The Relationship Between Long-term, Low-dose Macrolide Therapy and Acute Exacerbation in Idiopathic Bronchiectasis Classified by High-resolution Computed Tomography

ZENYA SAITO (zyst_0404@yahoo.co.jp)

Department of Respiratory Medicine, Atsugi City Hospital, 1-16-36 Mizuhiki, Atsugi-shi, Kanagawa 243-8588, Japan

Masahiro Yoshida

Atsugi city hospital

Saiko Nishioka

Atsugi city hospital

Kentaro Tamura

Atsugi city hospital

Nobumasa Tamura

Atsugi city hospital

Kazuyoshi Kuwano

Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku

Research

Keywords: High-resolution computed tomography (HRCT), Acute exacerbation (AE), low-dose macrolide therapy

Posted Date: November 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-112094/v1

Abstract

Background: High-resolution computed tomography (HRCT) and long-term, low-dose macrolide therapy has been established as a diagnostic method and treatment for bronchiectasis. HRCT correlates with clinical symptoms, respiratory function and quality of life in bronchiectasis. However, whether it will lead to reduction of macrolide therapy effects is unknown. We investigated the relationship between the efficacy of macrolide therapy and severity assessment performed by HRCT in idiopathic bronchiectasis.

Methods: Ninety-nine patients with idiopathic bronchiectasis were selected. Acute exacerbation (AE) incidence was set as a comparison factor for the treatment effect. First, patients were divided into the severe and non-severe group based on HRCT. The severe group was defined to have abnormal findings in three or more lobes and in both lungs and the non-severe group as having two or fewer lobes or one side of the lung. Next, each group was divided into subgroups with and without macrolide therapy. Finally, the relationship between macrolide therapy and the AE incidence in each subgroup was compared.

Results: Among the 99 idiopathic patients, 50 and 49 were included in the non-severe and severe groups, respectively. In the non-severe group, the subgroup with macrolide therapy had significantly less AE than the subgroup without macrolide (odds ratio [OR] = 0.10, $P < 0.036$). No significant difference was found in the severe group (OR = 0.70, $P = 0.57$).

Conclusions: HRCT may be useful in predicting the effect of long-term, low-dose macrolide therapy for idiopathic bronchiectasis.

Background

Bronchiectasis is classified as a chronic lower respiratory tract infection, referring specifically to a condition in which the bronchi are dilated by persistent inflammation [1–3]. While secondary bronchiectasis often results from systemic inflammatory diseases and infections such as rheumatoid arthritis, ulcerative colitis, nontuberculous mycobacteriosis, and diffuse panbronchiolitis (DPB), idiopathic bronchiectasis of unknown origin can also occur [4, 5] and accounts for approximately 50% of total cases [6–8].

Long-term, low-dose macrolide therapy, originally performed for DPB by Kudo et al. [9], was applied to bronchiectasis, and its effectiveness was reported in several randomized controlled trials [10–12]. These trials indicated a variety of anti-inflammatory and anti-microbial effects of macrolide therapy including suppression of inflammatory cell migration, reduction of active oxygen production, reduction of *Pseudomonas aeruginosa* biofilm formation, and reduction of excessive airway secretions. On the other hand, macrolide therapy has also a risk of side effects including antibiotic-resistant bacteria. One study recommended that this therapy can only be used for patients with repeat acute exacerbation (AE) and those with low risk of nontuberculous mycobacteriosis [13].

At present, high-resolution computed tomography (HRCT) has been established as the gold standard for diagnosing bronchiectasis. In 1991, Bhalla et al. suggested a detailed scoring system which was calculated by scoring each of the nine radiological categories and then adding up the total score [14]. Subsequently, the modified Reiff score based on the number of lobes and the severity of bronchial dilatation compared with the adjacent vessel was devised in 1995 [15]. The Bronchiectasis Severity Index (BSI) and the FACED (Forced expiratory volume in 1 second, Age, Chronic colonization, Extension, and Dyspnea) score, having excellent predictive power, were also devised to predict severity and prognosis by using several clinical parameters [16, 17]. In the latest study, the Bronchiectasis Radiologically Indexed CT Score (BRICS) was devised by using the parameters of bronchial dilatation and the number of bronchopulmonary segments with emphysema on HRCT, and it showed that radiological appearances alone can predict disease severity [18]. Currently, HRCT is useful in measuring the severity of bronchiectasis, and it may be possible to assess it using the simpler scoring system.

Thus, while some studies on severity and prognosis in bronchiectasis have been reported, no reports exist investigating the relationship between severity and the effectiveness of macrolide therapy. Considering the appearance of antibiotic resistance and the side effects associated with treatment, discussing appropriate treatment indication according to the severity classification of bronchiectasis is essential. The study aimed to examine the relationship between the effect of macrolide therapy and severity assessment performed by HRCT in idiopathic bronchiectasis, and this is the first report of its kind.

Methods

Study population and selection criteria

Medical records of patients diagnosed with idiopathic bronchiectasis between April 2014 and December 2019 at a single hospital were retrospectively reviewed. (1) Bronchial dilatation, visibility of peripheral airways, bronchial wall thickening, and small airway abnormality confirmed by multiple radiologists and pulmonologists on HRCT and (2) patient who has received regular follow-up for over 1 year were required for inclusion. (1) Secondary bronchiectasis due to rheumatoid arthritis, ulcerative colitis, DPB, nontuberculous mycobacteriosis, and cystic fibrosis ruled out by clinical symptoms, serological test, bacteriological examination, and/or endoscopy; (2) patients with a history of AE; (3) patients who were unable to continue macrolide therapy due to side effects; and (4) patients with interstitial pneumonia and malignant tumors were the exclusion criteria. This study was approved by the Atsugi City Hospital Ethics Committee. All patient records were anonymized prior to analysis, and informed consent was received from all patients (approval number, R2-02).

Data analysis and comparison factors

All patients who met the study criteria were divided into two groups, severe and non-severe, according to a severity assessment performed by HRCT. The severe group included patients with bronchial dilatation, visibility of peripheral airways, bronchial wall thickening, and small airway abnormality in three or more lobes and in both lungs. The non-severe group had the same abnormalities in two or fewer lobes or in one

side of lung. Patients in each group were also divided into subgroups based on treatment with and without long-term, low-dose macrolide therapy (shown in Fig. 1).

First, all patients were divided into subgroups, and clinical characteristics and AE incidence were compared across the groups. The patients were then divided into the non-severe and severe groups, and the same comparison was performed. Eventually, the differences in clinical characteristics between the subgroups with and without macrolide therapy were compared in the non-severe and severe groups, respectively, and the relationship between macrolide therapy and AE incidence in each subgroup was evaluated. Sex, age, body mass index (BMI), smoking status, clinical symptoms, forced vital capacity and forced expiratory volume in the first second of expiration percent predicted, bacterial colonization, treatment, and comorbidities were the variables set for comparison.

Review of radiology

All patients underwent HRCT, and radiologists' interpretation reports were made available for review. Patterns of abnormal findings were classified as bronchial dilatation, visibility of peripheral airway, bronchial wall thickening, and small airway abnormality by multiple radiologists and pulmonologists (shown in Fig. 2). Bronchial dilatation is the ratio between the diameter of the bronchus and pulmonary artery running parallel (bronchoarterial ratio) of one or more. Visibility of the peripheral airway is the bronchus found within 1 cm of the pleura. Small airway abnormality is the centrilobular granular shadow, tree-in-bud appearance, and mosaic attenuation.

Definition of long-term, low-dose macrolide therapy and AE

Low-dose macrolide therapy in all patients consisted of erythromycin or clarithromycin administration. Each dose for erythromycin or clarithromycin was set at 400–600 or 200–400 mg, respectively. All patients administered macrolide therapy continued receiving it for at least 1 year. AE presented with acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, and hemoptysis) and/or systemic upset.

Statistical analysis

The average, standard deviation, median, 25th and 75th percentile points, and range were calculated for continuous variables. Frequency and ratio were calculated for discrete variables. For intergroup comparisons, Fisher's exact test was used for discrete variables alongside the Bonferroni correction for pairwise comparisons. All groups were compared using analysis of variance and pair comparisons by *t*-test in the case of the parametric method for comparison of continuous variables. For the nonparametric method, all groups were compared using the Kruskal–Wallis test, and pair comparisons were made using the Mann–Whitney *U* test. A logistic regression analysis was performed to investigate the relationship between macrolide therapy and AE. $P < 0.05$ indicated statistical significance. Statistical analyses were performed with SPSS software, version 23.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

This study included 99 patients with idiopathic bronchiectasis. The patients were divided into with and without macrolide therapy groups (48 and 51 without and with macrolide, respectively). Tables 1 and 2 show no significant differences in clinical characteristics between these two groups, but patients in the macrolide group had significantly lower AE than without macrolide ($P < 0.05$). Of the 99 patients, 50 (31 and 19 without and with macrolide, respectively) and 49 (17 and 32 without and with macrolide, respectively) were included in the non-severe and severe groups, respectively. Table 1 shows the differences in clinical characteristics between the groups. Significant differences were observed in symptoms and respiratory function between the groups ($P < 0.05$). In addition, patients in the severe group were significantly more associated with *P. aeruginosa* colonization (20% vs 49%, $P < 0.05$). No significant differences were observed in the frequency of inhaled drug use; however, macrolide and L-carbocisteine were used more often in the severe group (38% vs 65%, 34% vs 90%, $P < 0.05$).

Table 3 shows the differences in clinical characteristics between the subgroups with and without macrolide therapy. In both non-severe and severe groups, no significant differences were found in age, sex, BMI, smoking history, symptoms, bacterial test, respiratory function, treatment, or comorbidities between subgroups. Tables 4 and 5 show that the subgroup with macrolide had significantly less AE than without macrolide in the non-severe group (OR = 0.10, 95% CI = 0.01–0.86, $P = 0.036$), while no significant difference was found in AE between the subgroups in the severe group (OR = 0.70, 95% CI = 0.21–2.37, $P = 0.57$).

Discussion

Bronchiectasis is a disease that causes repeated chronic respiratory tract infections and leads to gradual but irreversible lung distortion. The pathogenesis of bronchiectasis is currently considered to occur as follows. First, bacteria colonization weakened the bronchi, leading to an excessive immune response. Second, persistent inflammation in the bronchi leads to the destruction of bronchial elastic fibers, smooth muscle, and cartilage and promotes excessive mucus secretion, ciliary movement reduction, and airway macrophage dysfunction. Eventually, lung distortion and bacterial colonization takes place, leading to a cycle of destructivenflammation [3, 19]. The effects of genetic predisposition and environmental factors have both been considered for their roles in idiopathic bronchiectasis, but details have yet to be elucidated [2, 3, 19] Long-term, low-dose macrolide therapy has been proved to be an effective treatment for bronchiectasis [10–12]. However, one study has recently reported that erythromycin was shown to not affect AE incidence in patients without colonization of *P. aeruginosa* and promoted the replacement of *Haemophilus influenza* [20].

HRCT is currently established as the gold standard for the definitive diagnosis of bronchiectasis. Previous reports have already indicated that the severity of HRCT is significantly associated with respiratory function and clinical symptoms [21–23], and consistent with that report, patients in the severe group had a significantly lower respiratory function and more clinical symptoms than the non-severe group as

shown in Table 1. Moreover, *P. aeruginosa* colonization was observed more in the severe group and may reflect bacterial changes due to repeated infections. This time, AE incidence was set as a comparative factor, and significant differences in patients classified by HRCT was confirmed. Through this current study, the destruction of capillaries in the lung due to the progress of bacterial replacement and the destructive inflammatory cycle may have led to a reduction of the therapeutic effectiveness of macrolide in the severe group.

Next, the validity of the HRCT severity classification set in this study was discussed. As mentioned in the "Introduction" section, some reports on the severity scoring system, such as the Bhalla score, the modified Reiff score, the BSI, the FACED score, and the BRICS, already existed [14–18]. The oldest Bhalla score finely divided the HRCT findings into nine categories (severity of bronchiectasis, peribronchial thickening, number of bronchopulmonary segments involved, the extent of mucus plugging, sacculations or abscesses, generations of bronchial divisions involved, number of bullae, number of bronchopulmonary segments with emphysema, and collapse or consolidation) [14]. However, the latest BRICS was categorized only by bronchial dilatation (0 = absent, 1 = lumen just greater than the diameter of the adjacent vessel, 2 = lumen two to three times greater than the diameter of the adjacent vessel, 3 = lumen greater than three times the diameter of the adjacent vessel) and the number of bronchopulmonary segments with emphysema (0 = absent, 1 = 1–5, 2 = >5), and it showed that its simplified radiological score could assess clinical disease severity in bronchiectasis [18]. Based on these scoring systems, a severity classification focusing on imaging findings and distribution, keeping in mind the creation of a simpler classification, was defined.

Finally, the limitations of this study were discussed. First, because this was a retrospective study and the type and dose of macrolide were not completely consistent. Second, macrolide resistance was not routinely tested. Long-term macrolide therapy can cause the appearance of macrolide-resistant bacteria, but no evaluation was done on whether the appearance had any influence on the therapeutic effects. Third, although the AE incidence was compared as a marker of therapeutic effect, no comparison was done on the improvement of respiratory symptoms and respiratory function. In addition to these limitations, this study was conducted at a single hospital, and the number of patients registered was small. Despite these factors, it is strongly believed that this study has valuable implications for assessing the relationship between long-term, low-dose macrolide therapy and AE incidence in idiopathic bronchiectasis classified by HRCT. Furthermore, the need to investigate the relationship between the therapeutic effect of macrolide therapy, clinical symptoms, respiratory function, and bacterial colonization in patients classified by HRCT in the future is imperative.

Conclusions

In the non-severe group, the macrolide therapy subgroup experienced statistically less AE compared to the subgroup without macrolide. In the severe group, no significant difference between subgroups was found.

Severity assessment performed by HRCT may be useful for predicting the effect of long-term, low-dose macrolide therapy.

Declarations

Ethics approval and consent to participate

This study was approved by the Atsugi City Hospital Ethics Committee. All patient records were anonymized prior to analysis, and informed consent was received from all patients (approval number, R2-02).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author's contributions

Dr ZS designed the study and drafted the manuscript. Dr KK made substantial contributions to analysis and interpretation of data and editing of the final manuscript. Dr MY, SN, KT, NT contributed to data collection, analysis and review of this manuscript.

Acknowledgements

None.

References

1. Barker AF. Bronchiectasis. *N Eng J Med*. 2002; 346: 1383-93.
2. Boyton RJ, Altmann DM. Bronchiectasis: Current Concepts in Pathogenesis, Immunology, and Microbiology. *Annu Rev Pathol*. 2016; 11: 523-54.
3. King P. Pathogenesis of bronchiectasis. *Paediatr Respir Rev*. 2011; 12: 104-10.

4. Derek W, John E, Gerry O, Gregory T. Prevalence and economic burden of bronchiectasis. *Clin Pulm Med*. 2005; 12: 205-9.
5. Wilczynska MM, Condliffe AM, Mckeon DJ. Coexistence of bronchiectasis and rheumatoid arthritis: revisited. *Respir Care*. 2013; 58: 694-701.
6. Altenburg J, Wortel K, van der Werf TS, Boersma WG. Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital. *Neth J Med*. 2015; 73: 147-54.
7. Pasteur SM, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med*. 2000; 162:1277-84.
8. Kadowaki T, Yano S, Wakabayashi K, Kobayashi K, Ishikawa S, Kimura M, et al. An analysis of etiology, causal pathogens, imaging patterns, and treatment of Japanese patients with bronchiectasis. *Respir Investig*. 2015; 53: 37-44.
9. Kudoh S, Keicho N. Diffuse panbronchillitis. *Clin Chest Med*. 2012;33: 297-305.
10. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomized, double-blind, placebo-controlled traial. *Lancet*. 2012; 380: 660-7.
11. Atlenbur J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis. *JAMA*. 2013; 309: 1251-9.
12. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis. *JAMA*. 2013; 309: 1260-7.
13. Grimwood K, Bell SC and Chang AB. Antimicrobial treatment of non-cystic fibrosis bronchiectasis. *Expert Rev Anti Infect Ther*. 2014; 12: 1277-96.
14. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology*. 1991; 179: 783-8.
15. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM. CT findings in bronchiectasis: limited value in distinguishing between postinfective and specific types. *Am J Roentgenol*. 1995; 165: 261-7.
16. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The Bronchiectasis Severity Index. An international derivation and validation study. *Am J Respir Crit Care Med*. 2014; 189: 576-585.
17. Martínez-García MÁ, de Gracia J, Vendrell Relat M, Girón RM, Máiz Carro L, de la Rosa Carrillo D,et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J*. 2014; 43: 1357-1367.
18. Bedi P, Chalmers JD, Goeminne PC, Mai C, Saravanamuthu P, Velu PP, et al. The BRICS (Bronchiectasis Radiologically Indexed CT Score): A Multicenter Study Score for Use in Idiopathic and Postinfective Bronchiectasis. *Chest*. 2018; 153: 1177-1186.

19. Morrisey BM. Pathogenesis of bronchiectasis. *Clin Chest Med*. 2007; 28: 289-96.
20. Rogers GB, Bruce KD, Martin ML, Burr LD, Serisier DJ. The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomized, double-blind, placebo-controlled BLESS trial. *The Lancet Respir Med*. 2014; 2: 988-96.
21. Lee JH,Kim YK, Kwag HJ, Chang JH. Relationships between High-Resolution Computed Tomography, Lung Function and Bacteriology in Stable Bronchiectasis. *J Korean Med Sci*. 2004; 19: 62-8.
22. Eshed I, Minski I, Katz R, Jones PW, Priel IE. Bronchiectasis: correlation of high-resolution CT findings with health-related quality of life. *Clinical Radiology*. 2007;62: 152-9.
23. Başaran AE,Başaran A, Maslak İC, Arslan G, Bingöl A. Evaluation of Noncystic Fibrosis Bronchiectasis Using Clinical and Radiological Scorings in children. *Turk Thorac J*. 2018; 19: 159-64.

Tables

Table 1. Comparison of characteristics between without and with macrolide groups, non-severe and severe groups

Variable	Without Macrolide (N = 48)	With Macrolide (*N* = 51)	P	Non-severe group (N = 50)	Severe group (*N* = 49)	P
Age	74.7 ± 8.8	75.2 ± 6.9	NS	73.7 ± 8.7	76.4 ± 7.0	NS
Sex			NS			NS
Male	20 (42)	22 (43)		20 (40)	22 (45)	
Female	28 (58)	29 (57)		30 (60)	27 (55)	
BMI	20.7 ± 2.3	21.8 ± 2.5	NS	21.0 ± 2.2	21.6 ± 2.8	NS
Smoking history			NS			NS
Prior smoker	20 (42)	23 (43)		20 (40)	23 (47)	
Current smoker	4 (8)	2 (4)		4 (8)	2 (4)	
Non-smoker	24 (50)	27 (53)		26 (52)	24 (49)	
Symptoms						
Cough	40 (83)	42 (82)	NS	34 (68)	48 (98)	< 0.05
Sputum	33 (69)	39 (76)	NS	27 (54)	45 (92)	< 0.05
Bloody sputum	12 (25)	13 (25)	NS	8 (16)	17 (35)	< 0.05
Dyspnea	8 (17)	13 (25)	NS	2 (4)	19 (39)	< 0.05
Bacterial test						
P. aeruginosa	14 (29)	20 (39)	NS	10 (20)	24 (49)	< 0.05
H. influenzae	6 (13)	9 (18)	NS	5 (10)	10 (20)	NS
S. aureus	5 (0)	7 (14)	NS	5 (10)	7 (14)	NS
Respiratory function						
FVC, L	2.1 ± 0.5	1.9 ± 0.5	NS	2.4 ± 0.3	1.6 ± 0.5	< 0.05
FEV_1% pred	71.4 ± 6.8	66.6 ± 8.8	NS	73.2 ± 6.1	64.9 ± 7.8	

						< 0.05
Treatment			NS			
ICS/LABA	6 (13)	8 (16)	NS	7 (14)	7 (14)	NS
ICS alone	4 (8)	5 (10)	NS	5 (10)	4 (8)	NS
LABA alone	6 (13)	5 (10)	NS	6 (12)	5 (10)	NS
LAMA	5 (10)	6 (12)	NS	4 (8)	7 (14)	NS
L-carbocisteine	29 (60)	32 (63)		17 (34)	44 (90)	< 0.05
Macrolide	–	–		19 (38)	32 (65)	< 0.05
Comorbidities						
Asthma	3 (6)	4 (8)	NS	3 (6)	4 (8)	NS
Ischemic heart disease	4 (8)	7 (14)	NS	4 (8)	7 (14)	NS
Cerebrovascular disease	4 (8)	6 (13)	NS	4 (8)	6 (12)	NS
Diabetes mellitus	6 (13)	8 (16)	NS	6 (12)	8 (16)	NS

Values are presented as no. (%) or mean ± standard error. BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; % pred, percentage of predicted; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; NS, not significant.

Table. 2 Comparison of AE incidence between without and with macrolide groups

Variable	Without AE		With AE		P
	N	%	N	%	without vs with AE
Treatment					< 0.05
Without macrolide	21	36	27	66	
With macrolide	37	64	14	34	

Values are presented as no. (%). AE; acute exacerbation; CI, confidence interval; OR, odds ratio.

Values are presented as no. (%) or mean ± standard error. BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; % pred, percentage of predicted; ICS, inhaled

corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; NS, not significant.

Table 3. Comparison of characteristics between without and with macrolide in both non-severe and severe groups

	Non-severe group			Severe group		
Variable	Without (N = 31)	With (*N* = 19)	P	Without (N = 17)	With (*N* = 32)	P
Age	73.7 ± 9.0	73.6 ± 8.1	NS	76.9 ± 8.2	76.2 ± 6.3	NS
Sex			NS			NS
Male	13 (42)	7 (37)		7 (41)	15 (47)	
Female	18 (58)	12 (63)		10 (59)	17 (53)	
BMI	20.9 ± 2.0	21.3 ± 2.6	NS	20.5 ± 3.0	22.2 ± 2.5	NS
Smoking history			NS			NS
Prior smoker	13 (42)	7 (37)		7 (41)	16 (50)	
Current smoker	3 (10)	1 (5)		1 (6)	1 (3)	
Non-smoker	15 (48)	11 (58)		9 (53)	15 (47)	
Symptoms						
Cough	21 (68)	13 (68)	NS	17 (100)	31 (97)	NS
Sputum	17 (55)	10 (63)	NS	16 (94)	29 (91)	NS
Bloody sputum	6 (19)	2 (13)	NS	6 (35)	11 (34)	NS
Dyspnea	1 (3)	1 (6)	NS	7 (41)	12 (38)	NS
Bacterial test						
P. aeruginosa	6 (19)	4 (21)	NS	8 (47)	16 (50)	NS
H. influenzae	3 (10)	2 (11)	NS	3 (18)	7 (22)	NS
S. aureus	3 (10)	2 (11)	NS	2 (12)	5 (16)	NS
Respiratory function						
FVC, L	2.4 ± 0.3	2.3 ± 0.3	NS	1.6 ± 0.5	1.6 ± 0.5	NS
FEV_1% pred	73.6 ± 6.2	72.4 ± 6.0	NS	67.2 ± 5.4	63.8 ± 8.7	NS
Treatment						
ICS/LABA	4 (13)	3 (16)	NS	2 (12)	5 (16)	NS
ICS alone	3 (10)	2 (11)	NS	1 (6)	3 (9)	NS
LABA alone	4 (13)	2 (11)	NS	2 (12)	3 (9)	NS

LAMA	2 (6)	2 (11)	NS	3 (18)	4 (13)	NS
L-carbocisteine	11 (35)	6 (32)	NS	16 (94)	28 (88)	NS
Comorbidities						
Asthma	2 (6)	1 (5)	NS	2 (12)	2 (6)	NS
Ischemic heart disease	2 (6)	2 (11)	NS	3(18)	4 (13)	NS
Cerebrovascular disease	2 (6)	2(11)	NS	2 (12)	4(13)	NS
Diabetes mellitus	3 (10)	3 (16)	NS	3 (18)	5 (16)	NS

Values are presented as no. (%) or mean ± standard error. BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; % pred, percentage of predicted; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; NS, not significant.

Table 4.

Comparison of AE incidence between subgroups in non-severe group (Fisher's exact test and logistic analysis)

Variable	Without AE		With AE		P	OR	95% CI	P
	N	%	N	%	without vs with AE			
Treatment					0.01			
Without macrolide	20	53	11	92		1.00	Reference	
With macrolide	18	47	1	8		0.10	0.01-0.86	0.036

Values are presented as no. (%). AE; acute exacerbation; CI, confidence interval; OR, odds ratio.

Table 5.

Comparison of AE incidence between subgroups in severe group (Fisher's exact test and logistic analysis)

Variable	Without AE		With AE		P	OR	95% CI	P
	N	%	N	%	without vs with AE			
Treatment					0.76			
Without macrolide	6	30	11	38		1.00	Reference	
With macrolide	14	70	18	62		0.70	0.21-2.37	0.57

Values are presented as no. (%). AE; acute exacerbation; CI, confidence interval; OR, odds ratio.

Figures

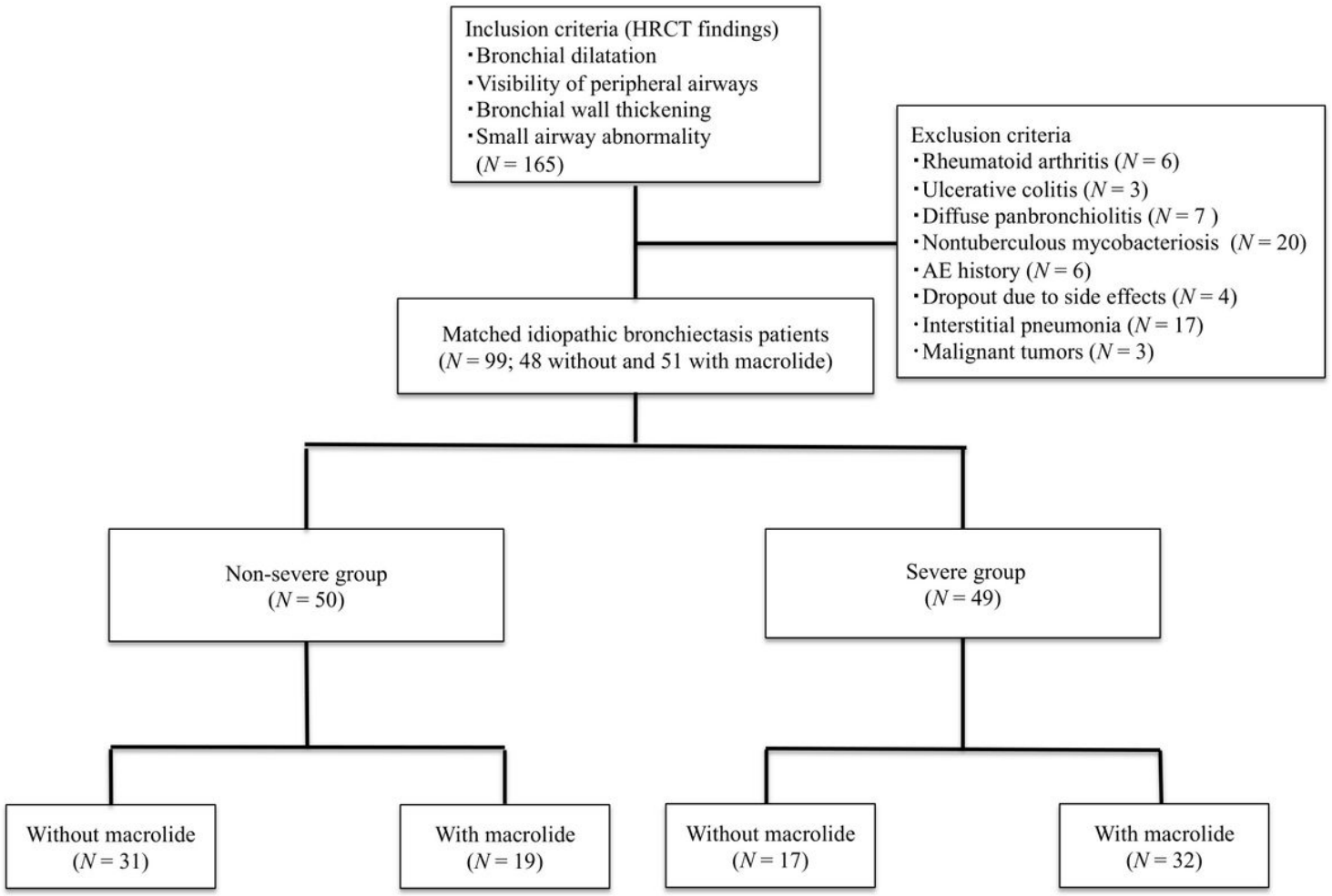

Figure 1

Patient selection flow chart. Legend: Of the 99 eligible patients diagnosed with idiopathic bronchiectasis, 49 were included in the severe group with abnormal findings of HRCT in three lobes or more and both lungs. The non-severe group included 50 patients with findings in two lobes or fewer or one side of lung. Of the 49 patients in the severe group, 32 were assigned to the with macrolide subgroup and 17 to the without macrolide. Of the 50 patients in the non-severe group, 19 were assigned to the with macrolide subgroup and 31 to the without macrolide.

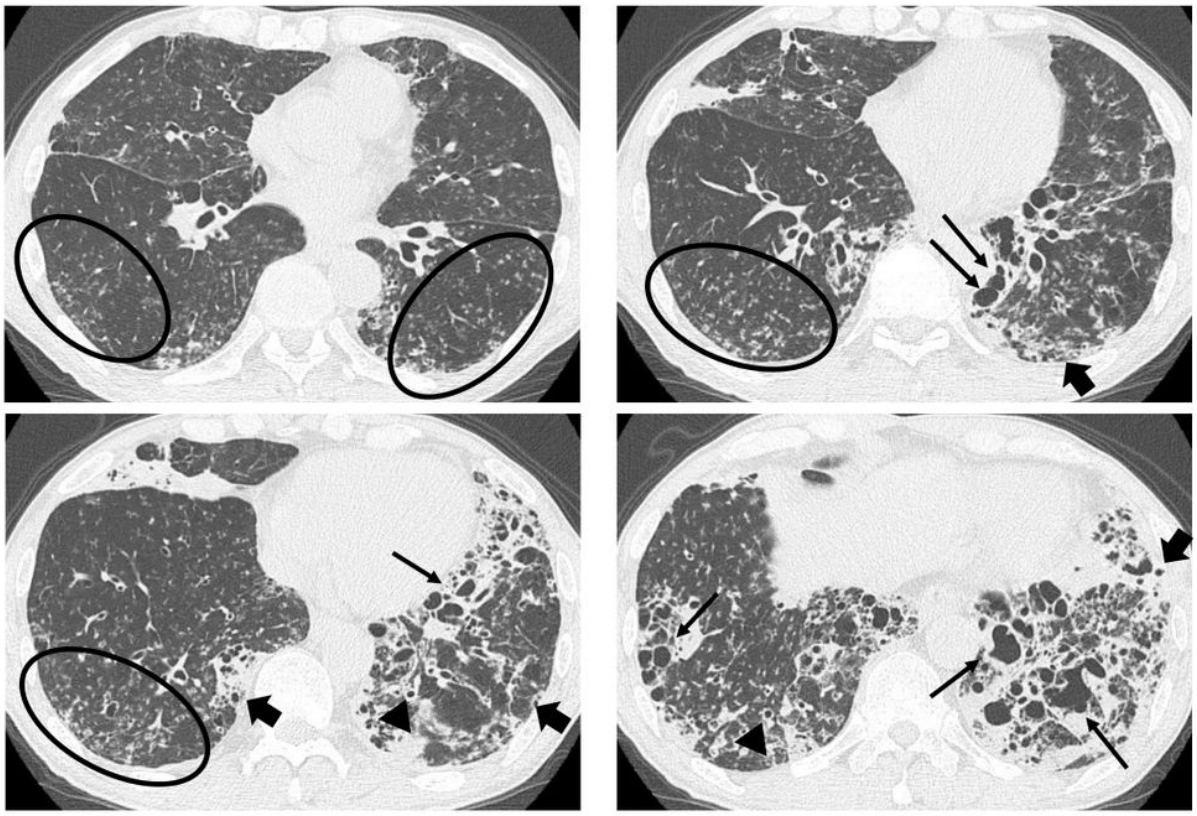

Figure 2

HRCT in a case of severe bronchiectasis. Legend: Bronchial dilatation (thin arrow), visibility of peripheral airway (thick arrow), bronchial wall thickening (triangle), and small airway abnormality (circle) were found in both lungs and in three lobes or more.