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Original article

Discontinuation rates attributed to adverse events and treatment outcomes between clarithromycin and azithromycin in *Mycobacterium avium* complex lung disease: A propensity score analysis

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ABSTRACT

Objectives: This study aimed to compare the discontinuation rates attributed to adverse events and treatment outcomes between clarithromycin (CLR) and azithromycin (AZM) in patients with *Mycobacterium avium* complex lung disease (MAC-LD).
Methods: Among patients diagnosed with MAC-LD during 2001–2013, 560 for whom treatment was initiated as a guideline-based therapy until May 2018 were selected for adverse event analysis. Of them, 316 who underwent treatment for ≥12 months were selected for outcome analysis. Their medical records were retrospectively reviewed. The discontinuation and treatment success rates were analysed after adjustments using the inverse probability of treatment weighted (IPTW) method.
Results: Among the 560 patients, 466 (83.2%) and 94 (16.8%) started CLR-containing and AZM-containing regimens, respectively. The IPTW method using propensity scoring revealed that the discontinuation rate attributed to adverse events was significantly higher with CLR than AZM use (24.6% vs. 9.6%; $P = 0.001$). The overall treatment success rate of the 316 patients who received guideline-based therapy for ≥12 months was 83.2%. Analysis adjusted by the IPTW method showed no significant difference in the treatment success rate between the use of CLR and AZM. Furthermore, 1-year and 3-year recurrence rates were similar with the two drugs (6.8% vs. 6.0%; $P > 0.999$ and 31.0% vs. 37.5%; $P = 0.482$, respectively).
Conclusions: These findings suggest that an AZM-containing regimen may be the better initial treatment choice for MAC-LD as it resulted in lesser discontinuation rates attributed to adverse events while offering similar patient outcomes when compared with CLR.

1. Introduction

The incidence and prevalence of nontuberculous mycobacterial lung disease have been increasing worldwide, including in South Korea [1,2]. Non-tuberculosis mycobacteria (NTM) is a diverse group of organisms; *Mycobacterium avium* complex (MAC) is the most frequently encountered group of mycobacteria in South Korea [3], and MAC lung disease (MAC-LD) is the most common clinical manifestation of infection with MAC [4,5].

The mainstay therapies for macrolide-susceptible MAC-LD are the newer macrolide/azalide drugs such as clarithromycin (CLR) and azithromycin (AZM) [4,6]. Guideline-based therapy (GBT)

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includes macrolide/azalide, ethambutol and rifamycin (rifampin or rifabutin) administered for 18–24 months, with 12 months of sputum culture negativity [4]. In patients with severe and advanced disease, the addition of an aminoglycoside is recommended [1]. The guidelines suggest that both CLR and AZM are equally acceptable for treatment and there is no preference between the two [7,8] as there are no data to show superiority of either drug in the treatment of MAC-LD [9]. However, very few studies have compared the efficacy of these two drugs in terms of their treatment success and disease recurrence rates in patients with MAC-LD [10]. In addition, although it is well established that a substantial portion of patients treated with macrolide/azalide-based regimen experience adverse events such as gastrointestinal (GI) irritation [11], no studies have analysed whether CLR and AZM differ in the incidence of adverse events. Therefore, this study aimed to compare the discontinuation rates attributed to adverse events and treatment outcomes between CLR and AZM in patients with MAC-LD.

2. Material and methods

2.1. Study subjects

Patients were retrospectively enrolled at the Asan Medical Center, which is a 2700-bed referral hospital in Seoul, South Korea. Of the patients who were diagnosed with MAC-LD between January 2001 and December 2013, 951 who had received any antibiotic treatment up to May 2018 were selected, based on the American Thoracic Society (ATS) diagnostic criteria. Patients' medical records were retrospectively analysed in October 2018. The study protocol was approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB No. 2018-1429), and the requirement for informed consent was waived because of the retrospective nature of the study.

2.2. Adverse events analysis

To compare treatment discontinuation rates attributed to adverse events, patients who had received at least one dose of CLR-containing or AZM-containing regimen were enrolled after applying the following exclusion criteria: (i) unclassifiable computed tomography (CT) findings, (ii) treatment not initiated with GBT, (iii) a history of previous MAC-LD treatment, and (iv) minimum inhibitory concentration of MAC isolates for CLR >8 μg/mL (Fig. 1).

In the present study, discontinuation of CLR or AZM attributed to adverse events was defined as permanent discontinuation of these antibiotics prior to the attending physician's initially planned treatment period owing to any adverse events. For patients in whom CLR or AZM was discontinued owing to adverse events, the attending physician could either (i) refrain from resuming the MAC-LD treatment and only observe the clinical course because of intolerance to CLR or AZM or (ii) switch the drug (e.g. prescribe an AZM-containing regimen to a patient in whom CLR was discontinued owing to adverse events and vice versa) as CLR and AZM are the mainstay therapeutics for MAC-LD treatment. Both cases were deemed as a discontinuation of CLR or AZM attributed to adverse events.

2.3. Treatment outcome analysis

Of the patients in whom treatment was commenced with GBT, only those who received treatment for ≥12 months were eventually selected for treatment outcome analysis of CLR-containing and AZM-containing regimens. Patients were excluded if they: (i) did not maintain GBT, (ii) were lost to follow-up, (iii) were transferred to another hospital, and (iv) died due to any cause. To fulfil the requirements of enrolment, patients should have received macrolide/azalide for the entire duration. After treatment initiation, the use of rifampin or ethambutol treatment could be switched to other drugs if newly developed adverse events occurred in response to either antibiotic. In such cases, the treatment regimen was regarded as GBT if both rifampin and ethambutol were prescribed for ≥80% of the total duration [12]. Among patients in whom treatment was subsequently switched to a CLR-containing or AZM-containing regimen after presenting with adverse events to the initial macrolide/azalide regimen, those who received the original or changed drug for ≥80% of the total duration were included in the treatment outcome analysis. As intermittent therapy was rarely adopted at the current centre prior to 2015, the majority of patients with the nodular bronchiectatic (NB) form of MAC-LD received daily therapy.

Treatment outcomes were categorised as follows [13,14]: (1) treatment success: sputum culture conversion, with the treatment duration post-conversion being ≥12 months; (2) treatment failure: no conversion to negative sputum culture even after ≥12 months of treatment; and (3) treatment completion: sputum culture conversion, with the treatment duration after conversion being <12 months. Only treatment success and treatment failure were selected for analysing treatment outcomes. Sputum culture

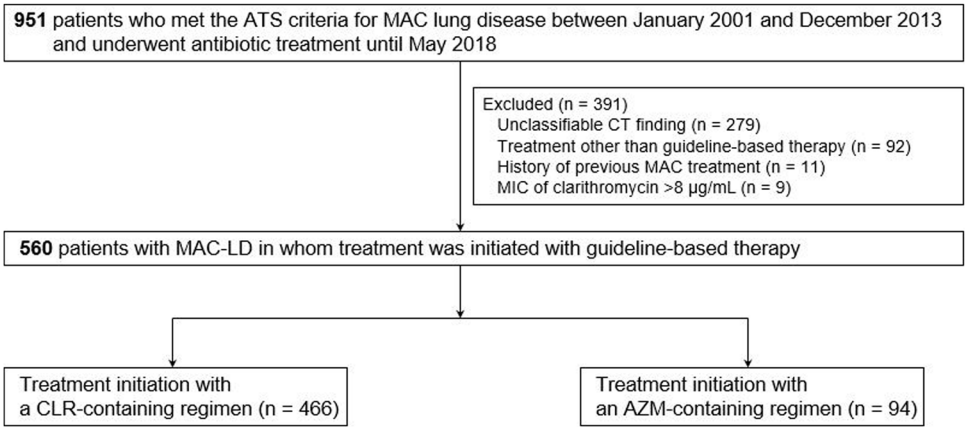

Fig. 1. Study flow chart for severe adverse event analysis.
Abbreviations: CLR, clarithromycin; AZM, azithromycin; ATS, American Thoracic Society; MAC, *Mycobacterium avium* complex; CT, computed tomography; MIC, minimum inhibitory concentration.

conversion was defined as three consecutive negative sputum cultures, with the time of conversion being defined as the date of the first negative culture. Recurrence of MAC-LD was defined as two or more positive cultures of a MAC species after treatment success for the same species [12].

2.4. Microbiological examination and radiologic evaluation

Acid-fast bacilli (AFB) smears were identified via Ziehl-Neelsen staining. Solid (Ogawa medium; Korean Institute of Tuberculosis, South Korea) and liquid (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA) media were used to detect AFB cultures. A polymerase chain reaction (PCR) assay using the Seeplex® TB detection kit (Seegen, Seoul, Korea) was used to differentiate between the *Mycobacterium tuberculosis* complex and NTM. The NTM species were identified using PCR and restriction fragment length polymorphism methods based on the *rpoB* gene [15].

As previously defined [16,17], radiographic abnormalities on chest CT at the time of diagnosis were classified into fibrocavitary, cavitary NB, noncavitary NB, and unclassifiable forms.

2.5. Statistical analysis

Data were compared using Student's *t*-test for continuous variables, and χ^2 or Fisher's exact test was used for categorical variables. Odds ratio (OR) and multivariate analysis were used to calculate the adjusted risk for treatment outcome analysis. Propensity scores to estimate the probability that patients would be selected for treatment with CLR or AZM were calculated using logistic regression to adjust for between-group differences in baseline characteristics based on covariates and factors. All variables listed in Table 1 were included in the propensity model. The inverse probability of the treatment weighted (IPTW) method was used to adjust for between-group differences, which were obtained from the propensity score. Using this approach, the weights for patients who received AZM were proportionally set to the inverse of the propensity score; for those who received CLR, the weights were set to the inverse of (1–propensity score). The calibration and discrimination abilities of the propensity score model were assessed using the Hosmer–Lemeshow statistic and C statistics, respectively. All tests for statistical significance were two-sided, and $P < 0.05$ was considered significant. All analyses were performed using R (3.5.1 version) and SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study subjects for discontinuation rates attributed to adverse events analysis

Eligibility screening identified 560 patients with MAC-LD (mean age, 61.6 years; predominantly female patients, 59.8%) in whom treatment was initiated with a CLR-containing or AZM-containing regimen as a GBT (Fig. 1). Daily therapy was administered to the majority of patients (99.3%, 556 of 560). The treatment was initiated with a CLR-containing regimen in 466 patients (83.2%) and an AZM-containing regimen in the remaining 94 patients (16.8%). In the 466 patients administered a CLR-containing regimen, the dose of CLR was gradually increased from 500 to 1000 mg/day in 23 patients (4.9%) over several weeks. The median time taken for dose escalation was 15 days (interquartile range [IQR] = 13–22). Among these 23 patients, one patient simultaneously received a supportive GI drug (H_2-blocker with bismuth subsalicylate) during dose escalation. In the remaining 443 patients, a complete dose of CLR was prescribed on the first day of treatment. A complete dose of AZM was prescribed at treatment initiation in all 94 patients treated with an AZM-containing regimen. Table 1 presents the baseline characteristics of the 560 patients according to the CLR-containing and AZM-containing regimens, before and after the IPTW method using propensity scoring.

3.2. Discontinuation rates attributed to adverse events

Among the 466 patients who were administered a CLR-containing regimen, discontinuation attributed to adverse events occurred in 113 patients (24.2%). Of the 94 patients who were administered an AZM-containing regimen, adverse events led to the discontinuation of the drug in nine patients (9.6%). Therefore,

Table 1
Clinical characteristics of 560 patients in whom treatment was initiated as a guideline-based therapy according to the treatment regimen.

Characteristics	Total (n = 560)	Unadjusted analysis			Inverse probability of treatment weighting		
		CLR-containing regimen (n = 466)	AZM-containing regimen (n = 94)	P value	CLR-containing regimen (n = 466)	AZM-containing regimen (n = 94)	SMD
Age (years)	61.6 ± 11.0	60.9 ± 10.8	64.7 ± 11.6	0.002	61.6 ± 10.8	61.6 ± 13.1	0.005
Age ≥60 years	326 (58.2%)	259 (55.6%)	67 (71.3%)	0.005	269 (57.7%)	58 (62.7%)	0.103
Female gender	335 (59.8%)	268 (57.5%)	67 (71.3%)	0.013	279 (59.8%)	59 (62.7%)	0.060
Body mass index (kg/m^2)	20.4 ± 3.0	20.5 ± 3.0	20.2 ± 2.9	0.334	20.5 ± 2.9	20.5 ± 2.9	0.013
Current or past smoker	175 (31.3%)	151 (32.4%)	24 (25.5%)	0.190	146 (31.3%)	29 (31.3%)	0.001
Previous history of TB treatment	236 (42.1%)	197 (42.3%)	39 (41.5%)	0.888	196 (42.1%)	38 (40.2%)	0.039
Comorbidities							
Malignancy	134 (23.9%)	116 (24.9%)	18 (19.1%)	0.234	112 (24.1%)	26 (27.8%)	0.085
COPD	79 (14.1%)	70 (15.0%)	9 (9.6%)	0.166	66 (14.1%)	11 (12.1%)	0.060
Diabetes mellitus	52 (9.3%)	42 (9.0%)	10 (10.6%)	0.620	44 (9.4%)	11 (11.5%)	0.067
Aetiology				0.498			<0.001
Mycobacterium avium	274 (48.9%)	231 (49.6%)	43 (45.7%)		227 (48.8%)	46 (48.8%)	
Mycobacterium intracellulare	286 (51.1%)	235 (50.4%)	51 (54.3%)		239 (51.2%)	48 (51.2%)	
Type of disease				0.068			0.060
Noncavitary NB	363 (64.8%)	308 (66.1%)	55 (58.5%)		301 (64.7%)	59 (62.9%)	
Cavitary NB	107 (19.1%)	81 (17.4%)	26 (27.7%)		90 (19.3%)	20 (21.7%)	
Fibrocavitary	90 (16.1%)	77 (16.5%)	13 (13.8%)		75 (16.0%)	15 (15.4%)	
Positive AFB smear	241 (43.0%)	204 (43.8%)	37 (39.4%)	0.430	200 (43.0%)	40 (42.6%)	0.008
Use of injectable aminoglycoside	267 (47.7%)	228 (48.9%)	39 (41.5%)	0.188	221 (47.4%)	40 (42.6%)	0.097

Abbreviations: CLR, clarithromycin; AZM, azithromycin; SMD, standardised mean differences; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; NB, nodular bronchiectatic; AFB, acid-fast bacilli.
Data are reported as mean ± standard deviation and numbers (%).

Table 2
Comparison of discontinuation rates attributed to adverse events between clarithromycin and azithromycin.

Analysis	CLR-containing regimen (n = 466)	AZM-containing regimen (n = 94)	P value
Unadjusted analysis			
Discontinuation of initial CLR or AZM attributed to adverse events	113 (24.2%)	9 (9.6%)	0.002
Not resuming treatment after discontinuation	57	8	
Attempt treatment by switching drug	56*	1†	
Inverse probability of treatment weighting			
Discontinuation of initial CLR or AZM attributed to adverse events	115 (24.6%)	9 (9.6%)	0.001
Not resuming treatment after discontinuation	58	8	
Attempt treatment by switching drug	57	1	

Abbreviations: CLR, clarithromycin; AZM, azithromycin.
Data are reported as numbers (%).
* Treatment of 56 patients was attempted to switch to an AZM-containing regimen. Among these 56 patients, 46 (82.1%) completed treatment with an AZM-containing regimen, whereas the remaining 10 (17.9%) failed to complete treatment because they demonstrated intolerance to AZM.
† A treatment change was attempted in one patient from the CLR-containing to the AZM-containing regimen. This patient failed to complete treatment because of intolerance to the CLR-containing regimen.

the proportion of patients in whom drug discontinuation was attributed to adverse events was higher in patients administered CLR than in those administered AZM (24.2% vs. 9.6%; P = 0.002; Table 2). Furthermore, the IPTW method using propensity scoring revealed almost similar results (24.6% vs. 9.6%; P = 0.001; Table 2).

Among the 113 patients with a discontinuation of CLR attributed to adverse events, treatment was not resumed in 57 because of patient refusal or because the attending physician decided against it. The remaining 56 patients were switched to an AZM-containing regimen; of these, 46 (82.1%) completed treatment with the AZM-containing regimen, whereas the remaining 10 (17.9%) failed to complete the treatment due to poor tolerance of the drug. Furthermore, in eight of the nine patients with discontinuation attributed to adverse events of AZM, treatment for MAC-LD was permanently discontinued, whereas in one patient, a CLR-containing regimen was attempted; this patient also failed to complete treatment because of intolerance to the drug. Table 3 displays the detailed adverse events that led to the discontinuation of CLR or AZM before and after adjusting the data using the IPTW method. The most common adverse event was GI disturbance. The median durations of administration of the initial CLR-containing and AZM-containing regimens until discontinuation were 49 (IQR = 19–153) and 22 (IQR = 14–216) days, respectively.

3.3. Study subjects for treatment outcomes analysis

Among the patients who received GBT for ≥12 months, treatment outcomes were analysed in 316 patients after excluding those in whom the outcome was treatment completion (Fig. 2). The majority of patients (98.7%, 312 of 316) underwent daily therapy. A total of 246 patients (77.8%) received a CLR-containing regimen, and the remaining 70 (22.2%) received an AZM-containing regimen. Table 4 summarises the baseline characteristics according to the treatment regimens.

3.4. Treatment outcomes

The overall treatment success rate for the 316 patients was 83.2% (263 of 316), and the failure rate was 16.8% (53 of 316). No difference was observed between the CLR-containing and AZM-containing regimens (82.9% vs. 84.3%; P = 0.788). The results showed that treatment success rates were similar between the use of AZM and CLR (OR = 0.906, 95% CI = 0.439–1.868; P = 0.788). Furthermore, multivariate analysis and analysis adjusted by the IPTW method also showed that the treatment success rate was not significantly different between the use of CLR and AZM (Table 5).

Of the 263 patients with treatment success, the median follow-up duration after the end of treatment was 44.0 months (IQR = 23.0–68.0). The median follow-up durations were 46.0 months (IQR = 23.0–74.0) and 39.0 months (IQR = 20.0–53.5) for patients who received CLR-containing and AZM-containing regimens, respectively (P = 0.015). Of 227 patients who were followed up for at least 1 year after the end of treatment, 15 (6.6%) had recurrence. The 1-year recurrence rate was similar between the use of CLR-containing and AZM-containing regimens [6.8% (12 of 177) and 6.0% (3 of 50), respectively; P > 0.999]. Furthermore, of the 161 patients who were followed up for at least 3 years after the

Table 3
Detailed causes of adverse events leading to discontinuation of clarithromycin and azithromycin.

Type of severe adverse event	Unadjusted analysis		Inverse probability of treatment weighting	
	Clarithromycin (n = 466)	Azithromycin (n = 94)	Clarithromycin (n = 466)	Azithromycin (n = 94)
Gastrointestinal disturbance	75 (16.1%)	7 (7.4%)	77 (16.6%)	6 (6.4%)
Rash	9 (1.9%)	0	9 (1.9%)	0
General weakness	5 (1.1%)	1 (1.1%)	5 (1.1%)	1 (1.2%)
Hepatotoxicity	4 (0.9%)	0	4 (0.8%)	0
Difficulty in swallowing the drug	3 (0.6%)	0	3 (0.7%)	0
Cytopenia	1 (0.2%)	1 (1.1%)	1 (0.2%)	2 (1.9%)
Dizziness	1 (0.2%)	0	1 (0.2%)	0
Febrile sensation	1 (0.2%)	0	1 (0.2%)	0
Tinnitus	1 (0.2%)	0	1 (0.2%)	0
Discoloration of tongue	1 (0.2%)	0	1 (0.2%)	0
Unrecorded	6 (1.3%)*	0	6 (1.2%)	0
Unknown	6 (1.3%)†	0	6 (1.2%)	0

Data are reported as numbers (%)
* Six patients discontinued treatment by themselves; however, the causes of discontinuation were not recorded.
† Six patients discontinued clarithromycin treatment as suggested by their attending physicians; however, the causes of discontinuation were unknown.

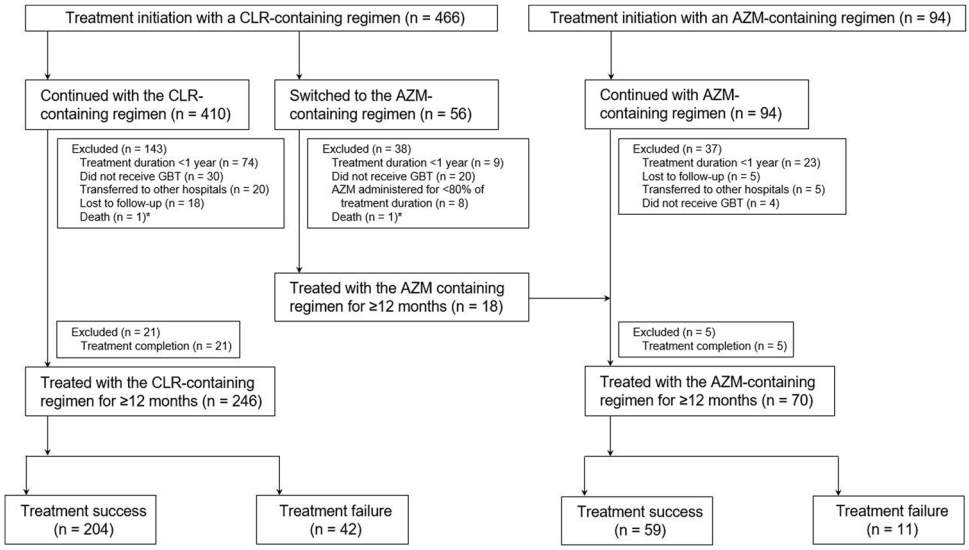

Fig. 2. Study flow chart for treatment outcome analysis.
Abbreviations: CLR, clarithromycin; AZM, azithromycin; GBT, guideline-based therapy.
*The cause of death in these two patients was pneumonia.

Table 4
Baseline characteristics of 316 patients who received guideline-based therapy for ≥12 months according to the treatment regimen.

Characteristics	Total (n = 316)	Unadjusted analysis			Inverse probability of treatment weighting		
		CLR-containing regimen (n = 246)	AZM-containing regimen (n = 70)	P value	CLR-containing regimen (n = 246)	AZM-containing regimen (n = 70)	SMD
Age (years)	59.9 ± 10.5	58.9 ± 10.2	63.4 ± 11.0	0.001	59.8 ± 10.2	60.0 ± 11.0	0.020
Age ≥60 years	165 (52.2%)	120 (48.8%)	45 (64.3%)	0.022	130 (52.6%)	37 (53.1%)	0.010
Female gender	201 (63.6%)	149 (60.6%)	52 (74.3%)	0.035	156 (63.3%)	44 (62.4%)	0.019
Body mass index (kg/m^2)	20.7 ± 2.5	20.8 ± 2.5	20.6 ± 2.5	0.695	20.7 ± 2.5	20.6 ± 2.4	0.007
Current or past smoker	85 (26.9%)	69 (28.0%)	16 (22.9%)	0.387	66 (26.9%)	20 (29.1%)	0.047
Previous history of TB treatment	131 (41.5%)	100 (40.7%)	31 (44.3%)	0.586	103 (42.0%)	33 (47.7%)	0.116
Comorbidities							
Malignancy	59 (18.7%)	48 (19.5%)	11 (15.7%)	0.472	47 (18.9%)	15 (22.0%)	0.077
COPD	43 (13.6%)	36 (14.6%)	7 (10.0%)	0.318	33 (13.5%)	8 (10.9%)	0.078
Diabetes mellitus	28 (8.8%)	20 (8.1%)	8 (11.4%)	0.392	22 (9.0%)	7 (10.3%)	0.045
Aetiology				0.696			0.025
Mycobacterium avium	160 (50.6%)	126 (51.2%)	34 (48.6%)		125 (50.6%)	36 (51.9%)	
Mycobacterium intracellulare	156 (49.4%)	120 (48.8%)	36 (51.4%)		121 (49.4%)	34 (48.1%)	
Type of disease				0.369			0.105
Noncavitary NB	223 (70.6%)	176 (71.5%)	47 (67.1%)		172 (69.8%)	46 (65.5%)	
Cavitary NB	55 (17.4%)	39 (15.9%)	16 (22.9%)		44 (18.0%)	15 (22.0%)	
Fibrocavitary	38 (12.0%)	31 (12.6%)	7 (10.0%)		30 (12.3%)	9 (12.5%)	
Positive AFB smear	126 (39.9%)	98 (39.8%)	28 (40.0%)	0.980	99 (40.2%)	32 (46.3%)	0.124
Use of injectable aminoglycoside	151 (47.8%)	126 (51.2%)	25 (35.7%)	0.022	118 (47.8%)	34 (48.9%)	0.022

Abbreviations: CLR, clarithromycin; AZM, azithromycin; SMD, standardised mean differences; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; NB, nodular bronchiectatic; AFB, acid-fast bacilli.
Data are reported as mean ± standard deviation and numbers (%).

Table 5
Analysis of azithromycin treatment success rate compared with clarithromycin treatment success rate.

	Treatment Success	P value
Crude OR (95% CI)	1.104 (0.535–2.278)	0.788
Adjusted OR (95% CI)*	1.032 (0.488–2.180)	0.935
Adjusted OR by IPTW (95% CI)	0.863 (0.447–1.749)	0.670

Abbreviations: OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.
* Adjusted for variables, including gender, smoking history, previous history of tuberculosis treatment, and positive acid-fast bacilli smear.

end of treatment, 52 (32.3%) had recurrence. The 3-year recurrence rate was comparable between the use of CLR-containing and AZM-containing regimens [31.0% (40 of 139) and 37.5% (12 of 32%), respectively; P = 0.482].

4. Discussion

This study investigated whether a difference exists between the use of CLR and AZM in terms of discontinuation rates attributed to adverse events and treatment outcome by retrospective analysis adjusted by IPTW using propensity score analysis for consecutive patients with MAC-LD in a tertiary referral centre in South Korea. It is believed that this is the first study to investigate this issue. The key findings are as follows: (i) the proportion of patients in whom the drug was permanently discontinued owing to adverse events was significantly higher in those administered CLR than in those administered AZM and (ii) no significant difference was observed in the treatment outcome (treatment success and recurrence rates) between the use of CLR-containing and AZM-containing regimens. As treatment discontinuation owing to adverse events is frequent (10–30%) in clinical

practice [10,18,19], an AZM-containing regimen could be the better initial choice because it resulted in fewer adverse events than the CLR-containing regimen while yielding similar patient outcomes in the present study.

In the present study, the decision of whether to administer CLR or AZM was made by the attending physician, as no information on the superiority of either drug was available. Notably, the number of patients who were administered AZM was lower than that of those who were administered CLR. It was not until 2011 that AZM was approved for MAC-LD treatment under coverage from the National Health Insurance in South Korea. In addition, the preference for a CLR-containing regimen might be due to the fact that treatment data pertaining to MAC-LD are mostly related to the outcomes of the administration of a CLR-containing regimen and not an AZM-containing regimen. Besides, some physicians prefer AZM because compared with CLR, AZM exhibits fewer interactions with rifamycin [20], although it remains unclear whether the low serum concentration of macrolide/azalide is the reason for suboptimal treatment outcomes [1,21].

The present study showed similar treatment outcomes (i.e. treatment success and recurrence rates) with the use of the two regimens. Wallace et al. reported that the rate of sputum conversion for NB-type MAC-LD was similar between patients administered CLR and AZM [10]. Compared with the aforementioned study, the present study included patients with fibrocavitary-type and NB-type MAC-LDs. In addition, only data from patients who received treatment for $\geq$12 months were analysed for determining treatment outcomes. This strategy was adopted to obtain the most accurate data on patient responses to MAC treatment [22]. Therefore, it is thought that these findings reflect the actual data of MAC-LD treated with macrolide/azalide regimen for $\geq$12 months. One of the hallmarks of MAC-LD treatment is a high recurrence rate of approximately 10–48% after successful treatment [14,23,24]. The current study showed that there was no difference in the short-term and long-term recurrence rates between the use of CLR-containing and AZM-containing regimens. Collectively, these results suggest that CLR and AZM have comparable potency against MAC-LD.

This study used the IPTW method using propensity scoring [25,26] to overcome the limitations of a retrospective design. Although propensity score matching is the most common among the four methods of propensity analysis [27], this method was not used as it would have resulted in a loss of information, given that the number of patients treated with AZM was relatively small. To circumvent loss of information, the IPTW method was used. Moreover, certain variables, such as age and gender, could have possibly influenced the choice of macrolide between CLR and AZM. The IPTW method using propensity score adjusted the influence of these variables on the choice of macrolide treatment.

Long-term therapy with CLR or AZM for MAC-LD can lead to side effects, with GI disturbance (such as nausea, vomiting and diarrhoea), hepatotoxicity, loss of olfaction and/or gustation, headache, tinnitus, and pruritus being the most commonly reported adverse events [9], which are often severe enough to warrant treatment discontinuation, particularly in elderly patients. The occurrence of such adverse effects is one of the reasons why early treatment for mild and indolent NB disease is not advised [6]. Of these side effects, GI disturbance is the most common, and it was observed in the present study (Table 3). As stated by Jeong et al., certain physicians prefer AZM over CLR because they believe that the latter causes more severe GI disturbance [28]. Although there has been no clear evidence to support such observations, the proportion of current patients who permanently discontinued medication because of GI disturbance was lower in those administered AZM than in those administered CLR, both when unadjusted and adjusted using the IPTW method (Table 3). Moreover, other adverse events such as skin rash and hepatotoxicity occurred to a lesser extent in patients administered AZM.

This study had several limitations. It was conducted at a single referral centre and had a non-randomised retrospective design, with a relatively small number of patients treated with AZM. Although it used the propensity score to try and overcome this limitation, this adjusts only for observed covariables, whereas randomisation can balance for both known and unknown factors in randomised trials. In addition, it is likely that a substantial number of the adverse effects, especially the mild ones, were not reported as data on adverse effects were not prospectively collected. However, the majority of the adverse events that led to permanent treatment discontinuation were recorded. The study subjects did not undergo electrocardiography examination during treatment despite recent guidelines recommending electrocardiography monitoring at regular intervals because of the known risk of QTc prolongation with long-term macrolide/azalide therapy [8]. Finally, it is uncertain whether the results of this study can be applied to patients undergoing intermittent therapy because the design of the study was such that the majority of the enrolled patients received daily therapy. This was because intermittent therapy was practically adopted at the centre only after a 2015 study revealed that treatment outcomes were comparable between intermittent regimens and daily regimens for noncavitary NB-type MAC-LDs [28], although 2007 ATS guidelines for NTM treatment had already recommended intermittent therapy for NB-type MAC-LD.

In conclusion, the treatment outcomes in terms of success and disease recurrence rates in patients with MAC-LD were similar between the CLR-containing and AZM-containing regimens. Nonetheless, the proportion of patients who required drug discontinuation attributed to adverse events was significantly higher with the former than the latter. The reduced incidence of adverse effects and similar treatment outcomes in patients administered AZM compared with those administered CLR suggest that the AZM-containing regimen may be the better initial choice for the treatment of MAC-LD.

Contributors

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Competing interests

None declared.

Ethics approval

The study was exempted by the Institutional Review Board of the Asan Medical Center.

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