TA07

FUNCTIONAL POLYMORPHISMS IN THE INTERLEUKIN-6 AND SEROTONIN TRANSPORTER GENES AND DEPRESSION AND FATIGUE INDUCED BY INTERFERON-ALPHA AND RIBAVIRIN TREATMENT

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Depression and fatigue are frequent side effects of interferon-alpha (IFN-α) treatment, and there is compelling evidence that the inflammatory response system (including interleukin-6/ IL-6) and the serotonergic system play a role in the pathophysiology of such symptoms. Functional polymorphisms in the promoter region of the IL-6 gene (rs1800795) and serotonin transporter gene (5-HTTLPR) have been identified as regulating these systems. The present study aimed to determine if these polymorphisms were associated with the development of symptoms of depression and fatigue during IFN-α and ribavirin treatment.

98 Caucasian patients receiving pegylated IFN-α and ribavirin treatment for hepatitis C at King's College Hospital, London and Emory Univ, Atlanta participated in this prospective cohort study. Symptoms of depression and fatigue were measured using self-report questionnaires, immediately before treatment began and at week 4, 8, 12 and 24 of treatment. Polymorphisms were determined using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism method, from DNA extracted from cheek swabs. A Mixed Linear Model approach for longitudinal data was used to investigate the effect of the polymorphisms during treatment.

The CC ("low IL-6" synthesizing) genotype was associated with significantly fewer depressive symptoms compared to the grouped GG/GC genotypes ($F=9.4$, $df=436$, $P=0.002$) but it was not associated with fewer symptoms of fatigue ($F=1.2$, $df=430$, $P=0.2$). The LL (high serotonin transporter transcription) genotype was also associated with fewer symptoms of depression, compared to the SS/SL genotype group ($F=4.5$, $df=436$, $P=0.03$) but not fatigue ($F=0.5$, $df=430$, $P=0.5$). Furthermore, there was an interaction between the genes ($F=5.0$, $df=434$, $P=0.02$): the "protective" effects of the 5-HTTLPR polymorphism were evident in the presence of the "low IL-6" genotype ($F=5.4$, $df=64$, $P=0.02$) but not in the presence of the "high IL-6" genotype ($F=2.2$, $df=369$, $P=0.1$).

Functional polymorphisms in the IL-6 and serotonin transporter genes are risk factors for developing symptoms of depression but not fatigue during IFN-α treatment. The association between these polymorphisms and depression confirms the role of the inflammatory response system and serotonergic system in the pathophysiology of IFN-α-induced depression.

TA08

POLYMORPHISMS IN CYTOSOLIC PHOSPHOLIPASE A2 AND CYCLOOXYGENASE 2 GENES AND RISK OF INTERFERON-INDUCED DEPRESSION

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Introduction. Interferon (IFN)-α in combination with ribavirin treatment is the standard treatment of hepatitis C virus (HCV) infection. However, there are 20~50% patients developed major depressive episode after received IFN-α treatment. Based upon the evidence from epidemiological data, case-control studies of PUFAs levels in human tissues, and antidepressant effect in clinical trials, phospholipid polyunsaturated fatty acids (PUFAs) might be etiologically important to cytokine-induced sickness behaviour and depression (Lin and Su 2007). Phospholipase A2 (PLA2) and cyclo-oxygenase 2 (COX2) are the key enzymes of the PUFA metabolism. This study aimed to investigate if polymorphisms of cPLA2 and COX2 genes have effects on the occurrence of IFN-induced depression.

Methods. Patients with chronic hepatitis C infection eligible for IFN-α treatment were recruited and were assessed regularly during 24 weeks of pegylated IFN-α and ribavirin combination therapy. Mini International Neuropsychiatric Interview (MINI) was used to determine presence of major depressive episode (IFN-induced depression). Six polymorphisms on cPLA2 and COX2 were chosen according to Wei and Hemmings's study (Wei and Hemmings 2004) and analysed by using PCR-based restriction fragmental length polymorphism.

Results. One hundred and thirty-five (93.1%) from 145 eligible patients were consent and completed at least two psychiatric assessments. Men comprised 60.1% of the sample. Mean age was 48.7 years (SD = 11.7; range, 22–70 years). Thirty-eight patients (28%) developed IFN-induced major depressive episode. Fatigue, neurotoxicity adverse events and depression scores increased significantly with a peak score at week 10 of treatment. One hundred and twenty-eight patients (94.8%) were genotyped. The allelic association of *Ban*I polymorphism of cPLA2 gene revealed that G allele had a significant effect on the development of IFN-induced depression ($\chi^2=4.44$, $p<0.035$). Subjects with the genotype G/G of *Ban*I polymorphism had an increased risk of IFN-induced depression (OR=4.01; CI=1.18 to 13.6). There were no significant effects on the development of IFN-induced depression for the other 5 examined SNPs on cPLA2 and COX2.

Conclusions: The occurrence of major depressive episode during IFN-α therapy was about one-third of patients with HCV in this Taiwanese sample. The significant effect of *Ban*I SNP of cPLA2 gene on IFN-induced depression implied that PUFA metabolism might be involved in the mechanism of psychoneuroimmunity in depression. Further studies are needed to clarify the functionality of this *Ban*I polymorphism, its effect on PUFA levels, and the effects of PUFA levels in the susceptibility of IFN-induced depression.

TA09

PHYSICAL HEALTH MONITORING IN A SCOTTISH COHORT OF BIPOLAR PATIENTS

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Introduction: Bipolar patients have increased risk of cardiovascular disease (CVD) and mortality. Consensus guidelines (Expert consensus Meeting 2005, J Psychopharmacology; 19(6) Suppl; 118-122) emphasise the need for monitoring of all relevant risk factors and include ECG and blood pressure (BP). Patient preference for this monitoring is to have this performed in secondary care. There is little reported naturalistic data on the number and severity of categorical abnormalities detected. Furthermore the ECG focus is often solely on QTc. Hypertension is a common finding in bipolar patients which commonly is untreated.

Method: A global health clinic was set up in 2006 to undertake systematic physical health monitoring in all bipolar outpatients at least once within Larkfield CMHT, one of 16 in Glasgow. Patients received 2 hour assessments performed by appropriately trained nurses. BMI, laboratory (non-fasting) parameters, ECG and BP routinely performed.

Results: Since 2006 from 67 bipolar patients within the CMHT 48 outpatients have been invited to attend screening of which 34 accepted (71%). Of those who accepted 38.2% were in current employment, 32.4% had known previous or current alcohol or substance misuse & 50% were current smokers. 88.2% were currently taking antipsychotic medication & 61.8% mood stabilisers. Mean BMI was 29.3 & mean waist circumference 94.8cm. ECGs – 27 available for analysis. ECG abnormalities were found in 6/27 patients (22%) of which 3 were significant findings (prior myocardial infarction), (11%). No patient had abnormal QTc >500 msecs. In 4 patients (15%) the ECG analysis was determined by the analyser to be difficult to analyse due to significant baseline patient movement. Normal blood pressure using guidelines from the British Hypertension Society (BHS) 2004 (<130/85) was determined in 29.4% (n=10), high-normal 32.4% (n=11) and varying grades of hypertension 38.2% (n=13). Grade 3 (severe) hypertension was found in 2.9% (n=1). Random glucose testing was performed in 28 patients of whom 2 were abnormal (7.1%).

Conclusion: Bipolar patients have found acceptable physical monitoring in a CMHT. Significant BP and ECG abnormalities are common and may require evaluation for treatment. QTc abnormalities > 500 msec were not detected. Using the most conservative definition of hypertension 38% of this cohort suffered from hypertension and an additional 32% were considered to have high-normal blood pressure and may benefit from lifestyle interventions.

TA10

ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION IN THREE EUROPEAN COUNTRIES: PREVALENCE AND IMPACT IN A CROSS-SECTIONAL SURVEY REPLICATION

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Sexual dysfunction is a common but often unrecognized side effect of many antidepressants. Building upon the results of a previous investigation (Williams et al, 2006, J Clin Psychiatry, 67:204-10), this study aimed to assess the prevalence and impact of antidepressant-induced sexual dysfunction (ADSD) in three European countries. Cross-sectional survey of 704 adults (497 women, 207 men) in Germany, Spain, and The Netherlands. All had started taking a selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI) within 3-6 months of the assessment. Information about other medications and conditions known to impair sexual functioning was sought, and changes in sexual functioning and the impact of such changes were assessed. The Medical Outcomes Study Short Form – 12 (SF-12) and Arizona Sexual Experience Scale (ASEX) were administered to measure health status and sexual functioning. ASEX scores generally exceeded the threshold defining sexual dysfunction (ASEX score > 19): 67.2% of subjects in the German (mean score 22.58), 79.4% in the Spanish (mean score 24.34), and 73.3% in the Dutch (mean score 22.94) samples. The prevalence of ADSD was conservatively estimated to be between 37.1% (German sample) and 61.5% (Spanish sample). Overall, 46.4% of men and 52.1% of women were classified as having ADSD. There were statistically significant differences between ADSD and non-ADSD patients in SF-12 Mental Component scores ($F1,665 = 8.01$, $p = 0.0048$), with ADSD patients displaying poorer mental well-being. Respondents with ADSD reported significantly worse quality of life, self-esteem, mood, and relationships with partners, compared with non-ADSD respondents ($p<0.001$, for all domains). Sexual dysfunction is a frequent adverse effect of antidepressant treatment and associated with reduced quality of life and self-esteem, and negative effects on mood and relationships.

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