Variables predicting clinical remission among adults with severe asthma treated with biologic agents

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ABSTRACT

Background: Although biologic agents promise a short- to medium-term remission in asthma, it is unclear whether they can fundamentally alter disease course and achieve long-term remission. We aimed to investigate the clinical remission success of biologics in patients with severe asthma and the factors associated with remission.

Methods: Adults followed-up due to severe asthma who were treated with mepolizumab or omalizumab were included in the study. Sociodemographic and clinical characteristics were reviewed. Subjects with and without clinical remission at 12 and 36 months were identified. Comparisons between the groups were made with univariate and multivariable analyses.

Results: Seventy-four patients were included in the study. The mean age of subjects was 51.85 (standard deviation: 11.43) years, and 50 (67.57%) were females. The 12- and 36-month remission rates were 72.97% and 51.79%, respectively. Patients with and without remission were similar in terms of age and gender distribution. FEV1% predicted ($p = 0.009$) and FEV1/FVC ratio ($p = 0.039$) were significantly higher in those with remission at 12 months compared to those without. FEV1 ($p<0.001$), FEV1% predicted ($p<0.001$) and FEV1/FVC ratio ($p = 0.004$) were significantly higher in those with remission at 36 months compared to those without. Multivariable logistic regression revealed that higher FEV1% predicted was the only factor independently associated with remission for both time points.

Conclusions: Omalizumab and mepolizumab provide significant clinical remission rates in severe asthma. FEV1% predicted is a variable that can independently predict clinical remission among severe asthmatics receiving biologic agents.

Keywords: Severe asthma, remission, biologics, omalizumab, mepolizumab, forced expiratory volume in 1 second

1. Introduction

Asthma is the most common chronic respiratory disease affecting more than 300 million people worldwide with significant morbidity and mortality (1). It is a heterogeneous disorder characterized by variable symptoms affecting breathing and airflow, and is usually associated with airway hypersensitivity and chronic inflammation (1,2).

Persistent or recurrent inflammation of the airways can cause changes in mucus-secreting cells, subepithelial fibrosis, muscle cell hyperplasia, angiogenesis, and airway structural changes such as epithelial hyperplasia and metaplasia (3,4). Although these changes sometimes pose the risk of irreversible airway remodeling and/or fixed airflow limitation, it is known that remission may be achieved in some patients (5,6). Although inhaled corticosteroids and bronchodilators are employed as the primary therapies, they have questionable efficacy in limiting progression (7). Biologic therapies spearheaded by anti-immunoglobulin (Ig) E, anti-eosinophilic (mepolizumab, benralizumab, reslizumab) and anti-interleukin (IL)-4/-13 (dupilumab) therapies have been investigated in order to block the pathophysiology of asthma (8,9). These agents have demonstrated remarkable success in reducing asthma exacerbations and systemic corticosteroid use, particularly in moderate to severe asthma (8). Although biologic agents can target the airway inflammation and promise to achieve short- to mid-term remission in asthma, there is no conclusive information on whether they can fundamentally alter the course of asthma and provide long-term remission (1).

Clinical remission is considered in the absence of significant asthma symptoms, optimization/stabilization of lung functions, patient/provider agreement on remission, and no use of

systemic corticosteroids for at least 12 months. Complete remission is considered if clinical remission is accompanied by resolution of asthma-related inflammation and if appropriate, negative bronchial hyperresponsiveness (5). In many studies, these definitions have been accepted as criteria for asthma remission with or without medication (10-12). Few studies have investigated remission of more than 12 months with the use of biologic agents in severe asthma (13-15). The proposed predictors of asthma remission are asthma severity (16,17), lung functions (16), asthma control (18), age at onset of asthma (19,20), duration of the disease (20), inflammation (21), comorbidities (20), and smoking status (16). Disease severity and treatment administration are the two most important factors that can affect remission in asthma. While the chance of remission of the disease is less in moderate to severe asthma, the probability of remission is higher in cases of mild asthma (22). In addition, remission rates are higher in patients who receive treatment compared to those who do not (23).

It may not be possible to achieve complete remission in all cases of asthma (8), despite the fact that biologic agents have increased the likelihood of clinical remission in severe asthma. Data is insufficient on demonstrating remission longer than 12 months and there is a lack of knowledge concerning factors that affect remission success. Retrospective real-life data is needed regarding this issue. Therefore, we aimed to investigate the clinical remission success of two biologic agents, omalizumab (anti-IgE) and mepolizumab (anti-IL-5), in patients with severe type 2 asthma and to investigate factors affecting remission.

2. Materials and methods

2.1. Study design, setting and population

This retrospective study was carried out at the allergy clinic in a tertiary chest diseases hospital. The study population consists of adults followed up with the diagnosis of severe asthma and treated with biologics in the clinic between January 2010 and December 2022. Exclusion criteria were using the biologic agent for less than a year, failure to attend follow-up visits regularly, switch in the biological agent administered and having missing data for the main variables included in the study.

2.2. Ethical considerations

Ethical approval was acquired from the local ethics committee (December 28th 2022/KAEK-15/2615). The study was carried out according to the ethical standards stated in the Declaration of Helsinki and its amendments, and all patients were examined and included with respect to good clinical practice guidelines.

2.3. Data collection

Study data were obtained by retrospective scanning of the hospital computerized registry and patient files. The following parameters pertaining to the time of initiation of the biologic agents were examined and recorded for the study: age and gender, body mass index (BMI), smoking status, concomitant conditions including nasal polyps, rhinitis, atopy history, respiratory disease triggered by non-steroidal anti-inflammatory drugs (NSAIDs) and other chronic and psychiatric diseases. The asthma-related parameters collected in detail were as follows: age at asthma onset, family history of asthma, biologic agent used (omalizumab or mepolizumab) and duration of treatment, oral corticosteroid (methylprednisolone) use and dosage, asthma control test (ACT) results, blood total IgE levels, eosinophil counts, and pulmonary function test results.

2.4. Definitions

2.4.1. Definitions related to asthma and its treatment

The diagnosis of severe asthma was made and the eligibility and administration protocol for omalizumab and mepolizumab treatments were assessed in accordance with the current guidelines (2). Briefly, patients with type 2 asthma and non-allergic eosinophilic phenotype were started on mepolizumab, whereas those with allergic phenotype were started on omalizumab. Omalizumab treatment dose and frequency of administration were calculated from a standard scale according to weight and total IgE value. According to this scale, patients received subcutaneous omalizumab at a calculated dose every 2 or 4 weeks. Mepolizumab was administered at a standard dose every 4 weeks. Clinical and biological data including ACT score, exacerbations, need of maintenance systemic corticosteroid treatment,

pulmonary function tests and laboratory analyses were recorded at each visit scheduled at 4-week intervals. Asthma exacerbations were documented by scanning the hospital records after the initiation of the biological agent. The requirement to use systemic corticosteroid for at least 3 days to control aggravated asthma symptoms was defined as an exacerbation (24).

2.4.2 Definition of remission

Clinical remission comprised 12 or more months with (i) absence of significant symptoms by validated instrument, (ii) lung function optimization/stabilization, (iii) patient/provider agreement regarding remission, and (iv) no use of systemic corticosteroids (5). ACT was used in the present study to confirm the absence of asthma symptoms. An ACT score of ≥20 was considered well-controlled asthma (25). An improvement of more than 10% from baseline FEV1 % predicted was considered to demonstrate lung function optimization/stabilization (4).

In the present study subjects who met all four remission criteria for at least 12 consecutive months while receiving biologic agents were defined as having remission for 12 months, and those who did so for at least 36 consecutive months were defined as having 36 months of remission.

2.5. Outcomes

The main outcomes of this study were to determine the 12-month and 36-month clinical remission rates in severe asthma patients receiving omalizumab or mepolizumab treatment, and to determine independent factors affecting remission success among recipients of these agents.

2.6. Statistical Analysis

Statistical significance was set at $p<0.05$ for all analyses. SPSS v25.0 (IBM, NY, USA) was used for data analysis. The normal distribution of continuous variables was assessed using Shapiro-Wilk tests. Normally distributed variables were analyzed with the Student's t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Contingency tables were primarily analyzed with appropriate Chi-square tests, while the Fisher's exact test or its extension, the Fisher-Freeman-

Halton test, were used when called for by the data. Multivariable logistic regression (forward conditional) was employed to identify independent factors associated with remission. The models created for each time point (12 months and 36 months) included significant variables from the respective univariate analyses.

3. Results

A total of 74 patients were included in the study. The mean age of the subjects was 51.85 (standard deviation: 11.43) years, and 50 (67.57%) were females. When the patients were evaluated according to the status of being in remission for 12 months, there were 54 (72.97%) patients who were in remission and 20 (27.03%) patients who were not. There was no significant difference between the two groups in terms of age and gender distribution ($p = 0.571$). The mean forced expiratory volume (FEV1) % predicted ($p = 0.009$) and FEV1/ forced vital capacity (FVC) ratio ($p = 0.039$) were significantly higher in those with 12-month remission. While 12-month remission rate was 66.66% in omalizumab users, this rate was 86.95% in mepolizumab users. However, there was no significant difference in 12-month remission between the users of the two drugs ($p = 0.124$). The groups were also similar with regard to other variables (**Table 1)**.

Multivariable logistic regression was performed to determine significant factors independently associated with 12-months remission. Higher FEV1% predicted (OR: 1.042, 95% CI: 1.009 - 1.076, $p=0.013$) was independently associated with greater likelihood of 12-month remission, whereas FEV1/FVC ratio ($p=0.665$) was non-significant (**Table 2)**.

When the 36-month remission assessment was made, 29 (51.79%) patients were in remission, while 27 (48.21%) patients were not in remission. The groups were similar in terms of age ($p = 0.360$) and gender distribution ($p = 0.848$). FEV1 ($p<0.001$), FEV1% predicted ($p<0.001$), and FEV1/FVC ratio ($p = 0.004$) were significantly higher in those with 36-month remission. As in the 12-month remission assessment, 36-month remission rates were not statistically different between omalizumab (50.00%) and mepolizumab (58.33%) users ($p = 0.852$). None of the remaining variables demonstrated any significant difference between the two groups (**Table 3)**.

Multivariable logistic regression was performed to determine significant factors independently associated with 36-months remission. Higher FEV1% predicted (OR: 1.089, 95% CI: 1.037 - 1.142, p = 0.001) was independently associated with greater likelihood of 36-month remission. Other variables in the model, FEV1 (p=0.208), and FEV1/FVC ratio (p=0.929) were found to be non-significant (**Table 4)**.

4. Discussion

In the present study 12-month and 36-month remission rates are 72.97% and 51.79%, respectively, among patients with severe asthma using biologic agents. Having a higher baseline level of FEV1% predicted is the only independent predictor associated with both 12-month and 36-month clinical remission.

Current biological agents such as omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab are effective on IL-4, IL-5, IL-13 and IgE, which are involved in the type 2 inflammatory cascade. Effective monoclonal antibody therapies are now increasingly used in asthma [26,27]. This offers promise for targeting asthma remission as a potential therapeutic goal. Omalizumab was approved in 2003 for severe allergic asthma and has been used safely and effectively to prevent asthma exacerbations (28). Mepolizumab was the first biologic targeting IL-5 and was approved in 2015 for the clinical treatment of severe eosinophilic asthma (8). In the current study, omalizumab was found to result in a 12-month remission rate of 66.66% and a 36-month remission rate of 50%. For mepolizumab, 12-month remission rate was 86.95% and 36-month remission rate was 58.33%. In the study Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO), 83.8% of subjects had uncontrolled asthma at baseline. About 50% of subjects achieved asthma control while using omalizumab (10). Exacerbation rates were also significantly reduced with omalizumab (from 3.00 ± 3.34 events at baseline to 0.78 ± 1.37 events at 12 months). Omalizumab therapy also resulted in a >50% event reduction in 77.8% of patients, while 64.7% of patients experienced a ≥3 points reduction in ACT score (10). In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, the results of 32-week mepolizumab treatments (75 mg

intravenously every 4 weeks, or 100 mg subcutaneously every 4 weeks) were compared to placebo (13). It was observed that both mepolizumab therapies significantly reduced the frequency of asthma exacerbations and improved post-bronchodilator FEV1 values compared to baseline; however, the effect of mepolizumab on remission was not investigated in this study (13). In the Open-label Long Term Extension Safety Study of Mepolizumab in Asthma Subjects (COLUMBA) study, it was reported that 33% of the patients did not experience exacerbation after an average of 3.5 years of mepolizumab treatment (15). In a recent observational multicenter retrospective study, the 12-month remission rates of mepolizumab treatment in severe asthmatic patients were investigated along with factors affecting remission (12). The percentage of patients in complete remission was reported as 30.12% among mepolizumab recipients (12). In a retrospective study, response to mepolizumab treatment was detected in 92.9% of patients (11). Eger and colleagues investigated treatment response and factors affecting treatment response over a 2-year period in patients with severe eosinophilic asthma receiving anti-IL-5 therapy. After 2 years of therapy, 14% of patients were defined as "super responders", 69% "partial responders", and 11% "non-responders" (14).

It is clear from aforementioned literature that the remission rates obtained with biological agents can vary considerably depending on the biological agent used, the patient population, and the accepted definition of remission. Apart from these, independent variables affecting remission rates are another subject of interest. Our results showed that having a higher FEV1% predicted value at baseline was the sole parameter independently associated with both 12-month and 36-month remission. In the study of Eger et al., those who were "super-responders" to anti-IL-5 therapy were defined to have shorter asthma duration and higher FEV1. Super-responders tended to have adult-onset asthma, no nasal polyps, and lower BMI (14). Higher eosinophil counts or higher exacerbation rates have been presented as factors predicting super-response to anti-IL-5 therapy in some studies that defined super-response as reduction of exacerbations or decreased use of oral corticosteroids (29,30). In a retrospective study, key features associated with "responder" and "super-responder" status to mepolizumab were found to be the presence of nasal polyposis, lower baseline score from the Asthma Control Questionnaire (ACQ)-6, lower BMI, and using lower oral prednisolone dosage at baseline (11). In the study by Harvey et al., higher

eosinophil and older age at asthma onset predicted better ACQ-5 results after receiving mepolizumab, while being male or having a BMI of ≥30 were associated with lower results.[24] In the PROSPERO study, it was noted that responders had baseline blood eosinophil levels greater than or equal to 300 cells/mL (10). In addition, in studies with other biologic agents, variables such as higher eosinophil (29-32,33) and basophil counts (34), a history of more frequent exacerbations (29,32), worse baseline lung function (16, 31-32,35,36), use of oral corticosteroids (37) and nasal polyposis (37) have been associated with better clinical remission rates.

The main goal of current asthma therapy is to control airway inflammation and minimize symptoms. At present, there is no effective treatment available to address the chronic alterations in airway remodeling and their impact on lung function. As the majority of previous studies assessed disease control rather than remission, it is difficult to accurately determine the efficacy of biological agents in achieving remission, particularly in relevance to prior research (23). This requires a thorough understanding of the pathophysiology of asthma remission and airway remodeling, supplemented by necessary tissue-level or cellular investigations. Data obtained from the present study suggest that biological agent therapy in patients with severe asthma achieves considerably high remission rates at 12 months and 36 months. However, the detection of a higher chance of remission in patients with better lung function at baseline suggests that more effective treatment approaches need to be developed for patients with severe asthma that have poor pulmonary function. However, there is still a need for comprehensive studies investigating predictors of optimal response to biologic therapy.

One of the strengths of our study is the investigation of two different biological. The second is the investigation of both 12-month and 36-month clinical remission rates of these agents. In most clinical studies, follow-up was limited to 12 months or less (10-12). Third, the factors affecting both 12-month and 36-month clinical remission rates with the extensive baseline characterization of the patients were investigated. However, the following limitations should be considered when interpreting the results of the study. It is a single-center study with relatively few participants, more so for the analyses of 36-month remission. Therefore, the generalizability of the results is limited. Due to the retrospective design, complete remission rates could not be obtained since this would necessitate prospective follow-up. Of

the patients' phenoendotypic characteristics, only eosinophilic or allergic status was included in the study.

Other endotypic and phenotypic characteristics may affect clinical remission rates; however, the current study does not account for these factors. Since the use of agents other than omalizumab and mepolizumab are not yet approved in our country, the present study reports data for only these two agents, and therefore, the results are relevant in this context. Although criteria for defining clinical remission, such as improvement of symptoms, absence of exacerbations and the need for oral steroids, and spirometric improvement are well defined, cut-off values to define spirometric improvement are not clearly defined. Since this study included patients with severe asthma, we did not set a criterion for spirometric improvement (such as FEV1 % predicted value exceeding 80%), which has been used in some previous studies (38). Instead, we used the following criterion: more than 10% improvement in FEV1 % predicted value, which has also been suggested in prior research (4). This ambiguity makes it difficult to clearly define clinical remission and to compare our findings with other studies.

5. Conclusion

Biological agents appear to provide significant clinical remission rates in severe asthma. However, due to the fact that higher FEV1% predicted is associated with higher likelihood of remission, there is an apparent need for more effective therapies in patients with poor pulmonary function at baseline. The data on this subject so far are from clinical studies. The present study is retrospective and thus reflects real life.

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Author contributions: KA constructed the research hypothesis; SY, KA, GTVS, ÖA, OT, HÇT, GKB, SNB, and ŞD contributed substantially to the study design; SY, KA, GTVS, ÖA, OT, HÇT, GKB, SNB, and ŞD contributed substantially to data collection; SY performed data analysis and interpretation; KA and SY substantially contributed to the writing of the manuscript; SY, KA, GTVS, ÖA, OT, HÇT, GKB, SNB, and ŞD approved the final manuscript.

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Table 1. Summary of patient and treatment characteristics with regard to 12-month remission

		12-months remission		
	Total (n=74)	No (n=20)	Yes (n=54)	p
Age, years	51.85 ± 11.43	52.45 ± 10.33	51.63 ± 11.90	0.786
Gender				0.571
Male	24 (32.43%)	8 (40.00%)	16 (29.63%)	
Female	50 (67.57%)	12 (60.00%)	38 (70.37%)	
Body mass index, kg/m^2	30.01 ± 5.51	28.69 ± 5.22	30.50 ± 5.58	0.211
Smoking status				0.193
Active smoker	7 (9.59%)	3 (15.00%)	4 (7.55%)	
Ex-smoker	21 (28.77%)	8 (40.00%)	13 (24.53%)	
Non-smoker	45 (61.64%)	9 (45.00%)	36 (67.92%)	
Atopy	54 (72.97%)	17 (85.00%)	37 (68.52%)	0.261
Respiratory disease triggered by NSAIDs	20 (27.03%)	6 (30.00%)	14 (25.93%)	0.956
Asthma history in family	25 (34.72%)	9 (47.37%)	16 (30.19%)	0.285
Nasal polyp	36 (48.65%)	8 (40.00%)	28 (51.85%)	0.520
Rhinitis/Rhinosinusitis	29 (39.19%)	8 (40.00%)	21 (38.89%)	1.000
Obstructive sleep apnea syndrome	13 (17.57%)	6 (30.00%)	7 (12.96%)	0.165
Gastroesophageal reflux disease	2 (2.70%)	1 (5.00%)	1 (1.85%)	0.470
Psychiatric disease	3 (4.05%)	1 (5.00%)	2 (3.70%)	1.000
Cardiovascular disease/Hypertension	21 (28.38%)	8 (40.00%)	13 (24.07%)	0.289
Diabetes mellitus	12 (16.22%)	3 (15.00%)	9 (16.67%)	1.000
Age at asthma onset	31.59 ± 12.50	29.95 ± 13.56	32.21 ± 12.16	0.495
Biological treatment				0.124
Omalizumab	51 (68.92%)	17 (85.00%)	34 (62.96%)	
Mepolizumab	23 (31.08%)	3 (15.00%)	20 (37.04%)	
Systemic corticosteroid use	46 (62.16%)	10 (50.00%)	36 (66.67%)	0.297
Asthma control test	15.74 ± 4.40	14.55 ± 4.37	16.19 ± 4.37	0.157
Total IgE, IU/mL	195 (81 - 409)	242.5 (73 - 330)	182.5 (81 - 471)	0.942
Eosinophil, cell/uL	273.5 (100 - 573.5)	165.5 (61.5 - 640)	334 (100 - 573.5)	0.255
FEV1	2026.70 ± 800.45	1756.50 ± 732.63	2126.78 ± 807.68	0.077
FEV1% predicted	69.64 ± 18.56	60.50 ± 15.16	73.02 ± 18.68	**0.009**
FEV1/FVC % predicted	74.89 ± 9.41	71.20 ± 10.89	76.26 ± 8.51	**0.039**
Biological agent treatment duration (months)	54.5 (35 - 67)	57.5 (43 - 67.5)	52 (28 - 67)	0.223

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables and as frequency (percentage) for categorical variables.

NSAID: Non-steroidal anti-inflammatory drugs, FEV1: Forced expiratory volume, FVC: Forced vital capacity

Table 2. Significant factors independently associated with the 12-months remission, logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95.0% CI for Exp(β)	
FEV1 % predicted	0.041	0.017	**0.013**	1.042	1.009	1.076
Constant	-1.753	1.105	0.113	0.173		

Nagelkerke R^2=0.133

CI: Confidence Interval, FEV1: Forced expiratory volume

Table 3. Summary of patient and treatment characteristics with regard to 36-month remission

		36-months remission		
	Total (n=56)	No (n=27)	Yes (n=29) [(1)]	p
Age, years	51.61 ± 11.45	53.07 ± 10.48	50.24 ± 12.32	0.360
Gender				0.848
Male	19 (33.93%)	10 (37.04%)	9 (31.03%)	
Female	37 (66.07%)	17 (62.96%)	20 (68.97%)	
Body mass index, kg/m^2	29.39 ± 5.17	29.58 ± 5.53	29.20 ± 4.90	0.787
Smoking status				0.669
Active smoker	7 (12.73%)	3 (11.11%)	4 (14.29%)	
Ex-smoker	13 (23.64%)	8 (29.63%)	5 (17.86%)	
Non-smoker	35 (63.64%)	16 (59.26%)	19 (67.86%)	
Atopy	43 (76.79%)	21 (77.78%)	22 (75.86%)	1.000
Respiratory disease triggered by NSAIDs	16 (28.57%)	7 (25.93%)	9 (31.03%)	0.899
Asthma history in family	20 (37.04%)	12 (46.15%)	8 (28.57%)	0.291
Nasal polyp	26 (46.43%)	10 (37.04%)	16 (55.17%)	0.275
Rhinitis/Rhinosinusitis	21 (37.50%)	10 (37.04%)	11 (37.93%)	1.000
Obstructive sleep apnea syndrome	12 (21.43%)	8 (29.63%)	4 (13.79%)	0.264
Gastroesophageal reflux disease	2 (3.57%)	1 (3.70%)	1 (3.45%)	1.000
Psychiatric disease	3 (5.36%)	1 (3.70%)	2 (6.90%)	1.000
Cardiovascular disease/Hypertension	17 (30.36%)	11 (40.74%)	6 (20.69%)	0.180
Diabetes mellitus	6 (10.71%)	3 (11.11%)	3 (10.34%)	1.000
Age at asthma onset	31.25 ± 12.55	30.74 ± 13.41	31.75 ± 11.89	0.769
Biological treatment				0.852
Omalizumab	44 (78.57%)	22 (81.48%)	22 (75.86%)	
Mepolizumab	12 (21.43%)	5 (18.52%)	7 (24.14%)	
Systemic corticosteroid use	30 (53.57%)	13 (48.15%)	17 (58.62%)	0.605
Asthma control test	15.14 ± 4.38	14.33 ± 4.41	15.90 ± 4.28	0.184
Total IgE, IU/mL	207 (85 - 441.5)	171 (84 - 328)	217 (86 - 567)	0.305
Eosinophil, cell/uL	205 (98 - 560)	200 (63 - 558)	222 (100 - 600)	0.516
FEV1	2116.96 ± 806.31	1698.15 ± 716.75	2506.90 ± 688.05	**<0.001**
FEV1% predicted	70.89 ± 19.69	59.70 ± 16.33	81.31 ± 16.76	**<0.001**
FEV1/FVC% predicted	74.13 ± 9.75	70.33 ± 9.53	77.66 ± 8.71	**0.004**
Biological agent treatment time, months	63 (48.5 - 69)	63 (43 - 69)	64 (50 - 69)	0.675

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables and as frequency (percentage) for categorical variables. (1) Eighteen patients were not included in the analysis due to follow-up time was lower than 36 months.

NSAID: Non-steroidal anti-inflammatory drugs, FEV1: Forced expiratory volume, FVC: Forced vital capacity

Table 4. Significant factors independently associated with the 36-months remission, logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95.0% CI for Exp(β)	
FEV1 % predicted	0.085	0.025	**0.001**	1.089	1.037	1.142
Constant	-5.905	1.750	0.001	0.003		

Nagelkerke R^2=0.412

CI: Confidence Interval, FEV1: Forced expiratory volume