預測 HMG-CoA 還原酶;抑制劑藥物治療期間糖尿病患發生肝毒性之預測量表建立

Development of a Risk Score for Predicting Hepatotoxicity during HMG-CoA Reductase Inhibitors Therapy in Diabetic Patients

中文摘要

HMG-CoA 還原酶抑制劑 (3-hydroxy-3-methyl-gutaryl-CoA reductase inhibitors, statins) 引起的肝毒性雖常見，但多數病人肝功能指數會自發性回復正常，因此臨床上糖尿病人使用時監測情形並不如藥品仿單建議的頻繁。但若嚴重肝毒性發生，就可能會降低病人的服藥配合度，甚至損害健康。糖尿病盛行率逐年增加，估計其中約有 50%患者會同時併有血脂異常，因此常需併用 statins 治療。除了高血脂，肝臟疾病也是一個重要卻常被忽略的糖尿病合併症。在糖尿病病人接受 statins 治療時，應要有符合臨床需要和經濟效應的肝功能監測建議，以有效的進行肝功能檢測，並避免肝臟相關不良反應導致服藥依順性低而造成浪費。

本研究目的爲利用糖尿病患者在 statins 治療期間發生肝毒性的危險因子，建立一套預測量表，以輔助肝功能監測的安排。收案地點爲台北醫學大學-市立萬芳醫院，共回溯 219 名糖尿病患之病歷，收集資料包括病人基本資料與合併疾病、生化檢驗數據，與使用藥物品項與劑量等。以 univariate analysis 評估潛在危險因子與 statins 使用期間發生的肝毒性之相關性。具有統計意義的危險因子再以 logistic regression 進行分析，並以危險因子進行配分，建立 statins 使用期間發生肝毒性的預測量表。量表之配適度以 Hosmer-Lemeshow test 評估，其檢測力則以 receiver-operating characteristic (ROC) curve 下的面積(AUC)、sensitivity 與 specificity 示之。

經過 logistic regression 分析並建立的量表總共包括五項危險因子：(1)男性，(2)三酸甘油脂的檢驗基準值，(3)糖尿病罹病期間，(4)合併疾病數，以及(5)病患所使用的 angiotensin-converting enzyme inhibitors (ACEI)之每日處方劑量(Prescribed Daily Dose, PDD) 與每日定義劑量(Defined Daily Dose,DDD) 的比率。ROC 曲線下面積爲 0.864，Hosmer-Lemeshow test 的 p 値爲 0.674,所得預測量最佳切點(cutoff point)爲 4.5 分。大於 50%以上的肝毒性發生在 statins 使用後半年內，因此建議 STH 預測量表得分大於 4.5 分的糖尿病患，應在 statins 開始使用的第三個月、第六個月、第十二個月，與第十八個月進行肝功能監測。

英文摘要

HMG-CoA reductase inhibitors (statins)-induced hepatotoxicity is a common adverse effect characterized by asymptomatic and transient elevations in liver enzymes. Due to the self-resolving nature, even without statin discontinuation, the frequency of

monitoring of liver function tests (LFT) in patients receiving statin therapy is usually lower than the manifacturers' recommendations. Although hepatotoxicity is rarely severe, once it occurs, patients are endangered directly by the event itself and indirectly from lowered patient compliance. Hyperlipidemia and liver diseases are important diabetic comorbidities. While statin is the most commonly prescribed lipid lowering agent, its hepatotoxicity in diabetic hyperlipidemic patients requires further evaluation. Current LFT monitoring recommendations should adjust to accommodate the clinical needs of diabetic patients during statins therapy.
This retrospective analysis was conducted to determine factors associated with hepatotoxicity among diabetic patients during statins therapy and to develop a risk score. Data of 219 patients were collected from the medical charts of Municipal Wan-Fang Hospital. Potential risk factors were assessed by univariate analysis for their association with hepatotoxicity during statin therapy. Factors significantly associated with the outcome were further evaluated in logistic regression analysis. A risk model was constructed by regression coefficients. Hosmer-Lemeshow test was performed to evaluate model fit. Discriminatory power was determined by area under receiver-operating characteristic curve (ROC curve).
Five risk factors were found significantly associated with hepatotoxicity during statin therapy and were incorporated to construct a risk model predicting hepatotoxicity. These factors included: (1) male gender, (2) baseline triglyceride level, (3) years since diabetes diagnosis, (4) number of diagnoses, and (5) PDD/DDD (Prescribed Daily Dose/Defined Daily Dose) ratio of angiotensin converting enzyme inhibitors. Area under ROC curve was 0.864 for the predictive model. Hosmer-Lemeshow test revealed a p-value of 0.674. Base on the findings in this study, it is advised that diabetic patients with STH score of 4.5 or above should monitor liver function at baseline, month 1, 3, 6, 9, 12, and 18 after initiation of statins.