Imipenem-Relebactam and Cefoxitin are Synergistic Against Clinical Isolates of Mycobacterium abscessu from People with Cystic Fibrosis.

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INTRODUCTION

- Mycobacterium abscessus (M. abs) is a group of rapidly growing, nontuberculous mycobacteria that is associated with rapid decline in lung function and shortened survival in people with cystic fibrosis (pwCF) (Illouz M et al, 2021).
- Over the last two decades, the incidence of nontuberculous mycobacteria (NTM) infections among Cystic Fibrosis patients has risen from 3.3% to 22.6%, (Degiacomi G et al, 2019).
- M. abs. is intrinsically resistant to many antibiotics, making it hard to treat.
- The current guidelines recommend a parental drug or a Oral Drug for the initial phase and 2 or more drugs for the continuation phase. Treatment can last up to 18 months.
- IMI/REL was found to be an effective and well-tolerated therapy for imipenem-non-susceptible bacterial infections (Hoffman, 2018).
- At the time of the study, there has been no research done on Imipenem/Relebactam with clinical isolates of m. abs from people with Cystic Fibrosis (pwCF). There is also no synergy studies on Imipenem/Relebactam with clinical isolates of m. abs from pwCF.

OBJECTIVES and AIMS

- This study will test the susceptibility of clinical isolates of m. abs from patients with cystic fibrosis with Imipenem/relebactam and other selected antibiotics.
- This study will also evaluate if Imipenem/relebactam can be synergistic with other antibiotics against clinical isolates of m. abs from people with cystic fibrosis.

METHODS

- Susceptibility and synergy studies were done using CSLI methods.
- Clinical isolates of M.abs from pwCF were used (n=29).
- Antibiotics were picked based on if they had oral or inhaled forms which may be more accessible to patients who have cystic fibrosis. Antibiotics that were used were also selected over previous data which may suggest synergistic effects with Imipenem.
- A lab isolate was used (ATCC19977) for comparison in both the susceptibility and synergy testing.
- For synergy MIC values, the MIC values displayed on the chart are a result of calculating the average value of the MIC seen on the plates
- Synergy was determined using the fractional inhibition concentration index equation.
- Synergy was defined by the fractional inhibition concentration index < 0.5, additive if between 0.5-4, and Antagonistic if >4.
- In all the assays, relebactam was fixed at 5ug/ml.

RESULTS

Cefoxitin MIC Results

Strain	MIC (ug/ml)
ATCC 19977	32
Isolates MIC 50	32
Isolates MIC 90	128

Table 1. Cefoxitin Susceptibility Results

Synergy Results

Drugs	Median MIC of drug alone (ug/ml)	Median MIC of drug with IMI/REL (ug/ml)	Median MIC of IMI/REL alone (ug/ml)	Median MIC of IMI/REL with drug (ug/ml)	FIC index	
Cefuroxime	512	64	4	0.375	0.21875	Synergistic
Cefdinir	192	24	4	1	0.38	Synergistic
Cefoxitin	48	8	8	2	0.42	Synergistic
Amoxicillin	2048	128	8	2	0.31	Synergistic
Rifabutin	8	2	4	1	0.5	Synergistic
NITD-916	2	0.5	8	1	0.38	Synergistic
Azithromycin	8	2	8	2	0.5	Synergistic
Moxifloxacin	16	4	6	2	0.58	Additive
Minocycline	256	96	4	2	0.88	Additive
Clofazimine	1	0.5	8	2	0.75	Additive
Omadacycline	2	1	8	4	1	Additive

Table 2. IMI/REL Synergy Results with Clinical Isolates

Intracellular Data

Drugs	Cmax (ug/ml)	Clinically achievable	Intracellular penetration
Cefuroxime	2.1-13.6	NO	LOW
Cefdinir	1.6-2.87	NO	LOW
Cefoxitin	110	YES	LOW
Amoxicillin	3.92-11.21	NO	MODERATE
Rifabutin	0.375	NO	VERY HIGH
NITD-916	-	NO	-
Azithromycin	0.5	NO	HIGH
Moxifloxacin	3.1	NO	VERY HIGH
Minocycline	2.63	N0	MODERATE
Clofazimine	0.9	YES	VERY HIGH
Omadacycline	1.507	YES	MODERATE

Table 3. Intracellular Concentration Data

CONCLUSIONS

- ✓ Cefoxitin had an MIC50 of 32 and MIC90 of 128.
- ✓ Based on the data collected, Moxifloxacin, Minocycline, Clofazimine, and Omadacycline were found to be additive with the samples.
- ✓ Cefuroxime, Cefdinir, Cefoxitin, Amoxicillin, Rifabutin, NITD-916, and Azithromycin were found to be synergistic with the samples.
- ✓ Cefoxitin, Clofazimine, and Omadacycline are clinically achievable based on their Cmax values. Among these, Cefoxitin is the only drug that is synergistic based on the experimental data
- ✓ Based on the results so far, IMI/REL and Cefoxitin would be beneficial, along with a third drug that has better intracellular penetration such as Azithromycin, Moxifloxacin, or Rifabutin
- ✓ Future research would look into three drug synergistic combos
- ✓ This research can aid future treatment guidelines of M. abs infections in pwCF.

CHALLENGES AND LIMITATIONS

- M. abs is a slow growing organism and takes several days to grow.
- Experiments took days, had to come in weekends to complete.
- Work is done in a BSL2 Lab, a specially certified lab. Special precautions had to be put in place.
- There was 29 samples to test with. When doing synergies in combinations, this created over 348 experiments (not including samples that had to be redone).
- Could only do 3-4 synergies at a time, which took 4 hours to do each time.

FUTURE RESEARCH

- Complete susceptibility and synergy on all clinical isolates (n=29)
- Three drug combination studies.
- Intracellular killing activity studies
- Invivo studies

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