Research Article

JOURNAL OF HEPATOLOGY

Minocycline hepatotoxicity: Clinical characterization and identification of *HLA-B**35:02* as a risk factor

Thomas Jacob Urban[1,2], Paola Nicoletti[3], Naga Chalasani[4], José Serrano[5], Andrew Stolz[6], Ann K. Daly[7], Guruprasad P. Aithal[8], John Dillon[9], Victor Navarro[10], Joseph Odin[11], Huiman Barnhart[12], David Ostrov[13], Nanye Long[1,2], Elizabeth Trilby Cirulli[12], Paul Brent Watkins[1,2], Robert John Fontana[14,*], on behalf of the Drug-Induced Liver Injury Network (DILIN), the Pharmacogenetics of Drug-Induced Liver Injury group (DILIGEN), and the International Serious Adverse Events Consortium (iSAEC)

[1]*Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA;* [2]*UNC Institute for Drug Safety Sciences, Durham, NC, USA;* [3]*Center for Computational Biology and Bioinformatics, Columbia University, New York, NY, USA;* [4]*Indiana University School of Medicine, Indianapolis, IN, USA;* [5]*National Institute of Diabetes Digestive and Kidney Diseases, Bethesda, MD, USA;* [6]*University of Southern California, Los Angeles, CA, USA;* [7]*Newcastle University, Newcastle upon Tyne, United Kingdom;* [8]*National Institute for Health Research Nottingham Digestive Diseases Biomedical Research Unit, Nottingham University Hospitals NHS Trust and University of Nottingham, United Kingdom;* [9]*University of Dundee, Dundee, United Kingdom;* [10]*Einstein Medical Center, Philadelphia, PA, USA;* [11]*Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [12]*Duke University, Durham, NC, USA;* [13]*University of Florida College of Medicine, Gainesville, FL, USA;* [14]*University of Michigan, Ann Arbor, MI, USA*

Background & Aims: Minocycline hepatotoxicity can present with prominent autoimmune features in previously healthy individuals. The aim of this study was to identify genetic determinants of minocycline drug-induced liver injury (DILI) in a well-phenotyped cohort of patients.

Methods: Caucasian patients with minocycline DILI underwent genome-wide genotyping and were compared to unexposed population controls. Human leukocyte antigen (HLA) binding of minocycline was assessed using AutoDock Vina.

Results: Among the 25 cases, 80% were female, median age was 19 years and median latency from drug start to DILI onset was 318 days. At presentation, 76% had acute hepatocellular liver injury, median ALT 1,077 U/L (range: 63 to 2,333), median bilirubin 4.5 mg/dl (range: 0.2 to 16.7), and 90% had a +ANA. During follow-up, 50% were treated with corticosteroids and no participants died or required a liver transplant. A significant association was noted between *HLA-B*35:02* and risk for minocycline DILI; a 16% carrier frequency in DILI cases compared to 0.6% in population controls (odds ratio: 29.6, 95% CI: 7.8–89.8, $p = 2.5 \times 10^{-8}$). Verification of *HLA-B*35:02* imputation was confirmed by sequence-based HLA typing. *HLA-B*35:02* carriers had similar presenting features and outcomes compared to non-carriers. *In silico* modeling studies support the hypothesis that direct binding of minocycline to this novel HLA risk allele might be an important initiating event in minocycline DILI.

Conclusion: *HLA-B*35:02* is a rare HLA allele that was more frequently identified in the 25 minocycline DILI cases compared to population controls. If confirmed in other cohorts, this HLA allele may prove to be a useful diagnostic marker of minocycline DILI.

Lay summary: Development of liver injury following prolonged use of minocycline for acne is a rare but potentially severe form of drug-induced liver injury. Our study demonstrates that individuals who are *HLA-B**35:02 carriers are at increased risk of developing minocycline related liver injury. These results may help doctors more rapidly and confidently diagnose affected patients and possibly reduce the risk of liver injury in individuals receiving minocycline going forward.

© 2017 Published by Elsevier B.V. on behalf of European Association for the Study of the Liver.

Introduction

Idiosyncratic drug-induced liver injury (DILI) is an important cause of acute and chronic liver injury in Western patients. In addition to being a leading reason for regulatory actions among drugs in development and in the marketplace, DILI also accounts for 13% of adults with acute liver failure.[1] A recent population based study indicated that the annual incidence of DILI was 19.1 per 100,000 person years in Iceland and that antibiotics were the most commonly implicated agents.[2] Similarly, analyses from the ongoing Drug-induced Liver Injury Network (DILIN) prospective study in the United States also identified antibiotics as the leading cause of DILI, with amoxicillin-clavulanate being most frequently implicated.[3] Prior reports have also implicated minocycline as a cause of DILI with characteristic clinical features

Keywords: Drug-induced liver injury; Single nucleotide polymorphism; Genetic association; Autoimmunity; Human leukocyte antigen.
Received 19 January 2017; received in revised form 2 March 2017; accepted 4 March 2017; available online 18 March 2017

* Corresponding author. Address: 3912 Taubman Center, Ann Arbor, MI 48109-0362, USA. Tel.: +1 (734) 936 4780; fax: +1 (734) 936 7392.
E-mail address: rfontana@med.umich.edu (R.J. Fontana).

including systemic arthralgias and detectable autoantibodies arising in young women.[4] Recent studies have suggested that various laboratory, histological and clinical features can help differentiate autoimmune like DILI from sporadic autoimmune hepatitis but confirmatory studies are needed.[4]

Several groups have begun studies to better define the presenting features, risk factors, and outcomes of patients with DILI. In addition to identifying improved causality assessment methods and DILI biomarkers, studies exploring the potential genetic susceptibility in these rare patients with DILI have been undertaken. Prior genome-wide association studies (GWAS) have identified single nucleotide polymorphisms in the human leukocyte antigen (HLA) locus that are associated with DILI susceptibility to several drugs.[5–8] The aim of the current study is to report upon the presenting clinical features and outcomes of patients with DILI attributed to minocycline that have enrolled onto the ongoing DILIN prospective and retrospective studies. In addition to exploring clinical phenotypes, we also set out to identify potential genetic susceptibility factors in patients with minocycline DILI compared to population controls, using GWAS and confirmatory sequence-based HLA typing. Finally, preliminary results exploring the potential mechanism of the *HLA-B**35:02 association with minocycline DILI using *in silico* modeling are presented.

Patients and methods

DILIN prospective study

Most of the participants were enrolled in the DILIN prospective study protocol. DILI onset was defined as the first date after a subject taking minocycline met the predefined laboratory criteria for study entry, of either a serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level that exceeded 5 × the upper limit of normal (ULN) (or 5 × pretreatment baseline if baseline abnormal), a serum alkaline phosphatase (AP) that exceeded 2 × the ULN (or 2 × pretreatment baseline if baseline abnormal), a total bilirubin >2.5 mg/dl, or an international normalized ratio (INR) greater than 1.5 on two consecutive blood draws. All study participants were enrolled within 6 months of DILI onset.

A detailed medical history was obtained at the baseline study visit and additional laboratory and radiological testing were performed to more fully characterize the DILI event and exclude competing etiologies. Specifically, testing for hepatitis A, B, C, HIV, autoantibodies including anti-nuclear antibody titers, CMV, and EBV infection were obtained at the local laboratory. Enrolled patients were seen for a follow-up study visit at 6 months after initial enrollment and those with evidence of chronic DILI within 6 months of DILI onset were asked to return for additional follow-up visits at 12 and 24 months.[9] Chronic DILI was defined as having a persistently elevated serum AST, ALT, or AP level, histological evidence of liver injury, or clinical evidence of portal hypertension at 6 months after DILI onset. Written informed consent was obtained from participants and the study was approved by the Institutional Review Boards of all participating clinical sites.

The severity of the DILI episode was categorized on a 5-point scale from mild,[1] moderate,[2] moderate-hospitalized,[3] severe,[4] and fatal,[5] where a fatal score was assigned only if the patient died or had liver transplant due to DILI.[9] Of note, the clinical features of some of the minocycline patients were previously presented in a separate report.[10] In addition, clinical features from two of these cases have been posted as brief vignettes on the LiverTox website (see http://livertox.nlm.nih.gov/minocycline).

DILIN retrospective study

DNA samples and phenotypic data from participants with minocycline hepatotoxicity enrolled in the DILIN retrospective study were included. Study inclusion criteria were patients that developed DILI due to one of 8 pre-specified drugs that included minocycline with a DILI onset date after 1994. Participants had to have a total bilirubin of >2.5 mg/dl and a complete set of laboratory tests at DILI onset, exclusion of competing causes, and outcome available for review. Retrospective study patients were either interviewed in person or over the phone to review the dose and duration of suspect medication use and facilitate collection of a DNA sample after obtaining written informed consent.

DILIGEN study

Only Caucasian participants with DILI attributed to minocycline enrolled in the DILIGEN study with an available DNA sample were included. All participants had (a) clinically apparent jaundice or bilirubin >40 μmol/L, or (b) a serum ALT >5 × ULN or (c) AP >2 × ULN plus any raised bilirubin above ULN.[7] All patients had a Roussel Uclaf Causality Assessment Method (RUCAM) causality score of 3 or greater.

Liver histopathology

Available liver biopsies were reviewed by a single expert liver histopathologist (DEK). All samples were scored for multiple histological features as well as an overall pattern of liver injury.[11]

Causality assessment

The causal relationship between the liver injury episode and the minocycline use were evaluated in a standardized fashion by the DILIN causality committee.[12] A DILIN expert opinion causality score varying from 1 (Definite >95% likelihood), 2 (Highly Likely 75–95% likelihood), 3 (Probable 50–74% likelihood), 4 (Possible 25–49% likelihood) to 5 (unlikely <25% likelihood) was assigned by consensus agreement of committee members for all of the retrospective and prospective DILIN cases. In addition, a RUCAM score was calculated for each case and implicated agent.[13] In participants with two or more implicated drugs, an overall causality score was assigned to the case and then an individual causality score for each drug was given.

Controls

Since DILI has a very low prevalence and minocycline is widely prescribed in healthy individuals with an estimated 4.2 million prescriptions of tetracyclines per year in the US, unselected population samples were used as study controls.[14] We selected 10,588 Caucasian controls from different available sources; the Welcome Trust Case Control Consortium (WTCCC) (http://www.wtccc.org.uk), the population reference sample (POPRES) and PGX4000118 and Spanish Bladder cancer cohort from dbGAP (phs000346.v1). Since all cases of minocycline DILI were determined to be of primarily Northern European ancestry, the set of ancestry-matched controls totaled 6,835 individuals. Since prior medication exposure history was not available for the controls, we presume that none of these patients previously received minocycline.

Genome-wide SNP and HLA analysis

Genome-wide genotyping of DILI cases was performed by the Broad Institute in Boston by Illumina Infinium HumanCoreExome BeadChip (n = 19) or at the Duke Center for Human Genome Variation on the Illumina 1Mduo array (n = 6). A total of 505,740 markers shared across the different genotyping platforms used for DILI cases and controls passed quality control (QC) and no samples were excluded for low quality profile.

For each cohort, single nucleotide polymorphisms (SNPs) with poor quality data were pruned before the imputation to avoid false positives. The imputation was performed by batches dividing the cohorts by the genotyping platform used. For each batch, we first phased the data by SHAPEIT (version v2.r727),[15] to increase the accuracy of the imputation. Then, imputation was carried out using IMPUTE2 (version 3) with the 1,000 Genomes Project (release v321) dataset as the reference panel.[16] We used an ethnically mixed panel to improve the quality of the imputation for rare variants. We retained imputed genotypes with: (a) posterior probability >0.9 in each genotyping batch, (b) no significant difference in missingness between cases and controls (χ^2 test, p value >0.0001), (c) no significant deviation from Hardy-Weinberg equilibrium (p value >0.0001), (d) missing data not greater than 5% in each single genotyping batch, (e) info score greater than 0.8 in each genotyping batch. Since the imputation quality is higher for common variants, we selected SNPs with minor allele frequency (MAF) in the 1,000 Genomes Project greater or equal of 0.01. The imputed cohorts were then merged and genotyped SNPs were used to replace imputed SNP genotypes if previously eliminated during the build of the batch groups. For each imputed SNP, possible

Download English Version:

https://daneshyari.com/en/article/5660717

Download Persian Version:

https://daneshyari.com/article/5660717

Daneshyari.com