Treatment Adherence of Anti-TNF Drugs in the Patients with Inflammatory Bowel Disease: A Scale Development Study

Nur Başak[1], *Berna Nilgün Özgürsoy Uran*[2], *Elif Sarıtaş Yüksel*[3]

[1]*Internal Medicine Nursing Department, Institute of Health Science, İzmir Katip Çelebi University, İzmir, Turkey*
[2]*Faculty of Health Science, İzmir Katip Çelebi University, İzmir, Turkey*
[3]*İzmir Katip Çelebi University Medical School, İzmir, Turkey*

Cite this article as: Başak N, Özgürsoy Uran BN, Sarıtaş Yüksel E. Treatment adherence of anti-TNF drugs in the patients with inflammatory bowel disease: A scale development study. *Turk J Gastroenterol.* 2022;33(4):336-345.

ABSTRACT

Background: *This work studies the validity and reliability of the Anti-TNF Alpha Treatment Adherence Scale, which has newly been developed to measure the compliance of inflammatory bowel disease patients using the anti-TNF alpha agents that are widely used in gastroenterology and rheumatology clinics.*

Methods: *The study group consisted of 165 irritable bowel disease patients aged 18 years and above who were using anti-TNF alpha drugs. After creating a question pool with 40 items, the pilot study was applied with 70 patients. SPSS 25.0 and AMOS programs were used. Item-total correlation coefficients, Cronbach's alpha and test-retest analysis, missing data, extreme value, normality, 27% sub-upper item discrimination analysis, and exploratory and confirmatory factor analyses were used.*

Results: *The factor structure of the scale was examined with exploratory and confirmatory factor analyses and the contribution of these components to the total variance was measured as 74.21%. The Anti-TNF Alpha Treatment Adherence Scale was found in relation to the scale structure consisting of 12 items and 4 sub-dimensions. According to the first level multifactorial analysis results, the goodness of fit identities of the scale were found at an acceptable level, with the following values: RMSEA 0.067; GFI 0.92; AGFI 0.87; CFI 0.95; and $\chi 2$ 79.876 ($P = .000$).*

Conclusion: *It was determined that the Anti-TNF Alpha Treatment Adherence Scale represents the area to be measured, measures the researched structure, has a high internal consistency between items, is interrelated, and is consistent over time. As a result of all measurements, it was determined that it is a valid and reliable scale.*

Keywords: *Anti-TNF alpha, IBD, reliability, scale development, treatment compliance, validity*

INTRODUCTION

Tumor necrosis factor (TNF) is a member of the large cytokine family. Cytokines are key actors in important biological functions, including conditions such as immunity, inflammation, cell growth, and fibrosis, apart from transmission of many messages.[1,2]

In 2009, the United States, European countries, and Turkey approved for chronic autoimmune arthritis a TNF-α inhibitor which has 5 clinical forms, namely, adalimumab, certolizumab, infliximab, golimumab, and etanercept. Anti-TNF-α agents are used in rheumatology, gastroenterology, and dermatology.[3-5] Although the selection of anti-TNF is a complex situation, especially in chronic inflammatory diseases such as inflammatory bowel disease (IBD) comprising remission and relapse periods, infliximab is the frequently preferred treatment method. The major purpose of treatment for IBD, which has many options such as amino salicylates, corticosteroids, antispasmodics, anticholinergics, and immune modulators, is to enhance clinical signs and to maintain remission. Besides these, biological agents play an important role in the treatment of advanced inflammation, in cases of non-response to corticosteroids, or the inability to use corticosteroids for over 8 weeks in ulcerative colitis (UC) and for over 12 weeks in Crohn's disease (CD).[6,7]

The World Health Organization defines long-term treatment compliance as 'the individual's drug use, the ability to transfer lifestyle changes to behavior, and compliance with the recommendations of healthcare professionals, and emphasizes that compliance is mainly affected by 5 factors: patient, medical condition, treatment, healthcare team, and socioeconomic status.[8] Personal experiences and health beliefs are among the most important factors affecting noncompliance in chronic diseases.[9] Although noncompliance with treatment and medication in chronic diseases adversely affects the

Corresponding author: ***Nur Başak****, e-mail:* ***nur.basak@yahoo.com***
Received: ***January 28, 2021*** *Accepted:* ***September 14, 2021*** *Available Online Date:* ***January 25, 2022***

DOI: ***10.5152/tjg.2022.211170***

treatment process financially and morally, it is a situation that healthcare professionals do not want because it will also cause relapse periods.[10] Treatment adaptation of anti-TNF alpha agents with regular and long-term use can be difficult. Therefore, it requires more frequent monitoring and testing.[3,11-13] Anti-TNF therapy may cause serious side effects, as it suppresses important beneficial effects such as inhibiting inflammation and tumor melting. Besides, it suppresses the harmful effects of TNF-α. Also, when patients experience side effects, they might quit the treatment. In different countries, the use of TNF alpha agents is accompanied by some checklists, developed with guidelines, before starting the treatment process, to minimize the risk of nonadherence to treatment.[14-17] Prior to the treatment in Turkey, there is no checklist used outside the tuberculosis directory or a form allowing the drug to be included in some tests.[18]

As a result of the screening, we concluded that although there have been many treatment and drug compliance studies, the existing studies have not specifically measured the compliance of anti-TNF alpha agents or have been limited. Only in a study conducted in 2017 by Martelli et al.[19] researchers prepared general questions and evaluated the treatment compliance of IBD patients, but they stated that this study could not be generalized. Further, the same research states that the most common reason why patients quit the anti-TNF-alpha treatment is the side effects seen during treatment.[19] Besides contributing to the literature, this scale development study, which was planned based on this deficiency, is thought to be a pioneer in future studies using the scale to detect noncompliance with treatment and provide training in treatment. This scale measures adherence to anti-TNF-alpha treatment. It includes the reasons for quitting treatment and the knowledge level in using the drug. Healthcare workers might determine the odds of patients quitting treatment before and during the therapy by using this scale. With these results, they can prevent nonadherence of treatment or educate the patients about the treatment if necessary. Moreover, there are no studies on this subject. These reasons necessitate this scale. The scale can be a guideline for anamnesis, can contribute a new tool to the literature, and can shed light on new studies.

Main Points

- *Anti-TNF alpha agents are a frequently used drug group, especially in gastroenterology and rheumatology.*
- *Physicians and nurses have important responsibilities in the use of these agents.*
- *The main factors affecting treatment compliance can be listed as the treatment process, lack of information, sociodemographic characteristics, etc.*
- *Measurability of treatment compliance plays an important role in determining the point where the patient experiences noncompliance and in facilitating compliance.*
- *The Anti-TNF Alpha Treatment Adherence Scale (ATA-TAS) was determined to be a valid and reliable scale.*

MATERIALS AND METHODS

Research Sample

The research was conducted between December 2019 and June 2020. While the universe of the research was formed by all patients who applied to the gastroenterology clinic of a training and research hospital, the sample comprised patients with IBD using anti-TNF alpha, over 18 years of age, literate, with no communication problems, who could speak Turkish, and volunteered for the study. In order for the factor analysis to be performed properly at the stage of determining the sample in the scale development studies, the sample size should be at least 5 times the number of draft scale items, or, according to the study of Preacher and MacCallum,[23] which stated that the minimum sample in the studies should be between 100-250, regardless of the number of items.[20-23] At the start of the main study, a 40-item question pool created within the scope of the literature was sent to a group of 14 experts, including physicians, nurses, and academicians working for the IBD patient group. With the suggestions and contributions of the experts, the number of items in the pool decreased to 33 and the draft scale was finalized. A total of 165 patients, 5 times the final version of the draft scale (33 items) and providing the minimum validity suggested by Preacher and MacCallum,[23] were determined as the target sample number of the study.

Data Collection

Research data were collected using the Patient Identification Form and the Draft of Anti-TNF Alpha Therapy Compliance Scale. Data collection forms were given to the patients, to be completed by the self-report method.

Patient Information Form

It consists of 11 questions prepared by the researchers, including the sociodemographic information of the patient such as age, gender, education, job, smoking, alcohol and drug consumption, medical knowledge, treatment time, experience of side effects, etc.[3,11,12]

Draft Anti-TNF Alpha Treatment Adherence Scale (ATA-TAS)

It consists of 33 items which include positive and negative statements prepared by the researcher on the basis of other treatment compliance scales in the literature, scale development resources, and other scales in the field (Appendix 1).[14-17,24-27]

Scale Development Process and Statistical Analysis

In order to evaluate treatment compliance in patients using anti-TNF alpha, an item pool of 40 questions containing positive and negative expressions was first created, taking into account the relevant guidelines, other drug compliance scales, and the questions and problems encountered during patient education. The Lawshe method was preferred for the content validity analysis of the items in the pool. The item pool was sent to a group of 14 experts who were asked to evaluate the items. After that, the draft scale consisting of the remaining questions was piloted with 70 patients.

All statistical analyses of the draft scale were carried out with SPSS 25.0 (IBM® SPSS® Statistics 25.0) and AMOS (IBM® SPSS® Amos) programs. Item-total correlation coefficients and Cronbach's alpha reliability analysis were performed in the pilot study. In the main study for the draft scale, the item-total correlation coefficients, Cronbach's alpha, missing data, extreme value, normality, 27% sub-upper item discrimination, and exploratory and confirmatory factor analyses were used. Statistically, a value of $P < .05$ was considered significant at 95% CI.

The construct validity of the scale was evaluated with the explanatory factor analysis (EFA) technique in order to determine the meanings of the scores obtained by the candidate scale and the characteristics it measured. Thus, the draft scale was divided into subitems and made more understandable. The contribution of these components to the total variance and the contribution of each subitem to the total variance were calculated separately, and reliability analyses were repeated for each sub-dimension. Confirmatory factor analysis (CFA) was conducted in order to verify the EFA and measure the goodness of fit of the scale.[28-33]

Reliability analyses are performed to show that sensitivity, consistency, and stability criteria are met in candidate scales.[29,30] In this study, reliability analyses were conducted to determine whether the draft scale was an appropriate measurement tool, whether it collected accurate data, and whether it was reproducible. To measure the stability of the scale, a retest was carried out 3 weeks after the first application and the correlation between the test-retest data was expected to be at least 0.70.[34,35] Cronbach's alpha reliability method was used to measure the internal consistency of the scale, and the ability of the candidate scale to give consistent results from application to application and to show stability over time was calculated.[28,33,35]

Ethical Aspect

All the procedures in the studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki. The study was approved by the ethical committee for scientific research of the University Non-Invasive Ethics Committee (approval date: December 26, 2019, approval no: 482). In addition, the application permission from the hospital where the study was conducted and written informed consent from the participants were obtained.

RESULTS

Scope Validity and Expert Opinion Results

The Lawshe method was used to calculate the content validity index (CVI). Forty questions created with the 5-point Likert response system in the item pool of the developed candidate scale were conveyed to 14 experts via mail or face-to-face interviews. Items below the acceptable content validity rate (CVR) value were removed, and the items that received regulation suggestions were rearranged. Thus, the item pool consisting of 40 questions was transformed into a candidate scale with 33 questions and a pilot implementation was initiated. The CVI of the scale was calculated as 0.84 after the items which below the CVR value were removed.

Pilot Results

The pilot study was conducted with 70 patients on the basis of at least twice the 33 items remaining in the pool. The 70 patients selected were determined by inclusion and exclusion criteria in the main study sample. While applying the scale, the face-to-face interview technique was used, and the patients' opinions about the clarity, understandability, and difficulty level of the items were obtained. At this stage, no questions were identified that were difficult to understand or required a detailed explanation. Item analysis was applied to all items deemed appropriate psychometrically to determine whether there was a problem in terms of item-total correlation and

internal consistency. As a result of the item analysis, the Cronbach's alpha value was calculated as 0.890, and all items were considered understandable and applicable to patients.

Main Study Practice and Analysis Results

After the pilot study, the main study was started and the scale adaptation study was conducted with 165 patients, who were selected in line with the inclusion and exclusion criteria, and as stated in the literature, 5 times the number of items. The 70 patients included in the pilot study were included in the main study sample.[28] The demographic characteristics of the patients are shown in Table 1.

Validity and Reliability Results of the Scale

Cronbach's Alpha reliability analysis was performed to measure the internal consistency of the scale and it was calculated as 0.892. While the total correlation for the item analysis result was calculated as positive for 31 items and was higher than 0.20, the value was lower than 0.20 for only 2 items, and these were removed from the scale and re-analyzed. The newly obtained Cronbach's alpha value for 31 items was calculated as 0.907. During the new analysis, an item came out slightly below 0.20 (0.17). This item was also removed and the Cronbach's alpha value was calculated as 0.909 with the analysis of the remaining 30 items, and its distinctiveness and understandability were deemed high.

Before the EFA was applied, the Kaiser–Meyer–Olkin (KMO) test was applied to measure whether the sample obtained was sufficient for analysis, and the result was calculated as 0.840. As this value approached 1, it was concluded that the sample size was "perfectly sufficient" since the sample was considered sufficient.[29]

After the data were found suitable for factor analysis, EFA was performed using principal components analysis and varimax rotation methods in order to examine the factor structure of the scale. According to EFA results, after removing 4 items with factor loads below 0.40, 9 items with overlap and 5 items under the wrong sub-dimension, the remaining 12 items were found to have 4 sub-dimensions as a result of the factor analysis. After the extracted items, the factor analysis was performed for 12 items, and the obtained new reliability analysis results (Cronbach's alpha and KMO) are shown in Table 2.

In Figure 1, which includes the eigenvalues on the vertical axis and the number of factors on the horizontal axis, it is seen that the fast decline decreased after the fifth point. The descents seen from the first point show the contribution of each sub-dimension to the variance. Considering the eigenvalue and variance percentages, the data obtained from the graph confirmed that there should be 4 factors toward EFA.[29] In order to measure the distinctiveness of the items, the raw scores obtained separately for the items in each sub-dimension were ranked in ascending order and the mean scores of the groups in the top 27% and bottom 27% were compared with the independent group *t*-test, The data are shown in Table 3.

In line with the results of the EFA, it was seen that CFA should be performed on the scale in order to measure the normal distribution of items, item significance, and the goodness of fit of the scale. The maximum likelihood calculation method was used for the CFA modeling of the scale with a normal distribution (multivariate/cr .= 9.045). According to the CFA results, the structural equation model result of the scale was found to be significant, with P = .000. The ATA-TAS was found to be associated with a scale structure consisting of 12 items and 4 sub-dimensions.

The opinions and recommendations of a gastroenterologist working with IBD patients and an IBD nurse were considered for naming the sub-dimensions of the scale. The first dimension is named "Personal Factors," the second dimension is "Awareness," the third dimension is "Leaving the Treatment," and the fourth dimension is "Concern and Coping" according to the items it contains and the factors affecting treatment compliance.

Some modifications have been made to the model (Figure 2). While making improvements, variables that reduce compliance were determined, and new covariances were created for those with high covariance among residual values (e7-e8; e10-e11). Table 4 shows that the accepted values for the fit indices are provided in the renewed fit index calculations afterward. Having GFI, AGFI, NFI, and CFI indices over 0.90, and RMSEA value below 0.08 corresponds to an acceptable fit.[33,36]

Table 4 shows the factor loadings of ATA-TAS according to the first level single-factor CFA result. According to the single-factor CFA result, it was determined that the factor loads varied between 0.472 and 0.932. Since the standardized regression weights are greater than 0.40, each item was considered significant. It has been shown that the fit indices obtained after

Table 1. Descriptive Characteristics of Patients Participating in the Study

	n	Minimum	Maximum	Mean	SS
Age (years)	165	18	74	41.44	12.81
				n	%
Gender					
Female				79	47.9
Male				86	52.1
Education					
Literate/primary education				40	24.2
High school				80	48.5
University or more				45	27.3
Job					
Housewife				20	12.1
Officer				20	12.1
Self-employed				30	18.2
Retired/unemployed				48	29.1
Other				47	28.5
Smoking					
Yes				85	51.5
Quit/no				80	48.5
Alcohol consumption					
Yes				46	27.9
Quit/no				119	70.1
Medical knowledge**					
Yes				148	89.7
No				17	10.3
Chronic illness					
Other than IBD***				61	36.9
Only IBD				104	63.1
Drug use					
Other than anti-TNF				63	38.1
Only anti-TNF				102	61.9
Treatment time					
Incipient				20	11.1
For 1-11 months				30	18
For 1-5 years				99	60
More than 5 years				16	10.9
Side effects experienced*					
Yes				113	68.5
No				52	31.5

*There is only side effect experience which is shown in anti-TNF alpha treatment.
**Have already received training from a health professional or other source on issues such as medication use, side effects, vaccination during treatment, and nutrition.
***Hypertension, diabetes, cerebrovascular accident, cancer, lung disease, thyroid diseases, kidney diseases, muscle-joint diseases, digestive diseases, and other.

Table 2. Factor Analysis and Reliability Analysis Results

Item Number	Factor Load Value	Load Value After Varimax				Cronbach's Alpha if Item Deleted
		Group 1	Group 2	Group 3	Group 4	
1	0.838	0.908				0.801
2	0.735	0.837				0.804
3	0.713	0.820				0.804
4	0.761		0.832			0.801
5	0.718		0.824			0.811
6	0.732		0.764			0.802
7	0.801			0.887		0.809
8	0.755			0.801		0.803
9	0.730			0.623		0.795
10	0.773				0.855	0.810
11	0.739				0.827	0.807
12	0.613				0.531	0.787
Explained Variance Total: 74.21% Group1: 21.29% Group2: 20.59% Group3: 17.12% Group4: 15.20%		Kaiser–Meyer–Olkin (KMO): 0.785 Bartlett's Test of Sphericity Approximate chi-square: 864.678 *df*: 66 sig: 0.000				Cronbach's Alpha: 0.816 Group1: 0.838 Group2: 0.802 Group3: 0.807 Group4: 0.722

sig, significant.

the modification are over 0.30 and are of acceptable value.[33] According to the first level multifactorial analysis results, the goodness of fit identities of the scale were found at an acceptable level, with values as follows: RMSEA 0.067; GFI 0.92; AGFI 0.87; CFI 0.95; χ^2 79.876 (P = .000).

Pearson moments correlation coefficient, which is the strongest and highest strength correlation method,[34] was calculated and data are given in Table 5. The minimum correlation value, which indicates the invariance of a newly developed scale against time, was determined as 0.70.[35] It was found that there is a statistically very high

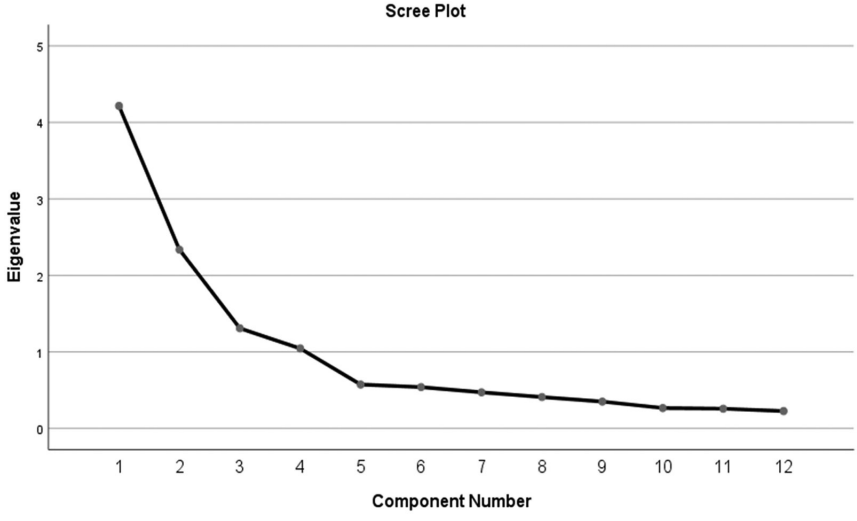

Figure 1. Factor Analysis of the Scale's self values and number of factors.

Table 3. Item Analysis Results of the Sub-Dimensions of the Scale

Item Number	Item Total Score Correlation	*t* (Bot 27%*-Top 27%*)	*P* sig. (Bot 27%*-Top 27%*)
1	0.489	–10.621	.000**
2	0.460	–18.099	.000**
3	0.470	–7.390	.000**
4	0.539	–21.819	.000**
5	0.386	–15.443	.000**
6	0.514	–15.319	.000**
7	0.399	–10.269	.000**
8	0.472	–17.245	.000**
9	0.556	–13.621	.000**
10	0.391	–17.220	.000**
11	0.429	–12.980	.000**
12	0.626	–13.725	.000**

n = 165, *n_1 = n_2 = 45, **A p-value < .05 (typically < .05) is statistically significant.

positive correlation between the first and the second application.

DISCUSSION

Although anti-TNF alpha agents do not affect all systems, they may cause serious side effects such as tuberculosis, uveitis, hepatitis B, optic neuritis, skin reactions, and even cancer, and they require close monitoring and follow-up.[37]

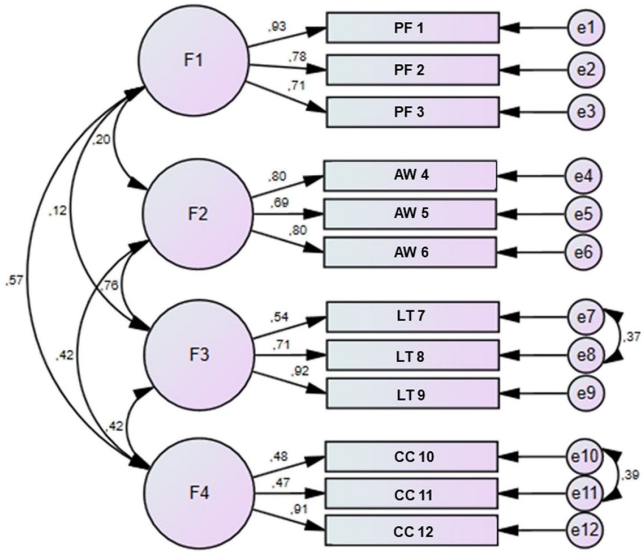

Figure 2. The Model of the Scale's First Level Multi-factor Confirmatory Factor Analysis. PF, personal factors; AW, awareness; LT, leaving the treatment; CC, concern and coping.

In the literature reviews, we found that studies evaluating treatment compliance for many diseases emphasize the need for disease-specific treatment compliance scales.[19,38-44] No scale evaluating the treatment compliance regarding anti-TNF use in patients with a diagnosis of IBD was found, and therefore, in this study, an attempt was made to add such a scale to the literature.

The physiological effects of TNF agents are harmless to the body at low levels. TNF is also an important protein in fighting cancer and infection. However, susceptibility to opportunistic infections which is developed during anti-TNF therapy is a serious side effect. Therefore, serious side effects such as tuberculosis can occur during the use of anti-TNF agents.[37-39] Among the anti-TNFs, infliximab has the most side effects because of IV use. For this reason, some researches show patients' inclination to quit the treatment. Also in subcutaneous forms, insufficient usage of information can be the cause of discontinuation of treatment.[19,37,39,40] The World Health Organization stated the lack of information, sociodemographic characteristics, and side effect experiences among the reasons for nonadherence to treatment of chronic diseases. Some anti-TNF studies have identified the leading causes of this incompatibility as occupational restrictions, deliberate non-compliance, and side effects such as injection site reactions, demyelinating disease, congestive heart failure, lupus-like clinical picture, vasculitis, uveitis, autoimmune hepatitis, lymphoma, and others.[37-44]

Based on the inclusion criteria, 52.1% of the population were male, the average age was 41.44 years, 48.5% were high school graduates and 29.1% were in retirement or were unemployed. In addition, 51.5% were smokers, 82.4% were not vaccinated regularly, and 64.8% had side effects while on treatment.

Studies on scale development state that for a Likert-type scale, an item pool of at least 2 to 4 times the number of items to be obtained or targeted should be created.[45,46] We created a question pool of 40 items in the literature review conducted in line with the specified purpose.[14-17,25-27] According to the Lawshe technique used in evaluating the harmony between experts, we conveyed the question pool created to a group of 14 experts,[36] and they said it expresses well the area to be measured for 33 items.

In order to ensure the construct validity of the developed scale, the minimum value for KMO should be

Table 4. Covariance Values and CFA Results Factor Loads Before and After Modification

Before Modification							
RMSEA	NFI	CFI	IFI	GFI	TLI	AGFI	CMIN/*df*
0.095	0.867	0.914	0.916	0.894	0.882	0.828	2.472
After Modification							
RMSEA	NFI	CFI	IFI	GFI	TLI	AGFI	CMIN/*df*
0.067	0.910	0.959	0.960	0.929	0.941	0.879	1.736

Factor Loads.
Item 1: 0.932; Item 2: 0.777; Item 3: 0.708; Item 4: 0.795; Item 5: 0.694; Item 6: 0.802; Item 7: 0.536; Item 8: 0.706; Item 9: 0.922; Item 10: 0.484; Item 11: 0.472; Item 12: 0.907.

0.70 (0.50 according to some sources), and the *P* value should be less than .05 for Bartlett's test.[29] The KMO and Bartlett's test results were found to be quite sufficient, according to the literature. The contribution of these components to the total variance is 74.21% for application of EFA. Similar to this research, considering that the total variance, explained in the multi-factor models, between 50% and 75% is sufficient, it is accepted as a valid and strong analysis.[47-50]

In the EFA conducted to reveal the factor design of the draft ATA-TAS, which aims to measure anti-TNF alpha treatment compliance, the acceptance level for factor load values was accepted as 0.40. It is known that a Cronbach's alpha value above 0.70 is sufficient for reliability.[30] Accordingly, it was determined that the developed scale and each of its sub-dimensions have high reliability (Table 2).

The raw scores obtained separately for the items in each sub-dimension were ranked for the distinctiveness of the items, and it was calculated that there was no statistically significant difference between the means of lower and upper group item scores. When the item-total test correlation and the relationship of each item with the total score are examined, having a high correlation means that the measuring tool is consistent. The correlation values for the developed scale vary between 0.391 and 0.626, and there is a relationship between all items. In the literature, the value for which the item-total test correlation is considered sufficient is specified as 0.300[31,32] (Table 3).

Since the draft scale has 12 items and 4 sub-dimensions, it was decided to apply the first-level multifactor CFA model.[31-33] There are some acceptable and good fit values when interpreting fit indices after the CFA model is applied. In order to provide these indices, an inter-item modification can be applied to the model, and 2 modifications have been applied to improve some of the fit indices in the ATA-TAS. According to the CFA results, the structural equation model result of the scale was measured as *P* = .000 and was significant. According to the first level single-factor CFA result of the draft scale, factor loadings vary between 0.484 and 0.932. Since the standardized regression weights are greater than 0.40, each item was considered significant.[33] The fit indices obtained after the modifications are mostly in good fit value ranges, but some of them are in the acceptable range. According to the outputs of CFA modeling, it has been confirmed that the sub-dimensions and items of the model are significant. All results are given in Table 4.

Table 5. Test-Retest Correlation Values

		ATA-TAS Pretest	ATA-TAS Final Test
ATA-TAS Pretest	Pearson Correlation	1	0.989
	Sig. (2-tailed)		0.000
	N	30	30
ATA-TAS Final Test	Pearson Correlation	0.989	1
	Sig. (2-tailed)	0.000	
	N	30	30

ATA-TAS, Anti-TNF Alpha Treatment Adherence Scale.

As a result, it was determined that ATA-TAS represents the area to be measured, measures the researched structure, has 4 subgroups with 12 items, has a high internal consistency between items, and is a valid and reliable scale. The scale includes positive and negative statements. Therefore, while developing the scale, some items were reverse-coded and measurements were made. A high score obtained from the scale shows the nonadherence with treatment. Score distribution indicates a good adherence if between 0 and 2, medium adherence if higher than 2 and lower than 3, and poor adherence for values 3 and above (up to 5).

The major factors affecting drug compliance can be listed as the treatment process, lack of information, sociodemographic characteristics, and other reasons that may develop because of these. Although these drugs are effective in combating diseases, full benefit is often not achieved since approximately 50% of the patients do not take their drugs as specified, which is why we need this scale. With this scale, which calculates adherence to treatment, health workers could be enabled to recognize any noncompliance early. For 165 individuals who were evaluated in the study, adherence was good in 71 of them, adherence was moderate in 72, and adherence was poor in 22 individuals. However, this result is only acceptable for patients who have IBD. With this developed scale, it is recommended to conduct studies with patients diagnosed with IBD who are receiving anti-TNF alpha treatment and to evaluate the validity and reliability analyses of the scale with different populations. Although patients with a diagnosis of IBD were included in the study, it is recommended that ATA-TAS should be tested in all inflammatory diseases using anti-TNF alpha (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, juvenile chronic arthritis, etc.) in terms of the structure and content of the questions, and it is recommended to be used in these disease groups by performing validity and reliability analyses.

Ethics Committee Approval: The study was approved by the Ethical Committee for Scientific Research of İzmir Katip Çelebi University Non-Invasive Ethics Committee (approval date: 26 December 2019, approval no: 482).

Informed Consent: All the procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki. Moreover, application permission from the hospital where the study was conducted and written informed consent from the participants were obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – N.B., B.N.O.U., E.S.Y.; Design – N.B., B.N.O.U., E.S.Y.; Supervision – N.B., B.N.O.U., E.S.Y.; Resources – N.B., B.N.O.U.; Materials – N.B., B.N.O.U., E.S.Y.; Data Collection and/or Processing – N.B.; Analysis and/or Interpretation – N.B.; Literature Search – N.B., B.N.O.U.; Writing Manuscript – N.B., B.N.O.U.; Critical Review – B.N.O.U., E.S.Y; Other – N.B., B.N.O.U., E.S.Y.

Acknowledgments: The authors would like to thank the statistician Murat Bayazıt for helping and checking statistical analysis, and the patients for allowing data collection.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. *Udalova I, Monaco C, Nanchahal J, Feldmann M. Anti-TNF therapy. Microbiol Spectr. 2016;4(4):1-11.* [CrossRef]
2. *Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. Crit Rev Eukaryot Gene Expr. 2010;20(2):87-103.* [CrossRef]
3. *Aydın V, Akıcı A. TNF-alpha inhibitor-induced infections in rheumatic diseases. tjtfp. 2018;9(1):13-24.* [CrossRef]
4. *Tezel A. İnflamatuvar barsak hastaliklarinda anti-TNF tedavilerin yeri ve Uygulamada dikkat edilecek noktalar. Güncel Gastroenteroloji. 2010;14(4):193-197.*
5. *van Hoeve K, Hoffman I, Vermeire S. Therapeutic drug monitoring of anti-TNF therapy in children with inflammatory bowel disease. Expert Opin Drug Saf. 2017;17(2):185-196.* [CrossRef]
6. *Üzerk M, Çetinkaya H. Ülseratif kolitin klasik tedavisine genel bakış ve anti-TNF ajanlarin rolü. Güncel Gastroenteroloji. 2009;13(1):41-47.*
7. *TİTCK. 2016/7 Genelgesi: Anti-TNF İlaçlar. Available at: https://www.sanliurfaeo.org.tr/indir3-225428JG8ANT%DD%20TNF.pdf, Accessed July 7, 2019.*
8. *Sabaté E, WHO Adherence to Long Term Therapies Project, Global Adherence Interdisciplinary Network, World Health Organization. Department of Management of Non-Communicable Diseases. Adherence to Long-Term Therapies: Evidence for Action. Geneva: World Health Organization; 2003.*
9. *Toh CT, Jackson B, Gascard DJ, Manning AR, Tuck EJ. Barriers to medication adherence in chronic heart failure patients during home visits. J Pharm Pract Res. 2010;40(1):27-30.* [CrossRef]
10. *Nitzan O, Elias M, Peretz A, Saliba W. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol. 2016;22(3):1078-1087.* [CrossRef]
11. *Ali T, Kaitha S, Mahmood S, Ftesi A, Stone J, Bronze MS. Clinical use of anti-TNF therapy and increased risk of infections. Drug Healthc Patient Saf. 2013;5:79-99.* [CrossRef]
12. *Vural B, Acar ÖT, Topsever P, Filiz TM. Modifiye Morisky Ölçeğinin Türkçe Geçerlilik Güvenilirlik Çalışması. Turk Fam Phys. 2012;3(4):17-20.*
13. *Aydın B, Gelal A, Kullanımı Aİ. Yaygınlaştırılması ve tıp Eğitiminin rolü. DEÜ Tıp Fak Derg. 2012;26(1):57-63.*
14. *Nordgaard-Lassen I, Dahlerup JF, Belard E, et al. Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment. Dan Med J. 2012;59(7):C4480.*
15. *Kelly MM, Turner BS, Kappelman MD, Lee EJ, Gulati AS. Implementation and evaluation of a standard operating procedure for pediatric infliximab infusions. Pediatr Qual Saf. 2019;4(1):e137.* [CrossRef]
16. *Miehsler W, Novacek G, Wenzl H, et al. A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohns Colitis. 2010;4(3):221-256.* [CrossRef]
17. *Mitoma H, Horiuchi T, Tsukamoto H, Ueda N. Molecular mechanisms of action of Anti-TNF-α agents – comparison among therapeutic TNF-α antagonists. Cytokine. 2018;101:56-63.* [CrossRef]
18. *Bakanlığı S. Anti-TNF Kullanan Hastalarda Tüberküloz rehberi. Toraks. Available at: https://www.romatoloji.org/Dokumanlar/Site/ATKHTR.pdf.*

19. Martelli L, Lopez A, Strobel S, et al. Adherence to infliximab therapy in inflammatory bowel disease patients in a real-life setting. J Dig Dis. 2017;18(10):566-573. [CrossRef]
20. Bayik Temel A, Yildirim JG, Kalkim A, Muslu L, Yildirim N. Parents' and teachers' expectations of school nurse roles: a scale development study. Int J Nurs Sci. 2017;4(3):303-310. [CrossRef]
21. Aksayan S, Bahar Z, Bayık A, et al. Hemşirelikte Araştırma İlke, Süreç ve Yöntemleri. 1. Baskı. Erefe İ (ed.), Hemşirelikte Araştırma ve Geliştirme Derneği. İstanbul: Odak Ofset; 2002:169-187.
22. Tavşancıl E. Tutumların Ölçülmesi ve SPSS ile Veri Analizi. 5. Baskı. Ankara: Nobel Yayıncılık; 2014:150-156.
23. Preacher KJ, MacCallum RC. Exploratory factor analysis in behavioral genetics research: factor recovery with small sample sizes. Behav Genet. 2002;32(2):153-161. [CrossRef]
24. Khan N, Shah Y, Trivedi C, Lewis JD. Safety of herpes zoster vaccination among inflammatory bowel disease patients being treated with anti-TNF medications. Aliment Pharmacol Ther. 2017;46(7):668-672. [CrossRef]
25. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23(suppl 2):1-70. [CrossRef]
26. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – short version – EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-2294. [CrossRef]
27. Royal College of Nursing. Assessing, Managing and Monitoring Biologic Therapies for Inflammatory Arthritis. RCN Guidance for Rheumatology Practitioners. 4th ed. Available at: https://www.readkong.com/page/assessing-managing-and-monitoring-biologic-therapies-for-4506556.
28. Bryman A, Cramer D. Quantitative Data Analysis with SPSS Release 10 for Windows: A Guide for Social Scientists. 1st ed. Londra: Routledge Yayıncılık; 2001:96-112.
29. Çokluk Ö, Şekercioğlu G, Büyüköztürk Ş. Sosyal Bilimler İçin Çok Değişkenli İstatistik: SPSS ve Lisrel Uygulamaları. Ankara: Pegem Akademi Yayıncılık; 2012.
30. Bayram N. Sosyal Bilimlerde SPSS İle Veri Analizi. Bursa: Ezgi Kitabevi; 2004.
31. Akyüz HE. Yapı Geçerliliği İçin Doğrulayıcı faktör analizi: Uygulamalı bir çalışma. BEÜ Fen Bilimleri Derg. 2018;7(2):186-198. [CrossRef]
32. Özdamar K. Paket Programlar İstatistiksel Veri Analizi. 7. Baskı. Eskişehir: Kaan Kitapevi; 2002.
33. Marsh HW, Hau KT, Artelt C, Baumert J, Peschar JL. OECD's brief self-report measure of educational psychology's most useful affective constructs: cross-cultural, psychometric comparisons across 25 countries. Int J Test. 2006;6(4):311-360. [CrossRef]
34. Tavşancıl E. Tutumların ölçülmesi ve SPSS ile veri analizi. Ankara: Nobel Yayıncılık; 2002.
35. Karakoç FY, Dönmez L. Ölçek geliştirme çalışmalarında temel ilkeler. Tıp Eğitimi Dünyası. 2014;40:39-49.
36. Yurdugül H, Çalışmalarında Kapsam ÖG. Ölçek Geliştirme Çalışmalarında Kapsam Geçerliği için Kapsam Geçerlik İndekslerinin Kullanılması, XIV. Ulusal Eğitim Bilimleri Bildiri Kitabı, 28-30 Eylül 2005, Denizli. 2005.
37. Özgürsoy Uran BN, Başak N, Yüksel ES. Güncel Kılavuzlar Işığında Anti Tümör Nekrozis Faktör-Alfa Biyolojik Ajanların Klinik Kullanımı. Güncel Gastroenteroloji. 2020;24(3):138-146.
38. van der Have M, Oldenburg B, Kaptein AA, et al. Non-adherence to anti-TNF therapy is associated with illness perceptions and clinical outcomes in outpatients with inflammatory bowel disease: results from a prospective multicentre study. J Crohns Colitis. 2016;10(5):549-555. [CrossRef]
39. Kane SV, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. Adv Ther. 2009;26(10):936-946. [CrossRef]
40. Depont F, Berenbaum F, Filippi J, et al. Interventions to improve adherence in patients with immune-mediated inflammatory disorders: a systematic review. PLoS One. 2015;10(12):e0145076. [CrossRef]
41. D'Incà R, Bertomoro P, Mazzocco K, Vettorato MG, Rumiati R, Sturniolo GC. Risk factors for non-adherence to medication in inflammatory bowel disease patients. Aliment Pharmacol Ther. 2008;27(2):166-172. [CrossRef]
42. Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication in inflammatory bowel disease. Am J Gastroenterol. 2003;98(7):1535-1544. [CrossRef]
43. Chan W, Chen A, Tiao D, Selinger C, Leong R. Medication adherence in inflammatory bowel disease. Intest Res. 2017;15(4):434-445. [CrossRef]
44. Wentworth BJ, Buerlein RCD, Tuskey AG, Overby MA, Smolkin ME, Behm BW. Nonadherence to biologic therapies in inflammatory bowel disease. Inflamm Bowel Dis. 2018;24(9):2053-2061. [CrossRef]
45. Erkuş A. Psikometri Üzerine Yazılar. 1. Baskı. Ankara: Türk Psikoloji Derneği Yayınları; 2003:34-158.
46. DeVellis RF. Scale Development: Theory and Applications. 2nd ed. Newbury Park: SAGE Publications; 2003:88-90.
47. Şencan H. Sosyal ve Davranışsal Ölçümlerde Güvenirlik ve Geçerlik. Ankara: Seçkin Yayıncılık; 2005:105-788.
48. Tabachnick BG, Fidell LS. Using Multivariate Statistics. 4th ed. London: Pearson Education Company; 2001.
49. Bryman A, Cramer D. Quantitative Data Analysis with SPSS Release 10 for Windows: A Guide for Social Scientists. 1st ed. London: Routledge; 2001:68-112.
50. Çakır A. Faktör Analizi (Doktora tezi). İstanbul: İstanbul Ticaret Üniversitesi, Sosyal Bilimler Enstitüsü; 2014.

Appendix 1. Anti-TNF Alpha Tedavi Uyum Ölçeği (Original Language)

Maddeler	Kesinlikle Katılıyorum	Katılıyorum	Kararsızım	Katılmıyorum	Kesinlikle Katılmıyorum
1. Tedavimin kullanım nedenini biliyorum.					
2. İlacımın olumsuz etkilerini biliyorum.					
3. Bu ilaçla, daha önceki deneyimlerimde bazı sorunlar yaşadım.					
4. Tedavimin uzun dönem yararlarını biliyorum.					
5. Tedavim hakkında yeterli bilgiye sahibim.					
6. İlacımı doktorun önerdiği şekilde kullanıyorum.					
7. Doktor ile görüşmeden tedavimi yarım bıraktığım oldu.					
8. İlacımı almak istemediğim zamanlar oluyor/oldu.					
9. İlacımı almayı unuttuğum zamanlar oluyor/oldu.					
10. İlacımı çoğunlukla zamanında almaya dikkat ederim.					
11. İlacımın beni rahatlattığını/iyileştirdiğini düşünüyorum.					
12. Daha önce ilaç dozumu azaltığım/arttırdığım oldu.					
13. Kendimi iyi hissettiğimde, tedavime ara veririm.					
14. İlaç dozumun artırılmasından korkuyorum.					
15. Bazen ilacımın bağımlılık yaptığı fikrine kapılıyorum.					
16. Tedavi sürecim yaşam kalitemi olumsuz etkiliyor.					
17. Tedavi sürecim aileme ve arkadaşlarıma endişe veriyor.					
18. Tedavi sürecimi çevremdeki insanlarla paylaşmaktan çekindiğim oldu.					
19. Tedavi sürecim bana endişe veriyor.					
20. Bazen başka bir tedavi yolu imkânım olmasını istiyorum.					
21. Tedavi sürecimin uzun olması beni olumsuz olarak etkiliyor.					
22. Mesleki kısıtlılıklar tedavi sürecimi olumsuz olarak etkiliyor.					
23. Çevremden olumsuz tepkiler görmek tedavi sürecimi olumsuz olarak etkiliyor.					
24. Sosyal yaşantım tedavi sürecimi olumsuz olarak etkiliyor.					
25. Seyahatler tedavi sürecimi olumsuz olarak etkiliyor.					
26. Unutkanlık tedavi sürecimi olumsuz olarak etkiliyor.					
27. Tedavi sürecim psikolojimi olumsuz olarak etkiliyor.					
28. Tedavimle ilgili çevremdeki insanların etkisinde kaldığım oluyor.					
29. Tedavi sürecimin uzun olduğunu düşünüyorum.					
30. Tedavi sürecimin maliyetli olduğunu düşünüyorum.					
31. Tedavi sürecim iş/okul yaşamımı etkiliyor.					
32. Tedavi sürecim sosyal yaşamımı ve arkadaşlarımla vakit geçirmemi etkiliyor.					
33. Tedavi sürecim uyku düzenimi etkiliyor.					

Appendix 2. Draft Anti-TNF Alpha Treatment Adherence Scale

Items	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1. I know why I received treatment.					
2. I know the side effects of my medication.					
3. I have had some problems with the previous experiences with this drug.					
4. I know the long-term benefits of my treatment.					
5. I have enough information about my treatment.					
6. I take my medicine as prescribed by the doctor.					
7. Sometimes I would leave my medication incomplete without talking to the doctor.					
8. There are/were times when I didn't want to take my medication.					
9. There are/were times when I forgot to take my medication.					
10. I usually take care to take my medicine on time.					
11. I think my medicine relaxes/heals me.					
12. I have decreased/increased my medication dose before.					
13. When I feel good, I take a break from my treatment.					
14. I am afraid of increasing my medication dose.					
15. Sometimes I get the idea that my medicine is addictive.					
16. My treatment process negatively affects my quality of life.					
17. My treatment process gives anxiety to my friends and family.					
18. I hesitate to share my treatment process with people around me.					
19. My treatment process gives me anxiety.					
20. Sometimes I wish I had another treatment opportunity.					
21. The length of my treatment process affects me negatively.					
22. Occupational limitations negatively affect my treatment process.					
23. Seeing negative reactions from people around me negatively affects my treatment process.					
24. My social life negatively affects my treatment process.					
25. Vacations/travels negatively affect my treatment process.					
26. Forgetfulness negatively affects my treatment process.					
27. My treatment process negatively affects my psychology.					
28. I am under the influence of the surrounding people on my treatment.					
29. I think my treatment process is long.					
30. I think my treatment process is costly.					
31. My treatment process is affecting my work/school life.					
32. My treatment process affects my social life and time spent with my friends.					
33. My treatment process is affecting my sleep patterns.					