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ORIGINAL ARTICLE

Features and outcomes from a retrospective study of 570 hospitalized Chinese patients with drug-induced liver injury

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KEYWORDS
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Summary
Aims: To investigate the clinical features and outcomes of hospitalized patients with drug-induced liver injury (DILI).
Methods: The medical records of hospitalized patients with DILI from January 1997 through July 2016 were reviewed.
Results: Five hundred seventy cases were reviewed, of which 381 (66.8%) were female. Four hundred fifty-eight cases (80.4%) presented with hepatocellular injury, 53 (9.3%) with cholestatic injury and 59 (10.4%) with mixed injury. Chronicity was more common in cholestatic and mixed injury cases than in hepatocellular cases ($P < 0.001$). In the hepatocellular injury group, patients in the severity score ≥ 3 group were younger than the patients in the severity score ≤ 2 group ($P = 0.040$). In the entire cohort, 487/570 (85.4%) patients resolved, 57/570 (10.0%) developed chronic liver injury, and 11/570 (1.9%) died. Thirty-two acute DILI patients with severity scores of 3 received steroid therapy, but no improvement was observed in the recovery time or resolution rate of these patients compared with that of the non-steroid group. Chinese herbal medicines were the most commonly used drugs, followed by antimicrobials, cardiovascular agents, endocrine agents, and nonsteroidal anti-inflammatory drugs (NSAIDs).
Conclusions: Hepatocellular injury was the most common DILI pattern, and 10.0% of patients developed chronic DILI. Steroid therapy was not associated with an improved recovery time or survival in acute severe DILI patients.

Introduction

Drug-induced liver injury (DILI) is a serious health problem faced by practicing physicians and the pharmaceutical industry and continues to be a barrier for new drug

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development and has led drugs to be removed from clinical use [1,2]. DILI is a rare adverse drug reaction that can lead to acute liver injury or even death [3]. The true incidence of DILI is difficult to determine. A few studies have reported an annual incidence of DILI ranging between 14 and 20 cases per 100,000 inhabitants in the general population in Europe, but this incidence may be underestimated [1,4–6]. DILI is usually a self-limiting disease but sometimes may have serious consequences. DILI accounts for approximately 13–17% of cases of fulminant liver failure and has replaced viral hepatitis as the most frequent cause of acute liver failure with high mortality [7–10]. The pathogenesis and risk factors for DILI are poorly understood [11,12]. The clinical presentation of DILI is not specific and varies from asymptomatic liver test abnormalities to acute or chronic liver disease [13]. Approximately 70% of the patients in the Drug-induced liver injury network (DILIN) and Spanish registries had jaundice, and patients with jaundice have worse outcomes [7,14]. DILI is a significant health problem in the general population [15]. However, definitive therapies for DILI with or without acute liver failure (ALF) are not available, and corticosteroid therapy is still controversial [3].

In China, traditional Chinese drugs are widely used, and herbal medicines are considered one of the leading causes of DILI [16,17]. Conversely, the most commonly implicated drugs in Western countries are antimicrobials [5,6,13]. Thus, the clinical features and outcomes of DILI in Chinese patients may differ from those observed in patients from the United States and Europe. A lack of evidence regarding the efficacy of steroid therapy for DILI has been noted. Herein, we retrospectively analyzed clinical data from 570 patients with DILI who were hospitalized at a single tertiary care center.

Materials and methods

Patients

Peking university first hospital is a tertiary hospital with 1574 beds and annual admission of about 80,000 patients. The patients were hospitalized with a principal diagnosis of DILI at the Peking university first hospital from January 1997 through July 2016. Cases of patients who were discharged with a principal diagnosis of DILI (ICD-10 code: K71.901, K71.601) were reviewed through electronic medical record system. The enrollment protocol is shown in Fig. 1.

Assessment of clinical patterns of liver injury

According to the Council for International organizations of medical sciences (CIOMS) criteria [18], DILI is classified as hepatocellular, cholestatic or mixed based on its *R*-value. The *R*-value is defined as the serum alanine aminotransferase (ALT)/upper limit of normal (ULN) ratio divided by the serum alkaline phosphatase (ALP)/ULN ratio. *R*-values > 5 were classified as hepatocellular, < 2 as cholestatic, and 2–5 as mixed injury.

Severity assessment

The severity assessment was completed according to the Chinese guidelines for the diagnosis and treatment of DILI in 2015 [19]. The severity was scored as follows: 1 (mild), serum enzyme elevations with TBIL < 2.5 × ULN and INR < 1.5; 2 (moderate), serum enzyme elevations and TBIL ≥ 2.5 × ULN or an INR ≥ 1.5; 3 (severe), serum enzyme elevations and TBIL ≥ 5 × ULN with or without an INR ≥ 1.5; and 4 (acute liver failure), serum enzyme elevations and TBIL ≥ 10 × ULN or a daily elevation of TBIL ≥ 17.1 μmol/L, an INR ≥ 2.0 or PTA < 40% and signs of hepatic or other organ failure related to DILI.

Definitions of DILI states

The resolution of DILI was defined as laboratory parameters that returned to normal ranges or values lower than the CIOMS laboratory criteria [18].

DILI chronicity was defined as persistent biochemical abnormalities and/or other signs or symptoms of ongoing liver disease lasting for more than 6 months after DILI onset.

Disease course: the course of the disease is defined as the time from symptoms appearance or biochemical tests abnormality to the time discharge from hospital.

The normal ranges of the laboratory parameters were as follows: ALT, 0–40 IU/L; ALP, 40–160 IU/L; TBIL, 1.7–20 μmol/L; and PTA, 75–158%.

Statistical analysis

All statistical analyses were performed using the SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, such as the means with standard deviations (SDs), medians with interquartile ranges (IQRs) and frequency distributions, were used to describe the cohort. Differences between groups were tested using the X^2 test and Fisher's exact test for categorical variables. Continuous variables were compared using the Mann-Whitney U test for two nonnormal datasets and the Kruskal-Wallis test for more than two nonnormal datasets. The t test was used for two normal datasets, and ANOVA was used for more than two normal datasets. The results were considered statistically significant when $P < 0.05$.

Results

Patient demographics and clinical features

Five hundred seventy patients whose clinical profiles met the inclusion criteria were included as study subjects. Our cohort comprised 189 men (33.2%) and 381 women (66.8%) with a mean age of 52 (range: 13–90) years. Of the 570 cases, 96 (16.8%) had fever, 68 (11.9%) had eosinophilia. All patients were tested for serum autoantibodies, which included antinuclear antibody (ANA), anti-smooth muscle antibodies (SMA) and antimitochondrial antibodies (AMA). 117 (20.5%) patients tested positive for ANA; a significant difference in gender was observed within this patient cohort, which included 93 (79.5%) females and 24 (20.5%) males ($P = 0.001$). Additionally, 6 of the patients in this ANA-positive cohort were positive for SMA, and 10 cases were positive for AMA. Combining titers of serum autoantibodies, serum IgG/erythrocyte sedimentation rate (ESR) level with

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