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Abstracts' Service

Heightened Plasma Levels of Heme Oxygenase-1 and Tissue Inhibitor of Metalloproteinase-4 as Well as Elevated Peripheral Neutrophil Counts are Associated with TB-Diabetes Comorbidity

Bruno B. Andrade, Nathella Pavan Kumar, , Rathinam Sridhar, Vaithilingam V. Banurekha, Mohideen S. Jawahar, Thomas B. Nutman, Alan Sher, and Subash Bab

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Background. The increased prevalence of type 2 diabetes mellitus (T2DM) in countries endemic for TB poses a serious complication in the clinical management of this major infectious disease. Understanding the impact of T2DM on TB and the determinants of comorbidity is critical in responding to this growing public health problem with better therapeutic approaches. Here, we performed an exploratory study assessing a series of biologic parameters that could serve as markers of pathogenesis in TB with T2DM.

Methods. Cross-sectional analyses of levels of heme oxygenase-1 (HO-1), acute phase proteins, tissue metalloproteinases, and tissue inhibitors of metalloproteinase (TIMPs) as well as cytokines and chemokines were performed in plasma samples from individuals with active pulmonary TB or with coincident TB and T2DM from South India.

Results. Compared with patients with TB without diabetes, those with coincident T2DM exhibited increased Mycobacterium tuberculosis bacillary loads in sputum. Plasma levels of HO-1 but not of other acute phase proteins were higher in patients with TB and T2DM than in patients without diabetes, independent of bacillary sputum loads. HO-1 concentrations also positively correlated with random plasma glucose, circulating glycosylated hemoglobin, and low-density lipoprotein levels. Moreover, patients with coincident TB and T2DM exhibited increased plasma levels of TIMP-4 and elevated peripheral blood neutrophil counts, which, when considered together with HO-1, resulted in increased power to discriminate individuals with active TB with and without T2DM.

Conclusions. Elevated plasma levels of HO-1 and TIMP-4 and peripheral blood neutrophil counts are potential single and combined markers of pathogenesis in TB and T2DM.

Use of Inhaled Corticosteroids in Patients with COPD and the Risk of TB and Influenza: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Yaa-Hui Dong, Chia-Hsuin Chang, Fe-Lin Lin Wu, Li-Jiuan Shen, Peter M. A. Calverley, Claes-Göran Löfdahl, Mei-Shu Lai, and Donald A. Mahler

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Background. The use of inhaled corticosteroids (ICSs) is associated with an increased risk of pneumonia in patients with COPD. However, the risks of other respiratory infections, such as TB and influenza, remain unclear.

Methods. Through a comprehensive literature search of MEDLINE, EMBASE, CINAHL, Cochrane Library, and ClinicalTrials.gov from inception to July 2013, we identified randomized controlled trials of ICS therapy lasting at least 6 months. We conducted meta-analyses by the Peto, Mantel-Haenszel, and Bayesian approaches to generate summary estimates comparing ICS with non-ICS treatment on the risk of TB and influenza.

Results. Twenty-five trials (22,898 subjects) for TB and 26 trials (23,616 subjects) for influenza were included. Compared with non-ICS treatment, ICS treatment was associated with a significantly higher risk of TB (Peto OR, 2.29; 95% CI, 1.04-5.03) but not influenza (Peto OR, 1.24; 95% CI, 0.94-1.63). Results were similar with each meta-analytic approach. Furthermore, the number needed to harm to cause one additional TB event was lower for patients with COPD treated with ICSs in endemic areas than for those in nonendemic areas (909 vs 1,667, respectively).

Conclusions. This study raises safety concerns about the risk of TB and influenza associated with ICS use in patients with COPD, which deserve further investigation.

Clinicopathologic and Prognostic Significance of c-MYC Copy Number Gain in Lung Adenocarcinomas

AN Seo, JM Yang, H Kim, S Jheon, K Kim, CT Lee, Y Jin, S Yun, JH Chung and JH Paik

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Background. c-MYC copy number gain (c-MYC gain) has been associated with aggressive behaviour in several cancers. However, the role of c-MYC gain has not yet been determined in lung adenocarcinomas classified by genetic alterations in epidermal growth factor receptor (EGFR), KRAS, and anaplastic lymphoma kinase (ALK) genes. We investigated the clinicopathologic and prognostic significance of c-MYC gain for disease-free survival (DFS) and overall survival (OS) according to EGFR, KRAS, and ALK gene status and stages in lung adenocarcinomas.

Methods. In 255 adenocarcinomas resected in Seoul National University Bundang Hospital from 2003 to 2009, fluorescence in situ hybridisation (FISH) with c-MYC probe and centromeric enumeration probe 8 (CEP8) was analysed using tissue microarray containing single representative core per each case. EGFR (codon 18 to 21) and KRAS (codon 12, 13, and 61) mutations were analysed by polymerase chain reaction and direct sequencing method from formalin-fixed, paraffin-embedded tissue sections. ALK rearrangement was determined by FISH method. c-MYC gain was defined as >2 copies per nucleus, chromosome 8 gain as ≥3 copies per nucleus, and gain of c-MYC:CEP8 ratio (hereafter, c-MYC amplification) as ≥2.

Results. We observed c-MYC gain in 20% (51 out of 255), chromosome 8 gain in 5.5% (14 out of 255), c-MYC amplification in 2.4% (6 out of 255), EGFR mutation in 49.4% (118 out of 239), KRAS mutation in 5.7% (7 out of 123), and ALK rearrangement in 4.9% (10 out of 205) of lung adenocarcinomas. c-MYC gain was observed in 19% (22 out of 118) of patients with lung adenocarcinomas with an EGFR mutation, but not in any patients with a KRAS mutation, or an ALK rearrangement. c-MYC gain (but not chromosome 8 gain or c-MYC amplification) was an independent poor-prognostic factor in the full cohort of lung adenocarcinoma (P=0.022, hazard ratio (HR)=1.71, 95% confidence interval (CI), 1.08-2.69 for DFS; P=0.032, HR=2.04, 95% CI, 1.06-3.91 for OS), as well as in stage I subgroup (P=0.023, HR=4.70, 95% CI, 1.24-17.78 for DFS; P=0.031, HR=4.65, 95% CI, 1.15-18.81 for OS), and in EGFR-mutant subgroup (P=0.022; HR=2.14; 95% CI, 1.11-4.10 for DFS).

Conclusion. c-MYC gain (but not chromosome 8 gain or c-MYC amplification) was an independent poor-prognostic factor for DFS and OS in lung adenocarcinomas, both in full cohort and stage I cancer, and possibly for DFS in EGFR-mutant adenocarcinomas. Additional studies are required to determine if patients with lung adenocarcinoma with c-MYC gain are candidates for additional first-line treatment to mitigate their increased risk for disease progression and death.

Prevalence of Night-time Dyspnoea in COPD and Its Implications for Prognosis

Peter Lange, Jacob Louis Marott, Jorgen Vestbo and Borge Gronne Nordestgaard

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The information on night-time symptoms in chronic obstructive pulmonary disease (COPD) is sparse.

We investigated the prevalence of night-time dyspnoea in 6616 individuals with COPD recruited from the general population in the Copenhagen area, Denmark, and described characteristics and prognosis of subjects with this symptom.

The prevalence of night-time dyspnoea was 4.3%: 2.1% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A, 12.9% in GOLD B, 2.6% in GOLD C and 16.3% in GOLD D. Compared with individuals without night-time dyspnoea, those with night time dyspnoea had lower forced expiratory volume in 1 s, higher daytime dyspnoea scores (modified Medical Research Council scale) and more wheezing, more often had chronic mucus hypersecretion, ischaemic heart disease and atrial fibrillation, and more often reported stress, nervousness and tiredness. After adjustment for age and sex, the presence of night-time dyspnoea was associated with future COPD exacerbations (hazard ratio (HR) 2.3, 95% CI 1.7-3.0), hospital admissions due to COPD (HR 3.2, 95% CI 2.3-4.4) and mortality (HR 1.7, 95% CI 1.2-2.3).

Prevalence of night-time dyspnoea in COPD increases with disease severity according to both spirometric and clinical GOLD classification, and is associated with presence of daytime respiratory symptoms and cardiac comorbidities. Night-time dyspnoea is a significant predictor of poor prognosis in individuals with COPD.

Predictors of Dyspnoea Prevalence: Results from the BOLD Study

Rune Grønseth, William M. Vollmer, Jon A. Hardie, Inga Sif Ólafsdóttir, Bernd Lamprecht, A. Sonia Buist, Louisa Gnatiuc, Amund Gulsvik, Ane Johannessen and Paul Enright

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Dyspnoea is a cardinal symptom for cardio-respiratory diseases. No study has assessed worldwide variation in dyspnoea prevalence or predictors of dyspnoea.

We used cross-sectional data from population-based samples in 15 countries of the Burden of Obstructive Lung Disease (BOLD) study to estimate prevalence of dyspnoea in the full sample, as well as in an *a priori* defined low-risk group (few risk factors or dyspnoea-associated diseases). Dyspnoea was defined by the modified Medical Research Council questions. We used ordered logistic regression analysis to study the association of dyspnoea with site, sex, age, education, smoking habits, low/high body mass index, self-reported disease and spirometry results.

Of the 9484 participants, 27% reported any dyspnoea. In the low-risk sub-sample (n=4329), 16% reported some dyspnoea. In multivariate analyses, all covariates were correlated to dyspnoea, but only 13% of dyspnoea variation was explained. Females reported more dyspnoea than males (odds ratio ~2.1). When forced vital capacity fell below 60% of predicted, dyspnoea was much more likely.

There was considerable geographical variation in dyspnoea, even when we adjusted for known risk factors and spirometry results. We were only able to explain 13% of dyspnoea variation.