中華民國 102 年消化系聯合學術演講年會

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* 中文題目

以肌苷三磷酸焦磷酸酶(ITPA)基因之單一核苷酸多型性為基礎之預測模式用以預測感染第一型病毒基因型之亞洲 C 型肝炎病患接受長效型干擾素合併 Ribavirin 治療時之溶血性貧血

* 英文題目

A Predictive Index using the Inosine Triphosphate Pyrophosphatase Gene Allele Status to Predict Ribavirin-induced Hemolytic Anemia in Genotype 1 Hepatitis C Virus-infected Asian Patients Receiving Pegylated Interferon and Ribavirin Combination Therapy

* 內 文

背景/Background :

Associations between single-nucleotide polymorphisms (SNP) in the inosine triphosphate pyrophosphatase (ITPA) gene and ribavirin (RBV)-induced anemia in hepatitis C virus (HCV)-infected patients receiving pegylated interferon and RBV combination therapy have been reported. Identification of HCV-infected patients at risk of anemia using ITPA status is a priority during combination therapy.

目的/Aims :

This study aimed to evaluate the impact of ITPA SNP status on severe anemia and treatment responses, to examine the association of severe anemia and treatment responses, and to construct a clinically practical predictive index for severe anemia during HCV combination therapy.

方法/Methods :

Genotype 1 HCV (HCV-1) infected Taiwanese patients (n = 311) received 24 or 48 weeks of combination therapy. Participants' DNA was genotyped for a functional ITPA SNP (C/C, A/A or C/A) on chromosome 20 at rs1127354. A predictive index was constructed by incorporating predictors identified through logistic regressions for severe anemia (hemoglobin < 10 g/dL). Areas under the receiver operating characteristic curves (AUCs) represent the diagnostic accuracies of the predictive index in the randomly assigned development and validation cohorts.

結果/Results :

Multivariate logistic regression analysis identified age (45-54 years: odds ratio,

OR = 5.9 (95% confidence interval, 95% CI = 2.4-14.2); 55-64: 7.5 (3.1-18.2); ≧ 65: 12.7 (3.7-43.9)), ITPA rs1127354 (C/C: 4.1 (2.1-8.0)), baseline hemoglobin (< 14.0 g/dL: 7.8 (3.7-16.2); 14.0-14.9: 3.2 (1.5-6.8)) as predictors of severe anemia throughout the course of treatment. Therefore, the predictive index incorporating age, ITPA SNP status and baseline Hb was expressed as 1/ (1 + exp [-x]), where x = -3.4803 + 1.7696 (if age = 45-54) + 2.0137 (if age = 55-64) + 2.5388 (if age ≧ 65) + 1.4107 (if ITPA SNP = C/C) + 2.0483 (if Hb < 14.0) + 1.1591 (if Hb = 14.0-14.9). For severe anemia, the predictive index incorporating age, ITPA SNP status and baseline hemoglobin yielded diagnostic accuracies (AUC) of 0.816 (95% CI = 0.764-0.868) in the development (n = 249) and 0.912 (0.841-0.984) in the validation (n = 62) cohorts.

結論/Conclusions :

In HCV-1-infected patients receiving combination therapy, the ITPA SNP-based index is an accurate and practical predictive solution for severe anemia in clinical practice.

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A Predictive Index using the Inosine Triphosphate Pyrophosphatase Gene Allele Status to Predict Ribavirin-induced Hemolytic Anemia in Genotype 1 Hepatitis C Virus-infected Asian Patients Receiving Pegylated Interferon and Ribavirin Combination Therapy

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Abstract

Background: Associations between single-nucleotide polymorphisms (SNP) in the inosine triphosphate pyrophosphatase (ITPA) gene and ribavirin (RBV)-induced anemia in hepatitis C virus (HCV)-infected patients receiving pegylated interferon and RBV combination therapy have been reported. Identification of HCV-infected patients at risk of anemia using ITPA status is a priority during combination therapy.

Methods: Genotype 1 HCV (HCV-1) infected Taiwanese patients (n = 311) received 24 or 48 weeks of combination therapy. Participants' DNA was genotyped for a functional ITPA SNP (C/C, A/A or C/A) on chromosome 20 at rs1127354. A predictive index was constructed by incorporating predictors identified through logistic regressions for severe anemia (hemoglobin < 10 g/dL). Areas under the receiver operating characteristic curves (AUCs) represent the diagnostic accuracies of the predictive index in the randomly assigned development and validation cohorts.

Results: Multivariate logistic regression analysis identified age (45-54 years: odds ratio, OR = 5.9 (95% confidence interval, 95% CI = 2.4-14.2); 55-64: 7.5 (3.1-18.2); ≧ 65: 12.7 (3.7-43.9)), ITPA rs1127354 (C/C: 4.1 (2.1-8.0)), baseline hemoglobin (<

14.0 g/dL: 7.8 (3.7-16.2); 14.0-14.9: 3.2 (1.5-6.8)) as predictors of severe anemia throughout the course of treatment. For severe anemia, the predictive index incorporating age, ITPA SNP status and baseline hemoglobin yielded diagnostic accuracies (AUC) of 0.816 (95% CI = 0.764-0.868) in the development (n = 249) and 0.912 (0.841-0.984) in the validation (n = 62) cohorts.
Conclusions: In HCV-1-infected patients receiving combination therapy, the ITPA SNP-based index is an accurate and practical predictive solution for severe anemia in clinical practice.
Keywords single-nucleotide polymorphisms (SNP); inosine triphosphate pyrophosphatase (ITPA); hemolytic anemia; hepatitis C virus (HCV)
感染第二型病毒基因型之 C 型肝炎病患接受長效型干擾素合併 Ribavirin 治療時肌苷三磷酸焦磷酸酶(ITPA)基因之單一核苷酸多型性與溶血性貧血之相關性
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背景：
最近的基因組關聯性研究報告指出， C 型肝炎病患接受長效型干擾素(pegIFN)合併 Ribavirin(RBV)治療時，肌苷三磷酸焦磷酸酶(ITPA)基因之單一核苷酸多型性(SNP)與溶血性貧血之間有顯著相關性。 然而， 有限的研究曾分析感染第二基因型 C 型肝炎病毒(HCV-2）之台灣患者。 本研究旨在探討這些 SNP， 對貧血， 血紅素（Hb）下降， 以及治療效果的影響。
材料與方法：
共有二百三十五位符合資格的 HCV-2 感染患者接受合併治療 24 週。 並從周邊血液單核球細胞基因組， 分析位於 20 號染色體 rs1127354 位置的功能性 ITPA 基因變異。 以確認重度貧血（血紅蛋白<10 克/dL）和血紅素下降（≧4 克/dL）的預測因子。
結果：
多變項邏輯斯回歸分析確定年齡（≧60 歲）(odds ratio, OR, 2.337; 95％confidence interval, CI, 1.180-4.627; P = 0.015)， 女性（OR, 3.463; 95％CI, 1.913-6.269, P <0.001)，和 ITPA rs1127354 C/C(OR, 2.227; 95％CI, 1.168-4.247, P = 0.015)，可以獨立預測整個 24 週的治療過程中的嚴重貧血。 年齡(≧60 歲)(OR, 1.633; 95％ CI, 0.832-3.203, P = 0.154)， 男性（OR, 2.224; 95％CI, 1.275-3.879; P = 0.005）和 ITPA rs1127354 C/C（OR, 3.135; 95％CI, 1.702-5.775; P <0.001)， 與血紅素下降相關。 多變項 Cox 回歸分析顯示年齡(≧60 歲)(hazard ratio, HR, 1.915; 95％CI, 1.226-2.993; P = 0.004)， 女性（HR, 2.712; 95％CI, 1.680-4.380; P < 0.001)， 和 ITPA rs1127354 C/C（HR, 2.162; 95％CI, 1.302-3.590; P = 0.003)， 亦可獨立預測整個 24 週的治療過程中的嚴重貧血。 持續病毒學反應(SVR)和貧血

或 ITPA SNP 不相關。

結論：

感染 HCV-2 之慢性 C 型肝炎台灣病患， 接受合併治療時， ITPA SNP 可預測 RBV 引起之溶血性貧血， 以及血紅素下降， 但並不影響 SVR 率。

關鍵語:

單一核苷酸多型性(SNP) ， 肌苷三磷酸焦磷酸酶(ITPA) ， 溶血性貧血， C 型肝炎病毒