Patient Preference and Adherence

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ORIGINAL RESEARCH

Association of the Driving Distance, Driving Time, and Public Transit Time to the Hospital with the Persistence of Tumor Necrosis Factor Inhibitors in Patients With Ankylosing Spondylitis: A Retrospective Cohort Study

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Purpose: Research on the impact of geographical distance from or travel time to healthcare facilities on treatment adherence among patients with rheumatic diseases is lacking. Therefore, we investigated the association of the driving distance, driving time, and public transit time to the hospital with the persistence of tumor necrosis factor-alpha (TNF-α) inhibitors in patients with ankylosing spondylitis (AS).

Patients and Methods: This 19-year retrospective cohort study was performed in the rheumatology department of a tertiary hospital in Korea and analyzed 313 adult patients with AS who were newly initiated on TNF-α inhibitors. The driving distance, driving time, and public transit time to the hospital were calculated using the Naver Map application. Drug persistence of TNF-α inhibitors was defined as the time duration between the index date and the date of discontinuation without exceeding a treatment gap of 90 days.

Results: The most commonly prescribed TNF-α inhibitor in patients with AS was adalimumab (69.3%), followed by etanercept (21.4%) and infliximab (9.3%). The median driving distance, driving time, and public transit time to the hospital were 16 kilometers (km), 0.6 hours, and 0.8 hours, respectively. In total, 120 (38.3%) patients with AS stopped TNF-α inhibitors over a median follow-up period of 67.1 months. After adjusting confounding factors, the driving distance to the hospital per 10-km increase (hazard ratio [HR] =1.09, p=0.017) and the driving distance to hospital ≧16 km (HR=1.9, p=0.001) were significantly associated with a higher risk of TNF-α inhibitor discontinuation. Neither the driving time nor the public transit time to the hospital was significantly associated with TNF-α inhibitor persistence.

Conclusion: Longer driving distances significantly increased the risk of treatment discontinuation, highlighting the need for healthcare systems to address these barriers.

Keywords: ankylosing spondylitis, biological products, treatment adherence and compliance, health services accessibility, medication adherence

Introduction

Ankylosing spondylitis (AS) is a chronic disabling rheumatic disease characterized by inflammation of the axial skeleton, peripheral arthritis, and various extra-articular manifestations, such as psoriasis, uveitis, and inflammatory bowel disease (IBD).[1] AS occurs mainly in the 30s and in rare cases after the age of 45[2] and prevalence of AS is reported to be 0.1% to 1.4% and is thought to be more common in people of lower socioeconomic status.[3] Persistent spinal inflammation can result in irreversible spinal ankylosis through new bone formation, which reduces spinal mobility and patients' quality of

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life.[4] The treatment of choice for the initial management of AS is non-steroidal anti-inflammatory drugs (NSAIDs), which help reduce musculoskeletal inflammation, thereby alleviating patients' pain and improving function.[1] If disease activity remains high despite adequate NSAID therapy, biologic agents, eg, tumor necrosis factor-alpha (TNF-α) or interleukin (IL)-17 inhibitors, are recommended.[1] Among these biologic agents, TNF-α inhibitors are the most widely used and have shown excellent efficacy in controlling disease activity.[5] After achieving the treatment goals of remission or low disease activity with TNF-α inhibitors in AS, experts recommend that patients continue long-term therapy without discontinuation, even if tapering is considered, as this helps control inflammation and improves long-term outcomes.[1] However, in clinical practice, adherence to TNF-α inhibitors in patients with AS is often insufficient, raising substantial clinical concerns;[6] thus, particular attention should be given to promoting treatment adherence.

The causes of nonadherence to treatment are multifactorial, involving not only disease-related and medication-related factors but also socioeconomic determinants and healthcare system-related issues, including medication cost, insurance coverage, and accessibility.[7] In particular, optimal healthcare accessibility is a critical factor that enables patients with chronic conditions, such as rheumatic diseases (RDs), to maintain consistent and effective long-term treatment. Additionally, geographical factors, eg, spatial and temporal distances to healthcare facilities, are key determinants of healthcare accessibility.[8] Indeed, a previous study reported a significant association between healthcare resource utilization and drug persistence to TNF-α inhibitors in patients with inflammatory joint diseases.[9] Therefore, it can be hypothesized that the time to and distance from healthcare facilities may also affect medication adherence. Previous studies have focused on the relationship between the driving distance to hospitals and clinical outcomes, investigating its associations with prognosis in lung cancer[10] and sepsis,[11] treatment outcomes for hip replacement[12] and lower extremity vascular revascularization,[13] and sustained use of hearing aids.[14] However, research on the impact of geographical distance from or travel time to healthcare facilities on treatment adherence among patients with RDs is lacking. Therefore, in the present study, we investigated the association between the driving distance, driving time, and public transit time to the hospital and the persistence of TNF-α inhibitors in patients with AS.

Materials and Methods

Ethics Statements

This study was approved by the Institutional Review Board of Pusan National University Hospital, which waived the requirement for informed consent owing to the retrospective nature of the study (IRB number: 2408–015-145, approval date: August 26, 2024) and was conducted in accordance with the Helsinki Declaration.

Study Design and Study Participants

This retrospective cohort study was conducted in the rheumatology department of a tertiary medical center in Busan, South Korea. Busan is located in southeastern South Korea and is the second most populous city in the country after Seoul. The distance between Seoul and Busan is approximately 325 km (202 miles) when traveling along a straight line. However, the driving distance is approximately 390–400 km (242–249 miles) depending on the route. Here, we analyzed 313 adult patients with AS aged 18 years or older who were newly initiated on TNF-α inhibitors between January 2005 and December 2023 at our center. AS was defined as meeting the 1984 modified New York criteria.[15] Patients who started TNF-α inhibitors for the treatment of diseases other than AS, those with a history of receiving another TNF inhibitor, other biologics (eg, IL-17 inhibitors) or JAK inhibitors at least one year prior to the initiation of TNF-α inhibitors, and patients younger than 18 years of age were excluded. The index date was defined as the date when the TNF-α inhibitor was newly initiated, and the study patients were followed up to until August 2024. During the study period, etanercept subcutaneous injection, adalimumab subcutaneous injection, and infliximab intravenous infusion were available at our center; therefore, these medications were included among the TNF-α inhibitors analyzed.

Data Collection

The clinical and demographic data of the patients were obtained through a comprehensive review of medical records. The following data were collected at the index date: age, sex, residential addresses, disease duration, type of TNF-α

inhibitors, erythrocyte sedimentation rate, C-reactive protein (CRP), human leukocyte antigen B27 status, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), concomitant medications, and extra-articular manifestations. In compliance with Korean privacy protection laws and bioethics regulations, patients' residential addresses were collected only up to the district ("dong") or street name level. Disease duration was defined as the period from the date of AS diagnosis to the index date and was described in months. Concomitant medications included NSAIDs, methotrexate, sulfasalazine, and glucocorticoids, and extra-articular manifestations included uveitis, psoriasis, peripheral arthritis, hip joint involvement, and IBD. Uveitis and psoriasis were defined as being diagnosed by an ophthalmologist and a dermatologist, respectively.[6] Peripheral arthritis was defined as the presence or history of swelling in one or more peripheral joints, excluding the hip joint.[16] Hip joint involvement was defined as the presence of local pain, limited range of motion, or lameness along with radiographic findings, such as joint space narrowing, bony ankylosis, subchondral erosion, progressive subluxation, or deformity.[17] IBD included Crohn's disease and ulcerative colitis and was defined using conventional endoscopic and pathological criteria.[17]

Exposure and Outcome

Driving distance was calculated as the shortest distance between the patient's residence and our center using the Naver Map application and was recorded in kilometers (km). It was also categorized as a binary variable on the basis of the median value (above the median value versus below the median value). The Naver Map application is a widely used navigation and mapping application developed by the Naver Corporation, a prominent information technology conglomerate in South Korea. This application offers comprehensive mapping services, including real-time navigation for walking, cycling, driving, public transit information, and various geolocation-based functionalities. Owing to South Korean restrictions on foreign mapping services, Naver Map is the preferred choice in South Korea, offering more detailed and accurate local information than Google Maps. The driving time and public transit time to the hospital were also calculated using Naver Map and were expressed in hours.

Drug persistence of TNF-α inhibitors was defined as the time duration between the index date and the date of discontinuation without exceeding a treatment gap of 90 days.[6,18] We set 90 days as the treatment gap because different reimbursement criteria apply in Korea when TNF-α inhibitors are restarted after being discontinued for >90 days compared with when they are restarted within 90 days. If treatment is discontinued for >90 days, restarting of the TNF-α inhibitor is considered a new treatment under the reimbursement criteria. However, if TNF-α inhibitors are prescribed within 90 days of discontinuation, this is regarded as a continuation of the previous treatment and the reimbursement applies accordingly. The discontinuation of TNF-α inhibitors was defined as meeting any of the following criteria: 1) discontinuing TNF-α inhibitors for >90 days (treatment gap) regardless of the cause after the index date; 2) restarting the index TNF-α inhibitor after >90 days of the first discontinuation; 3) switching from the index TNF-α inhibitor to another type of TNF-α inhibitor, or to another type of biologic disease-modifying anti-rheumatic drugs or targeted synthetic disease-modifying anti-rheumatic drugs. We also investigated the reasons for discontinuation, which were categorized as poor health literacy, lack of efficacy, adverse events, and miscellaneous, based on the medical chart review. Poor health literacy was defined as a lack of awareness of the importance of taking TNF-α inhibitors regularly.[6] Transfer to another hospital, loss to follow-up, or absence of discontinuation until the end of the study period were censored.

Statistical Analyses

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as number (percentage). Continuous variables were compared using the Student's *t*-test or Mann–Whitney *U*-test, whereas the categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. Drug persistence was graphed using the Kaplan–Meier method and compared using the Log rank test. The associated factors for the risk of TNF-α inhibitor discontinuation were analyzed using Cox regression models. To establish the independent statistical association between the driving distance and TNF-α inhibitor discontinuation, the following sequential Cox regression models were constructed: model 1, unadjusted; model 2, adjusted for age and sex; model 3, adjusted for all variables in model 1 plus baseline BASDAI and disease duration; model 4, adjusted for all variables in model 2 plus the presence of psoriasis; and model 5, adjusted for all variables in model 4 plus NSAIDs,

methotrexate, sulfasalazine, and glucocorticoids. The risk of TNF inhibitor discontinuation was quantified as hazard ratios (HRs) with 95% confidence intervals (CIs), using Cox regression models. All data were analyzed using STATA (version 15.0 for Windows; StataCorp LP, College Station, TX, USA) and SPSS (version 18.0 for Windows; IBM Corp., Armonk, NY, USA), with a p-value of <0.05 considered statistically significant.

Results

The baseline clinical characteristics of the study participants are described in Table 1. The mean patient age was 35 years and 17.3% of the patients were female. The most commonly prescribed TNF-α inhibitor in patients with AS was adalimumab (69.3%), followed by etanercept (21.4%) and infliximab (9.3%). The mean baseline BASDAI was 6.8, and the frequencies of uveitis, psoriasis, and IBD were 16.9%, 2.9%, and 2.9%, respectively. The median driving distance,

Table 1 Baseline Characteristics of Study Patients

	Patients with AS (n = 313)
Age, years, mean ± SD	35 ± 11.6
Female, n (%)	54 (17.3)
Disease duration, month, median (IQR)	8 (3.8–40.5)
Type of TNF-α inhibitors	
Adalimumab, n (%)	217 (69.3)
Etanercept, n (%)	67 (21.4)
Infliximab, n (%)	29 (9.3)
ESR, mm/hr, median (IQR)	27 (10–55)
CRP, mg/dL, median (IQR)	1.1 (0.3–2.6)
Baseline BASDAI, mean ± SD	6.8 ± 1.4
Positive HLA-B27, n (%)	277 (88.5)
NSAIDs, n (%)	234 (74.8)
Methotrexate, n (%)	68 (21.7)
Sulfasalazine, n (%)	113 (36.1)
Glucocorticoids, n (%)	110 (35.1)
Uveitis, n (%)	53 (16.9)
Psoriasis, n (%)	9 (2.9)
Peripheral arthritis, n (%)	139 (44.4)
Hip involvement, n (%)	73 (23.3)
IBD, n (%)	9 (2.9)
Driving distance to hospital, kilometer, median (IQR)	16 (9.2–26)
Driving time to hospital, hour, median (IQR)	0.6 (0.4–0.7)
Public transit time to hospital, hour, median (IQR)	0.8 (0.6–1.3)

Abbreviations: AS, ankylosing spondylitis; SD, standard deviation; IQR, interquartile range; TNF-α, tumor necrosis factor-alpha; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HLA, human leukocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease.

driving time, and public transit time to the hospital were 16 km, 0.6 hours, and 0.8 hours, respectively. Supplementary Table 1 presents the data comparing the clinical variables of patients with AS based on a median driving distance of 16 km. AS patients with a driving distance of ≧16 km tended to have higher CRP levels than those with a driving distance of <16 km, but the difference was not statistically significant. Patients with a driving distance of ≧16 km had a significantly higher frequency of sulfasalazine use than those with a driving distance of <16 km; however, there were no significant differences in the other variables between the groups.

In total, 120 (38.3%) patients with AS stopped TNF-α inhibitors over a median follow-up period of 67.1 months. Table 2 presents the causes of TNF-α inhibitor discontinuation. The most common reason for drug discontinuation was poor health literacy (47.5%), followed by a lack of efficacy (27.5%) and adverse events (21.7%). Drug persistence in all patients is shown in Figure 1. The drug persistence rates at 12, 24, and 60 months were 87.4%, 80.3%, and 69.9%, respectively. Figure 2 shows the Kaplan–Meier curve for drug persistence according to whether the driving distance was ≧16 km or <16 km. Patients with AS with a driving distance of ≧16 km had significantly lower drug persistence than those with a driving distance of <16 km (p=0.002).

The results of the univariable Cox regression analysis for factors associated with the risk of TNF-α inhibitor discontinuation are summarized in Supplementary Table 2. Driving distance to the hospital per 10-km increase (HR=1.08, 95% CI=1.01–1.16, p=0.028) and driving distance to the hospital of ≧16 km (HR=1.8, 95% CI=1.24–2.61, p=0.002) were significantly associated with a higher risk of TNF-α inhibitor withdrawal in patient with AS. However, neither the driving time to the hospital nor the public transit time to the hospital was significantly associated with the risk of TNF-α inhibitor discontinuation.

Table 3 shows the associations between the driving distance to the hospital and TNF-α inhibitor discontinuation using sequential Cox regression models. Cox regression model 5, which was adjusted for all potential confounding variables, revealed that driving distance to the hospital per 10-km increase (HR=1.09, 95% CI=1.02–1.17, p=0.017) and driving distance to the hospital of ≧16 km (HR=1.9, 95% CI=1.31–2.75, p=0.001) were independently associated with an increased risk of TNF-α inhibitor discontinuation in patients with AS.

Discussion

Here, we found that a longer driving distance to the hospital was significantly associated with a lower persistence to TNF-α inhibitors in patients with AS. In particular, if the driving distance to the hospital is ≧16 km (9.9 miles), the risk of discontinuation of TNF inhibitors increases by 90%. However, regardless of the mode of transportation, the time required to reach the hospital was not significantly associated with TNF-α inhibitor discontinuation. To our knowledge, this is the first study to evaluate the effects of geographical accessibility on treatment adherence in patients with AS. Our findings highlight the importance of considering patients' driving distance when formulating therapeutic strategies aimed at enhancing medication persistence.

Healthcare access is recognized as a complex concept comprising five main dimensions: the ability to perceive (approachability), seek (acceptability), reach (availability), pay (affordability), and engage (appropriateness).[19,20] Among these dimensions, geographic barriers, eg, long travel distances, inadequate transportation, and the uneven distribution of

Table 2 The Causes of Tumor Necrosis Factor-Alpha Inhibitor Discontinuation

	TNF-α Inhibitor Discontinuation (n=120)
Poor health literacy, n (%)	57 (47.5)
Lack of efficacy, n (%)	33 (27.5)
Adverse events, n (%)	26 (21.7)
Miscellaneous, n (%)	4 (3.3)

Abbreviation: TNF-α, tumor necrosis factor-alpha.

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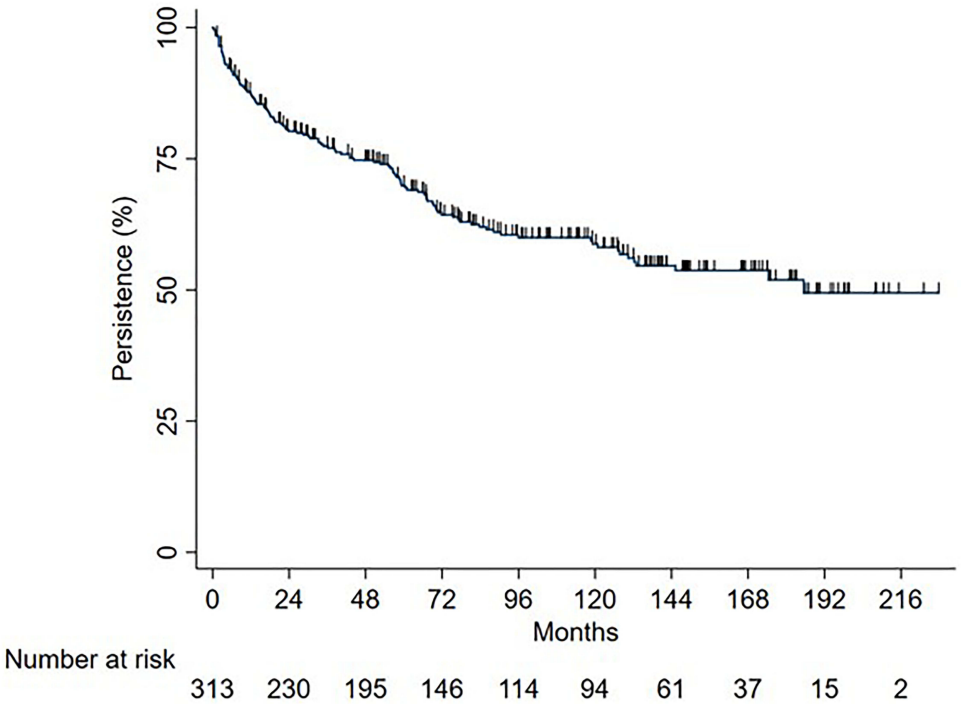

Figure 1 Drug persistence of tumor necrosis factor-alpha inhibitors in patients with ankylosing spondylitis.

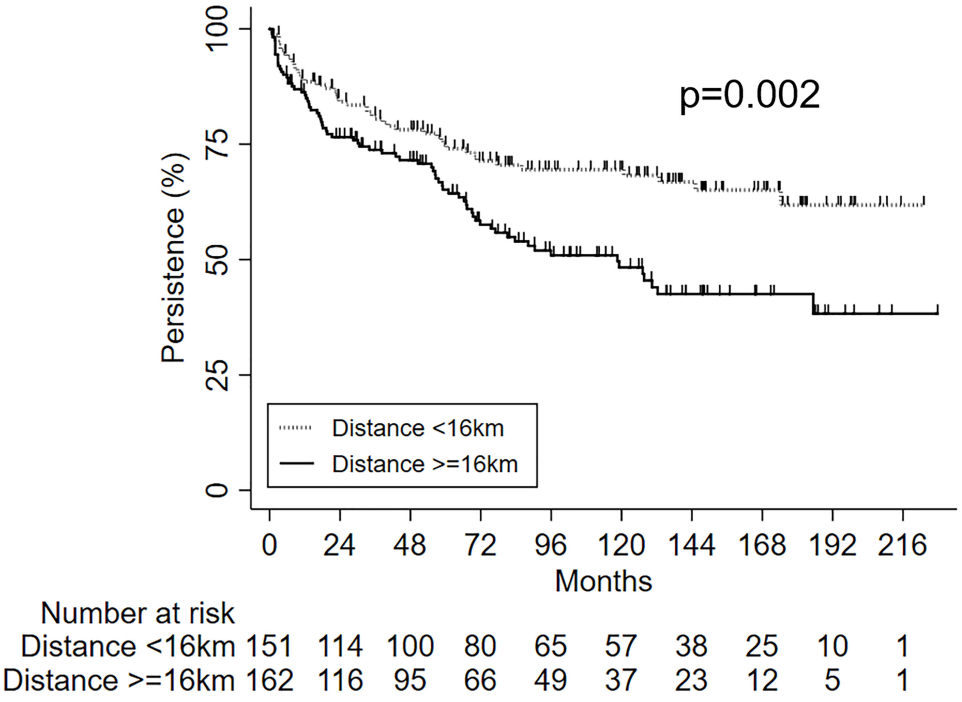

Figure 2 Drug persistence of tumor necrosis factor-alpha inhibitors according to whether the driving distance is greater than or less than 16 kilometers.

healthcare facilities, significantly hinder patients' ability to access (availability) healthcare services, particularly in rural and remote areas.[21,22] This barrier affects individuals' ability to physically access healthcare when needed, often resulting in delays or even complete avoidance of medical services, which in turn leads to untimely diagnosis and treatment, ultimately contributing to poor health outcome.[21–23] In our literature review, most previous studies analyzed the distance

Table 3 Associations of Driving Distance to Hospital and Tumor Necrosis Factor-Alpha Inhibitor Discontinuation in Patients with Ankylosing Spondylitis Analyzed by Sequential Cox Regression Models

	Driving Distance to Hospital, per 10 Kilometers		**Driving Distance to Hospital ≧16 Kilometers**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1	1.08 (1.01–1.16)	0.028	1.8 (1.24–2.61)	0.002
Model 2	1.09 (1.01–1.16)	0.02	1.9 (1.31–2.76)	0.001
Model 3	1.09 (1.01–1.16)	0.018	1.91 (1.31–2.77)	0.001
Model 4	1.09 (1.02–1.17)	0.017	1.9 (1.31–2.75)	0.001
Model 5	1.09 (1.02–1.17)	0.017	1.9 (1.31–2.75)	0.001

Notes: Model 1 indicates unadjusted model; Model 2 adjusted for age and gender; Model 3 adjusted for all variables in model 1 plus baseline BASDAI and disease duration; Model 4 adjusted for all variables in model 2 plus the presence of psoriasis; Model 5 adjusted for all variables in model 3 plus NSAIDs, methotrexate, sulfasalazine and glucocorticoids.
Abbreviations: HR, hazard ratio; CI, confidence interval.

or travel time to hospitals as key indicators of geographic barriers. These studies reported that greater distances are associated with lower hospitalization rates in patients with cognitive impairment[24] and chronic obstructive pulmonary disease,[25] and reduced hearing aid retention.[14] However, other studies found no significant impact of geographic barriers on outcomes, such as lung cancer surgery,[10] hip replacement surgery,[12] appendectomy outcomes,[26] or early mortality in patients with sepsis.[11] Thus, the impact of geographic barriers on healthcare use and clinical outcomes could vary depending on the nature of the condition, ie, whether it is acute or chronic, whether it requires surgical intervention, or whether it can be managed through medication.

The main study finding was that a longer driving distance to the hospital is associated with decreased drug retention rates of TNF-α inhibitors in patients with AS. A literature review revealed that previous studies have also analyzed driving distances to hospitals in the context of RDs. Similar to our study's findings, Wang et al, in a study of patients with inflammatory RDs in China, reported that long distances to the hospital, along with higher education levels, increased the risk of medication non-adherence.[27] Owing to China's larger land area compared with Korea, the median distance to hospitals in Wang et al's study was 30 km, which is approximately twice that in our study, and there are also differences in healthcare systems. Despite these factors, the distance to the hospital has consistently emerged as a key factor influencing medication adherence in RDs. In contrast, unlike the driving distance to the hospital, the time taken to reach hospitals showed no significant association with persistence to TNF-α inhibitors in patients with AS in our study. Although the exact reason for this is difficult to determine, it can be hypothesized that the physical, psychological, and social factors influencing a patient's regular hospital visits are affected more by the driving distance to the hospital than by the time taken to reach the hospital. Additionally, travel time is influenced by factors, such as the mode of transportation used or urban rush hour, making it more difficult to measure it accurately than distance, which may have contributed to these results. According to Polinski et al, who analyzed United States Medicare data, the odds of patients with rheumatoid arthritis being prescribed disease-modifying antirheumatic drugs increased with longer driving distances to hospitals.[28] Although the exact reason for this is unclear, the authors suggested that patients who live farther from the hospital may paradoxically have higher disease severity.[28] Therefore, it is difficult to rule out the possibility that disease-specific factors, eg, the severity of the illness, may have acted as confounding variables in the statistical relationship between the driving distance and persistence to TNF-α inhibitors in our study. Further prospective studies are warranted to explore this relationship in detail.

The outcome variable in our study, drug persistence, is considered a surrogate measure of the long-term efficacy and safety of medications.[6,18] Several studies have highlighted the importance of enhancing drug persistence in chronic conditions, such as RDs, which require lifelong treatment.[29,30] Drug persistence is linked to improved long-term

outcomes, such as better disease control and slower progression of RDs.[29,30] To achieve this, not only do physicians play a key role in personalized care and patient education but social and economic support is also crucial.[30,31] Our study found that a longer driving distance was associated with worse persistence to TNF-α inhibitors, suggesting that healthcare policies aimed at expanding transportation resources to reduce driving distance, as well as increasing and optimally distributing the workforce of rheumatologists, are essential to improving the prognosis of patients with AS. As the global population ages, the prevalence of RDs increases, leading to an increasing demand for rheumatology specialists.[32] Moreover, the combination of age-related physiological changes such as reduced muscle mass and function, decreased organ function and degenerative changes and AS-specific changes may put older AS patients at greater risk than younger AS patients.[33] The shortage of trained rheumatology professionals is becoming increasingly severe and is recognized as a considerable clinical and socioeconomic challenge.[32]

This study has several limitations. First, the driving distance and travel time to the hospital were not calculated on the basis of the actual routes or modes of transportation used by patients. Instead, they were estimated using the patients' home addresses via the Naver Map application. In addition, we could not collect data regarding available travel options to the hospital, patient preference type of transport, and necessity to come to the hospital to get treatment which can affect the study findings. Therefore, there may have been discrepancies between the estimated data and the actual travel conditions of our study patients. Second, the distance and travel time to the hospital were calculated on the basis of the patient's home address; however, there is a possibility that the patient may travel to the hospital from their workplace rather than from home. Third, the impact of the physical distance from the hospital may vary depending on the patient's socioeconomic status. Even if the distance is the same, access to healthcare facilities can differ between patients who are economically affluent or have strong social support and those who do not. However, this study does not fully account for these factors in its analysis. Fourth, as this was a retrospective study, establishing causality may be challenging. It is possible that a longer distance from the hospital is not a factor that reduces medication adherence. Rather, patients with higher medication adherence are more likely to live near the hospital. Patients with more insight into their condition may choose to live closer to a hospital to better manage their illness. Therefore, prospective studies are required to confirm these findings. Finally, as this study was conducted at a single institution, there may have been a risk of selection bias. Thus, future studies should include multicenter studies within the same region or nationwide to provide more generalizable results.

Conclusion

Geographical accessibility plays a crucial role in medication persistence among patients with AS receiving TNF-α inhibitors. Our results indicated that longer driving distances significantly increased the risk of treatment discontinuation, highlighting the need for healthcare systems to address these barriers. Given the increasing prevalence of RDs and the existing shortage of rheumatology specialists, it is imperative that healthcare policies focus on enhancing access to care, including optimizing the distribution of specialists and providing transportation support. Ultimately, by improving geographical access, better treatment adherence and outcomes can be achieved in patients with AS. Future research should continue to explore these relationships, considering a broader range of socioeconomic factors and employing prospective methodologies including qualitative semi-structured interviews of study patients to further validate these findings.

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Disclosure

The authors declare that they have no competing interests.

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