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ABSTRACT BOOK

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PC-396-01 Effects of high-dose vitamin D in patients with pulmonary tuberculosis in Tbilisi, Georgia

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Background: Patients with tuberculosis (TB) are commonly vitamin D deficient, which may impact immunity. We investigated whether high-dose oral vitamin D3 enhances the efficacy of anti-TB drugs in treatment of pulmonary TB.
Design/methods: Double blind, randomized, controlled, intent-to-treat (ITT) trial in adults with pulmonary TB in Tbilisi. Subjects were randomized to vitamin D3 (1 400 000 IU in divided doses) or placebo for 16 weeks concomitant with standard anti-TB drugs [RIPE] through directly observed therapy. Sputum AFB cultures (LJ) were performed at weeks 0, 2, 4, 6, 8, 12 and 16. Cox proportional analysis was used for the primary outcome (time to culture conversion).
Results: A total of 784 subjects were screened, with 585 excluded (345 met exclusion criteria; 240 declined to participate). Of 199 patients enrolled, 100 were randomized to receive vitamin D3 and 99 to receive placebo. The majority of subjects (>85%) were vitamin D deficient at entry [serum 25-hydroxyvitamin D [25(OH) D] < 50 nmol/L]. Baseline characteristics were similar between groups at entry. With vitamin D3, serum 25(OH) D levels peaked at 250 nmol/L at 8 weeks and decreased to 160 nmol/L by week 16. High-dose vitamin D treatment was safe, with similar adverse events and no differences in serum calcium levels between groups. A total of 192 subjects with sputum culture-confirmed TB were included in modified ITT efficacy analysis. A total of 23 (12%) had confirmed multi-drug resistant TB [MDR-TB; 12 vitamin D, 11 placebo]. Culture conversion rates were similar between vitamin D and placebo groups at 8 weeks and over time (HR = 0.84, 95%CI 0.62–1.15). However, the MDR-TB cohort showed enhanced culture conversion with vitamin D vs. placebo at 8 weeks (vitamin D3 88% vs. placebo 40%; P = 0.03) and over time (P = 0.02).
Conclusions: This regimen of vitamin D3 treatment was safe, but did not improve TB clearance in the overall cohort of TB patients. However, patients with MDR-TB randomized to vitamin D administration demonstrated a shorter time to culture conversion. Additional trials on the efficacy of high-dose vitamin D in MDR-TB patients are warranted.

PC-397-01 Could the common anti-inflammatories be the new coadjuvant treatment against tuberculosis?

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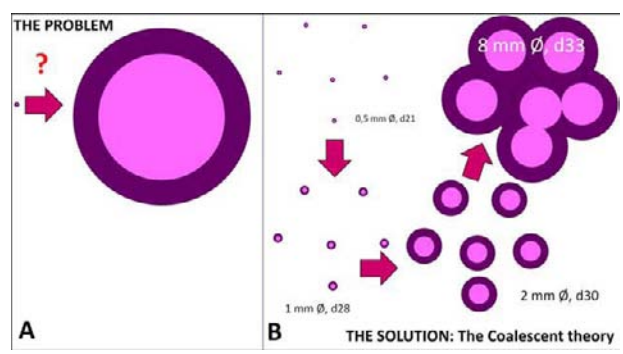
Background: Trying to discern the transformation of latent TB into cavitation in the lung has let us to the discover of ibuprofen as a clue treatment and prevention against TB. As seen in the minipig model, the lesions in LTBI are characterized by an early encapsulation because of the septae wich structure the lungs in big mammals (GilPLOSOne_2010_TB_minipigs). In this scenario the development of cavitary lesions—which requires a minimal size of 20 mm—appears to be impossible. In this process, the softening of the necrotic tissues appear to be paramount, and that's why—recalling previous experiences with SCID mice model treated with Ab (Guirado, Passive Serum Therapy, MicInfect 2006)—we looked after different necrotic models in mice, as C3HeB/FeJ.
Design/methods: Mice were intravenously infected with 2×10^4 *M. tuberculosis* H37Rv Pasteur. The histopathology, immune response, bacillary load and survival were evaluated. Anti-inflammatory treatments and C3H/HeN mouse strain were used to complete the characterization.
Results: Massive intra-alveolar neutrophilic infiltration related to the peripheric dissemination of infected foamy macrophages lead to the rapid growth of the granulomas. A central necrotic area appeared when they overpassed a certain size. This center evolved towards a progressive cellular destruction, the alveoli cell walls initially being conserved (caseous necrosis) but finally destroyed (liquefactive necrosis). From day 28 and on, lesions tended to coalesce into superlesions. The anti-inflammatory treated and C3H/HeN groups presented better outcome regarding bacillary load, histopathology and survival and an anti-inflammatory immune response profile.
Conclusion: Because of the role of the massive neutrophilic infiltration, inflammation might be a key factor in the progression towards active tuberculosis. These results highly support the idea of the introduction of ibuprofen in the treatment of active TB could be very benefitial to the patients, specially for those



suffering from MDR/XDR, which have no other hope. For all this, we strongly ask for scientists to perform Phase III Clinical Trials able to directly assess this effect in humans. Moreover, observational studies could be also be needed to compare the incidence of TB in different cohorts—currently treated or not with low-dose aspirin, for example patients suffering of diabetis or a cardiac situation requiring anti-aggregation treatment.

PC-398-01 Pyrazinamide-induced hepatoxicity: caution when using recommended daily dosage for body weight bands

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Background and challenges to implementation: World Health organization recommends formulations and fixed dose combinations (FDCs) of anti-TB drugs and proposes standardized daily dosage for body weight bands to facilitate procurement, distribution and administration of treatment to patients. Practices according to available dosage recommendation including National TB Program (NTP) guidelines in Thailand led to pyrazinamide (PZA) dosing in some weights higher than the upper limit of its recommended dose (30 mg/kg/day) (see Table).

Intervention or response: A prospective study was conducted at Phattalung provincial hospital in Thailand comparing the incidence rate of PZA-induced hepatotoxicity (diagnosed by doctor, and confirmed by increased liver enzyme and re-challenge result) among 3 patient groups treated with PZA dosing: A) 15–25 mg/kg/day B) >25–30 mg/kg/day C) >30–40 mg/kg/day. Study subjects were TB cases registered during October 2007–June 2009. All cases with age of ⩾15 years old and treated with isoniazid,rifampicin and PZA were included. Cases with renal failure and received PZA according to creatinine clearance were excluded. Data were analysed by survival analysis and multiple Cox regression.

Results and lessons learnt: Among 391 patients with age ranged between 16–103 years, 273 (70%) were male, 89 (23%) had co-morbidity associated with hepatotoxicity including HIV/cirrhosis/alcoholism/hepatitis,and 20 developed PZA-induced hepatotoxicity. Of 84 group A patients, 2 developed PZA-induced hepatotoxicity (2 per 1000 person-weeks [pw]) with incidence rate of 18/1000 pw at 2nd week. Five of 160 group B patients developed PZA-induced hepatotoxicity (4/1000 pw) with incidence rates of 5, 11, 6 and 6/1000 pw-week at 1st, 2nd, 3rd and 4th week, respectively. Thirteen of 147 group C patients developed PZA-induced hepatotoxicity (12/1000 pw) with incidence rates of 7, 29, 23, 24, 10 and 16/1000 person-week at 1st, 2nd, 3rd, 4th, 5th, 9th week, respectively. The risk of PZA-induced hepatotoxicity among those with PZA >30–40 mg/kg/day was greater than those with PZA 15–30 mg/kg/day with statistical significance (hazard ratio adjusted by age, sex and co-morbidity = 3.33, 95%CI 1.30–8.50, $P = 0.007$).

Table PZA dosing according to recommended daily dosage for body weight bands

Recommendation	Body weight bands (kg)			
4-FDCs (H75/R150/Z400/E275)	**30-37**	**38-54**	**55-70**	**>70**
PZA dose (mg/day)	800	1200	1600	2000
PZA dose (mg/kg/day)	21.6-26.7	22.2-31.6	22.8-29.1	28.2
Weights with PZA>30 mg/kg/day		38-39		
NTP 2005	**30-39**	**40-49**	**≥50**	
PZA dose (mg/day)	1000	1500	2000	
PZA dose (mg/kg/day)	25.6-33.3	30.6-37.5	≤40	
Weights with PZA>30 mg/kg/day	30-33	40-49	50-66	
NTP 2008	**30-39**	**40-49**	**≥50**	
PZA dose (mg/day)	1000	1250	1500	
PZA dose (mg/kg/day)	25.6-33.3	25.5-31.3	≤30	
Weights with PZA>30 mg/kg/day	30-33	40-41		

Conclusions and key recommendations: Incidence rate of PZA-induced hepatotoxicity was highest with PZA dosing of >30–40 mg/kg/day. Recommended dosage for body weight bands should be used with caution for some weights with PZA dosing of >30 mg/kg/day.

PC-399-01 Level of isoniazid metabolites in tuberculosis patients depending on acetylation genotype

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One is the putative reason of insufficient tuberculosis (TB) chemotherapy is a deficit of data concerning metabolism peculiarities of the most effective agent isoniazid in TB-patients. That's why the aim of the present work was an investigation of acetylisonizid (AcINH) and hydrazine (HZ) concentration in tuberculosis patients with consideration of their acetylation genotype.

NAT2 (N-acetyltransferase 2) polymorphisms C>T 481 NAT2*5A, G>A 590 NAT2*6A, G>A 857 NAT2*7A/B were analyzed with the help of polymerase chain reaction. Isoniazid (INH) and AcINH concentration was detected in venous blood 2, 4, 6 and 24 h. After ingestion of standard dose of INH, recommended by DOTS-strategy (4–6 mg/kg), according to Vollenberg method with modification of Shenderova R. I., 1975 with spectrophotometer. The concentration of HZ was detected by method of Filov V., 1982 with spectrophotometer. The blood samples were obtained from TB-patients with new cases from Odesa Regional Tuberculosis Dispensary in 2012.

Among 84 TB-patients according to NAT2 genotype 39.3% individuals belong to rapid or intermediate acetylators (RA/IA), others—60.7%—to slow acetylators (SA). In RA/IA the INH concentration 4