of motion of the lumbar spine in both the sagittal and frontal planes, and (c) limitation of chest expansion relative to normal values corrected for age and sex; (II) radiologic criterion—sacroiliitis grade 2 or above bilaterally or sacroiliitis grade 3-4 unilaterally.[9] Among eligible patients, we excluded those who had other connective-tissue disease, who were participating in another drug intervention study, who had difficulties completing a self-reported survey because of severe and irritable health status, or who were deemed by the investigator as unable to participate in this study. Before enrollment and study participation, all patients read and signed the written consent forms, which included data sharing. Patients who signed the informed consent form were enrolled in the sequence of patients' hospital visits.

2.3 | Data collection

Before the study was commenced, the Institutional Review Board of each participating center provided approval for the study.

Medical chart review and patient survey were used for data collection. Data on the patients' demographics, clinical characteristics, and treatment patterns were collected through medical chart review. Data on demographic and clinical characteristics were collected at the time of study enrollment, and treatment pattern, including TNFi available in Korea (infliximab, adalimumab, etanercept, and golimumab), and concomitant treatments were reviewed retrospectively from the time of diagnosis to the enrollment date.

Data on socio-economic status, disease activity, treatment satisfaction, and productivity loss were collected through cross-sectional patient survey.

Disease activity and physical functioning were measured using the Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI), respectively. BASDAI scores ranged from 0 to 10, with higher scores indicating worse physical function; BASFI scores ranged from 0 to 10, with higher scores indicating a higher degree of functional limitations.

The Treatment Satisfaction Questionnaire for Medication (TSQM), version 1.4, in Korean, certified on linguistic validation by the copyright holder (Appendix S1), was used to determine treatment satisfaction. This measure is a self-reported questionnaire consisting of 14 questions in four domains: effectiveness, adverse effects, convenience, and global satisfaction. Scores ranging from 0 to 100 were calculated in each domain according to the given scoring equation, with a higher score indicating better satisfaction in the domain.

Productivity loss was measured using the Korean version of the World Health Organization–Health and Work Performance Questionnaire (WHO-HPQ), which was translated by Woo et al.[10] The WHO-HPQ measures the productivity loss over the previous 4-week period. Absenteeism is defined as the sum of the number of absent workdays due to AS multiplied by 8 hours a day and of the number of partial-day absences due to AS multiplied by 4 hours a day. Presenteeism is considered actual hours worked multiplied by the self-rated level of job performance, a visual analog scale ranging from 0 (worst) to 10 (best), during the past 4 weeks. The calculation formula is shown in Figure S1. Actual hours worked over the past 4 weeks in the measuring system were calculated by subtracting absenteeism from the actual days worked, if not sick due to AS over the past 4 weeks.[10] To calculate the annual cost of lost productivity time (LPT), wage per hour by age group in Korea, reported by the Korean Statistical Information Service, was used.[11] All costs are presented in US dollars (USD) by applying the exchange rate of 1100 South Korean Won.

2.4 | Statistical analysis

Demographic and clinical characteristics of the study participants, including treatment patterns, and summary statistics of treatment satisfaction (TSQM) and productivity loss (WHO-HPQ) were presented as frequency (percentage) for categorical variables and as mean (standard deviation [SD]) for numeric variables. Univariate analysis was performed to compare TSQM and annual cost of LPT, according to demographic characteristics, clinical characteristics, and treatment patterns, using Student's *t* test and Kruskal-Wallis test, depending on whether the variable followed a normal distribution, and Pearson's correlation analysis. To identify associated factors, multiple linear regressions in each domain of the TSQM and cost of LPT were performed by adjusting with variables with $P < 1.0$ in the univariate analyses and variables selected under clinical judgment. Because of the existence of a strong colinearity between TNFi and device type in the multivariate analyses, separate models, including either TNFi or device type, were developed.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA), and a two-sided *P* value less than 0.05 was considered as the minimum level of statistical significance.

TABLE 1 Patient characteristics

	Total (N = 497)
Age (years), mean (SD)	40.3 (11.4)
Sex, male, n (%)	424 (85.3)
Education, n (%)	
High school or less	176 (35.6)
College or more	319 (64.4)
Annual household income (USD[a]), n (%)	
<45 455	285 (57.8)
≥45 455	208 (42.2)
Employment, n (%)	
Employed	385 (78.1)
Unemployed	108 (21.9)
BMI (kg/m^2), mean (SD)	24.7 (3.9)
Duration of disease (years), mean (SD)	10 (6)
Comorbidity, yes, n (%)	44 (8.9)
BASDAI, mean (SD)	3.1 (2.0)
BASFI, mean (SD)	1.7 (1.9)
Injection pain, VAS, mean (SD)	1.8 (2.1)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; KRW, South Korean won; n, number; SD, standard deviation; USD, US dollar; VAS, visual analog scale.
[a]1 USD = 1100 KRW.

3 | RESULTS

3.1 | Patient characteristics

Overall, 497 patients (mean age 40.3 years, SD 11.4 years; 85.3% male; mean duration of AS 10 years) were enrolled in this study. Table S1 provides a detailed list of the study sites and the proportions of patients enrolled across four university hospitals. Table 1 describes the patients' characteristics. Mean current disease activity and functional index scores were 3.1 (SD 2.0) and 1.7 (SD 1.9) in the BASDAI and BASFI, respectively. With regard to socio-economic status, more than half of all patients had graduated from college/higher education, were employed, and had an annual household income of less than 50 million South Korean Won (45 455 USD).

3.2 | Treatment patterns

Patients had been treated with any TNFi for a mean duration of 6.2 years (SD 3.4 years). Among the four TNFi considered in this study, adalimumab (39.6%) and etanercept (23.5%) were most commonly used at the time of study enrollment. Current TNFi had been prescribed for an average of 2.8 (golimumab) to 7.3 (etanercept) years and maintained at a low dose (defined as lower than the approved dose) for a considerable number of patients (24.7%) for the year before study enrollment. Compared with the other TNFi, etanercept was used at a low dose in the largest proportion of patients (41.4%). With low-dose TNFi, the disease activities of the patients were comparable to those of patients using high-dose TNFi. Approximately half of all patients treated with TNFi were prescribed a pen-type device for subcutaneous injection (Table 2).

With regard to concomitant treatments, cDMARD, nonsteroidal anti-inflammatory drugs, and steroids were used by 5.4%, 39.0%, and 8.3% of the patients, respectively (Table 2).

3.3 | Treatment satisfaction and associated factors

In the analysis of treatment satisfaction, the score in the convenience domain was the lowest (67.6), whereas scores in the other domains were 72.2, 96.9, and 71.4 for effectiveness, adverse effects, and global satisfaction, respectively (Figure 1).

In the TSQM, effectiveness showed an association with age, annual household income, and BASDAI score in models 1 and 2 (Table 3). Elderly patients reported lower satisfaction in the effectiveness domain but higher satisfaction in the convenience domain. Annual household income showed a positive association with effectiveness. The BASDAI score was negatively associated with the effectiveness, adverse effects, and global satisfaction domains in the TSQM. Severe injection pain was associated with lower satisfaction for treatment convenience. In model 1, patients who were treated with infliximab reported lower satisfaction than etanercept users did (coefficient −2.612). In model 2, subcutaneous syringe-type injection (coefficient 4.013) and intravenous injection (coefficient −7.671) were associated with statistically significantly lower patient satisfaction in terms of treatment convenience compared with subcutaneous pen-type injection (Table 3).

3.4 | Productivity loss and associated factors

Among the 497 enrolled patients, there were 50 missing reports of productivity loss. Overall, 447 patients reported that they would actually work for an average of 191.2 hours over the past 4 weeks if they did not have AS (Table 4). More than 87% of the patients never missed their work (data not shown). However, over the past 4 weeks, patients were fully absent from their work for a mean of 4 hours and partially absent from their work for an average of 2.8 hours due to

TABLE 2 Treatment patterns of patients with AS

	Total (N = 497)
Total duration from the beginning of any TNFi treatments (years), mean (SD)	6.2 (3.4)
Current TNFi treatments, n (%)	
Infliximab	109 (21.9)
Adalimumab	197 (39.6)
Etanercept	117 (23.5)
Golimumab	74 (14.9)
Duration of current TNFi treatment (years), mean (SD)	
Infliximab	5.6 (3.4)
Adalimumab	5.6 (2.7)
Etanercept	7.3 (4.1)
Golimumab	2.8 (1.3)
Doses of current TNFi treatment for the last year (doses/admission), n (%)	
Low	123 (24.7)
Approved	374 (75.3)
Infliximab	
<6 mg	29 (26.6)
>6 mg	80 (73.4)
Adalimumab	
<40 mg	46 (23.4)
>40 mg	151 (76.6)
Etanercept	
<50 mg	48 (41.0)
>50 mg	69 (59.0)
Golimumab	
<50 mg	0 (—)
>50 mg	74 (100.0)
BASDAI score according to treatment and dose, mean (SD)	
Low	3.3 (1.8)
Approved	3.1 (2.1)
Infliximab	
<6 mg	2.8 (1.5)
>6 mg	3.2 (2.1)
Adalimumab	
<40 mg	3.6 (2.0)
>40 mg	3.1 (2.1)
Etanercept	
<50 mg	3.3 (1.9)
>50 mg	3.3 (2.0)
Golimumab	
<50 mg	—
>50 mg	2.9 (2.2)
BASFI score according to treatment and dose, mean (SD)	
Low	1.6 (1.6)
Approved	1.7 (2.0)

TABLE 2 (Continued)

	Total (N = 497)
Infliximab	
<6 mg	1.2 (1.5)
>6 mg	1.9 (2.3)
Adalimumab	
<40 mg	1.4 (1.5)
>40 mg	1.6 (1.9)
Etanercept	
<50 mg	2.1 (1.8)
>50 mg	2.0 (2.3)
Golimumab	
<50 mg	—
>50 mg	1.4 (1.6)
Route of device type, n (%)	
Intravenous	111 (22.3)
Subcutaneous syringe	133 (26.8)
Subcutaneous pen	253 (50.9)
Concomitant use of NSAID, yes, n (%)	194 (39.0)
Concomitant use of cDMARD, yes, n (%)	27 (5.4)
Concomitant use of steroids, yes, n (%)	41 (8.3)

Abbreviations: AS, ankylosing spondylitis; cDMARD, conventional disease-modifying antirheumatic drugs; n, number; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

AS (Table 4). Self-reported job performance during the past 4 weeks was a mean of 7.5 on the visual analog scale, ranging from 0 (worst) to 10 (best). The mean values of time for each measured absenteeism, presentism, and LPT were 6.4, 47.6, and 54 hours, respectively. The annual cost of LPT was 12 578 USD (Table 4).

In both models 1 and 2, the annual cost of LPT differed significantly by gender, employment status, BASDAI score, and BASFI score. The annual cost of LPT in males and employed patients was significantly lower than in females and unemployed patients (Table 5). A 1-unit decrease in the BASDAI and BASFI scores increased the annual cost of LPT by 1860 USD and 987 USD in model 1 and by 1885 USD and 958 USD in model 2 (Table 5).

4 | DISCUSSION

In this multicenter cross-sectional study, we observed the treatment pattern, treatment satisfaction, and productivity loss of patients with AS in Korea who were treated with TNFi and associated factors, which are important for understanding the real-world use of TNFi and patients' disease burden in AS management.

Treatment for AS aims to reduce symptoms, improve and maintain spinal flexibility and normal posture, reduce functional limitations, maintain the ability to work, and decrease the complications associated with the disease.[12] The evidence for the efficacy of TNFi in AS is well established, and their use is embedded in clinical practice.[13] Globally, patterns of TNFi use vary among countries, as no particular TNFi drug is recommended over the others. This study showed that among the four TNFi available in Korea, adalimumab was the most frequently used, followed by etanercept. Sweden and Brazil have a pattern analogous to that of Korea, prescribing adalimumab the most often, whereas etanercept is prescribed more commonly in the USA and Canada.[14-16] Dose tapering is often considered in real-world clinical practice based on an individual patient's disease activity. In our study, approximately 24% of the patients were maintained on their current TNFi at a low dose for the previous year before study enrollment. Disease activities of patients treated with low-dose TNFi were as good as those of patients treated with an approved dose of TNFi. Among all TNFi evaluated in this study, etanercept, in particular, was maintained for a longer duration and prescribed at a low dose for a higher proportion of patients. The trend toward a longer use of etanercept in this study was consistent with the results from a previous study that showed a longer persistence with etanercept in second-line TNFi use in Korea.[17] In addition, previous studies revealed that clinical remission can be maintained after a dose reduction of etanercept, following a period of standard dosing.[18-20] Despite limited evidence for the efficacy and safety of cDMARD in treating AS, concomitant use of a TNFi with cDMARD was observed in this study, which may be used for patients with peripheral arthritis, as mentioned in the 2016 EULAR guidelines for the management of AS.[6]

Patient satisfaction with TNFi in this study—scores of 72, 97, 68, and 71 in the effectiveness, adverse effects, convenience, and global satisfaction domains of the TSQM, respectively—was considerably higher than treatment satisfaction reported for other chronic diseases in Korea. According to TSQM data from previous studies, patients with postmenopausal osteoarthritis reported their treatment satisfaction as 56, 64, 63, and 54 in the effectiveness, adverse effects, convenience, and global satisfaction domains, and patients with arterial fibrillation treated with vitamin K expressed their satisfaction as 58, 58, 58, and 56 in the corresponding TSQM domains.[21,22] Meanwhile, satisfaction in the treatment convenience domain was reported as the lowest among the four domains in this study and was statistically significantly lower with the use of subcutaneous syringe-type injection or intravenous routes compared with using a subcutaneous pen-type injection. According to the patients' perspectives, the pen-type device was a more satisfactory treatment option in several studies;[23,24] therefore, this type of device could be considered for future treatments to enhance patients' overall satisfaction with treatments. Younger age, higher annual household income, and lower disease activity were statistically significantly associated with higher patient satisfaction in the treatment effectiveness domain in this study. In a previous systematic review on the determinants of patient satisfaction with health services, the relationship between gender and patient satisfaction varied across studies; perceived health improvement was positively related to better satisfaction, and patients with a higher income tended to be more satisfied with overall health services.[25]

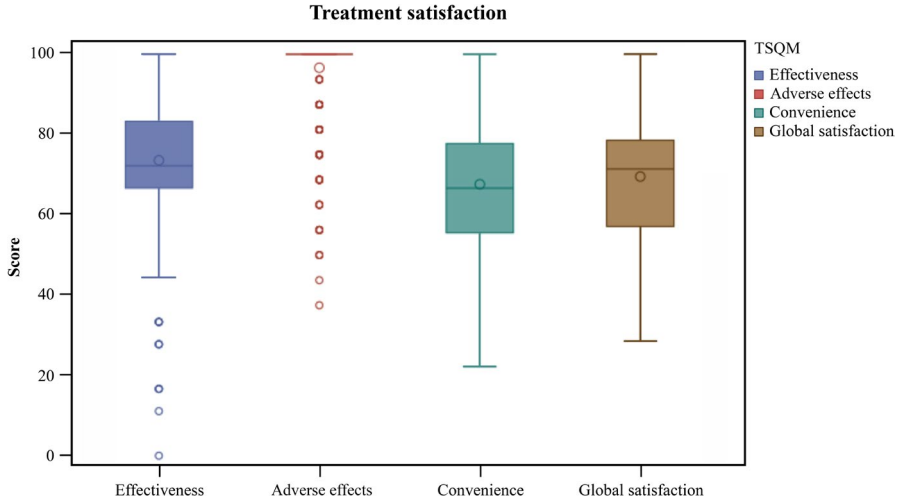

FIGURE 1 Boxplots for treatment satisfaction evaluated by the Treatment Satisfaction Questionnaire for Medication (TSQM)

TABLE 3 Risk factors for treatment satisfaction, based on the TSQM

	Effectiveness		Adverse effect		Convenience		Global satisfaction	
	Coefficient	*P* value[ab]	Coefficient	*P* value[ab]	Coefficient	*P* value[ab]	Coefficient	*P* value[ab]
Model 1[c]								
Age (years)	−0.210	0.002	0.036	0.430	0.179	0.013	−0.106	0.127
Male (Ref. female)	1.087	0.598	2.079	0.134	1.049	0.628	5.804	0.006
Annual household income (USD[a]) (Ref. <45 455)								
≤45 455	3.039	0.039	−0.285	0.773	−1.016	0.510	2.237	0.133
Type of current TNFi treatment (Ref. etanercept)								
Infliximab	−2.612	0.237	1.299	0.382	−3.585	0.123	−4.809	0.032
Adalimumab	−2.045	0.278	1.139	0.368	3.337	0.092	−2.945	0.123
Golimumab	1.344	0.588	−1.618	0.332	0.001	1.000	−2.853	0.256
BASDAI	−2.557	<0.0001	−1.004	0.001	−0.808	0.097	−2.697	<0.0001
Injection pain (as measured with a VAS)	−0.325	0.387	−0.376	0.137	−1.473	0.0002	−0.722	0.058
Model 2[c]								
Age (years)	−0.210	0.002	0.038	0.410	0.173	0.016	−0.106	0.126
Male (Ref. female)	1.102	0.594	2.081	0.135	1.101	0.609	5.877	0.005
BMI (kg/m^2)	0.222	0.231	−0.131	0.295	0.465	0.017	0.232	0.218
Annual household income (USD[a]) (Ref. <45 455)								
≤45 455	3.090	0.036	−0.283	0.774	−1.157	0.450	2.298	0.123
Route of device type (Ref. SC pen type)								
SC syringe type	2.174	0.206	−0.727	0.530	−4.013	0.026	1.034	0.552
Intravenous	−1.230	0.513	0.907	0.474	−7.671	<0.0001	−2.683	0.160
BASDAI	−2.561	<0.0001	−0.988	0.002	−0.810	0.094	−2.729	<0.0001
Injection pain VAS	−0.302	0.419	−0.343	0.175	−1.661	<0.0001	−0.626	0.099

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; cDMARDs, conventional disease-modifying antirheumatic drugs; KRW, South Korean won; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor; TSQM, Treatment Satisfaction Questionnaire for Medication; USD, US dollar; VAS, visual analog scale.

[a]1 USD = 1100 KRW.

[b]*P* value from multivariate linear regression models, adjusted following variables selected based on the results of univariate analysis and on clinical judgment; education, employment, BMI, duration of AS disease, total duration from the beginning of any TNFi treatments, doses of current TNFi treatment, BASFI, and concomitant use of NSAIDs, cDMARDs, or steroids.

[c]Adjusted R^2 values for model 1 were 0.1414 in effectiveness, 0.0420 in side effect, 0.0788 in convenience, and 0.1396 in global satisfaction and for model 2 were 0.1413 in effectiveness, 0.0372 in side effect, 0.0886 in convenience, and 0.1390 in global satisfaction.

TABLE 4 Productivity loss of patients with AS

Parameter	Mean (SD) (N = 447)
Actual days worked if not sick due to AS over past 4 weeks (days)	23.9 (5.2)
Absent work days over past 4 weeks (days); full day absent	0.5 (2.6)
Partial missing work days over past 4 weeks (days); partial-day absent	0.7 (2.7)
Self-rated job performance over past 4 weeks[a]	7.5 (1.9)
Lost productive time due to "absenteeism" over past 4 weeks (hours)	6.4 (27.0)
Lost productive time due to "presenteeism" over past 4 weeks (hours)	47.6 (38.2)
Lost productive time (hours)	54.0 (54.6)
Annual cost of absenteeism (USD[b])	1480 (6496)
Annual cost of presenteeism (USD[b])	11 098 (9216)
Annual cost of lost productive time (USD[b])	12 578 (13 096)

Abbreviations: AS, ankylosing spondylitis; USD, US dollar; VAS, visual analog scale.
[a]VAS, ranging from 0 (worst) to 10 (best).
[b]1 USD = 1,100 KRW.

TABLE 5 Risk factors of the annual cost[a] of lost productivity time

	Coefficient	*P* value[b]
Model 1[c]		
Male (Ref. female)	−4293.7	0.013
Employed (Ref. unemployed)	−6745.0	<0.0001
Type of current TNFi treatment (Ref. etanercept)		
Infliximab	1312.0	0.467
Adalimumab	1979.2	0.211
Golimumab	−190.1	0.926
BASDAI	2045.8	<0.0001
BASFI	1085.9	0.011
Model 2[c]		
Male (Ref. female)	−4290.9	0.013
Employed (Ref. unemployed)	−6781.4	<0.0001
Route of device type (Ref. Subcutaneous pen type)		
Subcutaneous syringe type	−864.0	0.547
Intravenous	−88.1	0.955
BASDAI	2073.7	<0.0001
BASFI	1053.3	0.014

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; cDMARDs, conventional disease-modifying antirheumatic drugs; IV, intravenous; KRW, South Korean won; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor; USD, US dollar; VAS, visual analog scale.
[a]In KRW: 1 USD = 1100 KRW.
[b]*P* value from multivariate linear regression model adjusted for the following variables selected based on the results of univariate analysis and on clinical judgment: age; BMI; education; household annual income; duration of AS disease; total duration from the beginning of any TNFi treatments; doses of current TNFi treatment; duration of AS disease; concomitant use of NSAIDs, cDMARDs, or steroids; and pain (as measured by the VAS) for the past year.
[c]Adjusted R^2 for model 1 was 0.2462 and for model 2 was 0.2442.

Previous studies have highlighted work-related restrictions due to pain and spine destruction in patients with AS.[26,27] In our study, patients were absent from their work for 0.5 full days (4 hours) and 0.7 partial days (2.8 hours) in the past 4 weeks. This is comparable to the results of a previous study in Korean workers that reported a mean of 5.22 hours of being absent from work due to back or neck disorders, with the greater number of hours of work absent among measured health problems. In research studies, productivity loss has been used as an aggregation of both absenteeism, which refers to being absent from work, and presenteeism, which signifies the efficiency of work done by an individual. Productivity loss is usually converted to annual cost and is often termed as an indirect cost.[27] Costs related to productivity loss in patients with AS have been reported in a systematic review and meta-analysis that identified 32 records on productivity loss in AS.[27] The annual indirect cost due to productivity loss in patients with AS using biologics has been reported to range from 191 USD to 45 954 USD per person (in 2013 USD prices).[27] Among the studies included in the meta-analysis, one study reported a considerable reduction in indirect cost after treatment with a biologic drug, with a decrease from 1968 USD at baseline to 191 USD after treatment with a biologic drug.[28] In our study, the annual cost of LPT was 12 578 USD, which is within the range of previously reported indirect costs in AS[27] and is comparable with that of patients with moderate or severe rheumatoid arthritis in Korea (moderate: 11 085 USD; severe: 13 157 USD).[29] A wide standard deviation (±13 096) of the annual cost of LPT was reported in our study as a result of the significant right-skewed data for absenteeism, as more than 87% of the patients reported no absence from their work.

Increased costs for productivity loss were strongly associated with female sex, unemployed status, higher disease activity, and higher functional limitations. This result strengthens the findings of previous studies indicating that higher disease activity and physical functioning are linked to lower work productivity in patients with AS.[26,30,31] Although the association between

productivity loss and gender in patients with AS is still controversial, many studies have reported that female patients have lower work productivity, which may be related to worse self-reported function and higher disease activity, both of which are known to affect work productivity.[32] In addition, the association between unemployment status and a higher cost of productivity loss in this study was consistent with the results of a previous study that the unemployed, including housewives and students, also suffered significant productivity loss.[33]

This study has several limitations. Because this study used a one-time cross-sectional design, the causal relationship between factors and patients' reported satisfaction and productivity loss could not be explored. Furthermore, because self-reported instruments were used, understanding of each question might have varied among individuals.

Notwithstanding these limitations, this study has remarkable strengths. This study included nearly 500 patients with AS in Korea from four major hospitals, all of which are well recognized as being representative of treating patients with AS in Korea. This study used validated measurements that have been widely used; the results of this study can therefore be applied as a source of comparison with results from future studies on the same individuals. In addition, because treatment patterns, treatment satisfaction, and costs for productivity loss can vary across countries, this study provides an in-depth understanding of those parameters in patients with AS in Korea.

5 | CONCLUSION

Among the four TNFi currently used for the treatment of patients with AS in Korea, adalimumab was the most frequently prescribed, followed by etanercept. Etanercept was used for the longest duration and often used at a low dose with comparable disease activity, suggesting that the use of etanercept could be sustainable in real practice even at a low dose. Patients with AS were quite satisfied with their current TNFi. However, among the four domains, a somewhat lower satisfaction in the treatment convenience domain was identified, and lower satisfaction with convenience was associated with subcutaneous syringe-type injection and intravenous injection compared with subcutaneous pen-type injection. More convenient treatment options may enhance overall treatment satisfaction. The mean annual cost of productivity loss due to AS in Korea was 12 578 USD per person. Further attention needs to be paid to the factors associated with treatment satisfaction and productivity loss when considering patients' perspectives with their treatment.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. TH Kim supervised the study. Sang-Hoon Lee, YG Kim, SG Lee, YJ Kim, JY Jeon, HJ Yoo, and TH Kim contributed to study conception and design. Sang-Hoon Lee, YG Kim, SG Lee, and TH Kim contributed to the acquisition of data. Sang-Hoon Lee, SH Lee, YJ Kim, JY Jeon, JY Jo, HJ Yoo, J Lee, and TH Kim contributed to the analysis and interpretation of data.

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REFERENCES

1. Braun J, Sieper J. Ankylosing spondylitis. *Lancet*. 2007;369:1379-1390.
2. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology*. 2014;53:650-657.
3. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int*. 2003;23:61-66.
4. Park JS, Hong JY, Park YS, Han K, Suh SW. Trends in the prevalence and incidence of ankylosing spondylitis in South Korea, 2010–2015 and estimated differences according to income status. *Sci Rep*. 2018;8:7694.
5. Gordeev VS, Maksymowych WP, Schachna L, Boonen A. Understanding presenteeism in patients with ankylosing spondylitis: contributing factors and association with sick leave. *Arthritis Care Res*. 2014;66:916-924.
6. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76:978-991.
7. Kang HB, Je NK. Analysis of drug utilization for patients with ankylosing spondylitis. *Korean J Clin Pharm*. 2015;25(4):246-253.
8. Borrás-Blasco J, Gracia-Pérez A, Rosique-Robles JD, Casterá MD, Abad FJ. Acceptability of switching adalimumab from a prefilled syringe to an autoinjection pen. *Expert Opin Biol Ther*. 2010;10:301-307.
9. 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;27:361-368.
10. Woo JM, Kim W, Hwang TY, et al. Impact of depression on work productivity and its improvement after outpatient treatment with antidepressants. *Value Health*. 2011;14:475-482.
11. Korean Statistical Information Service (KOSIS). Annual wage a labor time; 29 2020. Available from https://kosis.kr/statHtml/statHtml.do?orgId=118&tblId=DT_118N_LCE0004&conn_path=I3. Accessed 19 Feb 2021.

12. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. *N Engl J Med*. 2016;374:2563-2574.
13. Yates M, Keat A, Gaffney K. Do low-dose anti-TNF regimens have a role in patients with ankylosing spondylitis? *Rheumatology*. 2016;55:769-772.
14. Acurcio FA, Guerra Junior AA, da Silva MRR, et al. Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Curr Med Res Opin*. 2020;36:677-686.
15. Lie E, Lindström U, Zverkova-Sandström T, et al. Tumour necrosis factor inhibitor treatment and occurrence of anterior uveitis in ankylosing spondylitis: results from the Swedish biologics register. *Ann Rheum Dis*. 2017;76:1515-1521.
16. Walsh JA, Adejoro O, Chastek B, Park Y. Treatment patterns of biologics in US patients with ankylosing spondylitis: descriptive analyses from a claims database. *J Comp Eff Res*. 2018;7:369-380.
17. Lee MY, Shin JY, Park SY, Kim D, Cha HS, Lee EK. Persistence of biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: an analysis of the South Korean national health insurance database. *Semin Arthritis Rheum*. 2018;47:485-491.
18. Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. *Biologics*. 2013;7:1-6.
19. Lee J, Noh JW, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. *Clin Rheumatol*. 2010;29:1149-1154.
20. Yates M, Hamilton LE, Elender F, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. *J Rheumatol*. 2015;42:1177-1185.
21. Byun DW, Moon SH, Kim T, et al. Assessment of patient-reported outcomes (PROs): treatment satisfaction, medication adherence, and quality of life (QoL) and the associated factors in postmenopausal osteoporosis (PMO) patients in Korea. *J Bone Miner Metab*. 2019;37:563-572.
22. Oh S, Kim JS, Oh YS, et al. Quality of anticoagulation and treatment satisfaction in patients with non-valvular atrial fibrillation treated with vitamin K antagonist: result from the Korean atrial fibrillation investigation II. *J Korean Med Sci*. 2018;33:e323.
23. Paul C, Stalder JF, Thaçi D, et al. Patient satisfaction with injection devices: a randomized controlled study comparing two different etanercept delivery systems in moderate to severe psoriasis. *J Eur Acad Dermatol Venereol*. 2012;26:448-455.
24. Müller-Ladner U, Flipo RM, Vincendon P, Brault Y, Kielar D. Comparison of patient satisfaction with two different etanercept delivery systems. *Z Rheumatol*. 2012;71:890-899.
25. Batbaatar E, Dorjdagva J, Luvsannyam A, Savino MM, Amenta P. Determinants of patient satisfaction: a systematic review. *Perspect Public Health*. 2017;137:89-101.
26. Kruntorádová K, Klimeš J, Šedová L, Štolfa J, Doležal T, Petříková A. Work productivity and costs related to patients with ankylosing spondylitis, rheumatoid arthritis, and psoriasis. *Value Health Reg Issues*. 2014;4:100-106.
27. Malinowski KP, Kawalec P. The indirect costs of ankylosing spondylitis: a systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15:285-300.
28. Fautrel B, Benhamou M, Breban M, et al. Cost effectiveness of two therapeutic regimens of infliximab in ankylosing spondylitis: economic evaluation within a a randomised controlled trial. *Ann Rheum Dis*. 2010;69:424-427.
29. Bae SC, Cha JH, Choe JY, et al. Productivity loss of rheumatoid arthritis patients according to the their stages of the disease activity score. *J Rheum Dis*. 2018;25:122-130.
30. Frauendorf R, Pinheiro Mde M, Ciconelli RM. Variables related to work productivity loss in patients with ankylosing spondylitis. *Rev Bras Reumatol*. 2013;53:303-309.
31. Boonen A, Boone C, Albert A, Mielants H. Understanding limitations in at-work productivity in patients with active ankylosing spondylitis: the role of work-related contextual factors. *J Rheumatol*. 2015;42:93-100.
32. Haglund E, Bremander A, Bergman S, Jacobsson LT, Petersson IF. Work productivity in a population-based cohort of patients with spondyloarthritis. *Rheumatology*. 2013;52:1708-1714.
33. Filipovic I, Walker D, Forster F, Curry AS. Quantifying the economic burden of productivity loss in rheumatoid arthritis. *Rheumatology*. 2011;50:1083-1090.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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