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Treatment response and retention rates of bDMARDs in advanced spinal ankylosis or bamboo spine: Real-world data from the HUR-BIO registry

İleri spinal ankiloz veya bambu omurga olan hastalarda bDMARD tedavi yanıtı ve ilaç devamlılığı: HUR-BIO kayıt sisteminden gerçek yaşam verileri

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Abstract

Objectives: To evaluate clinical characteristics, biological disease-modifying antirheumatic drugs (bDMARD) treatment response and drug retention in patients with axial spondyloarthritis (axSpA) with advanced spinal ankylosis or bamboo spine, compared with patients without syndesmophytes.

Methods: Patients from the Hacettepe University Rheumatology Biologic Registry who had available cervical and lumbar radiographs were classified into three groups: advanced spinal ankylosis, bamboo spine, and a control group with at least ten-year disease duration and without syndesmophytes. Baseline characteristics, treatment responses [Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) and Assessment of Spondyloarthritis International Society partial remission (ASAS-PR)], and retention of first bDMARDs were evaluated.

Results: Of 770 patients, 99 had advanced spinal ankylosis, 78 had bamboo spine, and 92 constituted the control group. Patients with advanced structural damage were older, more often male, and had higher body mass index, greater smoking exposure, and more frequent hip involvement. Baseline disease activity was similar across groups. At follow-up, BASDAI50 and ASAS-PR responses were comparable among advanced spinal ankylosis, bamboo spine, and controls. Median retention of first bDMARDs did not differ significantly between groups (log-rank p=0.86). One-year retention rates were 75% (no syndesmophytes), 84% (advanced spinal ankylosis), and 78% (bamboo spine); at 5 years, retention rates were 67%, 64%, and 60%, respectively; and at 10 years, retention rates were 50%, 41%, and 43%, respectively. Median drug survival ranged from 104 to 126 months across groups.

Özet

Amaç: Bu çalışmanın amacı, ileri spinal ankiloz veya bambu omurgası olan aksiyel spondiloartrit (axSpA) hastalarında klinik özellikleri, biyolojik hastalık modifiye edici antiromatizmal ilaçlara (bDMARD) tedavi yanıtını ve ilaç devamlılığını, sindesmofiti olmayan hastalarla karşılaştırarak değerlendirmektir.

Yöntem: Hacettepe Üniversitesi Romatoloji Biyolojik Kayıt Sistemi'nde yer alan ve servikal ile lomber radyografileri mevcut olan hastalar üç gruba ayrıldı: ileri spinal ankiloz, bambu omurga ve en az 10 yıllık hastalık süresi olup sindesmofiti olmayan kontrol grubu. Başlangıç özellikleri, tedavi yanıtları [Bath Ankilozan Spondilit Hastalık Aktivite İndeksi 50'nin (BASHAİ50) ve Uluslararası Spinal Ankiloz Çalışma Grubu parsiyel remisyon (ASAS-PR)] ve ilk bDMARD tedavisinin devamlılığı değerlendirildi.

Bulgular: Toplam 770 hastanın 99'unda ileri spinal ankiloz, 78'inde bambu omurga saptandı ve 92 hasta kontrol grubunu oluşturdu. İleri yapısal hasarı olan hastalar daha ileri yaşta, daha sıklıkla erkek cinsiyette olup daha yüksek vücut kitle indeksi, sigara maruziyeti ve kalça tutulumu oranına sahipti. Başlangıç hastalık aktivitesi gruplar arasında benzerdi. İzlem sürecinde BASHAİ50 ve ASAS-PR yanıtları ileri spinal ankiloz, bambu omurga ve kontrol grupları arasında benzer bulundu. İlk bDMARD tedavisinin medyan devam süresi gruplar arasında anlamlı farklılık göstermedi (log-rank p=0,86). Bir yıllık ilaç devam oranları sırasıyla %75 (sindesmofit yok), %84 (ileri spinal ankiloz) ve %78 (bambu omurga) idi. Beş yılda bu oranlar sırasıyla %67, %64 ve %60; 10 yılda ise %50, %41 ve %43 olarak bulundu. Medyan ilaç sağkalımı gruplar arasında 104-126 ay arasında değişmekteydi.

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Abstract

Conclusion: Patients with advanced spinal ankylosis or bamboo spine achieve meaningful clinical improvement with bDMARD therapy and demonstrate long-term drug retention comparable to that of axSpA patients without syndesmophytes, supporting the initiation and continued use of bDMARDs in this population.

Keywords: Ankylosing spondylitis, axial spondyloarthritis, advanced spinal ankylosis, bamboo spine, bDMARDs, treatment response, retention rate

Öz

Sonuç: İleri spinal ankiloz veya bambu omurga varlığı olan hastalar bDMARD tedavisi ile anlamlı klinik iyileşme sağlamakta ve sindesmofiti olmayan axSpA hastalarına benzer uzun dönem ilaç devamlılığı göstermektedir. Bu bulgular, bu hasta grubunda bDMARD tedavisinin başlanmasını ve sürdürülmesini desteklemektedir.

Anahtar Kelimeler: Ankilozan spondilit, aksiyel spondiloartrit, ileri spinal ankiloz, bambu omurga, bDMARD'ler, tedavi yanıtı, ilaç devamlılığı

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that predominantly affects the axial skeletal.[1,2] In axSpA, structural spinal damage may occur through the formation of syndesmophytes.[3] Over time, progressive intervertebral ossification can lead to the development of bony bridges between consecutive vertebrae, ultimately resulting in advanced spinal ankylosis, and, in its most severe form, the characteristic "bamboo spine" appearance.[4] Advanced spinal disease is associated with impaired physical function,[5] reduced mobility,[6] and may lead to permanent disability and decreased quality of life.[7] In advanced spinal ankylosis or bamboo spine, which reflect irreversible structural damage,[8] identifying the presence of active inflammation remains important for disease management.

Biological disease-modifying antirheumatic drugs (bDMARDs) have been shown to be effective in controlling inflammation and disease activity in axSpA in randomized controlled trials (RCTs).[9] Many RCTs of bDMARDs did not include participants with severe spinal structural damage because it was assumed that they would have a lower therapeutic response. To date, two RCTs have shown that adalimumab[10] and etanercept[11] are effective in patients with advanced spinal ankylosis or bamboo spine who have high disease activity. In addition, two other studies have reported the efficacy of infliximab over 54 weeks[12] and adalimumab over 12 weeks[13] in this patient population. Overall, real-world evidence on the use of bDMARDs in patients with advanced spinal ankylosis or bamboo spine remains very limited.

This real-world study aims to compare baseline features, bDMARDs treatment response, and drug retention in patients with advanced spinal ankylosis and bamboo spine versus patients without syndesmophytes, all with at least 10-year disease duration.

Materials and Methods

Database, Study Population and Selection of Control Group

Hacettepe University Rheumatology Biologic Registry (HUR-BIO) is a prospective, single center database of biological treatments, established in 2005, and with a prospective design since 2012.[14] At the time of data collection, the HUR-BIO SpA registry had enrolled 2907 patients. Of these, 770 patients underwent lateral radiographs of the lumbar and cervical spine and were included in the study. Radiographic images of the lumbar and cervical spine were assessed by an experienced physician (UK) using predefined standardised definitions for the presence of syndesmophytes, spinal ankylosis, and bamboo spine. Radiographic data in the registry were recorded categorically (presence or absence of syndesmophytes and predefined structural classifications), and the exact number of syndesmophytes or bridged vertebral units was not systematically documented.

Three subgroups were established: 1) "advanced spinal ankylosis," defined by the presence of at least two intervertebral adjacent bridges and/or fusion at the lumbar and/or cervical spine,[11] without bamboo spine; 2) "bamboo spine," defined by the presence of a Bath Ankylosing Spondylitis Radiologic Index (BASRI)-spine grade 4,[15] with complete fusion of the cervical and lumbar vertebrae; "control group" of patients with at least 10-year disease duration without syndesmophytes at lumbar and cervical spine (BASRI 0, 1 and 2 without syndesmophytes). It was thought that this control group would be very unlikely to ever develop syndesmophytes of the spine.[16] Hip involvement was defined as BASRI-hip grade 2, 3, or 4.[17]

Data Collection, Outcome Measures and Response to bDMARD Treatment

Baseline (at the start of bDMARD treatment) demographic, clinical, laboratory, treatment and imaging data were collected from the HUR-BIO database: age, gender, age at disease onset, disease duration, body mass index (BMI), SpA family history (first-degree), human leukocyte antigen (HLA)-B27, history of uveitis, enthesitis, dactylitis, peripheral joint involvement, use of bDMARDs, use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and corticosteroid treatment.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score,[18] Bath Ankylosing Spondylitis Functional Index (BASFI) score,[19] axSpA Disease Activity Score containing C-reactive protein (ASDAS-CRP),[20] visual analogue scale (VAS)-patient global assessment (PGA) (0-100 mm), pain-VAS (0-100 mm), fatigue-VAS (0-100 mm),[21] erythrocyte sedimentation rate (ESR; mm/h)

and CRP (mg/L) levels were evaluated as outcome measures, at baseline (start of bDMARD treatment) and last visit.

bDMARDs evaluated in the study included anti-tumor necrosis factor (TNF) agents (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) and the anti-interleukin-17 (IL-17) agent secukinumab. During the follow-up period, bDMARD use, bDMARD switching (if yes, reasons for switching), and response to bDMARDs were assessed at each outpatient visit. Treatment response to bDMARDs was evaluated by the BASDAI50 response (defined as a 50% improvement of the initial BASDAI score)[22] and achievement of Assessment of Spondyloarthritis International Society partial remission (ASAS-PR) (defined as a value ≤2 for each of the following four domains on a 0-10 scale: PGA of disease activity, pain, function (assessed by BASFI), and inflammation [a mean of the BASDAI questions 5 and 6)][23] at the last visit. Drug retention was assessed as the time to treatment discontinuation of the first bDMARD, including switching to another bDMARD or loss to follow-up.

Ethics Committee Approval

Ethics committee approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/03-16, date: 02.02.2021). The study was conducted in accordance with the Declaration of Helsinki. This was a retrospective study. Written informed consent was obtained from all patients at enrolment into the HUR-BIO cohort.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether they were normally distributed. Descriptive analyses were presented using medians and interquartile range (IQR) for the non-normally distributed and ordinal variables, and mean ± standard deviation for normally distributed. One-way analysis of variance was used to compare normally distributed variables. Levene's test was used to assess the homogeneity of variances. Kruskal-Wallis tests were conducted to compare non-normally distributed parameters. The Mann-Whitney U test was performed to test the significance of pairwise differences, using the Bonferroni correction to adjust for multiple comparisons. The chi-square or Fisher's exact test, where appropriate, was used to compare proportions between groups. A 5% type-I error level was used to infer statistical significance.

Results

Characteristics of the Patient Subgroups

Among 770 axSpA patients with lumbar and cervical radiographs, 78 (10.1%) had bamboo spine, 99 (12.8%) had advanced spinal ankylosis, and 92 (11.9%) had at least 10-year disease duration and no syndesmophytes; these patients were included in the study (Figure 1). Detailed quantification of the extent of syndesmophytes or the number of bridged vertebral units was not available in the database, as radiographic data were recorded categorically.

Compared to the without syndesmophytes subgroup, both the advanced spinal ankylosis and bamboo spine subgroups had higher age (42.2±8.8, 51.3±10.2 and 55.5±9.3 years, respectively, p<0.001), higher age at disease onset [25.01 (IQR 11), 36.6 (IQR 19.7) and 33.3 (IQR 17.7), respectively, p<0.001], longer delay in diagnosis [12.02 (IQR 43.01), 36.01 (IQR 89) and 36.01 (IQR 100.5) months, respectively, p=0.013], more males (59.8%, 78.8% and 84.6%, p<0.001), higher BMI [26.3 (IQR 8.1), 29.7 (IQR 7.4) and 29.4 (IQR 6.8), respectively, p<0.001], more smoking packages-years [1.6 (IQR 7.6), 10 (IQR 18.9) and 14 (IQR 30), respectively, p<0.001] and more hip involvement (3.1%, 39.5% and 49.3%, p<0.001). There were no differences between the advanced spinal disease and bamboo spine subgroups in these parameters, except for age, with the bamboo spine subgroup being older than the advanced spinal disease subgroup.

Disease duration was higher in the bamboo spine subgroup compared with both the advanced spinal ankylosis subgroup and the subgroup without syndesmophytes [17.6 (IQR 13.1), 12.3 (IQR 14.6) and 13.8 (IQR 4.9) years, respectively, p<0.001; there was no difference between the advanced spinal ankylosis and without syndesmophytes subgroups]. However, tender joints at the start of the bDMARDs treatment were more common in the subgroup without syndesmophytes than in the advanced spinal ankylosis and bamboo spine subgroups (p<0.001), with no difference between the latter two subgroups. No significant differences were observed between the subgroups in terms of swollen joints, HLA-B27 positivity, enthesitis, dactylitis, uveitis, and concomitant use of methotrexate and sulfasalazine (Table 1).

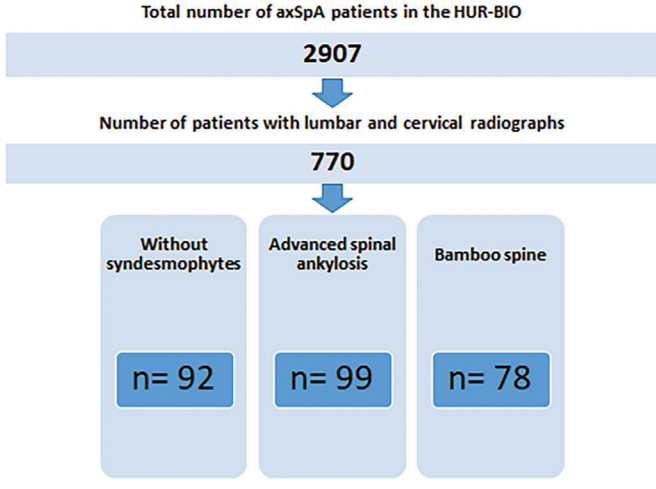

Figure 1. Study flow chart
axSpA: Axial spondyloarthritis, HUR-BIO: Hacettepe University Rheumatology Biologic Registry

Baseline Outcome Measures and Treatment Response of bDMARDs

The time from diagnosis to the start of bDMARD therapy was longer in the bamboo spine subgroup than in the advanced spinal ankylosis subgroup and the subgroup without syndesmophytes [118.7 (IQR 135), 59.7 (IQR 154) and 88.1 (IQR 102) months, respectively, p=0.007; there was no difference between the advanced spinal ankylosis and the subgroup without syndesmophytes].

ASDAS-CRP, BASDAI, BASFI, ESR, CRP, PGA-VAS, pain-VAS and fatigue-VAS levels were similar at the start of bDMARD treatment in all subgroups.

At the last visit, there was a significant difference among the three subgroups (without syndesmophytes, advanced spinal ankylosis, and bamboo spine) in terms of median CRP [0.35 (IQR 0.5), 0.65 (IQR 1), and 0.65 (IQR 0.7), respectively, p=0.001], median BASFI score [1.5 (IQR 3.7), 2.9 (IQR 4.8), and 3.9 (IQR 4.4), respectively, p=0.002], and percentage of patients with BASFI score >4 (23%, 29.8%, and 44.6%, respectively, p=0.01). The bamboo spine and advanced spinal ankylosis subgroups had significantly higher scores than the non-syndesmophyte subgroup for these parameters.

No significant differences were observed between subgroups in terms of ASDAS-CRP, BASDAI50 response, ASAS-PR, BASFI50 response, PGA-VAS, pain-VAS, and fatigue-VAS at the last visit (Table 2).

Distribution and Retention Rate of bDMARDs in the Subgroups

The median total bDMARDs usage time was longer in the bamboo spine subgroup compared to the advanced spinal ankylosis subgroup [110.02 (IQR 93.5) vs. 84.9 (IQR 82.5) months, respectively, p=0.004]; however, there was no significant

Table 1. Demographic and clinical characteristics of the study subgroups at baseline

	Without syndesmophytes (n=92)	Advanced spinal ankylosis (n=99)	Bamboo spine (n=78)	p-value
Age, years°	42.2 ± 8.8*^	51.3 ± 10.2*$^{\Sigma\times}$	55.5±9.3^$^{\Sigma\pi}$	**<0.001**
Age at onset of symptoms, years~	22.9 (11.6)*^$^{\infty}$	28 (19.4)*	27.01 (12.5)^	**<0.001**
Age at disease diagnosis, years~	25.01 (11)*^$^{\infty}$	36.6 (18.7)*	33.3 (18)^	**<0.001**
Delay in diagnosis, months~	12.5 (43)	36.01 (82)	36.01 (103)	0.054
Male, n (%)	55 (59.8)*^	78 (78.8)*$^{\times}$	66 (84.6)^$^{\pi}$	**<0.001**
Disease duration, years~	14.8 (5)^$^{\infty}$	13.4 (14.4)$^{\Sigma\times}$	18.9 (12.4)^$^{\Sigma\pi}$	**<0.001**
Family history of SpA (first-degree), positivity/total (%)	13/70 (18.6)^	21/67 (31.3)	25/61 (41)^$^{\pi}$	**0.013**
HLA-B27 positivity/total, (%)	21/42 (50)	31/45 (69)	16/28 (57)	0.19
BMI~	26.3 (8.1)*^	29.7 (7.4)*	29.4 (6.8)^	**<0.001**
Smoking, packages-year~	1.6 (7.6)*^	10 (18.9)*	14 (30)^	**<0.001**
Smoking, n (%)	*	*		**0.03**
Current	35 (38)	48 (48.5)	31 (39.7)	
Ex-smoker	21 (22.8)	32 (32.3)	27 (34.6)	
Never	36 (39.1)	19 (19.2)	20 (25.6)	
Enthesitis, positivity/total, n (%)	8/33 (24.2)	6/35 (17.1)	5/26 (19.2)	0.76
Dactylitis, positivity/total, n (%)	2/69 (3)	1/68 (1.5)	1/58 (1.7)	0.82
Uveitis, n (%)	16 (17.4)	24 (24.2)	26 (33.3)	0.055
Swollen joints, positivity/total (%)	5/43 (11.6)	2/53 (3.8)	0/29	0.08
Tender joints, positivity/total (%)	16/43 (37.2)*^	5/53 (9.4)*	0/29^	**<0.001**
Hip involvement, positivity/total (%)	11/84 (13.1)*^	34/86 (39.5)*	37/75 (49.3)^	**<0.001**
Corticosteroid use before bDMARDs, n(%)	24 (26.1)	13 (13.1)	13 (16.7)	0.06
Concomitant csDMARDs use, n (%)				
Sulfasalazine	19 (20.7)	19 (19.2)	17 (21.8)	0.91
Methotrexate	2 (2.2)	4 (4)	7 (9)	0.11

" Patients with syndesmophytes without advanced spinal ankylosis or patients without syndesmophyte with <10-year disease duration, ° mean ± SD, ~ median (IQR), * p<0.05 for comparison between subgroups "without syndesmophytes" and "advanced spinal ankylosis," ^ p<0.05 for comparison between subgroups "without syndesmophytes" and "bamboo spine," $^{\Sigma}$ p<0.05 for comparison between subgroups "advanced spinal ankylosis" and "bamboo spine," $^{\infty}$ p<0.05 for comparison between subgroups "without syndesmophytes" and remaining subgroups, $^{\times}$ p<0.05 for comparison between subgroups "advanced spinal ankylosis" and remaining subgroups, $^{\pi\times}$ p<0.05 for comparison between subgroups "bamboo spine" and remaining subgroups

bDMARDs: Biological disease-modifying antirheumatic drugs, BMI: Body mass index, csDMARDs: Conventional synthetic DMARD, HLA: Human leukocyte antigen, IQR: Interquartile range, SD: Standard deviation, SpA: Spondyloarthritis

difference compared to the subgroup without syndesmophytes [110.02 (93.5) vs. 105.03 (89.03) months, respectively, p=0.2]. Additionally, there was no significant difference between subgroups in the duration of use of the first bDMARD. Switching rates for bDMARDs were 42.4%, 43.4%, and 46.2% in the subgroups without syndesmophytes, with advanced spinal ankylosis, and with bamboo spine, respectively (p=0.88). The distribution of the first and last bDMARD treatments among subgroups is shown in Figure 2; no significant differences were observed between subgroups.

Retention rates for first bDMARDs in patients without syndesmophytes, advanced spinal ankylosis, and bamboo spine were 75%, 84%, and 78% at 1 year; 67%, 64%, and 60% at 5 years; and 50%, 41%, and 43% at 10 years, respectively. Median bDMARD therapy survival times in patients without syndesmophytes, without advanced spinal ankylosis, and without bamboo spine were 126.2 (104.2-148.1), 106.9 (80.8-133.1), and 104.0 (72.2-135.8) months, respectively. There was no difference between subgroups the retention rates of the first bDMARDs (log-rank test p-value=0.86) (Figure 3).

Discussion

In this real-world study, patients with advanced spinal ankylosis and bamboo spine demonstrated treatment responses and bDMARD retention rates comparable to those of patients without syndesmophytes. These findings provide important evidence supporting the continued and timely use of bDMARDs in patients with advanced structural spinal damage who exhibit high disease activity.

An important methodological consideration is the potential heterogeneity within the advanced spinal ankylosis group. The definition used (≥2 adjacent intervertebral bridges) may encompass a spectrum of structural severity, ranging from limited bridging to more extensive ankylosis. As the extent of structural involvement was not systematically quantified in the registry, this heterogeneity could not be explored further and may have influenced subgroup comparisons. In addition, the distinction between advanced spinal ankylosis and bamboo spine is based on a categorical threshold (BASRI-spine grade 4), which may introduce a threshold effect between near-complete and complete fusion. Patients with very similar structural burden may therefore be classified into different groups. Accordingly, these categories should be interpreted as pragmatic classifications rather than as strictly distinct biological states.

Table 2. Follow-up period and disease assessments at baseline and last visit, stratified by subgroup

	Without syndesmophytes (n=92)		Advanced spinal disease (n=99)		Bamboo spine (n=78)		p-value	
Time between diagnosis to start of bDMARD therapy~	88.1 (102)^		59.7 (154)$^{\Sigma}$		118.7 (135)^$^{\Sigma}$		**0.007**	
Follow-up duration, months~	94.6 (79.9)		78.8 (80.1)$^{\Sigma}$		102.3 (94.1)$^{\Sigma}$		**0.017**	
First bDMARD usage time, months~	61.7 (103)		46 (77)		59.2 (95)		0.76	
Total bDMARD usage time, months~	105.03 (89.03)		84.9 (82.5)$^{\Sigma}$		110.02 (93.5)$^{\Sigma}$		**0.013**	
bDMARD switch, n (%)	39 (42.4)		43 (43.4)		36 (46)		0.88	
	Baseline	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**
ESR, mm/h~	21.5 (34)	11 (13.5)	25.5 (29)	14 (16)	23 (31)	14 (13.5)	0.6	0.47
CRP, mg/dL~	1.5 (4)	0.35 (0.5)*^	1.7 (2)	0.65 (1)*	1.8 (3)	0.65 (0.7)^	0.4	**<0.001**
ASDAS-CRP~	3.6 (0.8)	1.86 (1)	3.4 (0.9)	2 (1.2)	3.4 (0.8)	1.87 (1.4)	0.4	0.23
BASDAI~	5.7 (2.6)	2 (4)	5.6 (3.3)	2.5 (3)	5.6 (3.2)	2.4 (3)	1	0.23
BASDAI50 response, positive/ total, n (%)		41/68 (60.3)		36/68 (52.9)		27/52 (51.9)		0.58
BASFI~	5.4 (4)	1.5 (3.7)^	4.5 (4)	2.9 (4.8)	6.5 (3)	3.9 (4.4)^	0.1	**0.002**
BASFI >4, n (%)	29 (59)	20 (23)^	29 (56)	28 (29.8)	27 (75)	33 (44.6)^	0.1	**0.012**
ASAS-PR, n (%)		26 (29.9)		15 (16)		17 (23)		0.08
PGA-VAS~	70 (30)	30 (40)	60 (30)	37.5 (30)	60 (20)	35 (40)	0.88	0.26
Pain-VAS~	70 (30)	40 (50)	70 (30)	40 (40)	70 (35)	40 (40)	0.87	0.54
Fatigue-VAS~	60 (37.5)	30 (45)	60 (50)	30 (30)	55 (52.5)	30 (50)	0.85	0.97

~ Median (IQR), * p<0.05 between subgroup 1 and 2, ^ p<0.05 between subgroup 1 and 3, $^{\Sigma}$ p<0.05 between subgroup 2 and 3. Four patients from the bamboo subgroup, 5 patients from each of the advanced spinal ankylosis subgroup and without syndesmophytes subgroup were excluded from the last visit evaluation because of missing data at final visit

ASAS-PR: Assessment in spondyloarthritis international society partial remission, ASDAS: Axial spondyloarthritis disease activity score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, bDMARD: Biological disease-modifying antirheumatic drug, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IQR: Interquartile range, PGA: Patient global assessment, SD: Standard deviation, VAS: Visual analogue scale

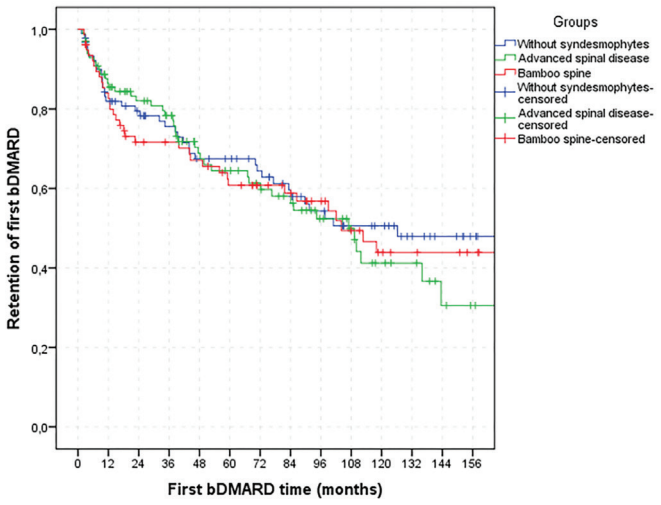

Figure 2. Retention rates of first bDMARDs treatment in the different subgroups. Log rank test p-value=0.86
bDMARD: Biological disease-modifying antirheumatic drug

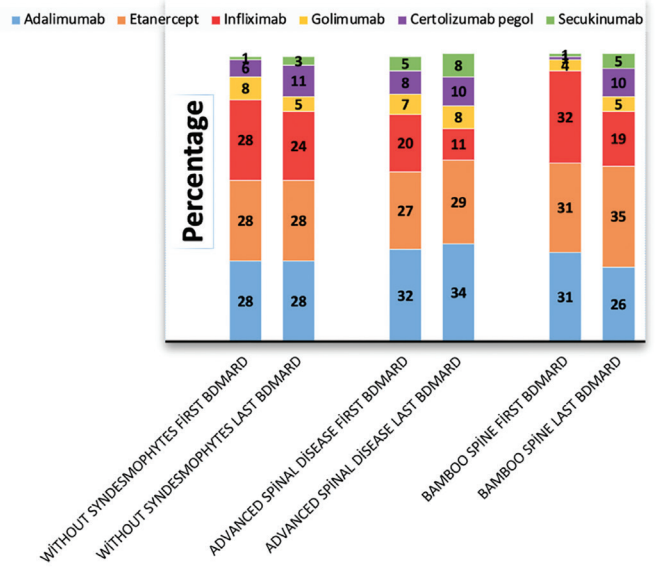

Figure 3. Distribution of bDMARDs treatment at the first and last visit
bDMARD: Biological disease-modifying antirheumatic drug

In the HUR-BIO cohort, treatment responses in patients with advanced spinal ankylosis and bamboo spine, including achievement of ASAS-PR and BASDAI50 responses, were comparable to those observed in the overall HUR-BIO axSpA population. Among individuals with advanced spinal ankylosis and bamboo spine, ASAS-PR was achieved by 16% and 23%, respectively, and a BASDAI50 response was achieved by 53% and 52%, respectively. Across randomised controlled trials and real-world studies of TNFi and IL-17i therapies in raxSpA, the proportion of patients achieving ASAS-PR ranged from 15% to 50.8%, and BASDAI50 responses ranged from 48% to 63% at various time points.[13,24-30] Only a few studies have specifically investigated treatment efficacy in advanced spinal axSpA. In a post-hoc analysis of an RCT assessing adalimumab treatment over two years in 11 patients with ≥50% spinal involvement, 62.5% achieved a BASDAI50 response (60% among those with bamboo spine), although ASAS-PR results were not reported.[10] In an observational study evaluating infliximab at week 54 in advanced spinal axSpA (≥50% spinal involvement), ASAS-PR and BASDAI responses were achieved in 18% and 82% of patients, respectively.[12] Another observational study assessing adalimumab at week 12 across different stages of spinal involvement, namely stages I-III (<50% of the spine; n=891), stage IV (50 to <80%; n=31), and stage V (≥80%, including bamboo spine; n=41), reported ASAS-PR rates of 30%, 26%, and 7%, and BASDAI responses of 57%, 58%, and 66%, respectively.

Another observational study assessing adalimumab at week 12 across different stages of spinal involvement—stages I-III (<50% of the spine; n=891),stage IV (50-<80%; n=31), and stage V (≥80%, including bamboo spine; n=41)—reported ASAS-PR rates of 30%, 26%, and 7%, and BASDAI responses of 57%, 58%, and 66%, respectively.[13] In a 12-week RCT investigating etanercept in advanced AS (defined by multiple intervertebral adjacent bridges: ≥2 in the lumbar or cervical spine or ≥3 in the thoracic spine), patients receiving etanercept (n=43) showed significantly higher BASDAI50 response rates than placebo (46% vs. 23%, p=0.031). However, ASAS-PR rates did not differ significantly between groups (18% vs. 5%, p=0.073).[11] Differences across studies likely reflect variation in definitions of advanced disease, disease severity, and study methodology. Collectively, these studies, including the present analysis, reinforce that bDMARDs remain effective in advanced structural disease.

Physical function as assessed by the BASFI followed the expected patterns. BASFI improved in all groups, but patients with bamboo spine had persistently higher scores at follow-up compared with individuals without syndesmophytes. This aligns with earlier findings that BASFI correlates with radiographic damage, particularly syndesmophytes and ankylosis.[31] Studies of bDMARDs in advanced disease have shown improvement in BASFI but consistently report higher absolute BASFI scores in those with bamboo spine or extensive ankylosis.[11-13] These observations support the concept that functional impairment in this population reflects both reversible inflammatory activity and irreversible structural damage. In our cohort, improvements in BASFI likely reflect suppression of inflammation with bDMARD therapy, whereas residual functional limitation is attributable to established ankylosis.[5,6,32]

A key strength of this study is the evaluation of long-term bDMARD retention in advanced spinal disease, an area with virtually no published evidence. Retention rates at 12 months (81-85%), 5 years (60-67%), and 10 years (41-51%) were similar across all groups and closely aligned with those reported in real-world axSpA cohorts.[26,28,29,33-35] These findings indicate

that individuals with advanced spinal ankylosis or bamboo spine maintain long-term adherence to bDMARD therapy and derive sustained benefit comparable to that of patients without structural progression.

Baseline phenotypic characteristics of the advanced spinal ankylosis and bamboo spine groups differed markedly from those without syndesmophytes. Patients with advanced structural damage were older, were more often male, had higher BMI, greater smoking exposure, and more frequent hip involvement—factors known to predict accelerated spinal radiographic progression. Bamboo spine was associated with longer disease duration, consistent with the cumulative nature of damage formation, whereas advanced ankylosis occurred despite a disease duration similar to that in those without syndesmophytes, suggesting more rapid structural progression in this subgroup. These patterns are in line with previous studies reporting that syndesmophyte development is associated with male sex, older age, and longer disease duration.[31,36-40] Furthermore, baseline differences between groups, including age, sex, BMI, smoking exposure, disease duration, and hip involvement, may contribute to residual confounding. As this was a registry-based observational study, analyses were not fully adjusted for all potential covariates, and findings should therefore be interpreted with appropriate caution.

Study Limitations

This study has limitations. First, some variables had missing data because of the cohort's long duration. Second, patients were grouped according to lumbar and cervical radiographs because most patients did not undergo thoracic radiography, and thoracic vertebrae could not be clearly evaluated on chest radiographs. Third, only 770 of 2,907 patients had both cervical and lumbar radiographs, and individuals with radiographs differed in some characteristics from those without them (Supplementary Table 1). Fourth, radiographic data were recorded categorically, and the exact number of syndesmophytes or bridged vertebral units was not available, limiting detailed assessment of structural severity. Therefore, potential heterogeneity within this subgroup could not be further explored. Additionally, the definition of advanced spinal ankylosis may include heterogeneous structural severity, and the categorical distinction between advanced ankylosis and bamboo spine may introduce a threshold effect. Fifth, radiographs were assessed by a single reader, and formal inter- and intra-observer reliability analyses were not performed. Sixth, although patients with radiographs represented a substantial proportion of the registry (26.4%), selection bias cannot be excluded; it may be related to indications for imaging—particularly neck pain or restricted movement—and to changes in patterns of radiograph use over time. Because analyses were not adjusted for all potential confounders, residual confounding cannot be excluded. Nonetheless, the study's strengths include its sizeable cohort of patients with advanced spinal ankylosis and bamboo spine, a population rarely captured in RCTs or observational studies, and the provision of long-term real-world treatment response and drug survival data.

Conclusion

In conclusion, this study contributes important evidence demonstrating that patients with advanced spinal ankylosis or bamboo spine can achieve meaningful clinical improvement with bDMARD therapy and maintain long-term treatment adherence comparable to that of patients without syndesmophytes.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/03-16, date: 02.02.2021).

Informed Consent: This was a retrospective study. Written informed consent was obtained from all patients at enrolment into the HUR-BIO cohort.

Footnotes

Authorship Contributions

Concept: B.F., G.K.Y., L.K., A.A., Ş.A.B., İ.E., S.K., Design: B.F., G.K.Y., L.K., A.A., Ş.A.B., İ.E., S.K., Data Collection and Processing: B.F., G.K.Y., E.B., E.Ç.B., E.S., G.A., L.K., A.A., Ş.A.B., İ.E., S.K., Analysis or Interpretation: B.F., P.M., Literature Search: B.F., P.M., Writing: B.F., P.M., G.K.Y., E.B., E.Ç.B., E.S., G.A., L.K., A.A., Ş.A.B., İ.E., S.K.

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