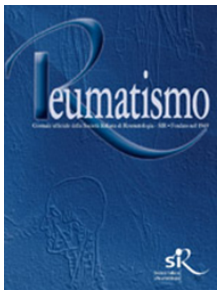

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Retention rate and predictor factors of drug discontinuation in axial spondyloarthritis: a focus on certolizumab and secukinumab

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Summary

Objective. Drug survival rate and time are important to demonstrate the effectiveness of treatment in patients with axial spondyloarthritis (axSpA) in real life. Therefore, we aimed to evaluate drug survival rate and predictors of discontinuation of certolizumab and secukinumab in axSpA patients.

Methods. This single-center retrospective cohort study included patients treated with certolizumab (n=239) and secukinumab (n=64) among axSpA patients followed up at the rheumatology clinic. Clinical, laboratory, and imaging findings, treatment duration, and reasons for discontinuation were evaluated between April 2019 and December 2022. Drug survival rate and time were analyzed using Kaplan-Meier analysis, and predictive factors associated with drug discontinuation were analyzed using multivariable Cox regression analysis.

Results. At 12 months, drug retention rates were 76% in the secukinumab group and 73% in the certolizumab group. The overall retention rate was similar in both groups (p=0.641). The median survival time was 66.0 months in the secukinumab group versus 62.8 months in the certolizumab group. A comparison of the patients who discontinued certolizumab treatment with those who continued showed that patients who discontinued certolizumab treatment had a higher frequency of female sex, peripheral arthritis, and inflammatory bowel disease. Comparison of the patients who discontinued secukinumab treatment with those who continued revealed that patients who discontinued secukinumab treatment only had a higher frequency of male sex. Multivariable Cox regression showed that male sex was independently associated with a lower risk of certolizumab discontinuation [hazard ratio (HR): 0.634, 95% confidence interval (CI): 0.41-0.97, p=0.036] and with a higher risk of secukinumab discontinuation (HR: 2.77, 95% CI: 1.18-6.49, p=0.018).

Conclusions. Our data showed that the drug survival rate of certolizumab and secukinumab was similar in patients with AxSpA. There was a lower risk of certolizumab discontinuation and a higher risk of secukinumab discontinuation in males.

Introduction

Spondyloarthropathies (SpA) are a heterogeneous group of chronic inflammatory diseases that include axial skeletal, peripheral joint, and inflammatory bowel involvement, as well as the presence of psoriasis and uveitis, which share a similar genetic basis and pathogenic mechanisms (1). Axial spondyloarthritis (AxSpA), formerly known as ankylosing spondylitis, is the most common subtype of SpA (2).

Over the past two decades, tumor necrosis factor inhibitors (TNFi) have transformed the treatment of SpA and have become an important treatment option for clinicians (3, 4) However, not all patients with SpA may benefit from TNFi, and the beneficial effects seen in some patients may disappear over time. Therefore, new therapeutic strategies are still needed to manage the disease activity in SpA. Interleukin 17 (IL-17) inhibitors and Janus kinase inhibitors have been shown to be effective and safe in the treatment of SpA (5, 6). Secukinumab, a fully human monoclonal antibody targeting IL-17A, has shown efficacy and safety in AxSpA (7). Certolizumab pegol, a PEGylated Fab fragment of the humanized monoclonal TNF-α antibody, is the most recently approved TNFi (8). Both can be used in TNFi-naive and TNFi-resistant SpA patients according to current guidelines (3, 4). Retention rate analyses, often used in observational studies to evaluate real-world data, provide important information about the efficacy, safety, and tolerability of treatments (9, 10). To date, comparative studies of SEC versus TNF inhibitors have mostly evaluated all TNFi as a group (9, 11-13).

There may be differences in efficacy between TNFi agents in some AxSpA clinical situations, such as severity of psoriasis, concomitant uveitis, inflammatory bowel disease, enthesitis, and/or dactylitis. Therefore, the evaluation of all TNFi agents in one group versus secukinumab is a limitation of these studies (14). Additionally, TNFi and IL-17 inhibitor treatments have different efficacies on the extra-articular involvements of SpA. IL-17 inhibitors have emerged as more effective treatments than TNFi for psoriasis (15). Unlike most TNFi treatments, studies have shown that neutralizing IL-17 is not effective in treating inflammatory bowel disease and may even exacerbate symptoms (16). Another limitation in real-life analyses is that since non-certolizumab TNFi were approved much earlier than secukinumab treatment in AxSpA, AxSpA patients treated with secukinumab included more difficult and resistant cases in terms of age, disease duration, and number of prior treatments (9, 11, 12).

Drug survival studies are needed to evaluate certolizumab and secukinumab treatment for AxSpA in real-life settings. Therefore, our study aimed to investigate the retention rate and predictive factors associated with discontinuation of certolizumab and secukinumab treatment in AxSpA patients.

Materials and Methods

The study included all patients with AxSpA treated with certolizumab and secukinumab at a single-center rheumatology clinic between April 2019 and December 2022. The diagnosis of AxSpA was made by a rheumatologist. A total of 370 patients with AxSpA were evaluated; 67 patients who received both drugs or patients who were pregnant and breastfeeding were excluded from the study. The biologics were dosed as follows: the initial dose of certolizumab is 400 mg at weeks 0, 2 and 4, and the maintenance dose is 200 mg every two weeks. The initial dose of secukinumab is 150 mg subcutaneously at weeks 0, 1, 2, 3, and 4, then 150 mg every 4 weeks. This study was approved by our hospital's ethics committee (reference number: E1-22-2826).

Patient data, including age, disease duration (years), age of first biological disease-modifying anti-rheumatic drug (bDMARD) use, body mass index (BMI), comorbidities, smoking history, C-reactive protein levels at the start of certolizumab and secukinumab, radiographic findings, and reasons for discontinuation were recorded retrospectively. The start and end dates of certolizumab and secukinumab were also recorded. The primary aim was to analyze drug retention rate, defined as the time to discontinuation of certolizumab and secukinumab or switching to another bDMARD or targeted synthetic disease-modifying antirheumatic drug. Temporary interruptions of certolizumab and secukinumab treatment (*e.g.*, due to infection or surgery) of <3 months were allowed. Drug survival was calculated as the number of months patients remained on the drug. Retention rate analysis was used to calculate drug survival. Predictors of treatment discontinuation during the entire

follow-up period were also assessed as a secondary endpoint. Obesity was defined as BMI≥30 kg/m^2. Asthma and chronic obstructive pulmonary disease were defined as pulmonary diseases. Radiographic examination of AxSpA patients was assessed for the presence of syndesmophytes and/or bamboo spine development. The reason for discontinuation of certolizumab or secukinumab was reviewed for each case and classified into the following three categories: primary-secondary inefficacy, adverse events, and patient preference.

Statistical analysis was performed using SPSS Statistics Version 22 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages (%) and, for continuous variables, mean with standard deviation (SD) or median with interquartile range (IQR), where appropriate. Comparisons of categorical variables between groups were examined using the Pearson chi-squared test. Independent-samples T and Mann-Whitney U tests were used for comparisons of continuous variables where appropriate. Survival rates for each biologic agent were examined using the Kaplan-Meier method and compared using the log-rank test. Predictors and confounders of survival were analyzed using Cox regression models for certolizumab and secukinumab discontinuation. A backward stepwise Cox proportional hazards regression model was used and p-values <0.05 were considered statistically significant.

Results

A total of 303 patients with AxSpA were included in the study, 52.5% of whom were male. The mean (SD) age was 45.2 (10.9) years, and the median (IQR) disease duration was 10.5 (7.0) years. Among the extra-axial findings in AxSpA patients, peripheral arthritis was the most common (28.6%), followed by enthesitis (23.1%), psoriasis (10.5%), uveitis (9.2%), inflammatory bowel disease (6.5%), and dactylitis (1.4%). The most common comorbidities were obesity (31.2%), hypertension (17.8%), diabetes mellitus (8.5%), chronic obstructive pulmonary disease/asthma (8.5%), hyperlipidemia (5.9%), coronary artery disease (4.4%), and history of malignancy (1.1%).

Of the 303 patients, 239 patients (78.8%) were treated with certolizumab, and 64 patients (21.2%) were treated with secukinumab. Table 1 compares the main characteristics of AxSpA patients according to treatment. Age, gender, disease duration, comorbidities, laboratory, and radiological findings were similar in the certolizumab and secukinumab groups. Comparing AxSpA patients receiving certolizumab and secukinumab, certolizumab patients had a lower frequency of enthesitis (19.2% *vs*. 37.7%, p<0.002) and were more frequently bDMARD-naive patients (49.0% *vs*. 34.4%, p<0.038). The median (IQR) follow-up for the entire cohort was 31.5 (43.5) months; 36.5 (51.5) months for certolizumab patients and 28.1 (30.9) months for secukinumab patients.

At 12 months, drug retention rates were 76% in the secukinumab group and 73% in the certolizumab group (p=0.382). The overall retention rate was similar in both groups, as shown in Figure 1 (p=0.641). The median survival time was 66.0 months in the secukinumab group *vs.* 62.8 months in the certolizumab group. The entire cohort (secukinumab and certolizumab) 12th-month retention rate and median survival time were 74 and 72.8 months, respectively. The most common reason for discontinuation was lack of efficacy (Table 1), and there was no difference between the certolizumab and secukinumab groups (p=0.136).

Comparison of patients who continued and discontinued certolizumab and secukinumab treatments is shown in Table 2. Predictors of discontinuation of certolizumab or secukinumab in the overall cohort and in each bDMARD group were as follows: smoking, age at first bDMARD (years), total comorbidity count, bDMARD resistance, presence of enthesitis, psoriasis, and bamboo spine. But no factors were found to be associated with discontinuation in the overall cohort (Table 3). In addition, factors that may be associated with discontinuation were evaluated separately in patients receiving certolizumab or secukinumab. Drug discontinuation was lower in male patients receiving certolizumab [hazard ratio (HR): 0.634, 95% confidence interval (CI): 0.41-0.97, p=0.036] and higher in patients with psoriasis (HR: 2.05, 95% CI: 0.98-4.27, p=0.054), whereas drug discontinuation was higher in male patients receiving secukinumab (HR: 2.77, 95% CI: 1.18-6.49, p=0.018) (Table 3).

Discussion and Conclusions

In this study, we showed that certolizumab and secukinumab were comparable in terms of drug retention in AxSpA patients. The drug retention rate at month 12 was approximately 75% for both drugs. According to the results of our study, the risk of discontinuation of certolizumab is 0.6 times lower in men, while the risk of discontinuation of secukinumab is 2.7 times higher in men when predictive factors for discontinuation in AxSpA patients receiving certolizumab or secukinumab are evaluated.

In our AxSpa patients, we found drug retention rates were 76% in the secukinumab group and 73% in the certolizumab group at 12 months. In a similar study with secukinumab, the drug retention rate was found to be as low as 55%. This result was due to the the fact that patients had longer disease duration and were more frequeently TNFi-resistant (17). In the literature, retention rates for secukinumab in SpA have been reported up to 78%, and similar rates were seen in our current results (18, 19). In a multicenter, prospective study, it was reported that 65% of the 218 patients with AxSpA who were treated with certolizumab were still on treatment at week 204 (8). In 325 AxSpA patients treated with certolizumab, the drug retention rate for one year was reported to be 72.5%, which is consistent with the rate we found in our study (20).

According to our results, male sex was independently associated with a lower risk of certolizumab discontinuation and with a higher risk of secukinumab discontinuation. There is conflicting information in the literature regarding drug retention and gender in SpA. According to a prospective multi-center observational study by García-Dorta *et al*. in patients with AxSpA and PsA, the best secukinumab retention rate was observed in female patients with AxSpA (95%) and in male patients with PsA (89%), whereas the worst retention rate was observed in female patients with PsA (66%) (19). A real-world, prospective, observational study has reported a higher survival rate with secukinumab in male patients with AS than in females (21). According to the results of another multicenter retrospective observational study, survival rates with secukinumab treatment in AxSpA and PsA patients were found to be better in males (22). Prospective longitudinal observational cohort studies showed that male sex predicts continuation of TNFi agents in ankylosing spondylitis, which is consistent with our findings (23-25). A retrospective multicenter study found a correlation between female gender and lower response rates and disease remission in AxSpA patients treated with TNFi agents (26). Psoriasis is an immune-mediated disease that affects patients with a genetic predisposition. It is characterized by inflammation of the skin and has a significant impact on quality of life. Drugs that affect the immune system, including biological treatments, are used to treat psoriasis. According to the recently published Cochrane analysis, which used many databases and had a very high level of evidence, anti-IL-17 drugs (ixekizumab, secukinumab, bimekizumab, and brodalumab) were more effective in treating psoriasis than anti-TNF drugs (adalimumab, certolizumab, and etanercept) (27). Even though it is not statistically significant, the low retention rate of certolizumab treatment in AxSpA patients with psoriasis that we found in our study may be explained by the fact that certolizumab is less effective than secukinumab in suppressing psoriasis-related symptoms. Studies in the literature report a higher secukinumab retention rate compared to TNF inhibitors in patients with psoriatic arthritis with axial involvement, which is consistent with our results (28-30).

Other factors such as patient age, disease duration (years), age of first bDMARD use, BMI, comorbidities, smoking history, C-reactive protein levels at baseline, and radiographic findings were not found to have an effect on drug retention. In our study, drug ineffectiveness was the most common reason for treatment discontinuation, which is consistent with the literature (17, 19).

The main limitations of our study were the lack of clinimetric measures and different sample sizes. The number of patients using certolizumab is higher than the number of patients using secukinumab because the drugs were approved on different dates. As this is an observational study, biased estimates may occur if the sample size is too small. Another limitation is that our study coincided with the pandemic period, so our objective disease assessments, such as disease activity (Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Disease Activity Score), functional status

(Bath Ankylosing Spondylitis Functional Index), radiological assessment (modified Stoke Ankylosing Spondylitis Spinal Score) and quality of life (Health Assessment Questionnaire, 36-Item Short Form Health Survey) were incomplete. Other limitations of our study are that it was conducted in a single center, the follow-up period was short, and that there were more bDMARD-naive certolizumab patients than bDMARD-naive secukinumab patients. Another limitation is that the reasons for discontinuation of biologic DMARD treatments used before certolizumab and secukinumab treatments were not evaluated.

As a result, the survival rates of both secukinumab and certolizumab used to treat AxSpA patients were found to be similar and good. Specifically, in secukinumab treatment, we concluded that male gender was a risk for drug retention. In contrast, in certolizumab treatment, male gender is a positive indicator for drug retention. These findings need to be supported by multicenter, randomized, prospective studies so that we can take gender into account in drug treatment preferences.

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Table 1. Baseline characteristics of axial spondyloarthritis patients receiving certolizumab or secukinumab

	Entire cohort* (n=303)	Certolizumab (n=239)	Secukinumab (n=64)	p
Demographic and clinical characteristics				
Male, n (%)	159 (52.5)	128 (53.6)	31 (48.4)	0.466
Age, years, mean (SD)	44.9 (10.5)	44.9 (10.6)	45.1 (10.3)	0.580
Age at first bDMARD, years, mean (SD)	38.3 (10.6)	38.0 (10.7)	39.2 (10.5)	0.272
Disease duration, years, median (IQR)	10.5 (7.0)	10.5 (6.5)	10.5 (9.3)	0.997
Current/former smoking	57 (41.9)	43 (38.7)	14 (56.0)	0.114
BMI, kg/m^2, mean (SD)	27.6 (5.5)	27.7 (5.4)	27.1 (5.7)	0.438
Peripheral arthritis, n (%)	84 (28.4)	64 (27.2)	20 (32.8)	0.391
Enthesitis, n (%)	68 (23.1)	45 (19.2)	23 (37.7)	**0.002**
Dactylitis, n (%)	4 (1.4)	3 (1.3)	1 (1.6)	>0.999
Uveitis, n (%)	27 (9.2)	20 (8.6)	7 (11.5)	0.486
Psoriasis, n (%)	31 (10.5)	21 (9.0)	10 (16.4)	0.095
Inflammatory bowel disease, n (%)	18 (6.2)	15 (6.5)	-	-
Comorbidity count, median (IQR)	1 (1)	1 (2)	1 (2)	0.150
Cardiovascular disease, n (%)	12 (4.4)	8 (3.8)	4 (7.0)	0.286
Hypertension, n (%)	48 (17.8)	36 (16.9)	12 (21.1)	0.467
Hyperlipidemia, n (%)	16 (5.9)	13 (6.1)	3 (5.3)	>0.999
Pulmonary disease, n (%)	23 (8.5)	18 (8.5)	5 (8.8)	0.938
Diabetes mellitus, n (%)	23 (8.5)	18 (8.5)	5 (8.8)	0.938
Obesity, n (%)	83 (31.2)	63 (29.9)	20 (36.4)	0.354
History of malignancy, n (%)	3 (1.1)	2 (0.9)	1 (1.8)	0.511
Laboratory and radiological findings				
Syndesmophyte, n (%)	59 (25.7)	45 (24.9)	14 (28.6)	0.598
Bamboo spine, n (%)	21 (9.2)	14 (7.8)	7 (14.6)	0.147
HLA-B27-positive, n (%)	28/50 (56.0)	18/36 (50.0)	10/14 (71.4)	0.215
Baseline CRP, mg/ml, median (IQR)	3.0 (12.)	3.0 (12.0)	4.6 (17.8)	0.525
Treatments				
bDMARD naive, n (%)	139 (45.9)	117 (49.0)	22 (34.4)	**0.038**
Number of biologic therapies, median (IQR)	2 (1)	2 (1)	2 (1)	0.963
Discontinued or switched, n (%)	144 (47.5)	118 (49.4)	26 (40.6)	0.213
Reasons of treatment discontinuation Primary-secondary inefficacy Adverse events Patient preference Unknown	 107 (74.3) 16 (11.1) 13 (9.0) 8 (5.5)	 84 (71.2) 14 (11.8) 13 (11.0) 7 (5.9)	 23 (88.8) 2 (7.7) 0 1 (3.8)	0.136
Treatment duration (months), median (IQR)	31.5 (42.0)	36.5 (51.5)	28.1 (30.9)	0.032
Drug retention rates (12th month), %	71	73	76	0.382
Drug retention rates (Overall), %	45	44	56	0.641

SD, standard deviation; IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; bDMARD, biological disease-modifying anti-rheumatic drug. *The entire cohort included axial spondyloarthritis patients receiving both certolizumab and secukinumab.

Table 2. Comparison of patients who continued and discontinued certolizumab and secukinumab treatments

	Certolizumab		p	Secukinumab		p
	Continue (n=121)	Stop (n=118)		Continue (n=38)	Stop (n=26)	
Demographic and clinical characteristics						
Age, years, mean (SD)	45.7 (11.2)	44.4 (10.5)	0.334	45.8 (10.2)	46.1 (12.6)	0.918
Age at first bDMARD, years, mean (SD)	37.7 (10.3)	38.6 (11.5)	0.496	38.8 (8.9)	40.0 (13.1)	0.994
Disease duration, years, median (IQR)	9.5 (6.0)	11.3 (7.0)	0.815	10.0 (8.0)	11.0 (8.7)	0.301
Male, n (%)	75 (62.0)	53 (44.9)	0.008	14 (36.8)	17 (65.4)	0.025
Current/former smoking	20 (37.7)	23 (39.7)	0.836			
BMI, kg/m^2, mean (SD)	27.3 (4.6)	28.2 (6.1)	0.258	26.9 (6.4)	27.3 (4.8)	0.836
Peripheral arthritis, n (%)	24 (20.2)	40 (34.5)	0.014	14 (38.9)	6 (24.0)	0.223
Enthesitis, n (%)	20 (16.8)	25 (21.7)	0.339	17 (47.2)	6 (24.0)	0.066
Dactylitis, n (%)	2 (1.7)	1 (0.9)	>0.999	0	1 (4.0)	0.410
Uveitis, n (%)	9 (7.6)	11 (9.6)	0.597	5 (13.9)	2 (8.0)	0.689
Psoriasis, n (%)	7 (5.9)	14 (12.2)	0.096	5 (13.9)	5 (20.0)	0.526
Inflammatory bowel disease, n (%)	3 (2.6)	12 (10.4)	0.017	-	-	
Comorbidity count, median (IQR)	1 (2)	1 (1)	0.161	1 (2)	1 (2)	0.812
Cardiovascular disease, n (%)	4 (3.8)	4 (3.7)	>0.999	3 (8.3)	1 (4.8)	>0.999
Hypertension, n (%)	15 (14.2)	21 (19.6)	0.286	7 (19.4)	5 (23.8)	0.697
Hyperlipidemia, n (%)	8 (7.5)	5 (4.7)	0.381	1 (2.8)	2 (9.5)	0.548
Pulmonary disease, n (%)	5 (4.7)	13 (12.1)	0.051	4 (11.1)	1 (4.8)	0.642
Diabetes mellitus, n (%)	9 (8.5)	9 (8.4)	0.983	3 (8.3)	2 (9.5)	>0.999
Obesity, n (%)	31 (29.2)	32 (30.5)	0.989	11 (35.5)	9 (37.5)	0.877
History of malignancy, n (%)	0	2 (1.9)	0.498	1 (2.8)	0	>0.999
Laboratory and radiological findings						
Syndesmophyte, n (%)	24 (27.3)	21 (22.6)	0.465	6 (23.1)	8 (34.8)	0.365
Bamboo spine, n (%)	10 (11.6)	4 (4.3)	0.093	3 (12.0)	4 (17.4)	0.696
HLA-B27-positive, n (%)	12/19 (63.2)	6/17 (35.3)	0.095	9/11 (81.8)	1/3 (33.3)	0.176
Baseline CRP, mg/ml, median (IQR)	4 (13.2)	2.4 (10.3)	0.075	4.6 (17.6)	3.5 (17.6)	0.577
Treatments						
bDMARD naive, n (%)	65 (53.7)	52 (44.1)	0.136	14 (36.8)	8 (30.8)	0.615
Number of biologic therapies, median (IQR)	2 (1)	1.5 (1)	0.538	1 (2)	2 (1)	0.469

SD, standard deviation; IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; bDMARD, biological disease-modifying anti-rheumatic drug.

Table 3. Cox regression analysis of drug discontinuation of entire cohort, certolizumab and secukinumab.

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Entire cohort*						
Smoking	1.136	0.64-2.01	0.662			
Age at first bDMARD, years	1.018	0.98-1.05	0.332	1.02	0.99-1.05	0.146
Total comorbidity count	1.097	0.89-1.34	0.365			
Enthesitis	0.785	0.40-1.52	0.477			
Psoriasis	0.484	0.16-1.39	0.179			
Bamboo spine	1.407	0.44-4.40	0.557			
bDMARD resistant	0.867	0.49-1.51	0.616			
Secukinumab (*vs.* certolizumab)	1.337	0.65-2.72	0.423			
Certolizumab						
Male	0.720	0.46-1.12	0.148	0.634	0.41-0.97	0.036
Total comorbidity count	1.118	0.95-1.30	0.158			
Psoriasis	2.238	1.02-4.87	0.043	2.05	0.98-4.27	0.054
Peripheral arthritis	1.273	0.79-2.04	0.318			
Inflammatory bowel disease	1.829	0.84-3.94	0.123			
CRP mg/dL	0.991	0.97-1.01	0.223			
Bamboo spine	0.445	0.15-1.27	0.131			
bDMARD resistant	0.817	0.52-1.28	0.382			
Secukinumab						
Male	2.567	1.07-6.12	0.034	2.77	1.18-6.49	0.018
Peripheral arthritis	0.614	0.23-1.59	0.316			
Enthesitis	0.691	0.26-1.82	0.456			

HR, hazard ratio; CI, confidence interval; bDMARD, biological disease-modifying anti-rheumatic drug; CRP, C-reactive protein. *The entire cohort included axial spondyloarthritis patients receiving both certolizumab and secukinumab.

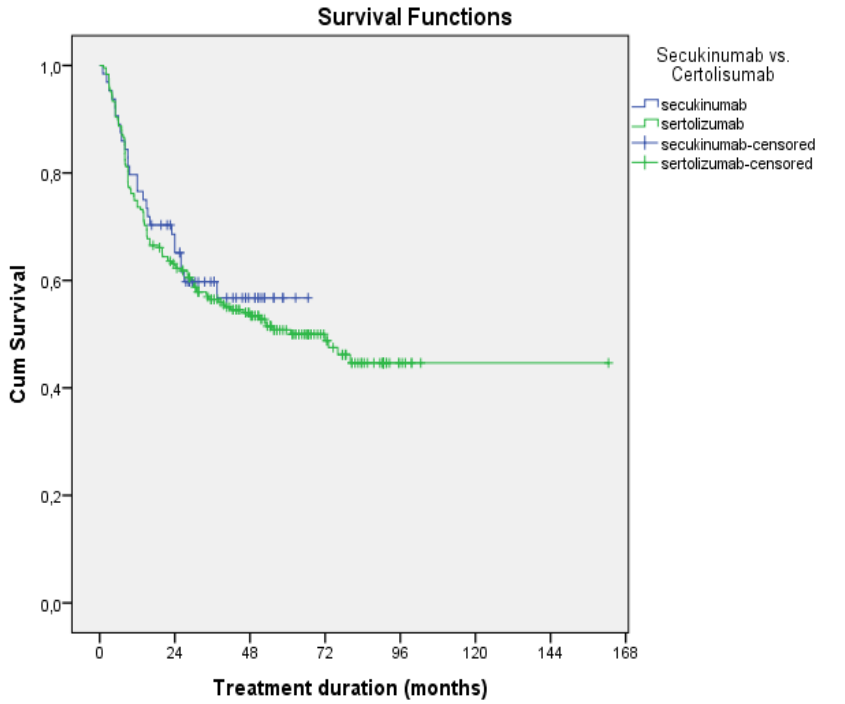

Figure 1. Kaplan-Meier curves for drug retention for secukinumab and certolizumab.