1633. Improving the diagnosis of extra-pulmonary tuberculosis (EPTB): experience from north India

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Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. Rapid and accurate diagnosis of extra-pulmonary tuberculosis (EPTB) is imperative for early treatment and better patient outcome. Loop-mediated Isothermal Amplification (LAMP) is a promising nucleic-acid amplification assay. LAMP assay could be carried out in simple water bath under isothermal conditions in 60 minutes, and can be performed in any laboratory even in rural setting in resource poor endemic countries. We evaluated LAMP assay using two different target regions LAMP primers specific for *Mycobacterium tuberculosis* complex for the diagnosis of EPTB.

Methods. LAMP assay using 6 primers (each for *IS*6110 and IS1081) specific for *Mycobacterium tuberculosis* complex were performed on patients suspected of EPTB on various EPTB samples(CSF, Synovial fluid, Lymaphnode and tissue biopsies and various other samples) of 150 patients (50 confirmed, 100 suspected) Clinically suspected of EPTB and 100 non-TB control subjects.

Results. Overall LAMP test (using any of the two targets) had sensitivity and specificity of 96% and 100% for confirmed (50 culture positive) EPTB cases. In 100 clinically suspected but unconfirmed EPTB cases, LAMP was positive in 87 out of 100 cases (87%). Sensitivity of *IS*6110 LAMP, 1S1081 LAMP and *IS*6110 PCR for clinically suspected cases was 78 (78%), 84 (84%) and 70 (70%), respectively. In total 150 EPTB patients, the overall sensitivity of microscopy, culture, *IS*6110 PCR, *IS*6110 LAMP, 1081 LAMP and the LAMP test (if any of the two targets were used) were 4%, 33.3%, 74.6%, 82.66%, 87% and 92%, respectively. Specificity of all the tests was 100%. There were 8 cases which were missed by *IS*6110 LAMP and 2 cases by 1081 LAMP.

Conclusion. LAMP assay using two targets is a promising technique for rapid diagnosis of EPTB in 60 minutes especially in a resource poor setting who are still battling with this deadly disease.

Disclosures. **All Authors**: No reported disclosures

1634. Meningeal Tuberculosis: Experience of a Series of Cases from Cali, Colombia, 2008 - 2018

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Grupo de Investigación en Tuberculosis, Fundación Valle del Lili- Universidad Icesi (GITB)

Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. Meningeal tuberculosis (MTB) is the most lethal and disabling form of Mycobacterium Tuberculosis infection. In Colombia, it represents the second most frequent extrapulmonary location. Co-infection with the Human Immunodeficiency Virus (HIV) is one of the factors that most impacts their clinical results. Therefore, in this article we present the experience of 10 years of managing patients with MTB, with and without HIV coinfection.

Methods. A retrospective observational study was conducted between January 2008 and December 2018, with clinical information from patients diagnosed with MTB at Teaching Hospital Fundación Valle del Lili. Using absolute and relative frequency tables, sociodemographic, clinical characteristics and treatment outcomes were described, according to HIV infection status. P values < 0.05 were taken as significant and 95% confidence intervals were used for comparison of proportions.

Results. 61 patients with MTB diagnosed were enrolled. They represented 6.43% of all TB locations in the institutional registry. HIV coinfection was found in 26.2% of cases (n=16). Most of patients were men (65.6%), from urban areas (78.7%), and a median age of 39 years. Acute and subacute evolution of the infection was observed in half of the patients (50.8%). Also 85% presented some degree of neurological impairment. Bacteriological demonstration was achieved in 60.6% of all cases. 88% received drugs for sensitive TB, for a median of 9.5 months, and 52.5% received concomitant steroids drugs. Of the 36 subjects with information about their outcome, 42.6% were successful at treatment, 1 failed in the non-HIV group and 9 died (1 with HIV). 77% of all deaths were associated with TB.

Conclusion. MTB generates a significant burden disease. The characteristics of its insidious clinical presentation and the difficulty in achieving bacteriological demonstration in all patients make its timely diagnostic and therapeutic approach challenging.

Disclosures. **All Authors**: No reported disclosures

1635. Oral Delivery of Amikacin-Lipid NanoCrystal Formulations Safely and Effectively Treat Macrolide Resistant *Mycobacteria* Infections in a Mouse Model of Cystic Fibrosis

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Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. In the cystic fibrosis lung, infections by intracellular pathogens, such as Mycobacteria, are problematic to treat due to a thick buildup of mucous as well as the difficulty of many anti-microbial agents, such as amikacin, to penetrate across the plasma membranes of infected cells. Lipid NanoCrystals (LNCs), mediate oral bioavailability for injectable drugs, reduce toxicity, and significantly enhance targeting to mycobacterial infected cells followed by intracellular drug delivery.

Methods. The oral efficacy of Amikacin-LNC (AmK-LNC) was evaluated in the cystic fibrosis (B6CFTR^{tm1UNC}/CFTR^{tm1UNC}) chronic mouse model against each of the three NTM strains having high resistance to macrolide antibiotics (*M. avium subsp intracellulare* 25292, *M. abscesus ssp abscessus* 1513, and *M. abscessus ssp bolletii* 1948). Mice were infected with a pulmonary aerosol of 1x10^8 CFUs of the macrolide resistant strain and treated daily starting on day 28 for a total of 8 weeks with saline control, oral LP-4 CAmK Lyophilized 50 mg/kg BID, oral LP-4 CAMK Lyophilized 100 mg/kg BID, IP Amikacin (AMI) 150 mg/kg QD, or oral Clarithromycin 250 mg/kg QD. Bacterial burden was measured on day 1, 27, 42, 56 and 84 after infection by plating serial dilutions of organ homogenates on nutrient 7H11 and charcoal agar and counting CFUs after 25-30 days incubation at 32°C. Results represent the average of six experiments (n=5 mice per experiment) bacterial load was expressed as the average Log_{10} CFU (± SEM) cells (± SEM). ANOVA, saline control compared to drug-treated groups, * denotes the compound that resulted in the highest bacterial reduction, *p< 0.05.

Results. Oral administration of AmK-LNCs safely and effectively treated all three macrolide resistant Mycobacteria infections. Colony counts showed that oral administration of AmK-LNC resulted in CFU lung, spleen and liver counts lower than treatment with IP amikacin or clarithromycin.

Lung pathology showed that lesions were more numerous and larger in infected mice treated with clarithromycin or amikacin compared to the smaller lesions after treatment with oral AmK-LNC.

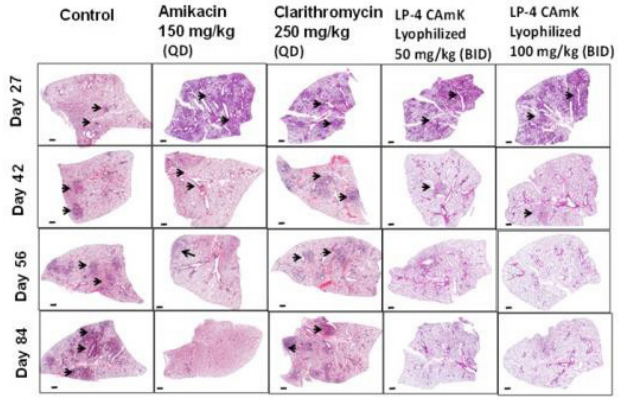
Bacterial Counts in the Lungs (A), Spleens (B) and Livers (C)

Bacterial counts in the lungs (A), spleens (B) and livers (C) of B6CFTR^{tm1UNC}/CFTRtm^{1UNC} mice infected with a pulmonary aerosol of 1x10^8 CFUs of a macrolide resistant strain of *M. abscessus* subspecies *abscessus* 1513

Group	Lung	Spleen	Liver
	Log10 CFU ±SEM	Log10 CFU ±SEM	Log10 CFU ±SEM
Day 1 Pretreatment Control (n=5)	5.87±0.03	5.83±0.04	6.01±0.01
Day 27 Pretreatment Control (n=5)	6.10±0.02	6.01±0.02	6.01±0.01
Day 42 Control (n=5)	6.21±0.18	6.18±0.17	6.16±0.03
IP Amikacin (AMI), 150 mg/kg QD (n=5)	4.85±0.22	4.96±0.09	4.90±0.08
Oral Clarithromycin 250 mg/kg QD (n=5)	6.33±0.11	6.30±0.04	6.38±0.08
Oral LP-4 CAmK Lyophilized 50 mg/kg BID (n=5)	5.19±0.04	5.23±0.03	5.20±0.01
Oral LP 1-4 CAmK 100 mg/kg BID (n=5)	4.10±0.08	4.13±0.06	4.15±0.07
Day 56 Control (n=5)	6.82±0.03	6.59±0.50	6.51±0.07
IP Amikacin (AMI), 150 mg/kg QD (n=5)	4.86±0.79	5.06±0.18	5.09±0.05
Oral Clarithromycin 250 mg/kg QD (n=5)	6.80±0.67	6.64±0.48	6.73±0.60
Oral LP-4 CAmK Lyophilized 50 mg/kg BID (n=5)	4.72±0.02	4.97±0.12	4.93±0.10
Oral LP 1-4 CAmK Lyophilized 100 mg/kg BID (n=5)	3.76±0.17	3.86±0.07	3.81±0.08
Day 84 Control (n=5)	7.20±0.02	6.84±0.48	6.87±0.46
IP Amikacin (AMI), 150 mg/kg QD (n=5)	3.79±0.21	4.01±0.20	4.13±0.13
Oral Clarithromycin 250 mg/kg QD (n=4)	7.20±0.03	6.94±0.24	6.89±0.50
Oral LP-4 CAmK Lyophilized 50 mg/kg BID (n=5)	4.05±0.26	4.34±0.31	4.40±0.26
Oral LP 1-4 CAmK Lyophilized 100 mg/kg BID (n=5)	3.20±0.19	3.36±0.28	3.34±0.20

Lung Pathology

Lung pathology in cystic fibrosis mice infected with a macrolide resistant strain of *M. abscessus* subspecies *abscessus* 1513. Sections of Formalin-fixed and paraffin-embedded lung tissue on days 27, 42, 56 and 84 after drug treatment were compared. Lesions (arrow) were more numerous and larger in infected mice that were treated with clarithromycin, and amikacin compared to the smaller lesions after treatment with **oral** LP-4 CAmK Lyophilized 50 mg/kg and **oral** LP-4 CAmK Lyophilized 100 mg/kg.



Conclusion: Conclusions

Oral administration of amikacin-LNCs safely and effectively treats macrolide resistant mycobacterial infections in a mouse model of Cystic Fibrosis.

Disclosures. Ruying Lu, n/a, Matinas BioPharma Inc. (Employee)Matinas BioPharma Inc. (Employee, Shareholder) Raphael J. Mannino, n/a, Matinas BioPharma Inc. (Employee, Shareholder)

1636. Risk of Latent Tuberculosis Reactivation in Patients Treated with Checkpoint Inhibitors Immunotherapy Compared to Other Anti-Cancer Therapies including Hematopoietic Cell Transplantation

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Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. The risk of latent tuberculosis infection (LTBI) reactivation in cancer patients during checkpoint inhibitor immunotherapy (CPI) remains largely unknown. We sought to evaluate LTBI therapy and outcomes between cancer patients receiving CPI versus conventional chemotherapy (CC) and hematopoietic cell transplantation (HCT) recipients.

Methods. We conducted a retrospective cohort study of adult patients with LTBI (positive T-SPOT TB test) at MD Anderson Cancer Center between April 2016 and May 2020, who received CPI or combined with other conventional chemotherapy. Thereafter we compared each group to patients treated with other anti-cancer therapies including CC alone or HCT.

Results. We identified 106 patients with LTBI, who were analyzed into 3 distinct groups: CPI (32 patients, 30%) CC alone (37 patients, 35%), and HCT (37 patients, 35% (7 autologous versus 30 allogeneic). The majority of patients in the CPI group (97%) had solid tumors compared to 54% in the CC group. Nivolumab was the most commonly used CPI agent in 13 patients (40%), followed by pembrolizumab 10 pts (31%). In the CPI group, 20 pts (62%) received LTBI therapy that included Isoniazid (INH), versus 18 patients (49%) in the HCT group and 16 patients (43%) in the CC group (p=0.26). Only 3 patients (CC group) had TB reactivations (8%; p=0.11). None of these 3 patients had received LTBI therapy or corticosteroids prior to the diagnosis. Immune-related adverse effect (IrAEs) were reported in 11 pts (34%) patients, and 9 (82%) of them received corticosteroids. Out of 20 of CPI patients whom received INH, 4 (20%) developed possible INH-induced liver toxicities leading to interruption of medication versus 1 (6%) patient which had mild hepatitis in CC group versus none of HCT patients (p=0.09).

Conclusion. Our data suggest that latent tuberculosis reactivation remains rare, especially in the severely immunocompromised patients on CPI, CC and steroids. However, hepatotoxicity is relatively common in patients treated with CPI and INH. Therefore, caution and close laboratory and clinical monitoring is required to avoid significant hepatic injury and interruption of LTBI therapy and lifesaving oncological therapy.

Disclosures. **Issam I. Raad, MD**, **Citius** (Other Financial or Material Support, Ownership interest)**Cook Medical** (Grant/Research Support)**Inventive Protocol** (Other Financial or Material Support, Ownership interest)**Novel Anti-Infective Technologies** (Shareholder, Other Financial or Material Support, Ownership interest)

1637. SPR720, A Novel Benzamidazole Gyrase Inhibitor, Demonstrates Potent Efficacy Against Mycobacterium avium ATCC 700898 in a Chronic C3HeBFeJ Mouse Infection Model

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Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. SPR719 (the active metabolite of phosphate prodrug SPR720) belongs to a novel class which targets the ATPase subunits of gyrase by a mechanism distinct from fluoroquinolones. SPR719 has potent antibacterial activity against nontuberculous mycobacteria strains (NTM), including *Mycobacterium avium*, and is under development for treatment of NTM pulmonary disease. Oral efficacy of SPR720 was evaluated alone and in combination treatment in the C3HeBFeJ chronic mouse infection model which produces necrotic granulomas, similar to humans.

Methods. Mice were infected with a pulmonary aerosol of $1x10^{8.5}$ CFU of *M. avium* ATCC 700898, (SPR719 MIC = 2 mg/mL). Treatment started on day 28 for 8 weeks with: saline, clarithromycin 250 mg/kg (CLR) QD, SPR720 at 10, 30 and 100 mg/kg QD, or SPR720 at 50 mg/kg BID. SPR720 at 30 mg/kg QD was also combined with CLR +/- ethambutol at 100 mg/kg (EMB), or CLR + rifabutin at 100 mg/kg (RFB) +/- EMB. Mice were evaluated for bacterial burden (CFU) on days 1, 27 and 60 after infection by plating serial dilutions of organ homogenates on nutrient 7H11 and charcoal agar plates. Lung pathology was evaluated by assessing prevalence and size of pulmonary lesions.

Results. CLR treatment for 28 days showed a significant reduction in the bacterial burden in the lung, spleen, and liver compared to the untreated control. SPR720 demonstrated a dose dependent reduction in bacterial burden, including at 100 mg/kg which showed a statistically significant reduction in the bacterial burden in the lung, spleen, and liver. CLR + EMB + SPR720 at 30 mg/kg reduction in the bacterial burden in the lung, spleen, and liver. RFB when added to the treatment regimen did not demonstrate enhanced efficacy compared the additive effect of EMB + CLR +/- SPR720. Lung pathology showed that lesions were less numerous and smaller in infected mice treated with all regimens.

Conclusion. Oral administration of SPR720 demonstrated a statistically significant reduction in the bacterial burden in all tissues with concomitant improvement in lung pathology, both alone and in combination with standard of care agents. These results support the continued development of SPR720 for treatment of NTM pulmonary infections.

Disclosures. Nicole S. Cotroneo, BS, Spero Therapeutics (Employee, Shareholder) Suzanne Stokes, PhD, Spero Therapeutics (Employee, Shareholder)

1638. Synchronous Video Observed Therapy for Monitoring Treatment of Tuberculosis: Experience in a Cases Series from Cali, Colombia, 2019

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Grupo de Investigación en Tuberculosis Fundación Valle del Lili - Universidad Icesi (GITB)

Session: P-72. Tuberculosis and other Mycobacterial Infections

Background. In Directly Observed Treatment (DOT) monitoring strategy for the treatment of tuberculosis (TB), the patient has to travel daily to the health institution to take the TB medication. Although has been usefulness, this strategy increases the catastrophic costs of the disease, rising the probability of rejection, abandonment, and failure to treatment. Therefore, a monitoring strategy was implemented through video calls phone known as Synchronous Video Observed Therapy (S-VOT), to document the experience and its results in a series of patients from a low-middle income country.

Methods. A prospective case series study was conducted involving 23 TB patients managed with standard treatment, who were supervised through daily video call phone, during 2019, Cali-Colombia. Adherence to VOT strategy and treatment were evaluated, as well as patient characteristics, adverse drug effects, perception and