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Factors associated with cause-specific discontinuation of long-term anti-tumor necrosis factor agent use in patients with ankylosing spondylitis: a retrospective cohort study

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Abstract

Object To investigate the factors associated with cause-specific discontinuation of long-term anti-tumor necrosis factor (TNF) agent use in patients with ankylosing spondylitis (AS).

Methods AS patients who initiated first-line anti-TNF treatment between 2004 and 2018 and continued treatment for at least two years were enrolled in the study. Enrolled patients were observed until the last visit, discontinuation of treatment, or September 2022. Reasons for discontinuation of the first-line anti-TNF agent were categorized into the following: (1) clinical remission, (2) loss of efficacy, (3) adverse events, and (4) other reasons including loss to follow-up, cost, or reimbursement issues. A cumulative incidence function curve was used to visualize the cumulative failure rates over time for each specific reason. Univariable and multivariable cause-specific hazard models were utilized to identify factors associated with cause-specific discontinuation of the first-line anti-TNF agent.

Results A total of 429 AS patients was included in the study, with 121 treated with adalimumab (ADA), 176 with etanercept (ETN), 89 with infliximab (INF), and 43 with golimumab (GLM). The median overall survival on the first-line anti-TNF agent was 10.6 (7.9–14.5) years. Among the patients, 103 (24.0%) discontinued treatment, with 36 (34.9%) due to inefficacy, 31 (30.1%) due to clinical remission, 15 (14.6%) due to adverse events, and 21 (20.4%) due to other reasons. Patients treated with ETN had a lower risk of discontinuation due to clinical remission compared to those receiving ADA (hazard ratio [HR] 0.45 [0.21–0.99], $P=0.048$). Higher baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; HR 1.31 [1.04–1.65], $P=0.023$) and INF use were linked to a higher risk of treatment discontinuation for inefficacy compared to ADA use (HR 4.53 [1.45–14.16], $P=0.009$). Older age was related to an increased risk of discontinuation due to infection-related adverse events (HR 1.07 [1.02–1.12], $P=0.005$), and current smoking was a risk factor for discontinuation due to other reasons (HR 6.22 [1.82–21.28], $P=0.004$).

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Conclusion AS patients on their first anti-TNF treatment for at least two years demonstrated a favorable long-term treatment retention rate, with a 24.0% discontinuation rate over a 10.6-year overall survival period. The predictors for discontinuation varied by causes, underscoring the complexity of treatment response and the importance of personalized approaches to treatment management.

Keywords Ankylosing spondylitis, Anti-tumor necrosis factor, Cause-specific discontinuation, Long-term outcome

Background

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by inflammatory back pain that can lead spinal ankylosis [1]. The introduction of anti-tumor necrosis factor (TNF) agents has significantly transformed the management of AS patients, especially for patients who do not respond well to or cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs) [2]. Currently, six anti-TNF agents have been approved for treatment of AS: adalimumab, etanercept, infliximab, golimumab, and certolizumab. Despite the benefits of these anti-TNF agents in controlling inflammation and symptoms, their effectiveness and persistence can vary, with some patients experiencing therapeutic failure, adverse events, or discontinuation of treatment for various reasons.

Measuring drug persistence (also referred to as drug survival), the time from treatment initiation to discontinuation, offers essential insights into their safety and effectiveness [3]. In general, drug retention rates for anti-TNF treatments tend to be higher in AS patients compared to individuals with rheumatoid arthritis (RA) [4–6]. Data from 12 European registries, encompassing 24,195 axial spondyloarthritis (axSpA) patients who initiated their first anti-TNF treatment, revealed an overall 12-month retention rate of 80%, with individual registries ranging from 71 to 94%. Over 24 months, the overall retention rates were 73%, with individual registries showing retention rates varying from 71 to 94% [7]. Research on the long-term retention rates of first-line anti-TNF agents in AS is relatively scarce, and the available studies have shown varying results, including an eight-year anti-TNF retention rate of 57.2% in a study with 316 axSpA patients and a 10-year anti-TNF survival rate of 28.9% in another study with 231 AS patients [4, 8].

Awareness of individual variability in drug retention has naturally led to an increased interest in understanding the factors associated with the response to anti-TNF agents. Several factors have emerged as predictors of a favorable response to anti-TNF treatment and improved survival rates. These factors include male sex [9–12], young age [9, 10, 13], high baseline levels of inflammatory markers [10, 12–14], a shorter disease duration, human leukocyte antigen (HLA)-B27 positivity [9, 11, 13], and non-smoking status [15].

However, applicability of these previous studies has been limited, due to relatively short observation periods. It is crucial to acknowledge that reasons for discontinuation of anti-TNF agent treatment can vary between short-term and long-term treatment periods [8]. Recognizing the clinical differences between discontinuations due to clinical remission and those due to lack of efficacy, it becomes evident that a deeper investigation into the causes of discontinuation is necessary, rather than focusing solely on the retention rate.

Therefore, the objective of this study was to explore and identify factors associated with cause-specific discontinuation after long-term treatment with first-line anti-TNF agents in AS patients.

Methods

Patient enrollment

We conducted a retrospective cohort study including AS patients who initiated first-line anti-TNF treatment with either adalimumab, etanercept, infliximab, or golimumab between 2004 and 2018. All patients met the 1984 modified New York criteria for AS [16]. To focus on the cause-specific discontinuation of anti-TNF treatment in the long term, we excluded patients who stopped using the anti-TNF agent within two years of initiation. Patients with inflammatory bowel disease were also excluded.

The index date was defined as that when the anti-TNF agent was initiated. Patients were observed until their last visit, discontinuation or switching of the anti-TNF agent, or end of the study in September 2022.

Data collection

We collected information on various demographics, including age and smoking status, as well as AS-related clinical factors including symptom and disease duration, HLA-B27 positivity, peripheral arthritis, uveitis, use of NSAIDs, and the specific type of anti-TNF agent used. To assess disease activity, we recorded the serum concentration of C-reactive protein (CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score at the index date and at three months after initiating anti-TNF treatment. To evaluate structural damage, the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) was used [17].

Discontinuation of treatment was defined as either stopping or switching anti-TNF therapy. The reasons for discontinuation were categorized as follows: (1) clinical remission, (2) loss of efficacy, (3) adverse events, and (4) other reasons, including loss to follow-up and issues

related to cost or reimbursement. Given the retrospective nature of our study, a comprehensive chart review was conducted, and each case was evaluated by a rheumatologist for classification into one of these categories.

Statistical analysis

Enrolled patients were divided into four groups according to type of anti-TNF agent; adalimumab, etanercept, infliximab, and golimumab groups. Demographic and clinical characteristics of each group are described in a descriptive analysis and all data are shown as median interquartile range [IQR] or frequency (percentage). The four groups were compared using the Kruskal-Wallis test for non-normally distributed numerical variables and chi-square test and Fisher's exact test for categorical variables.

Competing risks were taken into account for survival analysis. Gray's test was performed to analyze differences in the cumulative incidence between each anti-TNF agent group. We used Cox cause-specific hazards models to identify factors associated with discontinuation of anti-TNF treatment for specific causes, including clinical remission, loss of efficacy, overall adverse events, infection-related adverse events, and other reasons. An exploratory analysis was performed via univariable Cox cause-specific hazard models to determine which factors should be included in multivariable modes. Significant clinical factors including age, sex, disease duration, and type of anti-TNF agent or factors at a P-value < 0.2 in the univariable models were considered as candidates for the multivariable model.

Statistical analyses were 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). A P-values < 0.05 was regarded as statistically significant.

Results

Demographic and clinical characteristics of patients

Among 556 screened patients, 122 who discontinued anti-TNF treatment within two years and five with inflammatory bowel disease were excluded, resulting in the inclusion of 429 AS patients for the analysis (Fig. 1). Table 1 provides a summary of the demographic and clinical characteristics of the enrolled patients. The median age of the patients was 32.1 (26.9–38.5) years, with 88.8% being male. The median symptom duration was 10.4 (4.9–15.4) years. The most commonly prescribed anti-TNF agent was etanercept (176, 41.0%), followed by adalimumab (121, 28.2%), infliximab (89, 20.8%), and golimumab (43, 10.0%). At baseline, the median BASDAI score was 7.0 (6.0–8.0), and the level of CRP was 2.1 (0.9–4.6) mg/dL. After three months of anti-TNF treatment, the median BASDAI score decreased to 2.8 (2.0–4.0), and the level of CRP decreased to 0.8 (0.8–0.8) mg/dL. The median overall survival duration for anti-TNF agent treatment was 10.6 (7.9–14.5) years. During the observational period, 103 (24.0%) patients discontinued first-line anti-TNF treatment, with reasons of loss of efficacy (36, 34.9%), clinical remission (31, 30.1%), other reasons (21, 20.4%), and adverse events (15, 14.6%).

Cause-specific discontinuation of anti-TNF treatment

The overall survival duration differed among the anti-TNF agents, with adalimumab having a duration of 10.2 (7.8–12.0) years, etanercept 13.5 (10.2–16.7) years, infliximab 10.0 (7.4–12.5) years, and golimumab 7.7 (7.0-9.1) years (P < 0.001). The proportion of patients with uveitis was higher in the etanercept group (37.2% for adalimumab, 51.7% for etanercept, 40.5% for infliximab, and 23.3% for golimumab, P = 0.003). Other clinical characteristics, such as age, sex, baseline mSASSS, BASDAI, CRP, and smoking status, were comparable between the groups (Table 1).

The reasons for discontinuation varied depending on the anti-TNF agent used (P = 0.005). The most common reason for discontinuation of adalimumab was clinical remission (14, 45.2%), followed by other reasons (7, 22.6%), adverse events (6, 19.4%), and loss of efficacy (4, 12.9%). For etanercept, loss of efficacy (19, 38.0%) was the primary cause of discontinuation, followed by other reasons (12, 24.0%), clinical remission (11, 22.0%), and adverse events (8, 16.0%). In the case of infliximab, loss of efficacy (13, 68.4%) was the leading cause of discontinuation, followed by clinical remission (4, 21.0%), adverse events (1, 5.3%), and other reasons (1, 5.3%). Finally, for golimumab, the reasons for discontinuation were clinical remission (2, 66.7%) and other reasons (1, 33.3%).

The Kaplan-Meier survival curve for anti-TNF agents did not show significant differences among the agents (Fig. 2). Therefore, cause-specific discontinuation was compared based on the type of anti-TNF agent using the cumulative incidence function (Fig. 3). There were no significant differences in discontinuation due to clinical remission, overall adverse events, and other reasons (P = 0.083, P = 0.253, and P = 0.387, respectively). However, discontinuation associated with loss of efficacy differed significantly according to the type of anti-TNF agent used (P = 0.009).

Predictors for cause-specific discontinuation

We conducted univariable and multivariable cause-specific hazard models to identify predictors associated with cause-specific discontinuation. The multivariable cause-specific hazard models are presented in Table 2, while the univariable hazard models for each cause-specific discontinuation can be found in Supplementary Tables 1–5.

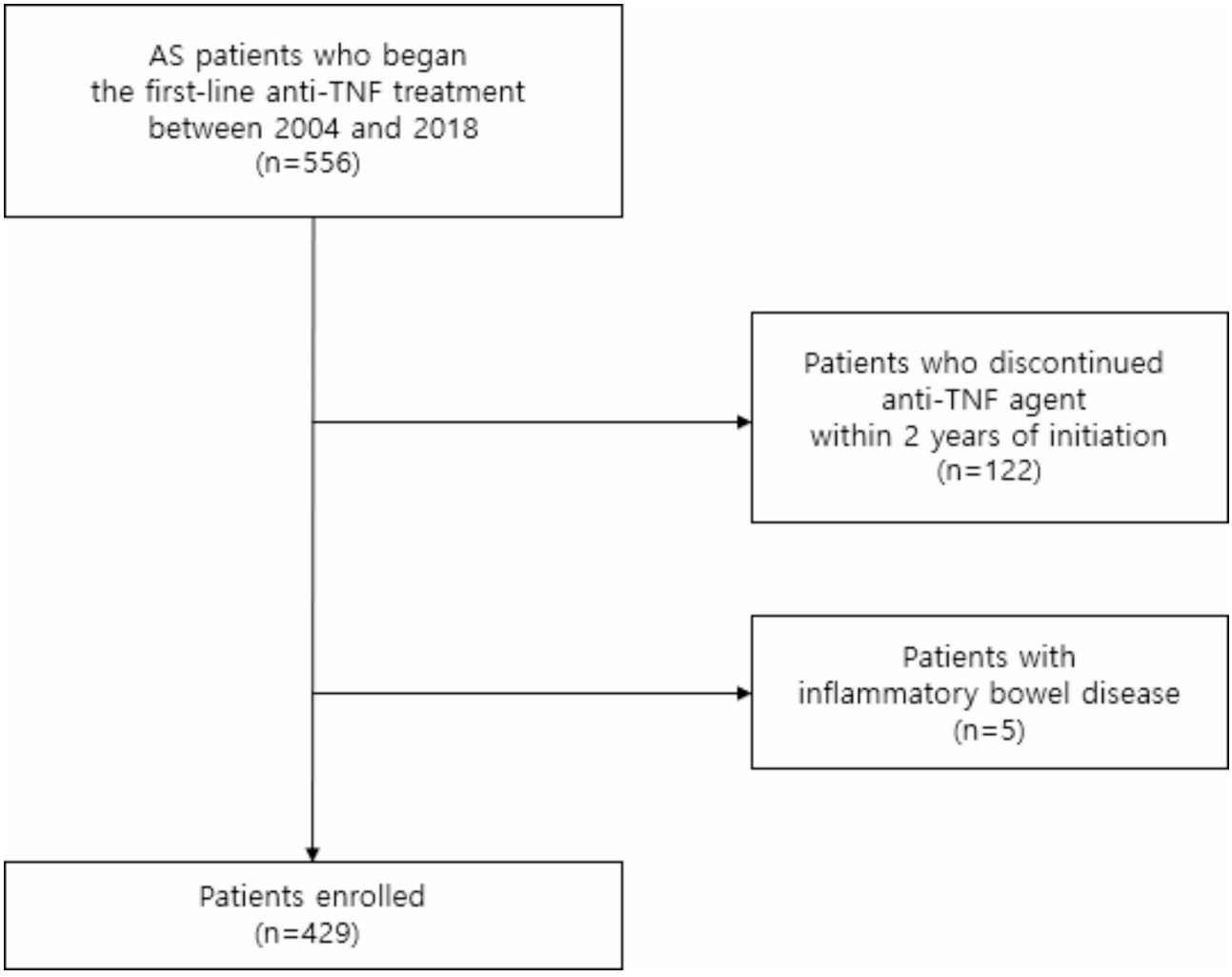

Fig. 1 Flow chart of patient selection
Ankylosing spondylitis, AS; TNF, tumor necrosis factor

In comparison to adalimumab, the use of etanercept was associated with a decreased likelihood of discontinuation due to clinical remission (Hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.21–0.99, $P=0.048$). Higher baseline BASDAI (HR 1.31, 95% CI 1.04–1.65, $P=0.023$) and the use of infliximab (HR 4.53, 95% CI 1.45–14.16, $P=0.009$) were predictors for discontinuation due to loss of efficacy. Increased age was a predictor for discontinuation due to infection-related adverse events (HR 1.07, 95% CI 1.02–1.12, $P=0.005$). Current smokers were more likely to discontinue anti-TNF treatment due to other reasons (HR 6.22, 95% CI 1.82–21.28, $P=0.004$).

Discussion

In this study using real-world data, we investigated cause-specific discontinuation in 429 AS patients receiving first-line anti-TNF treatment. We specifically focused on the long-term use of anti-TNF agents; therefore, only patients who continued treatment for at least two years were included; 21.9% (122 of 556) discontinued the therapy within the first two years. During an overall survival period of 10.6 (7.9–14.5) years, we observed a discontinuation rate of anti-TNF inhibitors in 24.0% of patients. The cumulative incidence function for cause-specific discontinuation was similar across types of anti-TNF agents, with the exception of discontinuation due to loss of efficacy. Specifically, the use of infliximab was associated with a higher risk of discontinuation due to loss of efficacy, as well as higher baseline BASDAI scores. The predictors for discontinuation varied depending on the specific cause, highlighting the complexity of treatment response and patient factors influencing therapy discontinuation. Etanercept use was associated with a decreased likelihood of discontinuation due to clinical remission compared to the use of adalimumab. Older age was associated with discontinuation caused by infections, while current smokers were more likely to discontinue anti-TNF treatment for other reasons.

Table 1 Clinical characteristics of patients

Variables	All patients (*N* = 429)	Adalimumab (*N* = 121)	Etanercept (*N* = 176)	Infliximab (*N* = 89)	Golimumab (*N* = 43)	*P*
Age, years	32.1 (26.9–38.5)	31.2 (26.7–37.6)	31.4 (25.9–38.1)	33.3 (28.5–40.8)	33.5 (28.5–42.8)	0.161
Male sex	381 (88.8)	110 (90.9)	150 (85.2)	81 (91.0)	40 (93.0)	0.260
Symptom duration						0.496
< 5 years	110 (25.6) 319 (74.4)	36 (29.8)	45 (25.6)	21 (23.6)	8 (18.6)	
≥ 5 years		85 (70.3)	131 (74.4)	68 (76.4)	35 (81.4)	
Disease duration, years	4.5 (1.2–8.8)	4.1 (1.3-8.0)	4.4 (1.0-9.5)	4.2 (1.0-7.5)	6.2 (3.3–10.9)	0.119
Overall survival, years	10.6 (7.9–14.5)	10.2 (7.8–12.0)	13.5 (10.2–16.7)	10.0 (7.4–12.5)	7.7 (7.0-9.1)	< 0.0001
Baseline mSASSS	8.7 (5.5–21.8)	8.0 (5.8–16.0)	9.4 (6.0-22.4)	8.0 (5.0-24.5)	11.0 (6.0–25.0)	0.528
Baseline BASDAI	7.0 (6.0–8.0)	6.8 (5.7-8.0)	6.8 (5.9–7.9)	7.2 (6.2-8.0)	7.3 (6.7–8.4)	0.146
BASDAI at 3 months	2.8 (2.0–4.0)	2.8 (2.0-3.8)	2.7 (2.0-3.8)	3.0 (1.9-4.0)	3.5 (1.6–5.4)	0.337
Baseline CRP	2.1 (0.9–4.6)	2.2 (0.9–4.7)	2.7 (1.1–4.9)	1.6 (0.8-4.0)	1.8 (1.2–3.6)	0.067
CRP at 3 months	0.8 (0.8–0.8)	0.8 (0.8–0.8)	0.8 (0.8–0.8)	0.8 (0.8–0.8)	0.8 (0.8–0.8)	0.628
HLA-B27 positivity	417 (97.2)	119 (98.4)	171 (97.2)	85 (95.5)	42 (97.7)	0.656
Psoriasis	16 (3.7)	6 (5.0)	8 (4.6)	2 (2.3)	0 (0.0)	0.485
Uveitis	182 (42.4)	45 (37.2)	91 (51.7)	36 (40.5)	10 (23.3)	0.003
Peripheral joint involvement	226 (52.7)	65 (53.7)	98 (55.7)	45 (50.6)	18 (41.9)	0.412
Use of NSAIDs	425 (99.1)	121 (100.0)	173 (98.3)	88 (98.9)	43 (100.0)	0.465
Anti-TNF discontinuation						0.005
Loss of efficacy	36 (34.9)	4 (12.9)	19 (38.0)	13 (68.4)	0 (0.0)	
Clinical remission	31 (30.1)	14 (45.2)	11 (22.0)	4 (21.0)	2 (66.7)	
Adverse events	15 (14.6)	6 (19.4)	8 (16.0)	1 (5.3)	0 (0.0)	
Infection	3 (2.9)	2	0	1	0	
Skin adverse events	3 (2.9)	2	1	0	0	
Others	9 (8.8)	2	7	0	0	
Other reasons	21 (20.4)	7 (22.6)	12 (24.0)	1 (5.3)	1 (33.3)	
Smoking status						0.424
Never	175 (40.8)	49 (40.5)	75 (42.6)	31 (34.8)	20 (46.5)	
Ex	55 (12.8)	15 (12.4)	25 (14.2)	8 (9.0)	7 (16.3)	
Current	199 (46.4)	57 (47.1)	76 (43.2)	50 (56.2)	16 (37.2)	

TNF, tumor necrosis factor ; mSASSS, the modified Stoke Ankylosing Spondylitis Spinal Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA, human leukocyte antigen; NSAID, non-steroidal anti-inflammatory drugs

Taking a closer look at the reasons for discontinuation, the discontinuation in the present study was primarily attributed to loss of efficacy (34.9%), followed by clinical remission (30.1%), other reasons (20.4%), and adverse events (14.6%). In contrast, a study conducted on Korean AS patients by Kim et al., reported a different ranking of reasons, with other reasons (32.6%) and loss of efficacy (32.6%) being the most common, followed by adverse events (23.6%), and clinical remission (11.2%) [11]. Remarkably, our study observed a relatively lower rate of discontinuation due to adverse events, which may be attributed to our research design; We excluded patients who discontinued anti-TNF agents within the first two years. It is important to note that adverse events, such as skin reactions, allergies, and severe infection, tend to be more frequent during the initial stages of anti-TNF therapy [18–20]. Additionally, our extended follow-up duration may have contributed to the relatively high rate of clinical remission. The longer follow-up duration likely led to more discontinuation attempts among individuals who had experienced sustained remission over an extended period [2].

Interestingly, our study demonstrated variations in discontinuation rates among anti-TNF agents. Infliximab showed a greater discontinuation rate due to loss of effectiveness compared to other anti-TNF agents, with similar results reported in previous studies [4, 5, 21]. This phenomenon may be attributed to drug antibodies that can potentially diminish efficacy by neutralizing the therapeutic effects or hastening its elimination from the body. Infliximab, in particular, is known to have the highest incidence of drug antibody formation among anti-TNF agents [22]. In contrast, etanercept, which is associated with the lowest generation of drug antibodies [22], was linked to a reduced likelihood of discontinuation due to clinical remission compared to the use of adalimumab. This observation may be explained, in part, by considerations related to uveitis. Uveitis incidence tends to

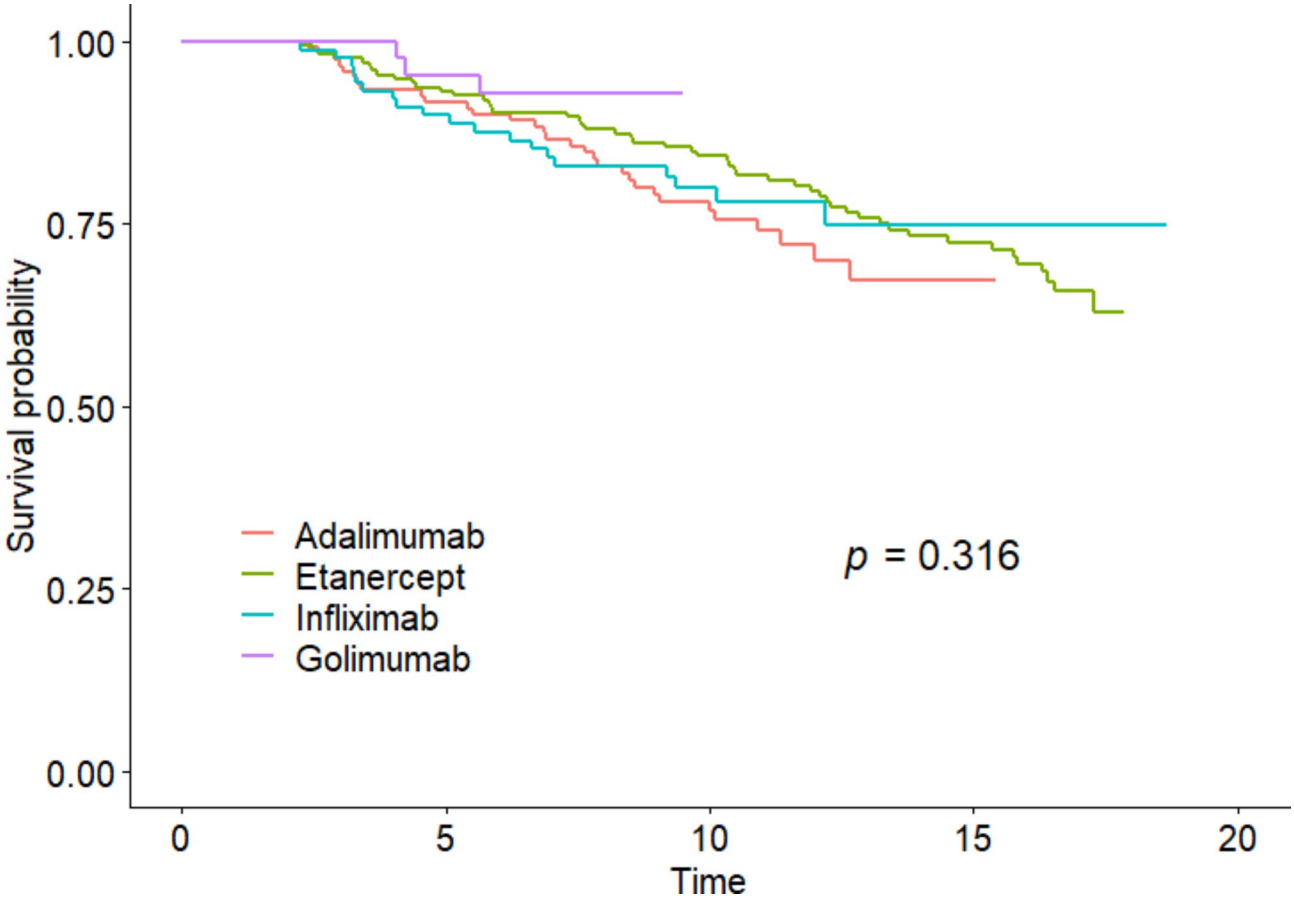

Fig. 2 Kaplan-Meier survival curve for anti-TNF agents

increase with disease duration [23], and given the focus of our study on the long-term use of anti-TNF agents, the unfavorable results may be attributed to uveitis. Etanercept has demonstrated clear inferiority in controlling uveitis compared to other anti-TNF agents such as infliximab or adalimumab [24, 25]. While adalimumab does induce drug antibody formation, albeit to a lesser extent than infliximab [22], it is not associated with an increased risk of uveitis. Moreover, the less frequent dosing regimen of adalimumab compared to etanercept may facilitate easier tapering when patients achieve clinical remission. A multicenter retrospective study demonstrating the eight-year retention rate of first-line anti-TNF in SpA patients showed similar findings. Adalimumab demonstrated the highest persistence, while infliximab exhibited the lowest retention rate in AS, although this trend did not reach statistical significance [8].

Higher baseline BASDAI scores, consistently demonstrated in prior research, have been linked to an increased risk of discontinuation due to loss of efficacy [10, 26–28]. Conversely, elevated objective inflammatory markers like CRP and acute inflammation detected on MRI have consistently shown a strong association with a clinical response to anti-TNF agents or treatment continuation [10, 12, 14, 29–32]. Consequently, recent guidelines emphasize the importance of evaluating these objective signs of inflammation before initiating biologics, as patients displaying these indicators tend to experience more favorable treatment outcomes [2]. The BASDAI solely reflects the patients' perspective, which may account for the disparities observed between BASDAI and objective inflammation markers in predicting treatment outcomes [33].

Smoking is a well-established poor prognostic factor in AS, linked to increased disease activity and radiologic progression [34]. An observational cohort study, based on the Danish nationwide DANBIO registry, revealed that both current and former smokers exhibited significantly poorer patient-reported outcomes at baseline, shorter treatment adherence, and inferior treatment responses compared to individuals who had never smoked [15]. Notably, our study found that current smokers were more likely to discontinue their anti-TNF treatment for other reasons including loss to follow-up, cost, or reimbursement issues. Given the strong recommendation for smoking cessation as a crucial component of AS patient treatment [35], we can interpret the link between

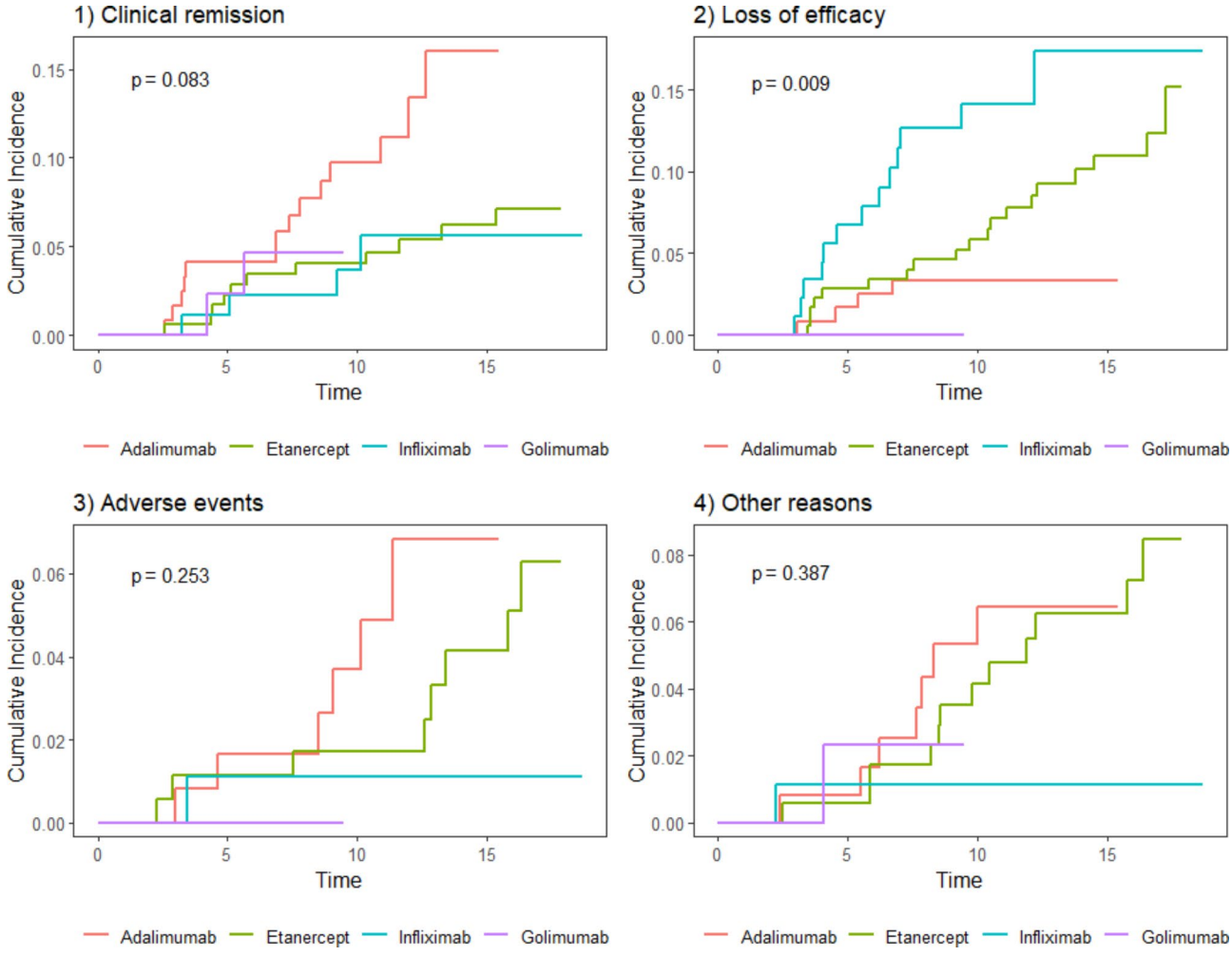

Fig. 3 Cumulative incidence function for individual anti-tumor necrosis factor agents

current smoking and discontinuation for other reasons as a potential sign of suboptimal treatment adherence.

There was no significant difference in overall adverse events among the anti-TNF agent groups. However, older age was a significant risk factor for discontinuation due to infection-related adverse events, in line with the well-established understanding that older age is associated with an increased risk of infections [36]. Remarkably, our study revealed that only three cases of infections resulted in discontinuation of anti-TNF therapy. This finding aligns with prior researches, suggesting that TNF inhibitors are generally safe for AS treatment [37–39]. In a recent meta-analysis of 3,564 AS patients from 18 randomized controlled trials, anti-TNF treatment was not associated with a significant increase in the risk of serious infection or upper respiratory tract infection compared to the placebo group (Odds ratio [OR] = 1.44, p = 0.36 and OR = 1.22, p = 0.16, respectively). The sole statistically significant difference was the higher occurrence rate of nasopharyngitis among AS patients treated with anti-TNF agents, at 8.69%, in contrast to the placebo rate of 5.67% (OR = 1.53, p = 0.03) [40].

The present study had several limitations. Firstly, it is a single-center observational study, which may introduce selection bias and sampling bias. Second, our results may be influenced by reimbursement policies in South Korea. Third, the number of patients using Golimumab and the duration of observation were limited, primarily due to the delayed approval of Golimumab compared to other biologics. Golimumab has been reported to exhibit better drug persistence than other anti-TNF agents [11, 21, 41], but this association was not observed in our study. Fourth, in cases where patients sustained clinical remission, dose tapering or extension of the interval of anti-TNF use is common practice. These alterations might contribute to the persistence of treatment. However, we did not account for doses and intervals of anti-TNF treatment. Additionally, extra-musculoskeletal manifestations, including uveitis, can influence treatment decisions and outcomes. The retrospective nature of our study

Table 2 Multivariable cause-specific hazard model

	Clinical remission		Loss of efficacy		Overall adverse events		Infection-related adverse events		Other reasons	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, years	0.99 (0.95–1.03)	0.516	1.03 (1.00-1.06)	0.052	1.02 (0.97–1.07)	0.486	1.07 (1.02–1.12)	0.005	0.98 (0.92–1.04)	0.445
Male	3.61 (0.46–28.27)	0.222	1.58 (0.49–5.07)	0.440	0.78 (0.15–4.19)	0.771			1.05 (0.12–9.25)	0.966
Symptom duration										
< 5 years	1.93 (0.95–3.93)	0.070	0.80 (0.35–1.81)	0.594	0.26 (0.03–2.25)	0.221			1.63 (0.65–4.08)	0.300
≥ 5 years	Reference		Reference		Reference				Reference	
Baseline mSASSS					1.02 (1.00-1.04)	0.062	1.02 (0.99–1.06)	0.228		
Baseline BASDAI			1.31 (1.04–1.65)	0.023						
Baseline CRP							0.83 (0.58–1.18)	0.290		
Uveitis					2.02 (0.70–5.86)	0.195				
Peripheral joint involvement			1.99 (0.98–4.03)	0.056						
Use of anti-TNF agents										
Adalimumab	Reference		Reference		Reference				Reference	
Etanercept	0.45 (0.21–0.99)	0.048	2.89 (0.98–8.51)	0.054	0.45 (0.16–1.26)	0.128			0.93 (0.36–2.37)	0.872
Infliximab	0.40 (0.13–1.25)	0.115	4.53 (1.45–14.16)	0.009	0.18 (0.02–1.55)	0.119			0.17 (0.02–1.46)	0.107
Golimumab	0.65 (0.14–2.92)	0.572	-	-	-	-			0.85 (0.11–6.96)	0.882
Smoking status										
Never									Reference	
Ex									1.46 (0.12–18.47)	0.768
Current									6.22 (1.82–21.28)	0.004

HR, hazard ratio; mSASSS, the modified Stoke Ankylosing Spondylitis Spinal Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive potein; TNF, tumor necrosis factor

meant that pre-existing uveitis could not be clearly determined. However, considering that we frequently encounter situations where uveitis develops over the follow-up period, even if not initially present. We believe that our strategy better reflects the real-world scenarios faced by AS patients and their healthcare providers. Despite these limitations, the value of this study lies in its examination of extended real-world retention of anti-TNF agents and the analysis of cause-specific discontinuation. Through the exclusion of early discontinuations, it provides valuable insights into the extended phase of anti-TNF use. With a median overall survival of 10.6 years, it effectively bridges a preceding research gap and enables a more in-depth exploration of long-term anti-TNF users.

To conclude, our study of 429 AS patients on first-line anti-TNF treatment for at least two years reveals a favorable long-term treatment retention rate, with a 24.0% discontinuation rate over an overall survival period of 10.6 years. Predictors for discontinuation differed by cause, highlighting the complexity of treatment response and emphasizing the need for personalized approaches to treatment management. Further research is warranted to uncover the underlying mechanisms behind these discontinuation patterns and to refine strategies for optimizing patient outcomes in the realm of AS treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-024-00410-w.

Supplementary Material 1

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Author contributions

Conceptualization: Nam B, Kim T-H, Koo BS. Formal analysis: Choi N, Kim J. Funding acquisition: Kim T-H. Investigation: Nam B, Kim T-H. Methodology: Nam B, Choi N, Kim J. Visualization: Choi N, Kim J. Writing - original draft: Nam B. Writing - review & editing: Koo BS, Kim T-H.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed according to the guidelines of the Helsinki Declaration and was approved by the Institutional Review Board (IRB) of Hanyang University Hospital (IRB file No. HYUH 2021-10-013). Informed consent was waived because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379–90.
2. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023;82(1):19–34.
3. Anghel L-A, Farcaş AM, Oprean RN. Medication adherence and persistence in patients with autoimmune rheumatic diseases: a narrative review. Patient Prefer Adherence 2018:1151–66.
4. Biggioggero M, Favalli EG. Ten-year drug survival of anti-TNF agents in the treatment of inflammatory arthritides. Drug Dev Res. 2014;75:S38–41.
5. Scirè C, Caporali R, Puttini S, Frediani P, Di Franco B, Tincani M. Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet database. Clin Exp Rheumatol. 2013;31(6):857–63.
6. Visman I, Atiqi S, Boers M, Twisk J, Nurmohamed M. Changes in TNF inhibitor drug survival in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis over 15 years. J Rhuematol 2023.
7. Ørnbjerg L, Brahe M, H C, Askling J, Ciurea A, Mann H, Onen F, et al. Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. Ann Rheum Dis. 2019;78(11):1536–44.
8. Favalli EG, Selmi C, Becciolini A, Biggioggero M, Ariani A, Santilli D, et al. Eight-year retention rate of first-line tumor necrosis factor inhibitors in spondyloarthritis: a multicenter retrospective analysis. Arthritis Care Res. 2017;69(6):867–74.
9. Benavent D, Franco-Gómez K, Plasencia-Rodriguez C, Novella-Navarro M, Bogas P, Nieto R, et al. Achievement rate and predictive factors of the recommended therapeutical target in patients with axial spondyloarthritis who remain on biological therapy: a prospective cohort study in Spain. BMJ open. 2022;12(4):e057850.
10. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Therapy. 2011;13(3):1–10.
11. Kim H-A, Lee S-K, Oh S, Park EH, Park Y-B, Shin K. Comparison of retention rates between tumor necrosis factor-α inhibitors in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics Registry. Front Med. 2021;8:689609.
12. Glintborg B, Østergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010;69(11):2002–8.
13. Vastesaeger N, Van Der Heijde D, Inman RD, Wang Y, Deodhar A, Hsu B et al. Predicting the outcome of ankylosing spondylitis therapy. *Annals of the rheumatic diseases* 2011;70(6):973 – 81.
14. Davis JC, Van der Heijde DM, Dougados M, Braun J, Cush JJ, Clegg DO, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rhuematol. 2005;32(9):1751–4.
15. Glintborg B, Højgaard P, Lund Hetland M, Steen Krogh N, Kollerup G, Jensen J, et al. Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry. Rheumatology. 2016;55(4):659–68.
16. Linden SVD, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. Arthr Rhuem. 1984;27(4):361–8.
17. Creemers M, Franssen M, Van't Hof M, Gribnau F, Van de Putte L, Van Riel P. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64(1):127–9.
18. Tong Q, Cai Q, De Mooij T, Xu X, Dai S, Qu W, et al. Adverse events of anti-tumor necrosis factor α therapy in ankylosing spondylitis. PLoS ONE. 2015;10(3):e0119897.
19. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology. 2011;50(1):124–31.
20. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Annals of the rheumatic diseases* 2007;66(10):1339-44.
21. Egeberg A, Rosenø NAL, Aagaard D, Lørup EH, Nielsen M-L, Nymand L et al. in *Seminars in Arthritis and Rheumatism*. 151979 (Elsevier).
22. 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.
23. Stolwijk C, Essers I, van Tubergen A, Boonen A, Bazelier MT, De Bruin ML, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. Ann Rheum Dis. 2015;74(7):1373–8.
24. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis. 2006;65(12):1631–4.
25. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheumatism: Official J Am Coll Rheumatol. 2007;56(10):3248–52.
26. Chiowchanwisawakit P, Katchamart W, Osiri M, Narongroeknawin P, Chevaisrakul P, Kitumnuaypong T, et al. Effectiveness and drug survival of anti–tumor necrosis factor α therapies in patients with spondyloarthritis: analysis from the Thai Rheumatic Disease Prior Authorization Registry. JCR: J Clin Rheumatol. 2019;25(1):9–15.
27. Ouardi NE, Maghraoui AE, Djossou H, Taoubane L, Ghassem A, Toufik H, et al. Discontinuation of biologic therapy in patients with rheumatoid arthritis and ankylosing spondylitis: analysis from multicenter cohort study. Rheumatol Int. 2023;43(1):79–87.
28. Pombo-Suárez M, Seoane-Mato D, Díaz-González F, Cea-Calvo L, Sánchez-Alonso F, Sánchez-Jareño M, et al. Long-term retention of golimumab treatment in clinical practice in a large cohort of patients with rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis. Musculoskelet Care. 2023;21(1):189–97.
29. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor α blockers in ankylosing spondylitis. Ann Rheum Dis. 2004;63(6):665–70.
30. Rudwaleit M, Schwarzlose S, Hilgert E, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis. 2008;67(9):1276–81.
31. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with

non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72(6):815–22.
32. Sieper J, Van Der Heijde D, Dougados M, Maksymowych W, Scott B, Boice J, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2015;67(10):2702–12.
33. Nam B, Koo BS, Lee T-H, Shin J-H, Kim J-J, Lee S, et al. Low BASDAI score alone is not a good predictor of anti-tumor necrosis factor treatment efficacy in ankylosing spondylitis: a retrospective cohort study. BMC Musculoskelet Disord. 2021;22(1):1–8.
34. Nam B, San Koo B, Choi N, Shin J-H, 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 2022;9.
35. Nam B, Koo BS, Nam SW, Shin J-H, Song Y, Cho S-K, et al. Gender differences in factors associated with low quality of life and depression in Korean patients with ankylosing spondylitis. Qual Life Res. 2021;30:2299–310.
36. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis. 2000;30(6):931–3.
37. Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. Ann Rheum Dis. 2010;69(10):1756–61.
38. Hou L-q, Jiang G-x, Chen Y-f, Yang X-M, Meng L, Xue M, et al. The comparative safety of TNF inhibitors in ankylosing spondylitis—a meta-analysis update of 14 randomized controlled trials. Clin Rev Allergy Immunol. 2018;54:234–43.
39. Xu Z, Xu P, Fan W, Yang G, Wang J, Cheng Q, et al. Risk of infection in patients with spondyloarthritis and ankylosing spondylitis receiving antitumor necrosis factor therapy: a meta–analysis of randomized controlled trials. Experimental Therapeutic Med. 2017;14(4):3491–500.
40. Feng H, Zhao Y, Kuang W, Dai Y, Cen X, Qin F. Adverse events of tumor necrosis factor alpha inhibitors for the treatment of ankylosing spondylitis: a meta-analysis of randomized, placebo-controlled trials. Front Pharmacol. 2023;14:1084614.
41. Dalén J, Svedbom A, Black CM, Lyu R, Ding Q, Sajjan S, et al. Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. Rheumatol Int. 2016;36:987–95.

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