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Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

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BACKGROUND: Bedaquiline is an oral antimycobacterial agent belonging to a new class of drugs called diarylquinolines. It has low equivalent minimal inhibitory concentrations for *Mycobacterium tuberculosis* and nontuberculous mycobacterial (NTM) lung disease, especially *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* (Mab). Bedaquiline appears to be effective for the treatment of multidrug-resistant TB but has not been tested clinically for NTM disease.

METHODS: We describe a case series of off-label use of bedaquiline for treatment failure lung disease caused by MAC or Mab. Only patients whose insurance would pay for the drug were included. Fifteen adult patients were selected, but only 10 (six MAC, four Mab) could obtain bedaquiline. The 10 patients had been treated for 1 to 8 years, and all were on treatment at the start of bedaquiline therapy. Eighty percent had macrolide-resistant isolates (eight of 10). The patients were treated with the same bedaquiline dosage as that used in TB trials and received the best available companion drugs (mean, 5.0 drugs). All patients completed 6 months of therapy and remain on bedaquiline.

RESULTS: Common side effects included nausea (60%), arthralgias (40%), and anorexia and subjective fever (30%). No abnormal ECG findings were observed with a mean corrected QT interval lengthening of 2.4 milliseconds at 6 months. After 6 months of therapy, 60% of patients (six of 10) had a microbiologic response, with 50% (five of 10) having one or more negative cultures.

CONCLUSIONS: This small preliminary report demonstrates potential clinical and microbiologic activity of bedaquiline in patients with advanced MAC or Mab lung disease but the findings require confirmation with larger studies. CHEST 2015; 148(2):499-506

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ABBREVIATIONS: AFB = acid-fast bacilli; Mab = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex; MDR-TB = multidrug-resistant TB; MTB = *Mycobacterium tuberculosis*; NTM = nontuberculous mycobacterial; QTc = corrected QT; TIW = three times weekly; UTHSCT = University of Texas Health Science Center at Tyler

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Nontuberculous mycobacterial (NTM) lung disease is a significant cause of morbidity and mortality among individuals with preexisting lung conditions such as bronchiectasis and COPD.[1,2] *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* (Mab) are the most common NTM respiratory pathogens in the United States. Treatment outcomes for noncavitary MAC lung disease have been generally favorable with macrolide-containing regimens.[3-5] Unfortunately, there are no predictable or reliably effective treatment strategies for lung disease caused by Mab with a functional erythromycin resistance methlyase gene (*erm*).[6] MAC and Mab lung diseases are similar to multidrug-resistant TB (MDR-TB) in that there are relatively few treatment options available, especially for patients who fail "standard" therapy. New drug therapies for MAC and macrolide-resistant Mab lung diseases are urgently needed.

Bedaquiline (Sirturo, TMC 207) was approved for treatment of MDR-TB by the Food and Drug Administration in December 2012 (e-Appendix 1). Bedaquiline is a diarylquinoline antibiotic that acts through a novel antimicrobial mechanism by inhibiting ATP synthase, an enzyme essential to generate energy for TB.[7] The US Food and Drug Administration approval of bedaquiline was based on two phase 2 studies involving 440 individuals with MDR-TB.[8,9] Bedaquiline, when given with other MDR-TB drugs, increased sputum conversion rates in the short term and reduced the amount of time to sputum conversion compared with non-bedaquiline-containing regimens. The approval of bedaquiline was also accompanied by controversy because in one study there was posttreatment excess mortality in the patient group receiving bedaquiline.

Bedaquiline has been shown to have bacteriostatic activity against MAC and Mab but with lower minimal inhibitory concentrations for MAC than for *Mycobacterium tuberculosis* (MTB); there are comparable minimal inhibitory concentrations for Mab in in vitro and mouse models.[10,11] Although bedaquiline has impressive in vitro activity for NTM, the clinical activity of the drug among individuals with NTM lung disease has not been studied. We describe the treatment with bedaquiline-containing regimens of individuals with refractory Mab or MAC lung disease who remained acid-fast bacilli (AFB) culture positive despite aggressive guidelines-directed therapy.[6]

Materials and Methods

Patients with MAC and Mab lung disease treated at the University of Texas Health Science Center at Tyler (UTHSCT), Tyler, Texas, are included in this report. This was a retrospective analysis of prospectively collected data as approved by the institutional review board of UTHSCT (IRB No. 957).

Patients were included in this study if they were ≥ 18 years of age, met the criteria for NTM lung disease as defined by the American Thoracic Society/Infectious Disease Society of America guidelines, and failed ≥ 12 months of therapy for MAC and ≥ 6 months for Mab.[6] Treatment failure was defined as persistent positive sputum cultures for NTM, with progressive symptoms and radiographic abnormalities. All were considered to have potentially life-threatening NTM disease. Bedaquiline was not available through the manufacturer for clinical trial purposes; therefore, only patients with approved commercial insurance or copay assistance were included in this study.

The necessity of obtaining the drug from a single pharmacy and the universal need for insurance reimbursement to obtain the drug precluded a blinded or randomized trial. All patients identified as possible candidates for bedaquiline were given information describing the drug and previously reported adverse events (e-Appendix 1). Specifically, the excess mortality seen with bedaquiline in the MDR-TB studies was discussed in detail.[12] Patients were given the same information about the excess bedaquiline-associated mortality that was provided to physicians by the Centers for Disease Control and Prevention.[13,14]

Patients were excluded from this study if they had a history of Torsade de Pointes; congenital long QT syndrome; a history of untreated hypothyroidism and bradyarrhythmia; uncompensated heart failure; serum calcium, magnesium, or potassium levels below the lower limits of normal; or HIV seropositivity; if they were pregnant or of childbearing age and not on adequate birth control; or if they had a history of alcohol abuse or active hepatitis B or C or other advanced liver disorders. We also assessed the short-term prognosis of each patient. With the exception of one patient early in the investigation who was approved for bedaquiline but did not receive it (see further discussion), patients perceived to have < 12 months anticipated survival were excluded.

Patients with macrolide-susceptible MAC were treated with azithromycin, 500 mg given three times weekly (TIW); ethambutol, 25 mg/kg given TIW; IM or IV streptomycin dosed at 7 mg/kg given TIW; or amikacin given IV at 7 mg/kg TIW. The macrolide was omitted if the MAC isolate was macrolide resistant. If the patient had macrolide-resistant MAC, rifabutin, 150 to 300 mg TIW, was used.[15] Doses for both aminoglycosides were titrated to achieve a peak level of 20 to 25 μg/mL. If the patient could not tolerate IM or IV aminoglycoside therapy, the injectable drug was stopped, and inhaled amikacin, 500 mg daily or TIW via a Pari LC nebulizer (PARI International), was used in combination with oral drugs.[16] Rifampin was omitted in almost all patients because of its significant induction of the hepatic metabolism of bedaquiline.[17] Bedaquiline was dosed at 400 mg (four tablets of 100 mg) po once daily with food for the first 2 weeks. The dose was then decreased to 200 mg (two tablets of 100 mg) TIW with food for a total of 600 mg per week.

Patients with amikacin-susceptible Mab were treated with IV amikacin, 7 mg/kg given at least five times weekly. Doses were titrated to achieve a peak level of 20 to 25 μg/mL. IV cefoxitin, up to 6 to 8 g daily in divided doses, imipenem, 500 to 1,000 mg bid, or tigecycline, 25 to 50 mg daily, and/or linezolid, 300 to 600 mg po daily, were given, depending on susceptibility patterns. Amikacin was omitted if the Mab isolate was resistant.[18] Bedaquiline was dosed as in the MAC protocol. If the isolate for Mab had a nonfunctional *erm* gene and in vitro susceptibility to macrolide/azalide, azithromycin was given at doses of 250 to 500 mg po daily.[19-21]

For both species, drug regimens were given for a minimum of 24 weeks. Pretreatment chest radiograph and high-resolution CT scan, sputum

for AFB smear and culture, CBC count, complete metabolic panel, serum magnesium and phosphorous levels, and ECG were obtained. An ECG, complete metabolic panel, CBC count, serum magnesium and phosphorous levels, and peak streptomycin or amikacin levels were obtained at 2 weeks and then every month while on bedaquiline. Patients were evaluated in clinic at least once per month while on therapy with drugs being distributed, and side effects were assessed at that time (e-Appendix 1). Sputum for AFB smear and culture was obtained at baseline and at least monthly, either by clinic visit or via mail.

Sputum samples were processed in the UTHSCT clinical laboratory using standard decontamination procedures, fluorochrome microscopy, solid media culture on a biplate of Middlebrook 7H10 agar with and without antibiotics, and a broth culture (ESP; Thermo Fisher Scientific, formerly TREK Diagnostic Systems) as described previously.[6,22] MAC isolates were identified using AccuProbe (Hologic Gen-Probe). Mab isolates were identified to species and subspecies using sequencing of region 5 of the *rpo*β gene and polymerase chain reaction restriction fragment length analysis of an approximately 441 base pairs heat shock protein gene (*hsp*)[23] using two restriction endonucleases, *Bst*EII and *Hae*III, as described previously.[24,25] A third restriction enzyme, *Sm*aI, was added to differentiate Mab subspecies *massiliense* from Mab subspecies *bolletii*. Semiquantitative AFB smear and culture results for each submitted clinical specimen during and after therapy were recorded as described previously (Table 1).[6,22] Macrolide/azalide susceptibilities for MAC used broth microdilution according to contemporary guidelines.[19] Clarithromycin was used as the class drug for both macrolide and azalide susceptibility. We were not able to perform in vitro susceptibility studies for bedaquiline on our clinical NTM isolates because the drug was not available. Routine radiographs, chest radiographs, and CT scans were performed at baseline. Chest radiographs were performed monthly and CT scans at the discretion of the provider. Baseline CT scans were compared with CT scans performed after 6 months of bedaquiline therapy and were read independently by two radiologists.

Results

We identified 17 patients between July and December 2013 who were deemed eligible for bedaquiline therapy. Six of the 17 patients (35%) were excluded because their insurance would not pay any part of the cost for bedaquiline (Table 2). No patient without insurance coverage opted to pay for the medication out of pocket. Eleven of the 17 patients (65%) were able to obtain bedaquiline via commercial insurance. One patient died prior to starting bedaquiline therapy because of advanced MAC lung disease. Ten patients described in this report completed ≥ 6 months of therapy. Two of these patients had cystic fibrosis.

Nine of 10 patients (90%) had symptomatic improvement as defined by less cough, less sputum production, improved energy level, and/or weight stabilization or gain at 2 months of therapy (Table 3). Forty percent (four of 10) had radiographic improvement at 6 months of therapy. Twenty percent (two of 10) were deemed stable or unchanged, and 40% (four of 10) suggested worsening. Of the four patients whose CT scan appeared worse, two patients with bronchiectasis but not cystic fibrosis had intercurrent pneumonia while receiving bedaquiline therapy, requiring additional antibacterial antibiotic therapy, and two patients had cystic fibrosis exacerbations while taking bedaquiline, requiring additional antibacterial therapy. Sixty percent (six of 10) had an improvement in semiquantitative sputum culture scores at 6 months, with 50% (five of 10) having one or more negative cultures (Table 1).

Twenty percent (two of 10) had no identifiable improvement in semiquantitative sputum scores but did not exhibit increased symptoms. Sixty percent (six of 10) had GI side effects, specifically nausea, which was felt to

TABLE 1] Semiquantitative Monthly Sputum Cultures of 10 Patients on a Bedaquiline-Containing Regimen

Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3 Mab	4+	28 colonies	Negative	8 colonies	Negative	Negative	32 colonies
4 Mab	4+	4+	4+	4+	4+	4+	4+
5 MAC	4+	3+	4+	4+	4+	4+	4+
6 MAC	4+	4+	Negative	Negative	2+	4+	3+
7 MAC	4+	4+	30 colonies	Negative	Negative	...[a]	...[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

Solid media with countable colonies = 0-49 colonies; 1+ solid media growth = 50-99 colonies; 2+ solid media growth = 100-199 colonies; 3+ solid media growth = 200-299 colonies; 4+ solid media growth = ≥300 colonies. Negative indicates no bacterial growth. Mab = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex. Negative = no bacterial growth.

[a]Unable to produce sputum.

TABLE 2] Clinical and Microbiologic Characteristics of 10 Patients Treated With Bedaquiline-Containing Regimens

Patient No.	Age, y	Sex	Species Pre-Rx Culture	Macrolide Susceptibility	Radiographic Feature	Prior Drugs Used in Treatment	Companion Drugs With Bedaquiline	New Drugs Started With Bedaquiline	Duration of Prior Rx, mo	Positive AFB Cultures Prior 12 mo	Negative AFB Cultures Prior 12 mo
1	36	M	Mab species *abscessus* 4+	Resistant (*erm* gene)	Nodular	Amikacin, linezolid, tigecycline	Amikacin, linezolid, tigecycline	None	96	5	0
2	31	M	Mab species *abscessus* 1+	Resistant (*erm* gene)	Nodular	Azithromycin, tigecycline, amikacin	Azithromycin, amikacin, tigecycline, moxifloxacin	Moxifloxacin	>12	15	0
3	64	F	Mab species *abscessus* 4+	Resistant (*erm gene*)	Cavitary	Clarithromycin, moxifloxacin, azithromycin, doxycycline, amikacin	Clarithromycin, moxifloxacin, azithromycin, doxycycline, amikacin, tigecycline	Amikacin, tigecycline	43	5	1
4	65	F	Mab species *abscessus* 4+	Resistant (*erm* gene)	Nodular	Linezolid, levofloxacin, amikacin	Linezolid, levofloxacin, imipenem, amikacin	Imipenem, amikacin	27	9	0
5	58	F	MAC 4+	Resistant	Nodular	Rifabutin, ethambutol, clarithromycin, amikacin, streptomycin	Rifabutin, ethambutol, streptomycin	Streptomycin	78	4	0
6	54	M	MAC 4+	Resistant	Cavitary	Linezolid, streptomycin, ethambutol, rifabutin, amikacin, clarithromycin	Streptomycin, ethambutol, rifabutin	None	96	2	0
7	64	M	MAC 4+	Susceptible	Cavitary	Ethambutol, clarithromycin, rifampin	Ethambutol, clarithromycin, rifabutin, (streptomycin added after 2 mo)	Rifabutin	20	3	0
8	60	F	MAC 4+	Susceptible	Nodular	Ethambutol, azithromycin, amikacin (inhaled and IV)	Ethambutol, azithromycin, amikacin, rifabutin (2 wk) streptomycin	Rifabutin	25	9	0

(Continued)

TABLE 2] *(continued)*

Patient No.	Age, y	Sex	Species Pre-Rx Culture	Macrolide Susceptibility	Radiographic Feature	Prior Drugs Used in Treatment	Companion Drugs With Bedaquiline	New Drugs Started With Bedaquiline	Duration of Prior Rx, mo	Positive AFB Cultures Prior 12 mo	Negative AFB Cultures Prior 12 mo
9	65	M	MAC 4+	Resistant	Cavitary	Amikacin, moxifloxacin ethambutol, rifampin, ciprofloxacin, azithromycin, clarithromycin	Ethambutol, rifabutin, streptomycin	Streptomycin (rifampin changed to rifabutin)	13	3	0
10	73	F	MAC 30 colonies	Resistant	Cavitary	Ethambutol, amikacin, moxifloxacin, ciprofloxacin rifabutin, rifampin, azithromycin, clarithromycin	Ethambutol, rifampin, streptomycin	Ethambutol, rifampin, streptomycin	96	5	1

AFB = acid-fast bacilli; F = female; M = male; Rx = prescription. See Table 1 legend for expansion of other abbreviations.

be related to bedaquiline (Table 4). There were no cardiac-related adverse events, significantly prolonged corrected QT (QTc) interval, or significant changes in biochemistry panels. The average change in the QTc interval by 12-lead ECG testing was 4.6 ms at 1 month, 6.5 ms at 3 months, and 2.4 ms at 6 months. No patients stopped the drug because of adverse events.

Discussion

In this evaluation of patients with refractory MAC and Mab lung disease, we found a modest favorable clinical response after 6 months of therapy with a bedaquiline-containing treatment regimen. Most patients had improved sputum AFB culture results. No patient had sustained sputum conversion to AFB culture negative. Bedaquiline was generally well tolerated, the most common side effect being nausea, which occurred primarily during the initial 2 weeks of high-dose bedaquiline therapy. We found no evidence of cardiac toxicity, specifically no clinically significant QTc interval prolongation.

Although not comparable to the more dramatic results with drug-resistant TB, the microbiologic results of bedaquiline in this small cohort of patients with NTM lung disease are still promising. A major difference between MTB and NTM is that bedaquiline is bactericidal for MTB but not for MAC or Mab. A difference in treatment response for MAC and MTB in a murine model was assumed to be attributable, in part, to the difference in killing activity of the two species.[11] Another factor is that virtually all patients had been on the complimentary drugs for prolonged periods of time with minimal or no response. A final factor is the possible development of bedaquiline resistance before any clinical or microbiologic benefit could be measured.

There have been and continue to be concerns about the safety of bedaquiline for the treatment of mycobacterial diseases because of the excess mortality found in a bedaquiline treatment arm for MDR-TB.[12] These deaths have been analyzed in detail and to date, there is not a clear connection between, or a known mechanism for, the deaths and the administration of bedaquiline itself. One concern about bedaquiline has been QTc interval prolongation and the risk of sudden death. We found no significant QTc interval prolongation. All patients in this study will continue to undergo follow-up for $\geq$ 24 months after discontinuation of the bedaquiline.

Based on the in vitro data showing activity of bedaquiline against NTM, it was inevitable that there would be interest in the use of bedaquiline for patients with NTM

TABLE 3] Monthly Clinical Symptom Response of 10 Patients to a Bedaquiline-Containing Regimen

Patient No.	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1	Unchanged	Worse	Improved	Unchanged	Worse	Unchanged
2	Improved	Improved	Improved	Worse	Unchanged	Unchanged
3	Improved	Improved	Improved	Improved	Improved	Unchanged
4	Unchanged	Improved	Improved	Improved	Improved	Improved
5	Unchanged	Improved	Improved	Unchanged	Improved	Improved
6	Unchanged	Improved	Worse	Improved	Unchanged	Unchanged
7	Unchanged	Improved	Improved	Improved	Improved	Improved
8	Worse	Improved	Worse	Improved	Unchanged	Worse
9	Improved	Improved	Improved	Unchanged	Improved	Unchanged
10	Unchanged	Improved	Unchanged	Unchanged	Improved	Improved

Symptoms were compared monthly with symptoms prior to bedaquiline therapy.

lung disease. We elected to pursue bedaquiline for selected patients for several reasons. As noted, treatment-refractory MAC and Mab lung disease is statistically less likely than MDR-TB to respond to medical therapy. There are fewer drugs currently available for the treatment of MAC and Mab than for MDR-TB.

TABLE 4] Tolerability and Laboratory Findings in 10 Patients on a Bedaquiline-Containing Regimen

Tolerability and Laboratory Findings	Baseline	1 mo	3 mo	6 mo
Side effects				
Nausea	…	6	2	3
Vomiting	…	2	2	1
Headache	…	1	0	1
Stomach pain	…	3	1	2
Arthralgia	…	4	1	2
Neuropathy	…	2	2	1
Anorexia	…	3	2	2
Fever	…	3	3	2
Diarrhea	…	1	3	3
Weight loss	…	0	1	1
Insomnia	…	1	2	3
Fatigue	1	0	1	1
Dizziness	…	1	0	0
Tinnitus	…	1	0	1
Ataxia	…	1	0	1
Blurred vision	…	1	0	0
Laboratory data				
Na^+	135.1 ± 4.15	133.9 ± 5.1	135.7 ± 5.28	135.3 ± 5.17
K^+	4.23 ± 0.5	4.14 ± 0.2	4.19 ± 0.45	4.28 ± 0.34
$Mg\ 2^+$	2.12 ± 0.2	1.99 ± 0.19	1.98 ± 0.13	2.0 ± 0.17
AST	20.8 ± 5.0	26 ± 9.12	21.5 ± 3.77	22.7 ± 10.64
ALT	19.2 ± 15.54	22.44 ± 9.75	18 ± 6.53	18.9 ± 7.84
ECG data				
QTc interval	405.4 ± 20.7	410 ± 21.97	412 ± 13.28	407.8 ± 10.97
Average lengthening		4.6 ± 10.9	6.5 ± 11.7	2.4 ± 13.3

Data are presented as No. and mean ± SD. ALT = alanine transaminase; AST = aspartate transaminase; QTc = corrected QT.

Aside from inhaled liposomal amikacin, there are no drugs currently in development for MAC or Mab lung disease.[26] From a safety perspective, the cornerstone of treatment of MAC and Mab are clarithromycin or azithromycin, both known to prolong the QTc interval, and both implicated in excess mortality after short-course treatment (days).[27-29] Unfortunately, there is no established animal model for NTM lung disease, so we are left to rely on human treatment trials. Admittedly, this report does not definitively answer the risk/benefit questions about bedaquiline therapy for NTM lung disease. However, we have shown short-term safety of the drug and modest therapeutic success, both of which should support future studies.

This report has several limitations. First, we studied bedaquiline in patients with NTM lung disease who had been treated with multiple antibiotics over long time periods without success. This group of patients is notoriously difficult to treat effectively. This is an observational evaluation based on a very small cohort of patients. The report was limited by our ability to obtain the drug only for patients with insurance coverage. We reported outcome characteristics and side effects at 6 months of therapy, and the duration of patient exposure to bedaquiline could have been insufficient to detect a more favorable response. Although many patients had symptomatic improvement attributed to bedaquiline, this result could have been complicated by the aggressive overall regimen, including an aminoglycoside. We were not able to perform in vitro susceptibility studies for bedaquiline on our clinical NTM isolates, and the possibility of the development of bedaquiline resistance remains.

A variety of in vitro-acquired resistant mechanisms are reported in MTB.[30,31] Milano et al[30] report that azole resistance in MTB is mediated by the MmpS5-MmpL5 efflux system, a mutation associated with clofazimine and bedaquiline cross-resistance in MDR-TB following bedaquiline treatment.[30] The mechanisms of bedaquiline resistance in Mab and MAC have not been determined. To avoid in vitro-acquired bedaquiline resistance, we chose as many potentially effective companion agents as possible to be given with bedaquiline. Despite this precaution, it is possible that patient isolates in this series acquired bedaquiline resistance, especially cases 6 and 8, who converted their sputum and then became heavily positive again (Table 1).

All six patients with MAC also received a rifamycin (rifabutin), which is known to decrease bedaquiline levels. Rifamycins also decrease macrolide levels, which have not been shown to adversely affect MAC treatment outcome. Additionally, it is not known if TIW bedaquiline dosing is sufficient for Mab, which is treated daily with other antimicrobials. Another major limitation that makes this a preliminary study is that the serious adverse events (deaths) noted in the MTB trials in bedaquiline occurred a mean of 12 months after stopping the drug.

Conclusions

There are limited treatment options for treatment-refractory NTM cases or for those with resistant NTM isolates. IV antibiotics are an essential element for aggressive MAC lung disease treatment and a necessity for Mab lung disease treatment. Unfortunately, oral and parenteral medication options are limited in both settings. Further study is clearly required to determine whether bedaquiline has a place in the management of NTM lung disease, and if so, to guide its appropriate use.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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