

Biological treatment in elderly and young patients with ankylosing spondylitis: TURKBIO real-life data results

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ABSTRACT

Objectives: This study aims to investigate the effect of age on disease activity and biological treatment in patients with ankylosing spondylitis (AS).

Patients and methods: A total of 811 AS patients registered in the TURKBIO registry database between 2011 and 2019 were categorized according to their age at the time of entry into the registry and assigned to one of two groups: young patients, defined as <60 years of age (n=610), and those aged ≥60 years (n=201) were recorded as elderly patients. Demographic, clinical, and laboratory characteristics, along with disease activity markers and other follow-up parameters, as well as current and prior treatments, were electronically recorded during each visit using open-source software.

Results: The mean age of the elderly patients was 67±5.8 years, while the mean age of the younger patients was 49.2±10.9 years. Male predominance was lower in the older AS group compared to the younger AS group (p=0.002). During follow-up period, 397 patients (comprising 318 young and 79 elderly individuals) had a history of using at least one biological disease-modifying agent (bDMARD). There was no significant difference between the groups in terms of DMARD and bDMARD-use distributions. First tumor necrosis factor inhibitor (TNFi) retention rates were found to be similar in both groups over 10 years of follow-up. Adverse events were found to be similar in young (19.9%) and elderly (26.8%) AS patients.

Conclusion: Research in the TURKBIO cohort reveals that both older and younger patients with AS exhibited similar disease activity levels with comparable treatment approaches. Moreover, the results of TNFi treatments in elderly patients were the same as those observed in younger patients, with no notable increase in safety concerns.

Keywords: Adverse event, ankylosing spondylitis, biological disease-modifying anti-rheumatic drug, geriatric, tumor necrosis factor inhibitor.

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by axial and peripheral joint involvement.¹ The prevalence of AS in Asia, Europe, and the United States of America (USA) is reported to be 0.17%, 0.12 to 1%, and 0.55%, respectively.²⁻⁴ The prevalence of AS is relatively low in Latin America (0.1%)

and Africa (0.07%), which is thought to be partly due to the low frequency of the genetic factor human leukocyte antigen-B27 (HLA-B27).^{5,6} In an epidemiological study conducted in Turkey, the prevalence of AS was found to be 0.49%.⁷ AS is more common in the young male population than in females. In patients

over 45 years of age, the initial symptoms of AS are rarer.^{8,9}

The elderly population has been increasing both in Turkey and globally. The World Health Organization (WHO) defines individuals aged 60 years and older as elderly. According to these distinction criteria, it is estimated that approximately 13% of the world population is elderly currently.¹⁰ As life expectancy continues to rise, there is a concurrent increase in the incidence of rheumatological diseases among the elderly population. The treatment approach in patients with geriatric rheumatological diagnosis is similar to that in adult patients. Nevertheless, treatment management admits of a greater degree of complexity and requires an enhanced level of care due to the heightened occurrence of comorbidities associated with advanced age, concerns about drug-related side effects, and variations in clinical outcome characteristics. The combination of age-related physiological changes (e.g., decreased muscle mass and function, decreased organ function, and degenerative changes) and AS-specific changes make elderly AS patients more vulnerable than younger AS patients.^{11,12} Elderly patients have higher comorbidity rates and more concomitant drug use. Differences in aging-related pharmacokinetics in patients result in variation in treatment responses and differences in the severity of adverse events associated with the use of immunosuppressive drugs.¹³ In elderly AS patients, the safety of biological drugs may be a matter of concern due to both organ/system function and polypharmacy.

Rheumatoid arthritis (RA) constitutes the majority of rheumatological disease experiences in which biological therapy is used in elderly patients. The tumor necrosis factor inhibitors (TNFi) are widely used in the treatment of AS. However, there are still limited data in the literature regarding the use of long-term TNFi treatment in patients with geriatric AS.¹⁴

In the present study, we aimed to evaluate the differences in disease activity and treatment choices between elderly and younger AS patients and to investigate the demographic, clinical, laboratory, treatment strategies and TNFi-related adverse events between younger and older AS patients.

PATIENTS AND METHODS

Study design

The data were obtained from the Turkish Biological (TURKBIO) database, which was approved as a Phase IV observational study. The TURKBIO data registry is the Turkish version of the Danish DANBIO rheumatological database.¹⁵ The main aim of this registry is to monitor the clinical course of rheumatic diseases and to collect and evaluate data on patients with RA, AS and psoriatic arthritis (PsA) treated with biological therapies. Large-scale national registries, such as this, provide researchers with an opportunity to study a large number of AS cases. This database collects data on the adverse effects and efficacy of biological disease-modifying agents (bDMARDs) in patients with AS, RA and PsA and serves as a nationwide prospective cohort.

A total of 811 patients diagnosed with AS according to the Modified New York criteria (mNY)¹⁶ criteria in the TURKBIO registry database between 2011 and 2019 were categorized according to their age at the time they were entered into the registry and were assigned to one of two groups: Patients aged <60 years were recorded as young (n=610), and patients aged ≥60 years were recorded as elderly (n=201). Exclusion criteria were as follows: (i) patients without follow-up data; and (ii) patients who withdrew informed consent. Patients' demographic and clinical characteristics (age, sex, and disease duration), laboratory findings (C-reactive protein [CRP], and HLA-B27), and treatment-related characteristics (DMARDs; methotrexate, leflunomide, sulfasalazine, and bDMARDs) were recorded electronically at each visit using open-source software. The AS patients were assessed using specialized instruments to measure disease activity, mobility and function: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),¹⁷ Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP),¹⁸ Bath Ankylosing Spondylitis Metrology Index (BASMI)¹⁷ and Bath Ankylosing Spondylitis Functional Index (BASFI).¹⁹ Visual Analog Scale (VAS) (0-10 mm)²⁰ was used for evaluation pain, fatigue and global assessment of all patients.

The VAS pain, fatigue, and global measurements of all patients were recorded

separately. Patient-reported outcome measures were recorded electronically by patients using touch screens. Drug retention rates and reasons for drug discontinuation were obtained from the enrollment system. The patients' extra-articular manifestations (psoriasis, dactylitis, uveitis, inflammatory bowel disease and other) were recorded from the database. The data related to side effects and infection related to the patients in our study were recorded through the cohort database. Bacterial and viral infections, tuberculosis reactivation, mild and serious drug-related side effects and cancer development were recorded.

Evaluation of adverse events

Data on safety and efficacy, which encompassed TNFi switch rates were collected. Bacterial and viral infections, tuberculosis reactivation, mild and serious drug-related side effects (paradoxical psoriasis, sarcoidosis, multiple sclerosis etc.) and cancer were recorded.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, US). The conformity of univariate

data to normal distribution was evaluated using the Shapiro-Wilk test, and the conformity of multivariate data to normal distribution was evaluated by the Mardia (Dornik and Hansen omnibus) test, with the homogeneity of variance evaluated by the Levene test. Continuous variables were expressed in mean \pm standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of a total of 811 AS patients, the mean age of the elderly patients was 67 ± 5.8 years, while the mean age of the younger patients was 49.2 ± 10.9 years (Table 1). Male predominance was lower in the older AS group compared to the younger AS group (125 patients [62.2%] vs. 439 [72%], $p=0.002$) (Table 1). The HLA-B27 positivity was similar in both groups (Table 1). Among the patients, 397 (318 young and 79 elderly) had a history of at least one bDMARD use. There was no significant difference in the distribution of disease-modifying agents and biological use between the groups (Table 2).

Table 1. Demographic and clinical characteristics of AS patients according to their age at the time of registration in TURKBIO

	<60 (n=610)			≥ 60 (n=201)			Total (n=811)			<i>p</i>
	n	%	Mean \pm SD	n	%	Mean \pm SD	n	%	Mean \pm SD	
Sex										0.002
Male	439	72		125	62.2		564	69.5		
Female	171	28		76	37.8		247	30.5		
HLA-B27 (+)	423	69.3		127	63.1		550	67.8		0.698
Age (year)			49.2 \pm 10.9			67 \pm 5.8			50.9 \pm 11.8	<0.001
Age at diagnosis (year)			32.8 \pm 11			44.8 \pm 11.8			33.9 \pm 11.6	<0.001
Symptom duration (year)			25.9 \pm 9.1			33.2 \pm 11.7			26.6 \pm 9.6	<0.001
BASDAI (baseline)			3.8 \pm 2.3			4.9 \pm 2.4			4.0 \pm 2.3	0.047
BASFI (baseline)			3.3 \pm 2.7			4.2 \pm 2.6			3.4 \pm 2.6	0.031
BASMI (baseline)			2.5 \pm 1.4			3.2 \pm 2.4			2.2 \pm 2.4	0.042
ASDAS-CRP (baseline)			2.9 \pm 1.1			3 \pm 1.5			2.9 \pm 1.1	0.795
VAS (Fatigue) (baseline)			5.1 \pm 27.1			5.3 \pm 2.6			5.1 \pm 2.6	0.665
VAS (Global) (baseline)			2.2 \pm 3.1			1.4 \pm 2.6			2.2 \pm 3.1	0.009
VAS (Pain) (baseline)			5.1 \pm 2.5			5.2 \pm 2.7			5.1 \pm 2.5	0.843
VAS (Physician) (baseline)			2.6 \pm 1.8			3.5 \pm 2.6			2.9 \pm 1.9	0.100

AS: Ankylosing spondylitis; SD: Standard deviation; HLA-B27: Human leukocyte antigen-B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-Reactive Protein; VAS: Visual Analog Scale.

Table 2. Clinical findings of AS patients using bDMARD

	<60 (n=318)		≥60 (n=79)		Total (n=397)		p
	n	%	n	%	n	%	
Sex							
Female	79	24.8	33	41.7	33	41.7	0.003
Male	239	75.1	46	58.2	46	58.2	
Uveitis							
Absent	262	82.3	62	78.4	62	78.4	0.429
Present	56	17.6	17	21.5	17	21.5	
Enthesitis							
Absent	194	61	44	55.6	44	55.6	0.390
Present	124	38.9	35	44.3	35	44.3	
Arthritis							
Absent	206	64.7	44	55.6	44	55.6	0.138
Present	112	35.2	35	44.3	35	44.3	
Dactylitis							
Absent	293	92.1	73	92.4	73	92.4	0.937
Present	25	7.8	6	7.5	6	7.5	
Inflammatory bowel disease							
Absent	304	95.5	75	94.9	75	94.9	0.803
Present	14	4.4	4	5	4	5	
Psoriasis							
Absent	309	97.1	78	98.7	78	98.7	0.428
Present	9	2.8	1	1.2	1	1.2	
1 st line bDMARD							0.32
Adalimumab	119	37.4	25	31.6	144	36.2	
Etanercept	82	25.7	24	30.3	106	26.7	
Infliximab	70	22	23	29.1	93	23.4	
Golimumab	22	6.9	2	2.5	24	6	
Certolizumab	15	4.7	2	2.5	17	4.2	
Secukinumab	10	3.1	3	3.7	13	3.2	
2 nd line bDMARD							0.42
Adalimumab	41	29.9	13	37.1	54	31.3	
Etanercept	31	22.6	3	8.5	34	19.7	
Infliximab	20	14.5	6	17.1	26	15.1	
Golimumab	18	13.1	7	20	25	14.5	
Certolizumab	16	11.6	4	11.4	20	11.6	
Secukinumab	11	8	2	5.7	13	7.5	
3 th line DMARD							0.211
Infliximab	11	19.2	1	9	12	17.6	
Secukinumab	13	22.8	5	45.4	18	26.4	
Certolizumab	12	21	2	18.1	14	20.5	
Etanercept	9	15.7	2	18.1	11	16.1	
Adalimumab	7	12.2	1	9	8	11.7	
Golimumab	5	8.7	0	0	5	7.3	
4 th line bDMARD							NS
Infliximab	2	33.3	0	0	2	33.3	
Adalimumab	1	16.6	0	0	1	16.6	
Etanercept	0	0	0	0	0	0	
Golimumab	0	0	0	0	0	0	
Certolizumab	2	33.3	0	0	2	33.3	
Secukinumab	1	16.6	0	0	1	16.6	

AS: Ankylosing spondylitis; bDMARD: Biological Disease-Modifying Anti-Rheumatic Drug; NS: Non-significant.

The distribution of extra-articular findings was similar in both groups (Table 2). The first and second most preferred bDMARD

was adalimumab, and the third most preferred bDMARD was infliximab. Etanercept was found to be the second most preferred TNFi in all

Table 3. bDMARD retention rates and drug survival

	<60 (n=318)				≥60 (n=79)				Total (n=397)				p
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	
Duration of bDMARD (month)			120.5	75-144			134	97-145			123	80-145	0.114
Retention of 1 st line bDMARD (month)			65.5	23-134			84	26-136			70	23-136	0.229
Retention of 2 nd line bDMARD (month)			20	9-53			31	13-73			21.5	10.5-54.5	0.286
Annually bDMARD switch bDMARD (year)			0.18	0.09-0.3			0.15	0.09-0.25			0.18	0.09-0.3	0.292
1 st bDMARD retention (12 month)													
No	38	11.9			13	16.4			51	12.8			0.346
Yes	280	88			66	83.5			346	87.1			
1 st bDMARD retention (24 month)													
No	84	26.4			18	22.7			102	25.6			0.504
Yes	234	73.5			61	77.2			295	74.3			
1 st bDMARD retention (36 month)													
No	109	34.2			22	27.8			131	32.9			0.271
Yes	209	65.7			57	72.1			266	67			
1 st bDMARD retention (48 month)													
No	132	41.5			26	32.9			158	39.7			0.163
Yes	186	58.4			53	67			239	60.2			
1 st bDMARD retention (60 month)													
No	156	49			29	36.7			185	46.5			0.048
Yes	162	50.9			50	63.2			212	53.4			
Reason for change/stop first bDMARD													
Primary inefficacy	6	40			4	50			10	43.4			0.524
Secondary inefficacy	4	26.6			3	37.5			7	30.4			
Adverse events*	5	33.3			1	12.5			6	26			
Severe allergic reaction	2	40			0	0			2	33.3			
Severe infection	1	20			0	0			1	16.7			NA
Cancer*	2	40			1	100			3	50			

bDMARD: Biological Disease-Modifying Anti-Rheumatic Drug; IQR: Interquartile range; NS: Non-significant; * Malignancy (<60 years: mediastinal germ cell tumor, colon cancer, ≥60 years: non-Hodgkin lymphoma) was observed in three patients.

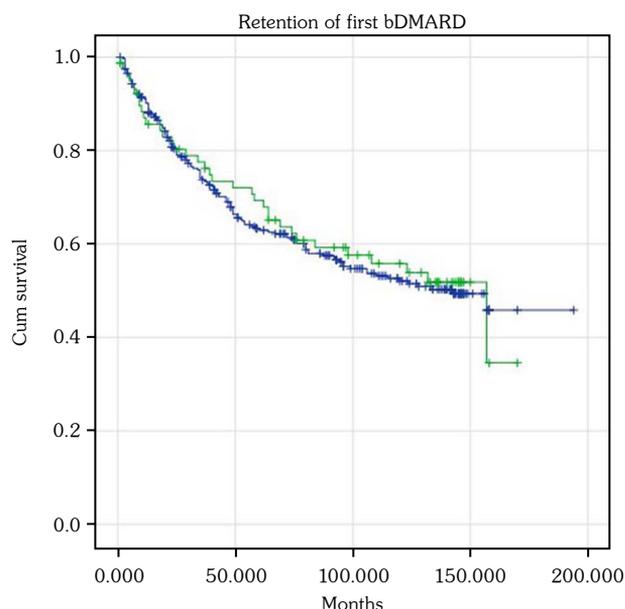


Figure 1. Drug survival rates of the groups (<60 years versus ≥60 years).

bDMARDs: Biological disease-modifying antirheumatic drugs.

ranks (Table 2). Data on their biological changes are given in Table 3 as an appendix. In most patients, the second switch was made, but since the number of lines with three or more drug changes was low, they were not included in the analysis tables.

During the more than 10 years of follow-up, the initial TNFi survival rates were comparable in both groups (Figure 1). Adverse effects were similar in both young (19.9%) and old (26.8%) AS patients. The frequency of infection (60 years >11%, and ≥60 years, 12.7%) and drug-related allergy (60 years >2.4%, and ≥60 years, 2.8%) was similar in both groups (data not shown). Biological therapy was discontinued in patients aged <60 years, due to severe allergic reaction in two patients, cancer in two patients, and serious infection in one patient, while biological therapy was discontinued in one patient aged >60 years due to cancer. Malignancy (<60 years; mediastinal germ cell tumor, colon cancer, ≥60 years; non-Hodgkin lymphoma) was observed in three patients (Table 3).

DISCUSSION

The TURKBIO database has made an important contribution to the assessment of

real-life experiences with biological therapies for rheumatological diseases in Türkiye. Registry data have shown not only a rise in the number of biological therapy regimens, but also an increasing diversity in routine rheumatology practice over the years.²¹ Based on the findings of our study, geriatric AS patients demonstrated reassuringly similar disease activity parameters and treatment modalities compared to younger AS patients. Clinical findings in AS rarely occur after the age of 50 years and, therefore, it is not a diagnosis that is primarily considered in older patients presenting with low back pain.²² Furthermore, the concept and definition of disease duration in AS patients remain unclear, and there may be a significant gap of several years between the onset of symptoms and the actual diagnosis.²³ This situation creates clinical difficulty in planning follow-up and treatment in patients with AS in the elderly patient group. In addition, elderly patients are often excluded from studies of newly developed bDMARDs. Randomized-controlled trials (RCTs) and prospective cohorts tend to include primarily healthy or mono-morbid volunteers rather than elderly and comorbid patients.²¹ This makes it difficult to evaluate drug efficacy and safety data with real-life outcomes in elderly patients.

Comparisons between studies conducted in elderly patients are difficult, as there is no consensus on the definition of age groups. Although elderly-onset RA (EORA) is usually defined as a disease that starts at the age of 60 years or older, some authors classify patients aged 65 years or older as “elderly” and those aged 75 years or older as “very old”.^{24,25}

Due to the absence of a consensus regarding the definition of age groups, making comparisons between studies involving elderly patients remains challenging. The BioStar data, which pertains to another cohort study conducted in Türkiye, revealed that the severity of comorbidities escalates in correlation with female sex, obesity, and advanced age (age >60 years).²⁶ Therefore, it has been reported that it is important to evaluate this age group, as it may also affect the selection of biological treatments in patients with AS diagnosed over 60 years of age.²⁶ Taken together, we decided to classify the patients in our study according to their age when they were enrolled in the TURKBIO registry.

In the CORRONA Registry, the toxicity associated with biological and/or DMARDs with a diagnosis of RA was similar in young and elderly patients.²⁷ In another cohort, it was emphasized that the rate of treatment discontinuation due to serious adverse events increased in elderly patients.²⁸ However, it has been emphasized that elderly patients have higher disease activity scores and additional comorbidities compared to younger patients, and it should be kept in mind that this may result in a biased higher incidence of bDMARD-related adverse events. Furthermore, studies have demonstrated that elderly patients are susceptible to infections, irrespective of their underlying disease or treatment.

In the REGISPONDER database, which is the registry of the Spanish rheumatology SpA study group, it was observed that sex distribution and basic characteristics such as the HLA-B27 frequency of 44 patients diagnosed with AS aged ≥ 50 years were similar to those in young AS patients.²⁹ In addition, Bodur et al.³⁰ showed that, according to the data obtained in the Turkish Rheumatism Research and War Association (TRASD)-IP (Monitoring Program) database study, the male sex was dominant (75.2%) in patients with AS with a mean age of 39.5 years. However, it has been shown that the sex distribution is similar with an increase in elderly patients, and in some studies, the female sex ratio increases. In Türkiye, Karaarslan et al.³¹ drew attention to the female predominance (62.7%) in this group in their report describing 27 geriatric AS cases followed in a single center. This study also drew attention to the fact that a similar treatment approach was adopted in the geriatric group regarding TNFi treatment approaches.

In Türkiye, in their demographic study, Bodur et al.²⁶ found that HLA-B27 positivity in young and adult AS patients was 73% versus 78.3%, respectively. Ozdemirel et al.³² found the frequency of HLA-B27 to be 70.1% in patients with AS with a mean age of 46.4 years. Similarly, previous studies have shown that the frequency of HLA-B27(+) decreases in patients diagnosed with AS at an advanced age. In our study, the rate in patients aged < 60 years was 69.3%, while this decreased to 63.1% in patients aged > 60 years. In our study, the HLA-27 positivity rate in

elderly AS patients was found to be lower than that in the general population.

In a study reported by Bendahan et al.³³ from Brazil, no significant difference was reported between BASDAI, Health Assessment Questionnaire (HAQ) scores and HLA-B27 frequency in AS patients aged > 45 years and younger AS patients. In this study, it is noteworthy that sulfasalazine and methotrexate usage was more frequent in AS patients aged > 45 years, although there was no significant difference in TNFi use. In our study, the sex distribution rate in the elderly AS group was equal and similar to that in other studies in terms of treatment strategy. In addition, there was no significant difference between young and elderly AS patients in terms of HLA-B27 positivity in accordance with previous studies.^{29,34,35}

Data on the use of TNFi therapies in geriatric patients are very limited and mostly come from RA experience.³⁶ Data from RCTs, observational drug trials, and real-life data suggest that biological therapies are almost as effective in geriatric RA patients as in younger patients. This result has also been obtained for AS and PsA with smaller numbers of patients.^{37,38} In more than five years of follow-up data of more than 1,000 RA patients > 65 years of age receiving etanercept treatment, no significant difference in efficacy and safety was found between both placebo and methotrexate treatments.^{38,39} The number of RCTs with other TNFi is limited. In a multi-center, retrospective study from Italy, TNFi treatments were well tolerated in 356 patients aged > 65 years with RA, AS, PsA and psoriasis indication; cardiovascular, malignancy and other adverse effects were not significantly different from those in the healthy population.⁴⁰ Knowledge of the effects and outcomes of TNFi treatments in geriatric AS patients would enable more effective treatment of this special patient group. The most commonly used bDMARDs in our study were TNFis, which is also the most studied bDMARD class. Adalimumab was the most frequently used TNFi in both groups, followed by etanercept and infliximab.

Geriatric patients have been shown to be prone to infection regardless of disease or treatment.¹² Some data obtained from national registries revealed that the frequency of infection

with TNFi increased slightly in the geriatric patient group.⁴¹ When TNFi treatments were evaluated in terms of cancer risk, no significant difference was found between the geriatric period and the young patient group according to Italian and Danish national registry data.^{42,43} Although there are insufficient data on heart failure, greater levels of cardiac care during TNFi treatments in elderly patients is suggested.⁴⁴ In all these real-life datasets, the information derived from a substantially smaller number of geriatric AS and PsA patient cohorts, compared to geriatric RA patients, appears to be compatible with the data observed in geriatric RA patients. The adverse effect data in our study were in parallel with previous studies and were similar in both age groups.

While young AS patients exhibited response rates comparable to the geriatric group concerning biological drug use, it is evident that new studies, which consider detailed definitions of advanced age groups, are necessary to conduct multicenter investigations with more extensive patient participation, particularly with regard to safety aspects.

Several recommendations regarding the use of TNFi's propose that they can be employed in older age groups.^{24,28} Although similar response rates have been found for the use of biological drugs in elderly patients compared to younger patients, there is a need for new studies that define advanced age groups in detail to conduct new multi-center studies with larger patient participation in terms of safety. Patients with late-onset/diagnosed AS represent a subgroup of patients with chronic diseases related to HLA-B27-related arthritis. Given the increase in life expectancy and new diagnostic criteria and imaging modalities to diagnose this group of disorders, the number of patients encountered and diagnosed with late-onset AS and SpA is likely to increase. Therefore, additional studies specifically evaluating the efficacy and safety (or benefit/risk ratio) of TNFi in elderly patients with AS are needed.

Nonetheless, there are some limitations due to its retrospective cohort design. Insufficient data were available to evaluate primary and secondary non-responsiveness and drug-switching findings

in patients with AS. It gives evidence of several differences from previous publications, including the use of age 60 to define elderly AS and the exclusion of patients with inflammatory bowel disease or psoriasis. On the other hand, our study exhibits important strengths with respect to AS. We believe that our study, which included 201 patients in the older AS group and 610 patients in the younger AS group, may be of clinical importance with a large number of patients assessed in relation to TNFi use status, their response to treatment and serious adverse effects. The results of our current study show that there is no significant increase in the risk of serious infections, cancer development and other serious adverse effects among younger and older patients with AS receiving TNFi treatment. Nevertheless, since TNFi treatment is typically employed for an extended duration, often lifelong, in AS patients, longer-term follow-up studies, particularly focusing on elderly patients, are essential to validate the findings of this study.

In conclusion, older and younger AS patients enrolled in the TURKBIO cohort had similar levels of disease activity and similar treatment modalities. The TNFi therapies used in geriatric patients were similar with respect to outcomes in younger patients and no additional safety risks were identified.

Ethics Committee Approval: The TURKBIO database project has been approved as a phase IV observational study by the Turkish Ministry of Health Drug Regulatory Agency and also by the Gaziantep University Ethics Committee (date: 20.06.2013, no: 20.06.2013/253). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed to the literature search, analysis and/or interpretation, and design. The first draft of the manuscript was written by Sadettin Uslu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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