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ORIGINAL ARTICLE

Frequency and the effects of spondyloarthritis-spectrum disorders on the clinical course and management of Takayasu arteritis: an observational retrospective study

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Abstract

Objectives Extravascular findings of Takayasu arteritis (TAK) often share features with the spondyloarthritis (SpA) spectrum of disorders. However, the characteristics of this overlap and its effect on the vascular manifestations of TAK are not fully known. Therefore, we aimed to investigate the frequency of SpA-related features in TAK patients.

Material and methods In this observational retrospective study, 350 patients with TAK classified according to ACR 1990 criteria, from 12 tertiary rheumatology clinics, were included and evaluated for the presence of axSpA, IBD, or psoriasis. Demographic, clinical features, angiographic involvement patterns, disease activity, and treatments of TAK patients with or without SpA were analyzed.

Results Mean age was 45.5 ± 13.6 years and mean follow-up period was 76.1 ± 65.9 months. Among 350 patients, 31 (8.8%) had at least one additional disease from the SpA spectrum, 8 had IBD, 8 had psoriasis, and 20 had features of axSpA. In the TAK-SpA group, TAK had significantly earlier disease onset, compared to TAK-without-SpA ($p = 0.041$). SpA-related symptoms generally preceded TAK symptoms. Biological treatments, mostly for active vasculitis, were higher in the TAK-SpA group (70.9%) compared to TAK-without-SpA (27.9%) ($p < 0.001$). Vascular involvements were similar in both.

Conclusion Our study confirmed that diseases in the SpA spectrum are not rare in TAK. Vascular symptoms appeared earlier in such patients, and more aggressive therapy with biological agents was required in the TAK-SpA group, suggesting an association between TAK and SpA spectrum.

Key Points

- *The pathogenesis of Takayasu arteritis is mediated by an MHC class I alelle (HLA-B*52), similar to spondyloarthritis-disorders.*
- *Extravascular findings of Takayasu arteritis are in the spectrum of spondyloarthritis disease.*
- *This frequent coexistence between Takayasu arteritis and spondyloarthritic disorders suggests a relationship rather than a coincidence.*

Keywords Takayasu arteritis · Spondyloarthritis · Inflammatory bowel diseases · Psoriasis · Sacroiliitis · Extravascular findings

Introduction

Takayasu arteritis (TAK) is a rare, chronic, granulomatous vasculitis of the large vessels characterized by stenosis, occlusion, and aneurysmatic involvement of the aorta and its major branches. The disease is more common in women, typically occurs in the second or third decades of life, impairs quality of life, and causes mortality [1, 2]. The etiology of the disease is still not known, but the role of genetic factors in the pathogenesis is prominent. The first genes were shown to be associated with TAK are *HLA-B*52* alleles encoded in the HLA class I region [3]. Additionally, the disease progresses more severely in *HLA-B*52* carriers [4–6]. Later on, *IL12B* and some other genes such as *PLCG2* and *ZMIZ1* that were associated with inflammatory bowel diseases (IBD) were also shown to be related with TAK.

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Among all inflammatory-mediated diseases, shared genetic risks seemed to be highest between IBDs and TAK [7, 8].

The typical features of TAK are constitutional, which can be seen in the early period of the disease (fever, malaise) and symptoms of the inflammation of the affected vessels (carotidynia, claudication, transient ischemic attacks) [9]. However, clinical findings independent of large vessel involvement such as skin, bowel, eye, and especially musculoskeletal involvement may also be encountered. These extravascular manifestations are similar to the symptoms of the spondyloarthritis (SpA) disease spectrum.

Co-occurrence of TAK and IBD or axial SpA (axSpA) has long been documented in case reports [10–13]. In a multicenter study of 470 patients, the prevalence of ulcerative colitis (UC) (6.4%) in TAK was found to be higher than the general population. Additionally, TAK with UC patients exhibited significant enrichment of *HLA–B*52.01* compared to TAK patients without UC [14]. In a single-center study investigating the frequency of inflammatory diseases accompanying TAK, high frequencies of axSpA (8%) and IBD (6%) were reported [15]. Likewise, in another two-center study examining extravascular findings, the frequency of sacroiliitis was 7.1% and IBD was 2.6% in TAK patients [16]. Although it is difficult to determine the incidence rate among rare diseases, studies exhibiting the relationship between SpA/IBD group and TAK implicate that this is not a simple coincidence and TAK may be a part of the newly described 'MHC-I-opathies' [17, 18]. In this multicenter study, we aimed to investigate the frequencies of axSpA, IBD, and psoriasis (PsO) in TAK patients and the effect of these disease associations on the clinical features of TAK.

Methods

All TAK patients ($n = 350$) followed in 12 tertiary rheumatology clinics across Turkey and classified according to 1990 ACR Criteria were included in the study [19]. Due to the retrospective design, patients' data evaluated within the scope of the study were collected from their follow-up files which are used for clinical management of the patients, from the diagnosis of the disease throughout the follow-up period, and so there was no need to obtain any informed consent from the patients. Data containing all demographic, clinical, and angiographic features; treatment outcomes; activity; and damage scores were acquired from the patient files retrospectively. For vascular involvement evaluation, computed tomography (CT) or magnetic resonance imaging (MRI) angiography scans encompassing the aorta and its branches were used. The distribution of vascular involvement was categorized as Type I to Type V according to the Hata angiographic classification [20]. Indian Takayasu's Arteritis Activity Score (ITAS) at the time of diagnosis and the follow-up examinations was used to determine disease activity [21]. Vasculitis Damage Index (VDI) was used to determine the damage associated with the disease and management [22].

SpA disease definitions

Patients were evaluated for the presence of axSpA, IBD, or PsO and then separated into two groups. AxSpA, IBD, and psoriasis classifications of the patients were made by scanning the patient files in terms of the diagnoses made during routine follow-ups in the past and ensuring that these diagnoses met the classification criteria. No additional questionnaire or investigation was conducted within the scope of this study. All investigations for this previous diagnosis (i.e., imaging, endoscopy) were performed according to standard clinical practice based on the symptoms reported by the patients. We classified patients with diagnosis of IBD, axSpA, or PsO as TAK-SpA group. AxSpA patients had to fulfill the Assessment of SpondyloArthritis international Society (ASAS) Classification Criteria for axSpA [23]. PsO was required to be diagnosed with a dermatology examination. Psoriatic arthritis (PsA) patients had to fulfill The ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria [24]. IBD patients were classified as Crohn's disease (CD) or UC by gastroenterologists who performed endoscopic examinations during the diagnosis of IBD.

Pelvis radiographs of the patients were evaluated based on the 1984 Modified New York criteria. Sacroiliac MRI images in terms of active sacroiliitis were also assessed according to the ASAS definitions [25, 26]. Non-infectious anterior uveitis detected by an ophthalmologist during the attack was considered as anterior uveitis. Physical examination by a dermatologist or a rheumatologist was sufficient for the diagnoses of erythema nodosum and recurrent aphthous stomatitis. Peripheral enthesitis and joint involvement were detected by physical examination, X-ray radiography, ultrasonography, or MRI.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used to measure the disease activity and function of all patients with axial involvement, respectively [27, 28]. For patients with sacroiliitis, the positivity of *HLA-B*27* (if available) was also determined.

Management

Data on treatments received for TAK or SpA were collected. We calculated the cumulative dose of corticosteroids received since the beginning of the treatment. We utilized Kerr and ITAS criteria for relapse and remission definitions of TAK [1]. The initial choice for biologic treatments was

divided into three groups: isolated TAK, isolated SpA, or both.

Statistical analyses

Data were analyzed using Statistical Package for the Social Sciences 22.0 (SPSS, Chicago, IL, USA). The continuous variables were expressed as mean (standard deviation) and median (interquartile range (IQR)) for normal and non-normal distribution, respectively. Frequency (%) was used for the description of categorical variables. Comparison of variables were evaluated by Mann–Whitney *U* test, independent-sample *t*-test, Wilcoxon test, or chi-square test.

The study was performed according to the Declaration of Helsinki and approved by the local ethical committee of Marmara University (09.2020–1078), Faculty of Medicine, Istanbul.

Results

Clinical features of the TAK with SpA patients

Mean (SD) age of TAK patients (F/M: 298/52) were 45.5 (13.6) years with a mean (SD) 76.1 (65.9) months of follow-up period. Among 350 TAK patients, 31 (8.8%) had diseases in the SpA spectrum. Among these 31 patients (F/M: 27/4), 8 (2.2%) patients had IBD, 8 (2.2%) had psoriasis, 5 (1.4%) had PsA, and 20 (5.7%) had axSpA. All male patients were in the radiographic axial-SpA group, and none had psoriasis or IBD. The distribution scheme of the patients was shown in Fig. 1. Spinal syndesmophyte formation was seen in only three patients; however, no bamboo spine was detected.

All of the eight patients with IBD were classified as Crohn's disease. The number of patients was low but when the onset age of disease-specific symptoms was evaluated, it was recognized that skin findings began at a relatively younger age, compared to the entire TAK and SpA findings. Median (IQR) were 18 (8–26) years, 26 (17–32) years, and 28 (22–30) years, for skin findings, inflammatory back pain, and vascular symptoms, respectively (Table 1). Initial clinical symptoms were SpA-related in 17 (54.8%) and TAK-related in eight (25.8%) patients, while six (19.4%) patients presented with symptoms attributable to both TAK and SpA.

Use of biological agents was significantly higher in TAK patients with SpA compared to those without SpA (TAK with SpA group, *n* (%): 22 (70.9%); TAK without SpA group, *n* (%): 85 (27.9%); $p < 0.001$). While biological agents were used for TAK in 12 patients, and for SpA in seven patients, three cases received due to severe symptoms of both TAK and SpA (Table 1).

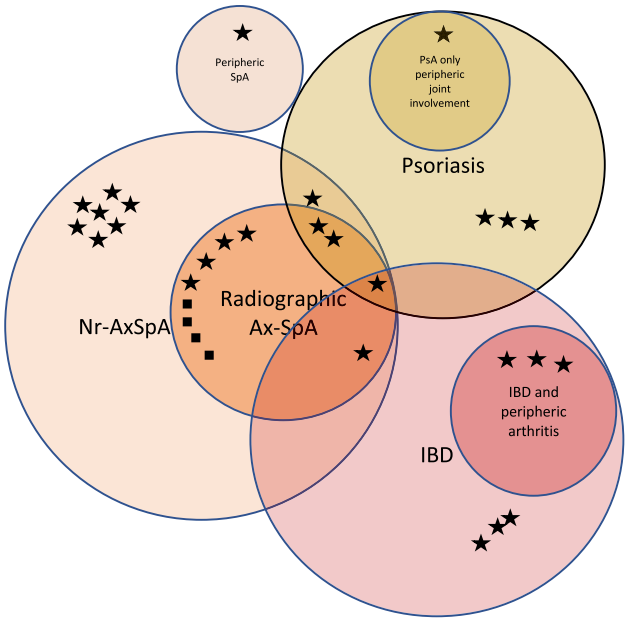

Fig. 1 Distribution clusters of TAK and SpA patients within the SpA disease spectrum

Vasculitis-related clinical features of patients according to SpA-spectrum presence

The symptoms attributed to TAK presented at a significantly earlier age in patients with additional SpA (26.03 ± 7.49 years), compared to those without SpA (31.59 ± 12.6 years, $p = 0.041$) (Table 2). Vascular involvement had similar distributions in both groups. Subclavian arteries, carotid arteries and branches, and aorta were the most frequently involved vessels in both groups (Table 3). Aortic involvement was observed in 41.4% of the TAK with SpA vs 54.7% in the TAK without SpA, without reaching significance ($p = 0.171$). Class distributions of both groups according to Hata Angiographic Classification were also similar ($p = 0.276$). Nevertheless, the most frequent class was type 1 in the TAK with SpA and type 5 in the TAK without SpA (Fig. 2). At the last visit, Physician Global Assessment (PGA) and ITAS scores of TAK with SpA patients were significantly lower compared to TAK without SpA (Table 2).

Discussion

In this study, we verified that SpA spectrum disorders accompanying TAK were not rare with a frequency of 8.8%. Initial symptoms of TAK with SpA patients were more commonly SpA-related, mostly with dermatological features. Consistent with our data, in the report of Riviere et al. on the

Table 1 Clinical features of TAK patients with TAK (TAK-SpA group, $n=31$)

Age mean (SD)	35.8 (5.8)
Female/male ratio	27/4
Inflammatory back pain, *n* (%)	20 (64.5)
Inflammatory back pain onset (years) ($n=20$), median (IQR 25–75)	26 (17–32)
BASDAI ($n=20$), median (IQR 25–75)*	2.4 (1.2–4.3)
BASFI ($n=20$), median (IQR 25–75)*	2.6 (1.9–3.6)
Peripheral arthritis, *n* (%)	14 (45.2)
Peripheral enthesitis, *n* (%)	7 (22.6)
Recurrent aphtous stomatitis, *n* (%)	5 (16.1)
Erythema nodosum, *n* (%)	5 (16.1)
Skin symptom onset (years) ($n=15$), median (IQR 25–75)	18 (8–26)
Anterior uveitis, *n* (%)	4 (12.9)
First uveitis attack (years) ($n=4$), median (IQR 25–75)	25 (20–49)
Crohn/ulcerative colitis, *n* (%)	8 (100)/0 (0)
Gastrointestinal symptom onset (years) ($n=7$), median (IQR 25–75)	22 (9–29)
SpA history in first-degree relatives, *n* (%)	4 (12.9)
HLA-B27 positivity, *n* (%)	5 (25)
Vascular symptom onset (years) ($n=31$), median (IQR 25–75)	28 (22–30)
Treatment with biologics, *n* (%)	22 (71)
Remission with first biologic treatment, *n* (%)	14 (63.6)
Biological treatment reason, only TAK/only SpA/both, *n* (%)	12 (54.5)/7 (31.8)/3 (13.6)

TAK Takayasu arteritis, *SpA* spondyloarthritis, *IQR* interquartile range, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index

*BASDAI and BASFI data were scores at patients' last examination

Table 2 Comparison of baseline characteristics and clinical features of TAK according to the presence of SpA-spectrum diseases

	TAK with SpA	TAK without SpA	*p*
Age at diagnosis, mean (SD)	29.5 (9.96)	34.1 (13.1)	0.087
Gender female/male	4/27	48/271	1
Age of onset: TAK-related symptoms, (years) mean (SD)	26 (7.5)	31.6 (12.6)	**0.041**
Diagnosis delay time (month), mean (SD)	31.2 (34.5)	34.7 (54.3)	0.557
Follow-up duration (month), mean (SD)	74.8 (69.6)	76.5 (65.4)	0.913
ITAS at diagnosis, mean (SD)	11.5 (6.4)	11.3 (5.3)	0.995
Fever at diagnosis, *n* (%)	6 (20)	76 (25.6)	0.507
Erythema nodosum, *n* (%)	5 (16.7)	5 (1.6)	**0.001**
Recurrent oral apthous stomatits, *n* (%)	4 (13.3)	23 (7.3)	0.477
Remission after first DMARDs, *n* (%)*	15 (68.2)	175 (70.8)	0.795
Relapse ever, *n* (%)	8 (34.8)	113 (40.3)	0.591
Annual relapse number, mean (SD)	0.07 (0.1)	0.11 (0.1)	0.365
Treatment with biologics, *n* (%)	22 (70.9)	85 (27.9)	**< 0.001**
Latest PGA Score mean (SD)	1.6 (1.6)	2.4 (2.1)	**0.035**
Latest ITAS Score mean (SD)	1.2 (2.4)	2.25 (2.6)	**0.007**
Latest VDI Score mean (SD)	3.7 (2.7)	3.7 (2.5)	0.771
Annual glucocorticoid use (g), mean (SD)	1.4 (1.3)	1.7 (1.6)	0.328
CRP (at diagnosis of TAK), mean (SD)	27.9 (8.5)	26.7 (9.2)	0.856

TAK Takayasu arteritis, *SpA* spondyloarthritis, *SD* standard deviation, ITAS Indian Takayasu Activity Score, *DMARD* Disease Modifying Anti-Rheumatismal Drugs, *PGA* Physician Global Assessment, *VDI* Vasculitis Damage Index

*DMARD: methotrexate, azathioprine, and leflunomide were used

Table 3 Comparison of vascular involvement of TAK patients according to the presence of SpA-spectrum diseases

	TAK with SpA	TAK without SpA	*p*
Carotid arteries and branches, *n* (%)	19 (65.5)	182 (60.8)	0.624
Subclavian arteries, *n* (%)	21 (72.4)	231 (77)	0.578
Vertebral arteries, *n* (%)	6 (20.7)	49 (16.3)	0.548
Aorta, *n* (%)	12 (41.4)	164 (54.7)	0.171
Ascending aorta, *n* (%)	6 (20.7)	79 (26.3)	0.507
Descending aorta, *n* (%)	6 (20.7)	104 (34.7)	0.128
Abdominal aorta, *n* (%)	7 (24.1)	84 (28)	0.657
Mesenteric arteries, *n* (%)	9 (31)	74 (24.7)	0.451
Renal arteries, *n* (%)	9 (31)	81 (27)	0.642
Iliofemoral arteries, *n* (%)	3 (10.3)	24 (8)	0.660
Pulmonary arteries, *n* (%)	2 (6.9)	16 (5.3)	0.724
Stenosis, *n* (%)	23 (79.3)	248 (84.3)	0.481
Occlusion, *n* (%)	16 (55.1)	178 (25.2)	0.573
Aneurism, *n* (%)	4 (13.7)	34 (11.6)	0.727

TAK Takayasu arteritis, *SpA* spondyloarthritis

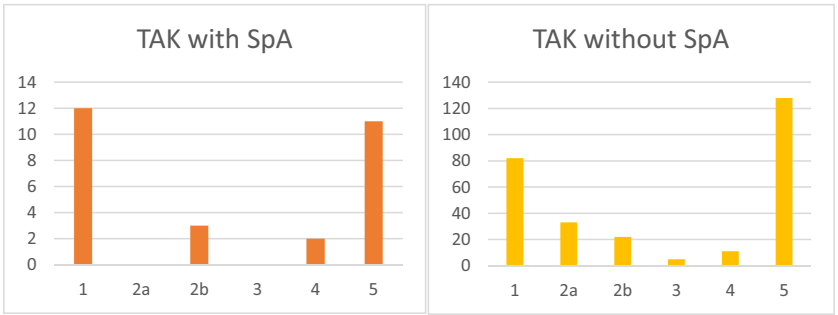

Fig. 2 Angiographic classifications of the TAK without SpA patients and the TAK with SpA patients

coexistence of TAK and SpA, SpA symptoms preceded TAK symptoms in 13 of 14 patients [29]. Similarly, skin findings usually appeared at an earlier age than musculoskeletal symptoms in PsA patients. However, our observation may also be explained by the fact that extravascular symptoms, especially skin and bowel symptoms, are relatively more striking than TAK symptoms which are more insidious and cause delays in diagnosis. Nevertheless, the differences at the time symptoms first appear can be supported by larger cohorts, which can then pave the way for new research to better understand pathogenetic processes and develop treatment options.

Axial involvement was the most common among the SpA-spectrum disorders. Similarly we also observed a high rate of sacroiliitis in the TAK population. In a study by Kwon et al., the frequency of sacroiliitis was reported as 7.1% in TAK patients, resembling our results (Table 4). TAK patients with sacroiliitis were predominantly female (89.5%) and exhibited a low incidence of *HLA-B*27* positivity (14.3%) [16]. Similar frequency of axSpA presence in TAK was also reported by Esatoğlu et al. [15]. In our study, the *HLA-B*27* positivity in patients with sacroiliitis was also low (25.0%), with a high majority of females (80.0%). However, Güzel Esen S. et al. reported higher frequency of axSpA with 14 (20.3%) patients diagnosed with ankylosing spondylitis fulfilling the ASAS criteria, again with a low *HLA-B*27* positivity [30].

Like axial PsA, *HLA-B*27* rates, which present with lower positivity than those found in classical axSpA, implicate that other pathogenetic factors may also be responsible for this entity [31]. Similarly, TAK is associated with another class-I allele, *HLA-B*52*, which might link TAK to spondyloarthropathy group of disorders [32]. Additionally, the most common non-HLA genetic association with TAK is IL-12B which encodes IL-12p40 subunit [8]. The same gene was also identified in axSpA and IBD. IL-12p40 and the p19 subunit form IL-23 are two of the key cytokines of the IL-17-driven pathogenetic pathway of SpA spectrum disorders [33]. Also together with IL-23, IL-12, which is formed by a combination of IL-12p40 and the p35 subunit, is the main inducer of IFNgamma which is the main cytokine responsible for granulomatous inflammation in the pathogenesis of TAK [34]. Similar interactions of cytokine pathways in addition to class-I MHC-related peptide presentation may provide a pathogenetic

Table 4 Data from other studies in the literature investigating the frequency of SpA features in TAK patients

	Güzel Esen et al. [31]	Kwon et al. [16]	Esatoglu et al. [15]	Our data	Total
Number of patients	69	268	198	350	885
TAK with SpA, *n* (%)	14 (20.3)	19 (7.1)	15 (8)	20 (5.7)	68 (7.6)
TAK with IBD, *n* (%)	4 (5.8)	7 (2.6)	12 (6)	8 (2.2)	31 (3.5)
CD/UC (%)	2/2 (50/50)	4/3 (57/43)	7/5 (58/42)	8/0 (100/0)	21/10 (68/32)
TAK with psoriasis, *n* (%)	3 (4.3)	No data	2 (1)	8 (2.2)	13 (2.1)
Uveitis, *n* (%)	4 (5.8)	2 (0.7)	6 (4)	4 (1)	16 (1.8)
Erythema nodosum, *n* (%)	3 (4.3)	4 (1.5)	17 (12)	10 (2.8)	34 (3.8)

SpA spondylarthritis, *TAK* Takayasu arteritis, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis

background for shared phenotypes but also demonstrate the need for further research.

In our study, the frequency of IBD was found to be 2.2%. Although higher rates (5.8–6.0%) were reported in some of the prior publications, a large series from Korea reported a similar frequency (2.6%) [16]. In addition to detecting sacroiliitis in two out of eight patients with TAK and IBD ($n=8$), IBD-associated peripheral arthritis were also detected in five patients. TAK patients with psoriasis ($n=8$; 2.2%) had a similar distribution of articular involvement. Since peripheral arthritis was present in five of these eight patients with psoriasis, they were followed up as PsA.

According to the Hata angiographic classification, type 5 was the most common subset in our TAK population. Although type I was more common in the TAK with SpA group, no significant difference was observed. In another study, a significant relationship was reported between the extravascular involvement and type 2b subset according to the Hata angiographic classification [16]. Such kind of different results may be due to the ethnic origins of the patient populations.

TAK-related symptoms presented at an earlier age in the TAK with SpA group than in patients without SpA in the present study. Similarly, in another study, TAK patients having additional UC developed TAK earlier compared to patients without UC. This difference may be related to increased common genetic burden of TAK and IBDs. However, in the aforementioned study, there was no significant difference in the severity of disease attributed to TAK between the two groups, similar to our data [14].

Biologic agents were also used more frequently in TAK-SpA group in our study, in accordance with the results of the study conducted by Güzel Esen et al. (64.3% vs. 29.1%, $p=0.014$) [30]. Although most of the indications for biologic use were active vascular disease, baseline ITAS scores were similar in TAK patients with or without SpA, implicating that concomitant SpA might also influence the need of biologic therapy. Lower current ITAS and PGA scores in TAK-SpA patients may be explained with the effects of biological agents on the assessment of global disease activity.

The retrospective design was the major limitation of our study. The number of patients in TAK-SpA group were also low. Besides, no disease activity score related to psoriasis, IBD, peripheral arthritis, and enthesitis were used, except for axial SpA. The fact that patients are under immunosuppressive treatments during the clinical course of TAK and SpA may mask some findings and thus may cause the frequency to seem low. In addition, in order to better understand the pathogenesis, investigating shared genetic and immunological components could provide a better understanding of this overlap mechanism. We think that these limitations will guide future studies.

In conclusion, our study confirmed that diseases in the SpA spectrum are not rare in TAK patients. In TAK-SpA group, not only SpA-related symptoms, but TAK related symptoms also appeared earlier compared to TAK patients without SpA. Although initial disease activity scores, remission with initial DMARD treatment, and subsequent relapse rates were similar in both groups, more aggressive therapy with biological agents was required in TAK-SpA group, mostly due to active vascular disease. Also, our results implicate that presence of SpA may lead to earlier disease onset. Obviously, there is a clear need for more comprehensive studies investigating the pathogenetic and clinical associations between TAK and SpA-spectrum diseases.

Author contribution All authors had full access to all of the data in the study and take responsibility for the data and the accuracy of the data analysis.

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Data availability Data are available on reasonable request. Not applicable.

Declarations

Ethics approval Approval for this study was obtained from the Marmara University Faculty of Medicine local ethics committee (09.2020–1078).

Patient and public involvement.
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication Not applicable.

Disclosures None.

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