2276. Evaluation of Ceffaroline-Avibactam Activity in vitro and ex vivo Against Mycobacterium abscessus Complex

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Background. M. abscessus complex strains are increasingly identified from immunosuppressed hosts, including those patients with cystic fibrosis and those undergoing transplantation. However, the treatment of M. abscessus infections is complicated as a result of its intrinsic resistance to antituberculous agents and its acquisition of multidrug resistance. Here, we used whole genome sequencing (WGS) coupled with in vitro (79H) and ex vivo (THP-1 cells) susceptibility studies to explore the activity of ceffaroline (CPT) and imipenem (IMI), alone, or in combination with avibactam (AVI). Methods. In a clinical study, 25 M. abscessus complex strains were compared by whole genome sequence analysis, and tested in vitro for susceptibility to CPT and IMI with or without AVI. Using a broth microdilution assay with 7H9 media, a range of drug concentrations from 0.25 to 128 µg/mL was evaluated with and without AVI. Additionally, the MIC of AVI was 4 µg/mL. On the basis of the MIC findings, we also analyzed the bactericidal activity of drug combinations against four clinical isolates (3 M. abscessus and 1 M. bolletii) in human THP-1 cells at an MOI of 1 organism to 10 cells. Bacteria were enumerated at 0, 24h, 48h and 72h post infection.

Results. WGS results distinguished the 25 M. abscessus complex into three clusters as M. massiliense, M. bolletii, and M. abscessus. Additionally, up to 16 amino acid substitutions were identified in the AmpC (bla_blaCC) gene. CPT MICs ranged from 0.5 to 128 µg/mL, but the MIC range was dramatically lowered to <0.125–16 µg/mL in the presence of AVI. IMI activity, in vitro, alone or in combination with AVI ranged from 0.5 to 16 µg/mL. Activity of CPT with AVI in THP-1 cells correlates with the in vitro activity against all 4 clinical isolates, while the activity of IMI with AVI in THP-1 cells was strain dependent. Increasing concentrations of AVI was active against one strain and had no effect on another strain. Conclusion. Our findings indicate that the in vitro activity of CPT in combination with AVI is predictive for ex vivo activity in human THP-1 cells and this combination may prove to be an effective regimen in treating infections caused by M. abscessus complex.

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2277. Clofazimine for Treatment of Mycobacterium abscessus Infections in Children

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Background. Mycobacterium abscessus infections are increasingly common and can be challenging to treat due to antimicrobial resistance. Clofazimine (CFZ), which is commonly used for treatment of leprosy, comes as a 50 mg capsule that must be swallowed whole. We evaluated in vitro activity against M. abscessus but there are limited reports of its use, particularly in children. During a healthcare associated outbreak of M. abscessus odontogenic infections, 27 children were treated with a CFZ containing regimen for several months.

Methods. Data was collected on all children who received CFZ for a proven or possible M. abscessus odontogenic infection via a Food and Drug Administration Investigational New Drug Application. Demographic, diagnostic and therapeutic information was evaluated, as were laboratory results, adverse events and clinical outcomes.

Results. Of 27 children who received CFZ, 13 were male, 22 were Hispanic and mean age at initial dosing was 5.8 years (range 3.0 – 9.4 years). Patients also received anti-infectives (rifampin or cefazolin) for a NTM was stopped an average of 31 days after CFZ started. All 27 children had osteomyelitis of the jaw and received aggressive surgical debridement; 10 had a positive stain for acid-fast bacilli (AFB) and 14 had a positive AFB culture (13 M. abscessus, 1 M. chelonae). CFZ was present in 16 children and granulomatus lymphadenitis (requiring surgery in 10. Patients received a mean of 105.6 total days of CFZ therapy (range 84–164 days) with a mean weekly dose of 7.6 mg/kg and with dosing occurring on a mean of 3 days a week. Every child was able to swallow the CFZ capsule. Minor skin discoloration was noted in 6 children, dry skin in 17, and gastrointestinal symptoms in 11. No child had a clinically significant change in corrected QT interval. All children showed evidence of jaw healing and resolution of lymphadenitis at the end of therapy, and 14 had resolved or improving lung nodules.

Conclusion. This the largest report of children receiving clofazimine for reasons other than leprosy. It is also the largest report of clofazimine use for extra pulmonary M. abscessus infections. Clofazimine appears to be safe in children and may be an effective part of a surgical and multi-drug regimen for M. abscessus infection.

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2278. A Randomized Controlled Trial of Anti-TNF a Bio-similar Adalimumab vs. Prednisolone in the Management of Leprosy Patients with New Type I Lepra Reaction

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Background. Leprosy Type 1 (T1) reactions are immune-mediated events leading to nerve damage and preventable disability affecting hands, feet and eyes. TNF-a is the main inflammatory cytokine associated. Type 1 Reactions are treated with oral corticosteroids. There is little evidence on alternative treatments for patients who do not respond to steroids or experience steroid adverse effects. We report the results of a randomized controlled trial testing the efficacy and adverse effect profile of Anti-TNF a Bio-similar Adalimumab and prednisolone in comparison to prednisolone only in patients with new T1R. Outcomes were measured using a clinical severity score, recurrence rate, adverse events and quality of life.

Methods. Seventy-three patients with new T1R were randomized to receive Adalimumab or Prednisolone for 20 weeks. TNF-a levels were correlated before and after the intervention. Results. Recovery rates in skin signs was similar in both groups (91% vs 88%). Improvements in nerve function both, new and old, sensory (66% vs 49%) and motor (75% vs 74%) loss were higher (but not significantly so) in the patients on Adalimumab. Recurrence rates of T1R (85%) were high in both groups, and recurrences occurred significantly earlier (8 weeks) in patients Adalimumab, who needed 10% more additional prednisolone than Adalimumab as compared with Prednisolone alone. Both groups had a significant improvement in their quality of life after the study, measured by the Short form survey SF-36.

Conclusions. This is the first double-blind RCT assessing adalimumab, in the management of T1R. It could be a safe alternative second-line drug for patients with T1R who are not improving with prednisolone or are experiencing adverse events related to prednisolone. TNF-a levels could be an important diagnostic marker to diagnose and prognosticate case for Type I Lepra reaction, which if not treated in time can lead to irreversible nerve damage.

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2279. Nontuberculous Mycobacteria Isolates at a Cancer Center: A 5-year Experience at H. Lee Moffitt Cancer Center in Tampa, Florida

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Background. Nontuberculous Mycobacteria (NTM) are widely distributed in natural environments and are known to cause human diseases distinct from tuberculosis. NTM caused diseases may lead to significant morbidity and mortality, particularly in immunocompromised hosts such as cancer patients. We present here a 5-year experience of NTM isolates at the Moffitt Cancer Center and research institute in Tampa, Florida.

Methods. We conducted a single center, retrospective study of patients with NTM from January 2011 to February 2016. Records were searched to identify patients with NTM. Specimens included bronchial lavage, swabs, blood, body fluids and biopsy or excised surgical specimens. Basic demographics of patients, clinical attributes, presentation and sites from which the NTM were isolated and associated necrotic or plastic lesions were tabulated for each NTM type and category.
Results. There were a total of 208 isolates of NTM during the 5-year study period. 86/208 (41%) of the isolates were Mycobacterium avium complex (MAC). Mycobacterium abscessus, gordonae and fortuitum accounted for 26%, 11% and 6% of the top four isolates respectively. There was no significant difference in types of NTM isolated based on the type of underlying neoplasm. Over half of the cases were from the respiratory tract, majority with lung nodule referred to rule out cancer. Skin/ wound isolates accounted for 13% (majority from breast lesions) and blood/serologic diagnosis accounted for 7% of the isolates. Average age of patients was 68 ± 11 years, 92% were US born and over 70% had smoking history.

Conclusion. NTM isolated in a referral cancer center setting are likely to be from the work up of PET positive pulmonary nodules and the majority isolates were MAC, followed closely by M. abscessus. With high level of resistance and few therapeutic options, the rise of M. abscessus pulmonary diseases is cause for concern. Even though the respiratory tract was the most common site of NTM isolation, we did not find association between types of NTM and a given neoplasm. Our finding may have been confounded by referral pattern to our center and the retrospective design. Future studies that lead to improved testing and scoring algorithms for NTM could reduce the rate of surgical excision of pulmonary nodules.

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2280. Potts’ Disease Caused by Mycobacterium bovis Following Intravesical BCG Therapy for Bladder Cancer
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Background. Bacillus Calmette-Guerin (BCG) are attenuated strains of Mycobacterium bovis, which is part of the Mycobacterium tuberculosis complex. BCG is used for bladder cancer therapy.

Case/Methods. 80 year old man presented with severe back pain, paraplegia, urinary retention. Past history included rheumatoid arthritis, bladder cancer. He was diagnosed with recurrent bladder cancer (T1, high grade lamina propria superficial invasion) in June 2016 (previously diagnosed 14 years ago, treated with BCG). Patient had tranurethral resection of tumor in August 2016, after which he got 6 weekly cycles of intravesical BCG. He underwent cystoscopies with no evidence of residual disease. No history of concurrent illness during therapy.

He was initially admitted 1 month ago with back pain: MRI showed thoracic (T6-T7) epidural abscess, vertebral osteomyelitis/diskitis; he underwent T6-T7 hemilaminectomy, drainage of abscess, cord decompression. Operative cultures were initially negative. He was discharged with empiric broad spectrum antibiotics. Repeat MRI during this admission showed extensive inflammation at T6-T7: diskitis, osteomyelitis, epidural abscess, more non enhancing material in the disc space, progressive edema in pedicles and lamina, worse cord compression. Neurosurgery evaluated patient deemed to be poor surgical candidate given his extensive comorbidities, advanced age. His operative AFB cultures turned positive 4 weeks after surgery (MTB complex by DNA probe). Therapy started with Isoniazid, Rifampin, Ethambutol, Pyridoxine, Dexamethasone. The isolate was sent to state lab: whole genome sequencing showed M. bovis BCG strain. Susceptibility testing is pending.

Discussion/Results. BCG therapy of superficial bladder cancer is a recommended treatment modality. Early infectious complications occur within 3 months, late infections after 1 year. In >2000 patients treated with BCG, infectious complications occurred in ~5%. Potts disease following BCG therapy is rare but has been described; the time of onset can be from 14 days to 12 years after therapy.

Conclusion. In patients treated with BCG for bladder cancer, clinicians must have a high index of suspicion for infectious complications, as early initiation of therapy yields better outcomes.

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2281. Treatment Regimens Prescribed for Mycobacterium avium complex Infections Diagnosed in Hospitalized Patients throughout the United States, 2008–2013
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Background. Nontuberculous mycobacteria (NTM) are associated with human lung disease, with 80% of cases caused by Mycobacterium avium complex (MAC). American Thoracic Society (ATS)-led treatment guidelines exist for MAC (macrolide/ethambutol/rifampycin), although studies suggest poor concordance with clinician practice. Using a national database of hospitalized patients with MAC isolated, we sought to characterize US treatment practices and trends.

Methods. Linked demographic and microbiological data from Premier Healthcare Database were extracted for all inpatient encounters from 2009 to 2013. Patients with ≥1 positive MAC culture were identified as cases; concomitant pathogens were also identified. Antibiotics ordered within 3-months post-positive culture were evaluated. Regression models were used to estimate the relative risk (RR) for factors associated with receiving an ATS regimen or macrolide monotherapy.

Results. Of 3629 MAC cases, 2285 (63%) received an evaluated antibiotic regimen. Most (59%) were treated with a quinolone-based regimen, and 481 (21%) received an ATS regimen. Concordance with ATS guidelines improved over time from 12% in 2009 to 20% in 2013, peaking in 2012(23%). Concordance was highest at facilities in the South (24%) and lowest in the Midwest (13%). Regimens associated with macrolide resistance were given to 160 (7%) cases, including macrolide monotherapy (4%). Guideline concordance was 69% more likely in the South (RR: 1.6, P = 0.01) and 5-fold greater among those who received initial tuberculosis-specific therapy (isoniazid/pyrazinamide, RR: 4.7, P < 0.01). Cases in the Northeast (RR: 2.3, P = 0.02) and without co-infection (only MAC isolated) (RR: 1.7, P = 0.05) were more likely to receive macrolide monotherapy.

Conclusion. Prescribing concordance with ATS guidelines increased over time. However, regimens associated with macrolide-resistance are still ordered nationally. Clinicians managing hospitalized patients with suspected MAC infections should avoid use of regimens associated with macrolide resistance, which can result in worse clinical outcomes.

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Figure 1. Treatment regimens prescribed among a national cohort of inpatients with MAC isolated by co-infection status.

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