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The long-term safety of chronic azithromycin use in adult patients with cystic fibrosis, evaluating biomarkers for renal function, hepatic function and electrical properties of the heart

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ABSTRACT

Background: Azithromycin maintenance therapy is widely used in cystic fibrosis (CF), but little is known about its long-term safety. We investigated whether chronic azithromycin use is safe regarding renal function, hepatic cell toxicity and QTc-interval prolongation.

Methods: Adult CF patients (72 patients using azithromycin for a cumulative period of 364.8 years and 19 controls, 108.8 years) from two CF-centers in the Netherlands with azithromycin (non)-use for at least three uninterrupted years were studied retrospectively.

Results: There was no difference in mean decline of estimated glomerular filtration rate (eGFR), nor in occurrence of eGFR-events. No drug-induced liver injury could be attributed to azithromycin. Of the 39 azithromycin users of whom an ECG was available, 4/39 (10.3%) had borderline and 4/39 (10.3%) prolonged QTc-intervals, with 7/8 patients using other QTc-prolonging medication. Of the control patients 1/6 (16.7%) had a borderline QTc-interval, without using other QTc-prolonging medication. No cardiac arrhythmias were observed.

Conclusion: We observed no renal or hepatic toxicity, nor cardiac arrythmias during azithromycin use in CF patients for a mean study duration of more than 5 years. One should be aware of possible QTc-interval prolongation, in particular in patients using other QTc-interval prolonging medication.

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1. Background

Maintenance therapy with azithromycin in Cystic Fibrosis (CF) patients infected with *Pseudomonas aeruginosa* is associated with reduced pulmonary exacerbations and improved pulmonary function [1,2]. Azithromycin maintenance therapy is included in the guidelines for CF patients aged ≥ 6 years of age and is currently widely used [2]. The beneficial effect of azithromycin in patients with CF is thought to emerge from a combination of its antibacterial activity as well as its anti-inflammatory and immune-modulatory properties.

Azithromycin is generally well tolerated and one of the safest macrolides [3].

Side effects are mostly mild, like gastrointestinal adverse events or headache [4]. However, a major point of concern of azithromycin use is cardiovascular toxicity with QTc-interval prolongation [5]. In addition, antimicrobials are the most common causative medication class of drug-induced liver injury (DILI), of which azithromycin belongs to the top three [6]. Furthermore, renal toxicity has been described, for example an interstitial nephritis in a single patient after a short course of azithromycin [7]. In patients with Chronic Obstructive Pulmonary Disease long-term azithromycin use is associated with hearing loss [8]. Another concern with the use of macrolides is emergence of bacterial resistance [9].

Long-term data of azithromycin use are mostly derived from non-CF populations [9,10]. However, assessing safety of chronic azithromycin therapy specifically in the CF population is of utmost importance. Since CF is a multisystem disease, with for example CF-related liver disease affecting around 30% of patients [11], there may be a higher risk of adverse events. Furthermore, as CF encompasses polypharmacy, this leads to potential risk of drug-drug interactions with azithromycin. Finally, most studies evaluating long-term azithromycin use have a follow up of a maximum of one year, while in CF patients azithromycin is often used much longer.

All in all, there is an urgent need for long-term safety data of azithromycin in the CF population. Therefore, the aim of this study is to describe the effects of long-term azithromycin

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use in CF, evaluating biomarkers for renal and hepatic function, and electrical properties of the heart.

2. Methods

This was a retrospective cohort study from 01–01-2008 till 01–01-2016 and consisted of adult CF patients from two CF-centers in the Netherlands; the University Medical Center Groningen (UMCG) and the Amsterdam University Medical Center, location Academic Medical Center (AMC). We included adult CF patients who were on azithromycin for at least 3 uninterrupted years as chronic azithromycin users and adult CF patients not using azithromycin for at least 3 uninterrupted years as controls. Inclusion and exclusion criteria are shown in Table 1, together with an overview of the endpoints and covariates. Data were extracted from electronic patient files. The laboratory results for renal and hepatic function were reviewed every year during the study period. Where available, the most recent electrocardiogram (ECG) within the study period was taken. In none of the patients a baseline ECG prior to the initiation of azithromycin was available. Azithromycin dose was evaluated every four months and then converted to a mean azithromycin dose per year, with which the influence of azithromycin dose on the endpoints could be compared between patients.

All statistical analyses were performed with IBM SPSS Statistics (version 23). Student T-test, Fisher's exact test and Fisher-Freeman-Halton exact test were performed for the comparison of the chronic azithromycin users and the controls. The biomarkers of renal and hepatic function were analyzed with Linear Mixed Models. The Medical Ethics Committee of the UMCG granted a waiver for both hospitals (METc2014.328), as they concluded that this study was not subject to the Medical research Involving Human Subjects Act (WMO).

Table 1. Inclusion and exclusion criteria, endpoints and covariates.

Inclusion criteria	- Patients diagnosed with CF with clinical signs consistent with CF and sweat chloride > 60mEq/L and/or two CF-causing mutations identified - Adult age of 17 years or older on 01–01-2008 - Chronic azithromycin users, defined as azithromycin use for at least three uninterrupted years [a] - Controls, defined as patients who did not use azithromycin for at least three uninterrupted years [b]
Exclusion criteria	- Azithromycin use as treatment for Non-Tuberculous Mycobacterium infection - Lung or liver transplantation before inclusion in the study - Incomplete exposure/outcome data
Endpoint renal function	- eGFR [c] - eGFR events, defined as ≥25% decline from baseline eGFR [d]
Endpoint hepatic function	- Liver enzymes: ALT, AST, GGT, AP, and total bilirubin. - Laboratory criteria of DILI, defined as [12]: - Hepatocellular DILI when ALT ≥3 times ULN and ALT/AP ratio ≥5 times ULN. - Cholestatic DILI was characterized by AP ≥2 times ULN and ALT/AP ratio of ≤2 times ULN. - Mixed DILI was defined as ALT ≥3 times ULN, AP ≥2 times ULN and ALT/AP ratio <5 but >2 times ULN.
Endpoint QTc-interval	QTc ranges defined as follows[e]: normal QTc ≤ 430 ms for men and ≤ 450 ms for women; borderline QTc 431–450 ms and 451–470 ms respectively; prolonged QTc > 450 ms and > 470 ms respectively [13].
Covariates	Potentially hepatotoxic, nephrotoxic or cardiotoxic co-medications were assessed according to the Pharmacotherapeutic Compass ('Farmacotherapeutisch Kompas'; the Dutch reference for prescription drugs), as A (percentage chance of toxicity > 10%), B (1–10%), C (0.1–1%), D (0.01–0.1%), E (<0.01%) and F as no toxicity [14]. For each year during the study period the most toxic label was used. [f]

[a] A break of azithromycin therapy during the included period was allowed when this was no more than 10% of the total included time.

[b] Because of the scarcity of clean controls, incident azithromycin use (less than three months in total) was allowed. Laboratory results and/or electrocardiogram (ECG) within three months after this short azithromycin use were not taken into account for these controls.

[c] Calculated with the CKD-EPI equation [15], as this equation performs better than the MDRD equation, especially at higher GFR.

[d] This threshold was similar to the one chosen by other studies that included this higher range of eGFR values [16].

[e] A list of QTc prolonging medications used: ciprofloxacin, claritromycin, cotrimoxazole, levofloxacin, moxifloxacin, fluconazole, itraconazole, voriconazole, granisetron, amitriptyline, aripiprazole, citalopram, irtazepine, pipamperon, risperidone, sertraline, venlafaxine, furosemide, hydrochlorothiazide, domperidone, ondansetron, rupatadine, formoterol, fenoterol/ipratropium, methadon, fluoxetine, metoclopramide, droperidol.

[f] The QTc value for each patient was a signal-averaged QTc from the ECG machine.

Abbreviations used: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CF = cystic fibrosis; DILI = drug-induced liver injury; eGRF = Estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; ULN = upper limit of normal

3. Results

85 adult CF patients from the UMCG and 97 from the AMC were assessed for eligibility, and respectively 44 and 47 were included. Main reasons for exclusion were not meeting the inclusion criterion of three uninterrupted years of azithromycin (non-)use (UMCG 13, AMC 22), lung/liver transplantation before start of study (UMCG 15, AMC 11) and missing data (UMCG 13, AMC 17).

We studied 91 patients: 72 azithromycin exposed patients (37 UMCG, 35 AMC) and 19 controls (7 UMCG, 12 AMC), for a total of 473.6 observation years (azithromycin group 364.8 years, controls 108.8 years). Baseline clinical characteristics are displayed in table 2 and 3. Mean FEV_1 and BMI were lower in the azithromycin group and CF-related diabetes was more common, indicating increased disease severity in this group in contrast to the control group. On the contrary, the use of nephrotoxic and hepatotoxic comedication was more common in the control group.

3.1. Renal function (Table 4)

Decline in eGFR over time was not significantly different between both groups. Intra-individual analysis of eGFR events, defined as ≥25% decline, showed no difference between both groups. The eGFR of all patients was never less than 60 ml/min/1.73 m^2.

3.2. Drug-induced liver injury (Table 4)

Baseline liver enzymes were not significantly different between both groups, except for GGT, with a mean value of 22.09 U/l in the control group and 36.85 U/l in the azithromycin group (p = 0.005). No significant differences were found for

Table 2. *Baseline demographic and clinical characteristics; mean* [SD] *and numbers (%) are given.*

	Index patients (n = 72)	Control patients (n = 19)	p-value
Age (years)	28.8 [8.1]	28.9 [9.1]	0.95
Gender			0.20
Male	36 (50.0%)	13 (68.4%)	
Female	36 (50.0%)	6 (31.6%)	
Mutation type			0.10
Phe508del/Phe508del	39 (54.2%)	7 (36.8%)	
Phe508del/other	28 (38.8%)	9 (47.4%)	
Other/other	2 (2.8%)	3 (15.8%)	
Unknown	3 (4.2%)	0 (0.0%)	
FEV_1 (% predicted)	65.5 [24.0]	84.7 [22.2]	0.002
BMI	21.4 [3.1]	23.1 [2.5]	0.03
CF-related diabetes	33 (45.8%)	1 (5.3%)	0.001
CF-associated liver disease	23 (31.9%)	4 (21.1%)	0.41
CF-related bone disease	18 (25.0%)	2 (10.5%)	0.23
Study duration	5.1 [1.5]	5.7 [1.3]	0.09
Use of nephrotoxic co-medication (mean AUC score)	41.3	63.7	0.001
Use of hepatotoxic co-medication (mean AUC score)	40.8	65.7	0.001

For analysis of the distribution of nephrotoxic and hepatotoxic co-medication between index and control group the AUC (area under the curve) is calculated per patient individually, using the aforementioned toxicity levels A-F. Then the AUC score is calculated by dividing the AUC by the patients' total study days. Thereafter the distribution is analyzed with the Mann-Whitney U test.

Abbreviations used: AUC = area under the curve; BMI = body mass index; CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second.

Table 3. *ECG-specific patient characteristics; mean* [SD] *and numbers (%) are given.*

	Index patients (n = 39)	Control patients (n = 6)	p-value
Age (years)	34.3 [9.4]	35.4 [8.6]	0.78
Gender			1.00
Male	20 (51.3%)	3 (50.0%)	
Female	19 (48.7%)	3 (50.0%)	
Use of QTc-interval prolonging comedication			1.00
Yes	27 (69.2%)	4 (66.7%)	
No	12 (30.8%)	2 (33.3%)	

changes over time between both groups for all liver enzymes including GGT (p = 0.65).

Six patients fulfilled the laboratory criteria of cholestatic DILI , of whom five used azithromycin and one did not (Fisher's exact test, p = 1.0). However, in none of the cases the definitive diagnosis of DILI was made, as there appeared to be no association between azithromycin and the abnormal liver values. In three azithromycin users, liver enzymes returned to normal without cessation of azithromycin. In the other two patients cholestatic DILI persisted, yet DILI was already present prior to azithromycin initiation. Next to this there were two patients with mixed DILI , in whom liver enzymes also returned to normal without discontinuation of azithromycin therapy.

3.3. QTc-interval (Table 5)

In none of the patients a baseline ECG prior to the initiation of azithromycin was available. Of 45 persons (49.5%), an ECG was available during the study period (39 azithromycin users, 6 controls). Of the 6 control patients, 1 had a borderline QTc-interval (male, QTc of 448 ms). This person did not use any other QTc-prolonging medication. Of the 39 azithromycin users, 4 had a borderline QTc-interval (10.3%) ranging from 435 ms to 463 ms, with 1 not using other QTc-prolonging medication (QTc 435 ms). In 4 of the 39 azithromycin using patients (10.3%) QTc was prolonged, ranging from 453 ms to 493 ms. All 4 used other QTc-prolonging drugs at the time the ECG was taken. Of the in total 36 persons with a normal QTc-interval 24 persons (66.7%) used other QTc-prolonging medication. During the study period, no cardiac arrhythmias were reported.

4. Discussion

We observed no renal or hepatic toxicity during azithromycin use for a mean study duration of more than 5 years. From half of the study population ECG data were available, showing no cardiac arrhythmias, although prolonged QTc was observed in four patients, three of whom were also using other QTc-prolonging drugs.

Data in the literature about prolongation of QTc-interval by azithromycin are still conflicting. Observational studies in the general population suggest an increased risk of cardiovascular events in patients treated with azithromycin, which have led to a warning by the FDA to prescribers [17,18]. In addition, from 2000–2013 a total of 12 cases of azithromycin associated Torsade des Pointes were published. All subjects (non-CF) had at least two risk factors: preexisting cardiovascular conditions and concomitant use of other QTc-prolonging drugs [19]. However, in a prospective study, also in non-CF patients, Strle [20] showed no statistically significant increase in the QTc-interval, even when using a higher dosing regimen than commonly prescribed. For the CF population on chronic azithromycin treatment, and also regularly receiving polypharmacy with other medications that can cause QTc prolongation, few data exist regarding the prevalence of cardiovascular events. The two available studies show similar results as this study. Lenehan [21] found no clinically prolonged QTc intervals in pediatric CF patients with chronic azithromycin therapy for 2–6 months. Of the 23 adolescent males 4, however, demonstrated a borderline increase in QTc interval. A retrospective cohort study by Avedissian [22] in CF patients showed no association between chronic azithromycin therapy and longer QTc intervals or significant QTc prolongation. Of the 68 patients on chronic azithromycin therapy 6 had a borderline (5) or prolonged (1) QTc-interval. Additionally, the study did not identify a dose-response relationship between chronic azithromycin and borderline/prolonged QTc. According to the FDA [23], discontinuation of a potentially proarrhythmic drug is recommended with a QTc-interval greater than 500 ms or a QTc-prolongation >60 ms above baseline (QTc-interval prior to initiation of medication), as the majority of cases of Torsade des Pointes have occurred in patients fulfilling these conditions. None of our patients had a QTc-interval greater than 500 ms. Unfortunately, no baseline ECG prior to the initiation of azithromycin was available. Over the period we studied, no cardiac arrhythmias were reported.

Table 4. Results regarding renal function and liver function.

	Index patients (n = 72)	Control patients (n = 19)	p-value	p-value, adjusted for covariates
Renal function				
- Baseline eGFR	117.25 ml/min	114.65 ml/min	p = 0.049	p = 0.42
- Slope eGFR	−1.68 ml/min/year	−1.98 ml/min/year	p = 0.40	p = 0.69
- eGFR events[a]	4 (5.6%)	1 (5.3%)	p = 1.00	
Liver function				
- Baseline ALT	29.35	35.92	p = 0.18	p = 0.80
- Slope ALT	−0.17	0.49	p = 0.58	p = 0.59
- Baseline AST	30.39	34.02	p = 0.41	p = 0.71
- Slope AST	−0.54	−0.31	p = 0.81	p = 0.85
- Baseline ALP	122.93	108.17	p = 0.012	p = 0.78
- Slope ALP	1.78	−0.84	p = 0.20	p = 0.21
- Baseline GGT	36.85	22.09	p = 0.002	p = 0.005
- Slope GGT	0.23	1.83	p = 0.29	p = 0.65
- Baseline Bilirubin	8.58	7.61	p = 0.09	p = 0.99
- Slope Bilirubin	−0.08	−0.20	p = 0.44	p = 0.27
- Hepatocellular DILI	0	0		
- Cholestatc DILI[b]	5 (6.9%)	1 (5.3%)	p = 1.00	
- Mixed DILI[c]	1 (1.4%)	1 (5.3%)	p = 1.00	

Renal function and liver cell damage are analyzed with Linear Mixed Models. The slope represents the annual change in eGFR and liver enzymes, where a negative slope means a decrease and a positive slope means an increase.

[a]One of the patients in the control group had an eGFR event with a decline of 32.3%. The 4 persons in the azithromycin group with an eGFR event had a decline between 10.9% and 42.0%. The eGFR of all patients never dropped below an eGFR of 60 ml/min.

[b]Clinically the elevated liver enzymes were interpreted as matching with liver cirrhosis with biliary pathology. In 3 of the 5 azithromycin users and the 1 non-user, liver enzymes returned back to normal without therapy or cessation of azithromycin. In the other 2 patients the cholestatic conditions persisted, in these both patients the elevated liver enzymes were however already present prior to start of the azithromycin.

[c]In both patients the liver enzymes returned back to normal without changing policy.

Abbreviations used: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CF = cystic fibrosis; DILI = drug-induced liver injury; eGRF = Estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; ULN = upper limit of normal.

Table 5. Results regarding QTc-interval prolongation.

	Index patients (n = 39)	Control patients (n = 6)
QTc-interval prolongation[a]		
- Normal QTc	31 (79.5%)	5 (83.3%)
- Borderline QTc[b]	4 (10.3%)	1 (16.7%)
- Prolonged QTc[c]	4 (10.3%)	0

[a]Time between date of ECG to end of study existed of 478.1 days in the index group, versus 648.0 days in the control group.

[b]The 1 control patient with a borderline QTc-interval was male with a QTc of 448 ms, this person did not use any other QTc-prolonging medication. The 4 persons in the azithromycin group had a borderline QTc-interval ranging from 435 ms to 463 ms, 1 of them did not use any other QTc prolonging medication (male with a QTc-interval of 435 ms).

[c]The 4 index patients with a prolonged QTc had a QTc-interval ranging from 453 ms to 493 ms. All 4 persons were male and had concomitant use of other QTc-prolonging drugs at the time the ECG was taken.

The main limitation of this study is that it is a retrospective study potentially subject to biases. Azithromycin users may have been using this drug for multiple years before inclusion in this study, potentially selecting patients who tolerate azithromycin. The second limitation is the presence of a small control group, limiting power. Also, significant differences exist between both groups regarding FEV_1, BMI and CF-related diabetes, indicating higher disease severity in the azithromycin group. Of note, the use of nephrotoxic and hepatotoxic comedication was more common in the control group. Although with our statistical analysis we adjusted for possible confounders like comedication, it is difficult to fairly compare both groups. For example, concurrent medications that can prolong QTc-interval will not all have the same potential for increase, making it hard to control. Another limitation of the study is the availability of an ECG in only half of the study cohort, with in addition the absence of baseline ECGs for start of azithromycin treatment. For renal function we used an eGFR instead of a measured GFR, and did not evaluate urine samples, blood pressure or imaging. However, these data were not available for the majority of patients, and eGFR is recognized as the best index of kidney function [24].

As stated earlier, an important shortcoming of the current cohort is the absence of an ECG before the start of azithromycin and an ECG in only half of the population being on azithromycin. Even though no cardiac arrhythmias have been observed in our study, it is advisable to make an ECG before the initiation and shortly after starting with azithromycin in patients with other QTc prolonging medication or other risk factors. Since we observed no renal or hepatic adverse events which could be attributed to azithromycin, we believe it is not necessary to add extra monitoring for renal and hepatic toxicity in addition to the usual yearly CF follow-up. The current study did not evaluate the possible risk of ototoxicity in chronic azithromycin use in the CF population. As CF patients are already at increased risk for ototoxicity due to the frequent use of aminoglycosides, this could be important to investigate.

In conclusion, in this observational study in adult CF patients we did not observe major differences in biomarkers for renal and hepatic function between patients on chronic azithromycin therapy and control patients. No cardiac arrhythmias were observed over an observation period of 5 years. We conclude that although long-term use of azithromycin appears safe in CF, one should be aware of possible QTc-interval prolongation, in particular in patients using other QTc-interval prolonging medication.

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Declaration of interest

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Reviewer disclosures

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References

1. Jaffe A, Francis J, Rosenthal M, et al. Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet. 1998;351(9100):420.
2. Mogayzel PJ, Naureckas ET, Robinson KA, et al., Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187(7): 680–689.
3. Rubinstein E. Comparative safety of the different macrolides. Int J Antimicrob Agents. 2001;18:71–76.
4. Summary of product characteristics azithromycin, NL/H/0956/001, 28. 02.18
5. Herath SC, Normansell R, Maisey S, et al. Prophylactic antibiotic therapy for chronic obstyructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018;10. 10.1002/14651858.CD009764.pub3.
6. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology. 2015;148(7):1340–1352.
7. Woodruff AE, Meaney CJ, Hansen EA, et al. Azithromycin-induced, biopsy-proven acute interstitial nephritis in an adult successfully treated with low-dose corticosteroids. Pharmacotherapy. 2015;11:e169-74.
8. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. NEJM. 2011;365(8):689–698.
9. Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Resp Med. 2014;108(10):1397–1408.
10. Tian B, Wuan N, Wang Y, et al. The efficacy and safety of azithromycin in asthma: a systematic review. J Cell Mol Med. 2019;23(3):1638–1646.
11. Siano M, De Gregorio F, Boggia B, et al. Ursodeoxycholic acid treatment in patients with cystic fibrosis at risk for liver disease. Dig Liver Dis. 2010;42(6):428–431.
12. Katarey D, Verma S. Drug-induced liver injury. Clin Med. 2016;16(6):104–109.
13. Straus AM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006;47(2):362–367.
14. Pharmacotherapeutic Compass/Farmacotherapeutisch Kompas: https://www.farmacotherapeutisch kompas.nl. Consulted on 2015 September 30.
15. Mula-Abed WS, Al Rasadi K, Al-Riyami D. Estimated glomerular filtration rate (eGFR): a serum creatinine-base test for the detection of chronic kidney disease and its impact on clinical practice. Oman Med J. 2012;27(2):108–113.
16. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. Pharmacoepidemiol Drug Saf. 2013;22(6):623–631.
17. Svanstrom H, Paternak B, Hviid A. Use of azithromycin and death fromcardiovascular causes. N Engl J Med. 2013;368(18):1704–1712.
18. Mortenson EM, Halm EA, Pugh MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. JAMA. 2014;311(21):2199–2208.
19. Hancox JC, Hasnain M, Vieweg WVR, et al. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. Ther Adv Infect Dis. 2013;1(5):155–165.
20. Strle F, Maraspin V. Is azithromycin treatment associated with prolongation of the QTc interval? Wien Klin Wochenschr. 2002;114(10–11):396–399.
21. Lenehan PJ, Schramm CM, Collings MS. An evaluation strategy for potential QTc prolongation with chronic azithromycin therapy in cystic fibrosis. J Cyst Fibros. 2016;15(2):192–195.
22. Avedissian SN, Rhodes NJ, Ng TMH, et al., The potential for QT Interval prolongation with chronic azithromycin therapy in adult cystic fibrosis patients. Pharmacotherapy. 2019;39(6):718–723.
23. International Conference on Harmonization. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0
24. Soares AA, Eyff TF, Campani RB, et al. Glomerular filtration rate measurement and prediction equations. Clin Chem Lab Med. 2009;47(9):1023–1032.