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BRIEF REPORT

Clarithromycin–Rifampin-Based Treatment for Nontuberculous Mycobacteria Infections in Immunocompromised Patients who Require Concomitant CYP-Metabolized Medications

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Clarithromycin (CYP inhibitor) can be used instead of azithromycin for nontuberculous mycobacteria therapy in patients requiring CYP substrates to mitigate rifampin's CYP induction. We found no differences in adverse events (10/13 vs 14/17; $P = .73$), drug intolerability (1/5 vs 4/11; $P = 1$), or 90-day mortality (0/13 vs 1/17; $P = 1$) in patients receiving clarithromycin vs azithromycin.

Keywords. clarithromycin; immunocompromised host; *Mycobacterium avium* complex; nontuberculous mycobacteria.

Nontuberculous mycobacteria (NTM) are common in the environment [1, 2] and can cause pulmonary and extrapulmonary disease in both immunocompetent and immunocompromised hosts [3]. NTM pulmonary disease is increasing worldwide, with *Mycobacterium avium* complex (MAC) being the most common etiological agent [4]. American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) and British Thoracic Society guidelines recommend [3, 4] treatment with a macrolide-based, multidrug regimen that includes rifampin and ethambutol for at least 12 months after a negative sputum culture in NTM pulmonary disease [3].

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Given its favorable safety profile and lower risk of drug–drug interactions (DDIs), azithromycin is often preferred for NTM treatment [5] and can be used in conjunction with rifabutin to mitigate possible DDIs. However, 19% of solid organ transplant recipients receiving rifabutin develop grade 3 thrombocytopenia [6], making this combination less attractive for immunocompromised patients receiving cytochrome (CYP) substrates. While there are several strategies to mitigate DDIs, one method is to use rifampin with clarithromycin, as their relative CYP induction and inhibition might be offset for most concomitant drugs [7].

Immunocompromised patients commonly receive complex drug regimens that often include calcineurin inhibitors, glucocorticoids, or chemotherapy. They frequently require other concurrent medications such as antidepressants, statins, antihypertensives, or antimicrobials, many of which are metabolized by CYP enzymes. The addition of rifampin, a potent CYP inducer and a first-line agent for NTM therapy, often poses significant challenges in terms of managing DDIs [8]. One potential way to mitigate the effects of rifampin on drug metabolism is through concurrent administration of a potent CYP inhibitor such as clarithromycin. This observation prompted us to consider the potential advantages of the opposing CYP3A effects of clarithromycin with rifampin for the treatment of NTM disease, a strategy that might facilitate DDI management without altering the safety or efficacy of the NTM regimen. One concern with using a clarithromycin-based regimen is that CYP induction from rifampin may result in lower serum clarithromycin concentrations, with adverse clinical outcomes [9]. Therefore, we evaluated the safety and clinical outcomes of NTM therapy in immunocompromised patients receiving a clarithromycin-based regimen compared with azithromycin-based regimens.

METHODS

We included adult patients with immunocompromising conditions, including a solid or hematologic malignancy, solid organ or hematopoietic cell transplantation, or an autoimmune disease with a positive culture for an NTM. Patients who received rifamycin (rifampin or rifabutin) with a macrolide (azithromycin or clarithromycin) for at least 1 week of treatment were included. Participating institutions included Brigham and Women's Hospital from January 1, 2011, to October 18, 2020, and Dana-Farber Cancer Institute from June 3, 2015, to July 1, 2020.

We reviewed electronic medical records to collect patient demographics, underlying comorbid conditions, and characteristics of NTM disease. We evaluated the incidence of infection recurrence and any adverse events (AEs) potentially related to NTM therapy in patients receiving a clarithromycin-based

regimen compared with patients receiving an azithromycin-based regimen using the Common Terminology Criteria for AEs, version 5 (CTCAEv5). This assessment included hepatic and renal function, QTc prolongation, drug discontinuation, interacting medication dose adjustments, out-of-range drug levels, and an adjudication of the severity of AEs.

We compared NTM disease response in 3 domains: (i) symptom evolution, (ii) radiologic, and (iii) microbiologic cure (definitions in Supplementary Table 2) [10]. We also assessed 90-day mortality rates, cause of death, and infection recurrence. We analyzed continuous data using the Wilcoxon rank sum test and categorical data using the Fisher exact test. We used RStudio, version 1.2.5033, for these analyses. This study was approved by the Mass General Brigham Institutional Review Board.

RESULTS

Baseline characteristics were similar between the 2 groups (Table 1). However, patients who received clarithromycin-based regimens were older (median [interquartile range {IQR}], 67 [65–72] years vs 61 [49–64] years; $P = .02$) and less likely to receive rifabutin (0% vs 5%; $P = .05$) compared with those receiving an azithromycin-based regimen. The median duration of treatment (IQR) was 407 (331–600) days among patients who received a clarithromycin-based regimen and 416 (207–551) days among patients who received an azithromycin-based regimen. The median time from MAC diagnosis to start of treatment was also similar (30 vs 45 days, respectively; $P = .36$). Among patients who received a clarithromycin-based regimen, 8 (62%) were culture-positive for MAC, 3 (23%) had *Mycobacterium chimaera*, and 2 (15%) had *Mycobacterium kansasii*. Among patients who received an azithromycin-based regimen, 10 (59%) were culture-positive for MAC, 5 (29%) had *M. chimaera*, 1 had *M. palustre*, and 1 had *M. xenopi*. Of the 30 eligible patients with NTM, 13 (43%) received clarithromycin-based regimens (500 mg once daily [QD]), with 5 of these not receiving concomitant immunosuppressants (IS). Seventeen patients (57%) received azithromycin-based regimens (7 patients receiving 500 mg three times a week [TIW], 6 patients receiving 250 mg QD, 2 patients receiving 500 mg QD, 1 patient receiving 250 mg QD, and 1 patient receiving 1000 mg QD), with 11 of these not receiving concomitant IS. Both groups received other medications with major and moderate interactions. Patients received clarithromycin-based regimens to allow for concomitant CYP substrate administration (76%), or due to provider preferences (15%) or azithromycin allergies (8%). All clarithromycin regimens were first-line therapy, except in 1 patient who received an azithromycin regimen previously and switched due to provider preference.

We identified 35 immunocompromised patients diagnosed with NTM disease who met our inclusion criteria. We excluded 3 patients who lacked clinical and safety outcomes, 1 whose treatment was discontinued after 4 days, and 1 due to severe acute allergic reactions to both clarithromycin and azithromycin during MAC treatment.

In the clarithromycin-based group, 10 patients experienced at least 1 AE vs 14 patients in the azithromycin-based group (77% vs 82%, respectively; $P = .73$). The most common AEs included liver function test elevation (54% vs 24%; $P = .13$), QTc prolongation >450 ms (38% vs 35%; $P = 1.0$), gastrointestinal AEs (nausea, vomiting, diarrhea, and/or constipation; 23% vs 41%; $P = .13$), worsening of baseline comorbidities (15% vs 47%; $P = .11$) and hearing loss (0% vs 24%; $P = .11$) among patients receiving a clarithromycin-based regimen compared with those receiving an azithromycin-based regimen (Supplementary Table 1). Most patients experienced CTCAE, version 5, grade 1–3 AEs, and only 1 patient in the azithromycin group experienced a grade 4 visual alteration. No patients were found to have treatment-emergent thrombocytopenia, nor did we find them to have unrelated thrombocytopenia grade ≥3.

Dose adjustments for interacting medications were similar in the clarithromycin and azithromycin groups (23% vs 29%; $P = .76$). The proportions of out-of-range tacrolimus levels were also similar in both groups (8% vs 6%; $P = 1.0$). Among those receiving azithromycin-based regimens, 1 had worsening graft-vs-host disease and 2 had flares of their underlying conditions (sicca syndrome and rheumatoid arthritis); these were attributed to challenging management of concomitant medications (ruxolitinib and prednisone, respectively) due to high-rate metabolization per CYP induction.

Only 1 patient presented a grade 3 elevation in liver enzymes (Supplementary Table 1). There were no differences between groups in terms of resolution of NTM symptoms, median time to symptomatic resolution, radiologic resolution, or microbiological cure (Supplementary Table 2). There were no differences between the groups in intolerability (8% vs 24%; $P = 1$), recurrence (9% vs 31%; $P = .12$), 90-day mortality (0% vs 6%; $P = 1$), or cause of death (bronchiolitis obliterans syndrome [8% vs 0%; $P = .43$], cancer progression [0% vs 12%; $P = .48$], *Aspergillus* infection [0% vs 6%; $P = 1$]).

DISCUSSION

We found in this study that clarithromycin-based regimens were as effective as azithromycin-based regimens in immunocompromised patients receiving other CYP substrates. We did not observe a higher incidence of NTM-related AEs in patients who received clarithromycin-based regimens, compared with azithromycin-based regimens. Specifically, we did not observe significant differences in alanine transaminase, aspartate transaminase, QTc, or creatinine when comparing median maximum values on therapy. More significant differences could be seen if the study were repeated with a larger sample size, allowing the

Table 1. Baseline Characteristics

	Clarithromycin-Based Regimen (n = 13)	Azithromycin-Based Regimen (n = 17)
Median age [IQR], y	67 [53.57–72.14]	61 [30.82–64.8]
Male sex, No. (%)	5 (38.5)	8 (35.3)
Median weight [IQR], kg	66.2 [50.8–80.7]	64.2 [54.5–72.3]
Race, No. (%)		
White	12 (92.3)	15 (88.2)
Non-White	1 (7.7)	2 (11.8)
Comorbidities, No. (%)		
Hypertension	6 (46.2)	5 (29.4)
Arrythmia	4 (30.8)	2 (11.8)
Chronic pulmonary disease	3 (23.1)	0
Peripheral vascular disease	2 (15.4)	0
Diabetes	1 (7.7)	3 (17.6)
Moderate to severe renal disease	1 (7.7)	1 (5.9)
Lymphoma	1 (7.7)	1 (5.9)
Myocardial infarction	0 (0)	2 (11.8)
Rheumatologic disease	0 (0)	2 (11.8)
Cerebrovascular disease	0 (0)	1 (5.9)
Immunocompromising condition, No. (%)[a]		
Solid tumor	7 (53.8)	9 (52.9)
Hematologic malignancy	7 (53.8)	6 (35.3)
Transplant	1 (7.7)	3 (17.6)
Autoimmune disease	1 (7.7)	3 (17.6)
Risk factor for *Mycobacterium* lung disease, No. (%)		
Asthma	3 (23.1)	1 (5.9)
Bronchiectasis	5 (38.5)	4 (23.5)
COPD	3 (23.1)	2 (11.8)
None	3 (23.1)	1 (5.9)
Others[b]	5 (38.4)	5 (29.4)
Smoking	1 (7.7)	7 (41.2)
Radiotherapy	3 (23.1)	2 (11.8)
Reason for treatment, No. (%)		
Lung disease	11 (84.6)	16 (94.1)
Cutaneous disease	1 (7.7)	0
Tenosynovitis	1 (7.7)	0
Lymphadenitis	0	1 (5.9)
Mycobacterium spp., No. (%)		
Mycobacterium avium complex	8 (61.5)	10 (58.8)
Mycobacterium chimaera	3 (23.1)	5 (29.4)
Mycobacterium kansaii	2 (15.4)	0
Mycobacterium palustre	0	1 (5.9)
Mycobacterium xenopi	0	1 (5.9)
Median duration from positive culture to start of treatment [IQR], d	30 [11–64]	45 [22–113]
Reason for clarithromycin regimen, No. (%)		-
To allow for concomitant CYP substrate administration[c]	10 (76.9)	
Provider's preference	2 (15.4)	
Allergy to azithromycin	1 (7.7)	
Other antimycobacterial agents used in combination, No. (%)		
Rifampin	13 (100)	13 (76.5)
Ethambutol	13 (100)	16 (94.1)
Linezolid	1 (7.7)	0 (0)
Pyrazinamide	1 (7.7)	1 (5.9)
Isoniazid	1 (7.7)	3 (17.6)
Rifabutin	0 (0)	5 (29.4)
CYP-interacting immunosuppressant, No. (%)		
Prednisone (20 mg/d ≥2 wk)	5 (38.5)	1 (5.9)
Tacrolimus	2 (15.4)	2 (11.8)
Venetoclax	1 (7.7)	0 (0)

Table 1. Continued

	Clarithromycin-Based Regimen (n = 13)	Azithromycin-Based Regimen (n = 17)
Ibrutinib	0 (0)	1 (5.9)
Other[d]	5 (38.5)	4 (23.5)
None	5 (38.5)	11 (64.7)
Other interacting medications, No.[e]		
Moderate interaction	21	37
Major interaction	2	9
Median baseline ALT [IQR], U/L	18 [9.5–22.5] (n = 11)	14.5 [11–18.75] (n = 16)
Median baseline AST [IQR], U/L	18 [15.5–20.5] (n = 11)	19 [15–22.5] (n = 16)
Median baseline alkaline phosphatases [IQR], U/L	86 [73–98.5] (n = 11)	78.5 [57.25–88.25] (n = 16)
Median baseline serum creatinine [IQR], mg/dL	0.72 [0.68–0.895] (n = 11)	0.655 [0.6–1.09] (n = 16)
Median baseline QTc [IQR], ms	440 [439–443] (n = 6)	449 [420–476] (n = 6)

Abbreviations: ALT, alanine transaminase; AML, acute myeloid leukemia; AST, aspartate transaminase; c/GVHD, concomitant graft-vs-host disease; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; CYP, cytochrome; EGFR, estimated glomerular filtration rate; HCT, hematopoietic cell transplant; IQR, interquartile range; MUD-HSCT, matched unrelated donor-hematopoietic stem cell transplant; P-ALL, philadelphia-positive acute lymphoblastic leukemia; QTc, corrected QT interval; s/p, status post; SCT, stem-cell transplant.

[a]Specific immunocompromising condition: breast cancer (3), myelodysplastic syndrome (2), non-Hodgkin's lymphoma (1), AML s/p MUD-HSCT (1), prostate cancer (1), metastatic lung cancer (1), CLL (2), multiple myeloma (1), P-ALL s/p HCT (1), metastatic non–small cell cancer (1), follicular lymphoma (1), melanoma and basal cell carcinoma (1), melanoma metastasized to lung (1), heart transplant, non–small cell carcinoma (1), EGFR+ lung adenocarcinoma (1), cord blood SCT c/GVHD (1), arthritis rheumatoid and lupus (1), myelofibrosis (1), autoimmune hemolytic anemia (1), multiple myeloma s/p HCT (1), ulcerative colitis (1), endometrial cancer metastasized to lung (1), sicca syndrome (1).

[b]Other risk factor for *Mycobacterium* pneumonia: lung cancer, necrotizing pneumonia, pneumonitis, alveolar proteinosis, interstitial lung disease, allergic rhinitis, hypogammaglobulinemia, bronchiolitis obliterans syndrome, pulmonary embolism.

[c]CYP substrates: methotrexate, prednisone, ruxolitinib, tacrolimus, tadalafil.

[d]Other interacting immunosuppressant: methotrexate (1), methylprednisolone (1), mycophenolate (1), paclitaxel (2), hydroxychloroquin (1), prednisone (1), pomalidomide (1), ruxolitinib (1).

[e]Other interacting medications that at least 1 of the patients was receiving concomitantly: Major interaction: amiodarone, atovaquone, sulfamethoxazole and trimethoprim, warfarin, fluconazole, phenytoin, pravastatin, tadalafil, tamsulosin, coumadin, solifenacin. Moderate interaction: zolpidem, amitriptyline, amlodipine, atorvastatin, carvedilol, citalopram, clonazepam, warfarin, meperidine, diazepam, everolimus, fluconazole, glimepiride, hydrocortisone, ivabradine, labetalol, levothyroxine, losartan, metoprolol, mirtazapine, nifedipine, omeprazole, ondansetron, oxycodone, prednisone, primidone, propranolol, remeron, rosuvastatin, sertraline, simvastatin, trazodone, solifenacin, olanzapine.

detection of clinically relevant differences. Liver enzymes and baseline drug levels should still be monitored routinely in patients receiving NTM treatment; our findings suggest that patients with abnormal values mostly developed these changes ~4 weeks into NTM treatment.

NTM treatment is long and complex. Previous studies show that 82% of patients receiving treatment including a macrolide, ethambutol, and rifamycin met sputum conversion within 12 months of initiating antibiotic therapy [11]. Our data show similar percentages for microbiological status of presumed or documented cure, regardless of the macrolide received. We found no significant difference in the recurrence of NTM post-treatment.

Our study has several limitations, primarily related to its retrospective design. First, the incidence of AEs may have been underestimated and NTM symptoms potentially documented incompletely or underreported in the electronic health record. Additionally, our study was conducted at 2 institutions in the Northeastern United States with a predominantly White, homogeneous population, which may limit the generalizability of these findings to patients with more variable CYP metabolism.

Overall, our analysis suggests that clarithromycin-based regimens for NTM therapy in immunocompromised patients receiving concomitant CYP substrates are not associated with increased AEs compared with azithromycin-based regimens and are comparably well tolerated.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Availability of data. De-identified data can be shared upon request.

Ethics approval. This study was approved by the Mass General Brigham Institutional Review Board.

Patient consent. This study was considered exempt from patient consent by Mass General Brigham Institutional Review Board.

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